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Studies on synthesis and evaluation of quantitative structure–activity relationship of 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]-azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides

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Abstract—A new series of 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides has been synthesized and subjected to acute antibacterial and antifungal screening studies. All the derivatives belonging to this series delineated remarkable activity as compared to standard drugs (ampicillin and clotrimazole). Compounds are quantitatively analyzed in relation to their different physicochemical parameters. Significant correlations were obtained between biological activity and polarizability parameter (MR).

1. Introduction

Indolizines and azetidines, the nitrogen containing heterocyclic systems, have been widely distributed in nature. In particular, indolizines have been the subject of substantial attention by chemists due to their biological properties such as antifungal,[1] antimycobacterial,[2] antiherpes[3] and antineociceptive.[4] The other well-known pharmacological applications associated with this ring compounds are well documented in the literature.[5,6] This nucleus acts as the prototype molecule for the large class of azolozines particularly, aza-indolizine. Likewise, compounds containing azetidine ring are present in many drugs exhibiting potent analgesics[7] and antiviral activities.[8,9] Recent discoveries had also displayed other pharmacological profile of these compounds.[10] These findings had led to a spate of synthetic studies of various azetidine analogues.[11,12]

Although, a number of antimicrobial agents have been developed in order to resist various pathogenic microbes, but still there is a lack of an ideal drug, which can eradicate this problem easily. Based on these facts and in continuation of our interest in developing simple and efficient route for the synthesis of heterocycles,[13–16] it was aimed to compose an elegant synthetic route for condensed system containing both indolizine and azetidine nuclei. We report herein the synthesis and studies on biological evaluation of 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides.

2. Chemistry

Initially, 1,3-disubstituted-propane-1,3-dione[(3-hydroxypyridin-2-yl)hydrazones] **1a**–**r** was prepared from 2-amino-3-hydroxypyridine under diazotization conditions using hydrobromic acid according to the reported[17] procedure modified by us. Compounds **1a**–**r** were nitrated to provide yellowish crystals of *N*-protected derivatives, that is, 1,3-disubstituted 2[(3-hydroxypyridin-2-yl)(*N*-nitro)hydrazono]propane-1,3-diones **2a**–**r**. It was then added to a constantly stirred solution of 1,4-dioxan, triethylamine and chloroacetylchloride to give disubstituted-3-chloro-1-[(3-hydroxypyridin-2-yl)(*N*-nitro)amino]-4-oxoazetidine-2,2-dicarboxylates **3a**–**r**. Furthermore, treatment of **3a**–**r** with a pertinent alkyl/aryl halide and phosphorus trichloride

Keywords: Indolizine; Azetidine; Synthesis; Antibacterial; Antifungal; QSAR; Molar refractivity.
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resulted in the formation of a ylide as an intermediate, which on treatment with phosphorus trichloride and acetonitrile in presence of triethylamine yielded 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides **4a**–**r**.

3. Biological activities

The in vitro antimicrobial activity of the 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides were investigated against several representative pathogenic bacteria and fungi. Nutrient agar media and saboured dextrose agar was employed for bacterial and fungal growth, respectively. Inocula containing approximately 10^7 CFUs/mL of bacteria and 10^6 CFUs/mL of fungi were prepared from broth culture in log phase. Bacterial and fungal plate was incubated at 37 °C for 24 h for bacteria and 30 °C for 28 h for fungi. Four microbial strains including *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 2943 as bacteria and *Aspergillus niger* ATCC 16404, *Candida albicans* ATCC10231 as fungus were used in antimicrobial assay. Ampicillin and clotrimazole were also screened under similar conditions as reference antibacterial and antifungal drug, respectively. All the synthesized compounds delineate profound antimicrobial potency on both bacteria and fungi as compared to reference drugs, which is further supported by biological investigations shown in Table 1. The screening results reveals that reported compounds showed a remarkable effect on the bacteriocidal/bacterostatic potency. However, these compounds have been found to show least to moderate activity on the growth of *A. niger*. The pattern followed by tested compounds is shown below:

$$S.\ aureus > B.\ subtilis > C.\ albicans > A.\ niger$$

3.1. QSAR analysis

In order to deduce the correlation of observed activity, expressed in terms of MIC of reported compounds with different structural parameters, systematic QSAR investigations have been carried out using the linear free energy relationship (LFER) model proposed by Hansch and Leo.[18]

$$\log\frac{1}{C} = k_1 a + k_2 b + k_3$$

where C is molar dose that produces or prevents certain biological response, a and b are the descriptors to be investigated and k_1, k_2, k_3 are the constants.

