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Studies on synthesis and evaluation of quantitative structure–activity relationship of 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides

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Abstract—A new series of 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides **11a**–**p** has been synthesized and evaluated as antimicrobial agents. Structures of all the synthesized compounds were established on the basis of elemental analysis and spectroscopic data. Quantitative structure–activity relationship (QSAR) investigations were applied to find out the correlation between the experimentally evaluated activity with various parameters of the compounds studied. QSAR equations showed that the molecular refractivity correlates significantly with the antimicrobial activity.

Benzodiazepines (BDZs) and their derivatives are well known to the chemists mainly because of the broad-spectrum biological properties exhibited by this class of compounds.[1–5] Interest in the chemistry, synthesis and biology of this pharmacophore continues to be fuelled by their activity against a variety of CNS disorders as well as due to wide biological properties such as antianxiety, anticonvulsant, sedative/hypnotic, muscle relaxing and tranquilizing.[6–8] Many drugs incorporating BDZ core nucleus which extensively binds to plasma and tissue proteins have been developed over the past two decades and they became the most commonly prescribed group of psychotherapeutic drugs worldwide.[9,10] After the discovery of benzodiazepine receptors in the CNS and peripheral tissues[11,12] many attempts have also been made to correlate the molecular structure with the biological activity of these compounds.[13] In an attempt to prepare even more potent drugs, the ability of BDZ analogues to adjoin with another four- or five-membered ring has been investigated.[14–16] It has been reported that the introduction of an additional five-membered heterocyclic ring to seven-membered azepine nucleus tends to exert profound influence in conferring novel biological activities in these molecules.[17] The attachment of a five-membered ring often produces potent anti-HIV active compounds.[11–13] These compounds exert their biological activity by covalently binding to the N-2 of guanine in the minor groove of DNA through the imine or equivalent functionality at N10–C11 of the BDZ. The aminal linkage thus interferes with DNA function.[18] Furthermore, these molecules have been shown to interact with DNA in a sequence-selective manner as a result they may have the potential to inactivate particular genes.[19]

Hence, in view of the variegated importance associated with the five-membered phosphole ring system, we decided to link up this moiety with the benzodiazepine nucleus in order to frame the novel molecular architecture of annulated heterophospholobenzodiazepines. Keeping this in mind and in continuation of our enduring research on the synthesis of biologically significant compounds,[20–25] we have attempted the synthesis of hitherto unknown, 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides **11a**–**p** with fascinating structural features.

Keywords: 1,4-Benzodiazepine; Azaphohole; Intramolecular cyclocondensation; Antimicrobial activity; QSAR; Molecular refractive index (MR).
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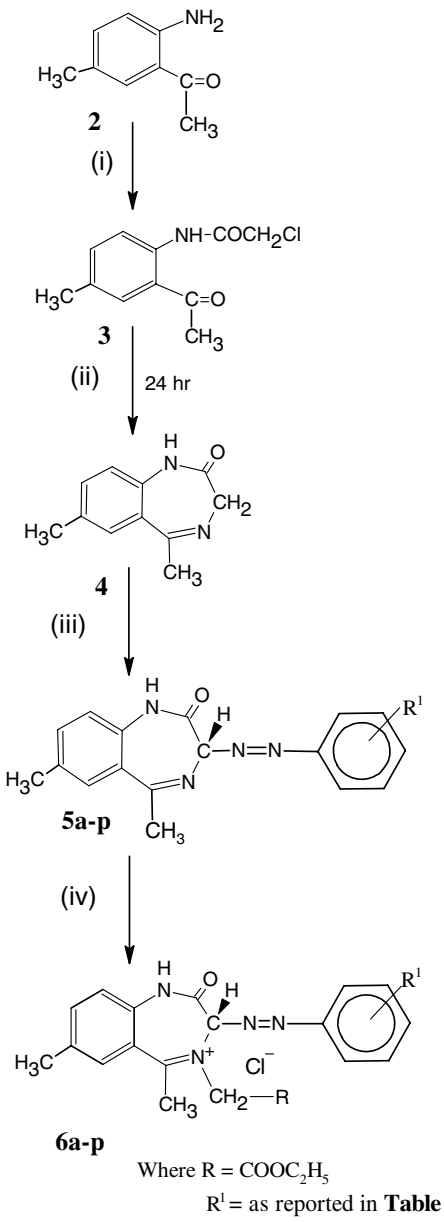
Moreover, to find a role of this nucleus against the problem of multidrug-resistant pathogens, the constructed molecules were screened for their antimicrobial activity.