The activity data, MIC represents the minimal concentration of compounds that inhibits visible growth. The same are further expressed as −log MIC on molar basis and used as dependent variables to get linear relationship in QSAR model. The calculated parameters used in present studies include molar refractivity (MR), Van der Waals volume (VDW), connolly accessible area (CAA), connolly molecular area (CMA), connolly solvent excluded area (CSEV), dipole–dipole energy (DDENE), partition coefficient (PC). The above-mentioned parameters were calculated by using Chem 3D 6.0 software.[19] Further, HOMO and LUMO energies were calculated by semiempirical PM3[20] studies using MOPAC 6.0 package.[21] Some indicator variables were

Table 1. The in vitro antimicrobial activity of 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides **4a**–**r**

Compound	R	R′	R″	−log MIC (μg/mL)			
				Bacteria		Fungi	
				SA	BS	CA	AN
4a	COOH	C_6H_5	C_6H_5	4.980	4.870	4.745	4.649
4b	COOH	OC_2H_5	CH_2Br	4.367	4.246	4.191	4.171
4c	COOH	OC_2H_5	OC_2H_5	4.304	4.201	4.128	4.109
4d	COOH	OCH_3	OCH_3	4.147	4.107	4.036	4.020
4e	COOH	OC_2H_5	CH_3	4.179	4.115	4.043	4.034
4f	COOH	NHC_6H_5	CH_3	4.549	4.406	4.373	4.342
4g	COOH	C_6H_5	CH_3	4.451	4.316	4.262	4.250
4h	COOH	CH_3	CH_3	4.063	4.045	4.008	3.972
4i	COOH	CN	OC_2H_5	4.208	4.154	4.083	4.073
4j	COOH	CH_3	OCH_3	4.114	4.067	4.016	4.000
4k	C_6H_5	OC_2H_5	CH_2Br	4.881	4.794	4.631	4.578
4l	C_6H_5	OC_2H_5	OC_2H_5	4.689	4.599	4.502	4.441
4m	C_6H_5	OC_2H_5	CH_3	4.703	4.606	4.527	4.460
4n	C_6H_5	NHC_6H_5	CH_3	5.116	5.037	4.970	4.773
4o	C_6H_5	C_6H_5	CH_3	5.106	4.902	4.850	4.691
4p	C_6H_5	CH_3	CH_3	4.399	4.256	4.193	4.181
4q	C_6H_5	CN	OC_2H_5	4.566	4.491	4.408	4.372
4r	C_6H_5	CH_3	OCH_3	4.471	4.341	4.267	4.254
A	—	—	—	3.907	4.606	—	—
C	—	—	—	—	—	3.139	3.236

SA = *S. aureus*; BS = *B. subtilis*; CA = *C. albicans*; AN = *A. niger*; A = ampicillin; C = clotrimazole.

also used to describe the effect of specific binary alterations such as presence of –COOH (IN1) and $-C_6H_5$ (IN2).

All the calculated parameters were first subjected to correlation studies and only those parameters considered further with intercorrelation <0.5, depending on their individual correlation with biological activity. The best fit between −log MIC values and these explaining parameters were obtained through multiple regression analysis (MRA) employing the method of least square using VALSTAT software.[22] Calculated parameters and correlation matrix needed for MRA is shown in Tables 2 and 3.

Only, molar refractivity exhibited ($r^2 > 0.95$) a good correlation with biological activity (Table 3). The statistical quality of the resulting models, as depicted in Eqs. 1–4, is determined by r^2 (coefficient of determination), s (standard error of estimate), F (F-statistics). It is worth mentioning that no outliers have been detected and the equations were derived using the entire data set ($n = 18$).

QSAR model for *S. aureus*

$$-\log \mathrm{MIC} = [1.4216(\pm 0.328851)] + \mathrm{MR}\ [0.228041(\pm 0.0241034)]$$
$$n = 18, \quad r^2 = 0.962, \quad s = 0.068, \quad F = 406.477 \tag{1}$$

QSAR model for *B. subtilis*

$$-\log \mathrm{MIC} = [1.56255(\pm 0.383329)] + \mathrm{MR}\ [0.210531(\pm 0.0280963)]$$
$$n = 18, \quad r^2 = 0.938, \quad s = 0.079, \quad F = 254.977 \tag{2}$$

Table 2. Values of descriptors calculated for 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides **4a**–**r**

Compound	HOMO	LUMO	VDW	DDENE	PC	CSEV	CMA	CAA	MR	IN1	IN2
4a	−9.198	−1.592	8.606	12.522	3.456	436.444	449.403	768.382	15.541	1	0
4b	−9.341	−1.702	5.241	23.562	1.533	383.819	390.942	677.648	12.840	1	0
4c	−9.337	−1.704	8.679	23.828	2.029	384.103	410.083	717.713	12.680	1	0
4d	−9.357	−1.720	7.483	23.700	0.971	349.299	369.095	649.029	11.753	1	0
4e	−9.344	−1.707	5.068	19.515	1.280	359.136	376.871	659.563	12.063	1	0
4f	−9.186	−1.569	2.037	3.543	1.756	398.978	403.948	695.953	13.863	1	0
4g	−9.235	−1.620	5.734	11.594	1.993	386.834	402.233	693.863	13.494	1	0
4h	−9.287	−1.663	2.714	10.786	0.530	336.285	352.242	617.191	11.447	1	0
4i	−9.433	−1.787	4.950	33.917	0.577	361.607	374.047	694.692	12.077	1	0
4j	−9.356	−1.716	4.510	19.410	0.750	342.607	356.737	623.714	11.600	1	0
4k	−8.512	−1.029	12.019	20.009	3.725	446.627	435.674	730.893	14.793	0	1
4l	−8.601	−1.262	14.941	16.280	4.221	460.477	444.276	741.482	14.633	0	1
4m	−8.575	−2.044	12.303	14.544	3.613	452.818	431.799	726.599	14.716	0	1
4n	−8.965	−1.533	11.222	10.247	2.687	450.559	452.654	758.411	15.933	0	1
4o	−8.834	−1.478	11.927	5.7062	4.471	465.652	397.882	659.709	15.564	0	1
4p	−8.704	−1.323	7.849	10.312	2.722	420.085	372.68	636.698	13.399	0	1
4q	−8.669	−1.367	12.5969	23.404	1.408	417.145	422.921	724.031	14.325	0	1
4r	−8.717	−1.339	10.171	13.247	2.943	411.407	386.837	660.928	13.552	0	1
A	−9.337	−0.827	7.445	0.675	−1.204	280.439	304.619	555.251	9.144	—	—
C	−8.956	−0.228	14.212	2.072	5.254	285.356	295.911	538.175	10.395	—	—

A = ampicillin; C = clotrimazole.

Table 3. Correlation matrix of molecular descriptor calculated for **4a**–**r**

	SA	BS	CA	AN	MR	HOMO	LUMO	VDW	DDENE	PC	CSEV	CMA	CAA	IN1	IN2
SA	1.000														
BS	0.993	1.000													
CA	0.993	0.996	1.000												
AN	0.996	0.996	0.995	1.000											
MR	0.981	0.970	0.970	0.984	1.000										
HOMO	0.586	0.579	0.557	0.594	0.659	1.000									
LUMO	0.388	0.378	0.344	0.381	0.397	0.600	1.000								
VDW	0.663	0.677	0.649	0.664	0.704	0.806	0.442	1.000							
DDENE	0.464	0.419	0.465	0.454	0.472	0.299	0.201	0.014	1.000						
PC	0.825	0.793	0.778	0.801	0.835	0.744	0.447	0.765	0.458	1.000					
CSEV	0.915	0.896	0.888	0.910	0.949	0.804	0.454	0.815	0.411	0.929	1.000				
CMA	0.223	0.208	0.206	0.195	0.148	0.087	0.096	0.055	0.292	0.398	0.185	1.000			
CAA	0.153	0.179	0.135	0.165	0.163	0.140	0.104	0.104	0.071	0.009	0.023	0.044	1.000		
IN1	0.342	0.356	0.329	0.342	0.338	0.124	0.031	0.023	0.128	0.233	0.189	0.173	0.848	1.000	
IN2	0.501	0.483	0.505	0.500	0.578	0.775	0.302	0.730	0.330	0.578	0.694	0.163	0.342	0.197	1

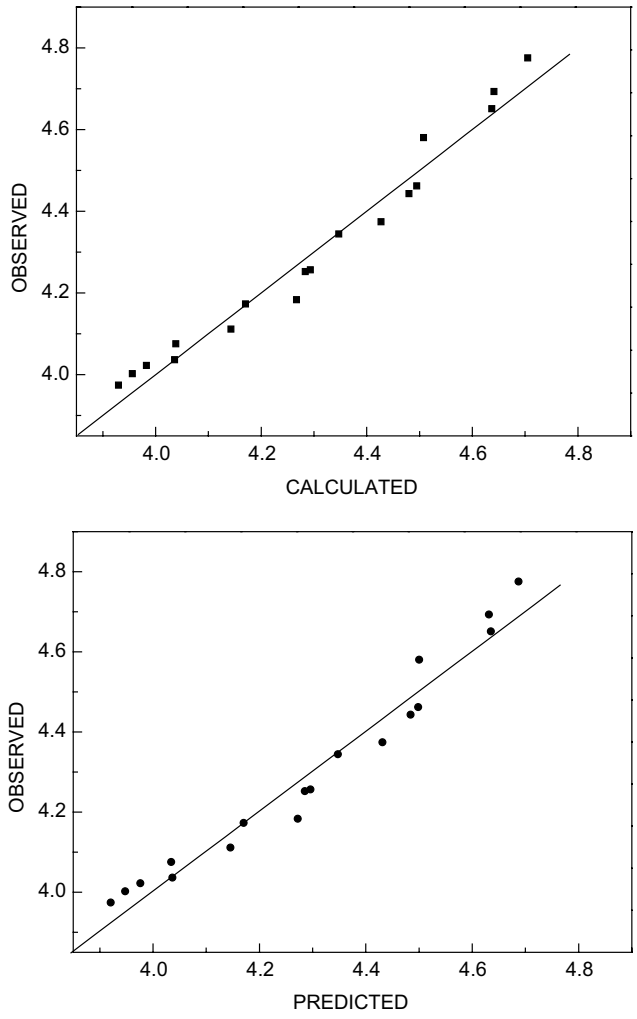


Figure 1. Plots of observed versus calculated and observed versus predicted activity of **4a**–**r** against *S. aureus* (Eq. 1).

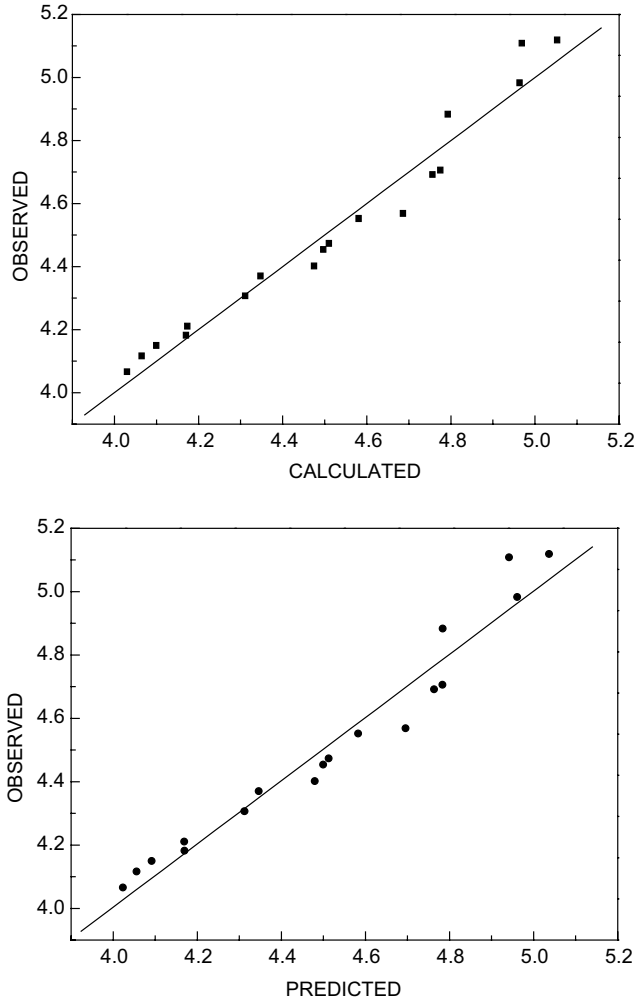


Figure 2. Plots of observed versus calculated and observed versus predicted activity of **4a**–**r** against *A. niger* (Eq. 4).

QSAR model for *C. albicans*

$$-\log \mathrm{MIC} = [1.61463(\pm 0.369476)] + \mathrm{MR}\ [0.20129(\pm 0.027081)]$$
$$n = 18, \quad r^2 = 0.940, \quad s = 0.076, \quad F = 250.889 \tag{3}$$

QSAR model for *A. niger*

$$-\log \mathrm{MIC} = [1.95319(\pm 0.229365)] + \mathrm{MR}\ [0.172809(\pm 0.0168114)]$$
$$n = 18, \quad r^2 = 0.968, \quad s = 0.047, \quad F = 479.831 \tag{4}$$

The F-value obtained in Eqs. 1–4 are found statistically significant at >99.90% level since all the calculated F value are far higher as compared to tabulated value, that is, $F_{1,16}\alpha_{0.001} = 16.1$. Similarly, cross validation of obtained equations were subsequently checked by employing the LOO method and calculation of all the related cross-validation parameters viz. PRESS (predicted residual sum of the square), S_{PRESS} (uncertainty of prediction), SDEP (standard error of prediction), r^2_{CV} (cross-validated correlation coefficient) and r^2_{bsp} (bootstrapping r^2). The calculated and predicted activities of the synthesized compounds were in good accordance with the observed activities as shown in Figures 1,2.

Table 4. Cross-validation parameters

Eq.	Compds used	PRESS	SSY	PRESS/SSY	S_{PRESS}	SDEP	$r^2{}_{\mathrm{CV}}$	$r^2{}_{\mathrm{bsp}}$
1	18	0.0934	1.9236	0.0486	0.0765	0.0721	0.9514	0.9525
2	18	0.1269	1.6764	0.0757	0.0891	0.0840	0.9243	0.9377
3	18	0.1237	1.5334	0.0807	0.0879	0.829	0.9193	0.9375
4	18	0.0453	1.0982	0.0413	0.0532	0.0502	0.9587	0.9596

Table 5. Physical and spectral assignments for 5-[3′-chloro-4′,4′-disubstituted propane-1,3-dione-2-oxoazetidinyl(*N*-nitro)amino]-6-hydroxy-3-phenyl[1,3]azaphospholo[1,5-*c*]pyridin-1-yl phosphorus dichlorides

Compd	Yield	Mp (°C)	Found (calcd) (%)			IR ν_{max} (cm^{-1})	^{1}H NMR (δ ppm)	Mass [*m*/*z* (% RA)]
			C	H	N			
4h	75	158–159	33.00 (33.14)	1.93 (2.04)	10.20 (10.31)	3825 (OH), 3040 (–C=H_{as}, sp^2), 2951 (C=H_s, sp^2), 2738 (C–H_{as}, sp^3), 2550 (br, COOH, characteristic), 2353 (C=P), 2676 (C–H_s, sp^3), 1750 (C=O, four-membered), 1715 (C=O), 1646 (C=C/C=N), 1520, 1473, 1396 (C–···C ring str.), 1396 (N–NO_2), 1173 (C–P), 671 (P–Cl)	2.0 (s, 6H, $2\times CH_3$), 4.1 (s, CH–Cl), 10.37 (s, OH), 12.3 (br s, OH), 7.1 (d, Ar-H_1, Ar-H_2)	543 [M^+ (12)], 545 [M^++2 (36)], 547 [M^++4 (36)], 549 [M^++6 (12)], 93 (100)
4l	70	177–178	41.40 (41.57)	2.92 (3.01)	8.71 (8.81)	3831 (OH), 3050 (–C=H_{as}, sp^2), 2940 (C=H_s, sp^2), 2748 (C–H_{as}, sp^3), 2676 (C–H_s, sp^3), 2357 (C=P), 1750 (C=O, four-membered), 1715 (C=O), 1646 (C=C/C=N), 1520, 1473, 1398 (C–···C ring str.), 1396 (N–NO_2), 1173 (C–P), 671 (P–Cl)	1.44 (t, 6H, $2\times CH_3$), 3.20 (q, 4H, $2\times CH_2$), 4.25 (s, CH), 6.57, 7.04 (br s, m, Ar-H_1, Ar-H_2), 7.42 (s, C_6H_5)	636 [M^+ (13)], 638 [M^++2 (39)], 640 [M^++4 (39)], 642 [M^++6 (13)], 93(100)
4n	68	165–166	45.85 (46.00)	2.72 (2.78)	10.69 (10.73)	3432 (OH), 3265 (NH–C_6H_5), 3138 (=C–H_{as}, sp^2), 3080 (=C–H_s, sp^2), 2364 (C=P), 1760 (C=O, four-membered), 1715 (C=O, NH–C_6H_5), 1663 (C=O, $COCH_3$), 1603 (C=C/C=N), 1548, 1498, 1444 (C–···C ring str.), 1361 (N–NO_2), 1240 (C–P), 557 (P–Cl)	2.26 (s, 3H, CH_3), 7.08 (d, virtually coupled, Ar-H_1), 7.11 (d, virtually coupled, Ar-H_2), 7.30 (s, C_6H_5), 9.28 (s, NH), 12.9 (s, OH)	653 [M^+ (10)], 655 [M^++2 (30)], 657 [M^++4 (30)], 659 [M^++6 (10)], 224 (6), 177 (9), 135 (2), 119 (4), 93 (100), 65 (21), 64 (14), 52 (19)]

PRESS is a good estimate of the real prediction error of the model. Its value less than SSY indicate that the proposed model has good predictive power and is better than chance. In this regard, all the four models proposed by us (Eqs. 1–4) are statistically significant. Further, to be a reasonable QSAR model PRESS/SSY ratio should be smaller than 0.4, and its value smaller than 0.1 indicates an excellent model. The data pertaining to Table 4 indicate that for all the four proposed models this ratio is $\ll$0.1 suggesting all of them to be excellent model. Moreover, the value of cross-validated correlation coefficient (r^2_{CV}) and bootstrapping r^2 are further supporting the predictive power of these explaining models (Eqs. 1–4).

Since, molar refractivity accounts for the polarizability and thus for the size and polarity of the groups as indicated by Eqs. 1–4, suggesting that MR plays a significant role towards the expressed biological activities, which is possible due to steric interactions occurring in polar spaces. It can be suggested that the presence of –COOH group at C-3 of indolizine nucleus further increases the inhibitory action on the growth of tested panel of bacteria and fungi as revealed by Table 1.

4. Experimental

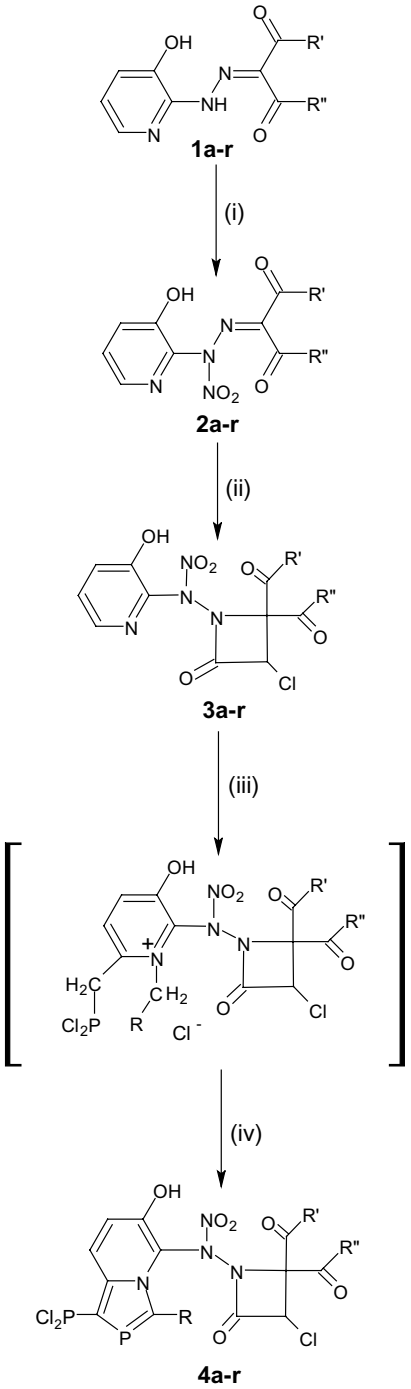
All the chemicals used are of analytical grade. Melting points were taken in open capillary tubes using an electric melting point apparatus. All the melting points reported are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz with a Bruker advance DRX 300 instrument using TMS as an internal stranded. IR spectra were run on a Perkin Elmer model 377-spectrophotometer using KBr pellets. Analytical thin layer chromatography was performed using E. Merck Silica gel a 0.50 mm plate (Merck no. 5700).

4.1. Synthesis of disubstituted-3-chloro-1-[(3-hydroxypyridin-2-yl)(*N*-nitro)amino]-4-oxoazetidine-2,2-dicarboxylates (3a–r)

2-Amino-3-hydroxypyridine (2.2 g, 0.02 M) was diazotized by hydrobromic acid using different active methylene compound (0.02 M) as per the procedure reported[17] and modified by us to give 1,3-disubstituted propane 1,3-dione[(3-hydroxypyridin-2-yl)hydrazones] **1a**–**r**. In a 250 cm^3 round-bottom flask, 3-disubstituted propane 2,4-dione[(3-hydroxypyridin2-yl)hydrazone] **1a**–**r** (0.02 M), was taken and subjected to nitration to give 1,3-disubstituted 2[(3-hydroxypyridin-2-yl)(*N*-nitro)-hydrazono]propane-1,3-diones **2a**–**r**. To this, triethylamine (2.4 mL, 0.02 M), chloroacetyl chloride (1 mL, 0.02 M) and measured quantity of 1,4-dioxane (50 mL) were added and all the contents were stirred for 4 h to afford disubstituted-3-chloro-1-[(3-hydroxypyridin-2-yl)(*N*-nitro)amino]-4-oxoazetidine-2,2-dicarboxylates **3a**–**r**.

4.2. Synthesis of 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides (4a–r)

Disubstituted-3-chloro-1-[(3-hydroxypyridin-2-yl)(*N*-nitro)amino]-4-oxoazetidine-2,2-dicarboxylates **3a**–**r** (0.01 M) was taken in 250 cm^3 round-bottom flask and an equimolar quantity of a solution of an alkylating agent viz. benzyl chloride, monochloroacetic acid in tetrahydrofuran (25 mL) was added. All the contents were stirred for 30 min at room temperature and resulted in the formation of a solid compound. It was then washed with diethyl ether (10 mL), filtered and dried in vacuum. The resultant compound (0.01 M) thus obtained was then suspended in acetonitrile (20 mL) in a beaker and cooled to 0–5 °C. To this, triethylamine (4 mL, 0.04 M) was added and the mixture was stirred for 30 min. Further, a solution of phosphorus trichloride (0.02 M) in acetonitrile (1 mL) was added dropwise. The reaction mixture gradually changes from pale yellow to brown and allowed to stand at room temperature for 30 min and then stirred further for 10 h. The compounds 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides (**4a**–**r**) obtained were recrystallized from methanol. Structures of all the synthesized compounds have been ascertained on the basis of consistent physical and spectroanalytical data (Table 5). Synthetic pathway of all sequential steps is depicted in Scheme 1.



Scheme 1. Reagents and conditions: (i) HNO_3/H_2SO_4, 0–5 °C; (ii) $(C_2H_5)_3N$, 1,4-dioxane, $ClCOCH_2Cl$, stirring, 4 h; (iii) RX, THF, PCl_3; (iv) CH_3CN, PCl_3, $(C_2H_5)_3N$, stirring, 10 h.

Conclusively, a series of compounds incorporating azetidine and phosphaindolizine heterocyclic nuclei viz., 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)-(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides has been synthesized as potent antimicrobial agents. Furthermore, QSAR studies performed on these compounds have revealed that the substitution of bulky group with higher polarizability probably enhances the potency of these compounds as antibacterial and antifungal agents. Influence of other substituents at this site will be the matter of further investigation.

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