Additionally, the systematic quantitative structure–activity relationship (QSAR) studies have also been carried out to reach a thorough understanding of the effect of substituents on the observed activities of the synthesized compounds.

The synthetic route to the desired target molecule 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides **11a**–**p** includes the cyclization (**3** → **4**) (Scheme 1) to generate the imine moiety of the B-ring. The approach involves the initial preparation of precursor, viz., chloroacetamidoacetophenone[26] **3** as the representative of B-ring fragment. Subsequently, this was allowed to reflux in ammonia/methanol for 24 h, which leads to cyclization to give 5,7-dimethyl-1, 3-dihydro-2*H*-1, 4-benzodiazepin-2-one **4** in an excellent yield (80%). Moreover, stereochemical asymmetry at C11a of **5a**–**p** was accessible by introducing a diazonium fragment in an electrophilic substitution mode which resulted in the formation of compound (3*S*)-3-arylazo-5,7-dimethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **5a**–**p**.[27] This in turn was allowed to react with an equimolar quantity of a pertinent alkyl halide in THF and stirred for 36 h at room temperature to give the N-alkylated product **6a**–**p** in good yield.[28]



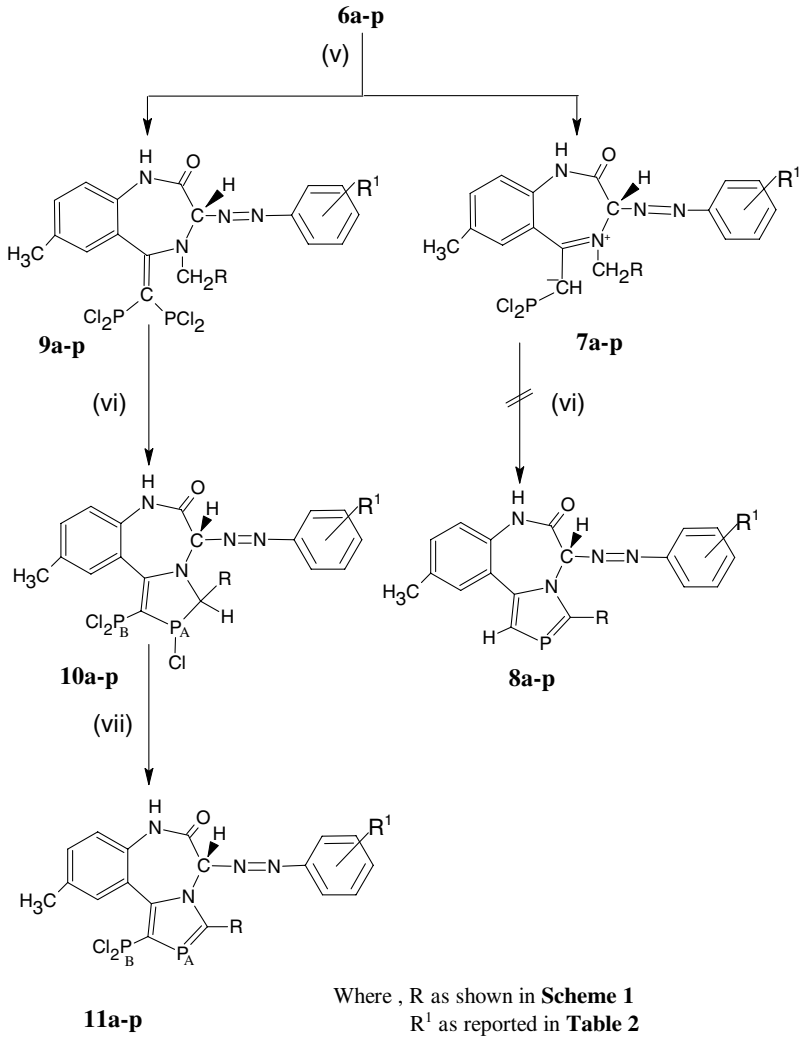
Scheme 1. Reagents and conditions: (i) 1,4-di-oxan, $ClCH_2COCl$, 3 N NaOH, CH_2Cl_2, 30 min; (ii) NH_3/CH_3OH; (iii) $RC_6H_4NH_2$, $NaNO_2$/HCl, 0–5 °C; (iv) $ClCH_2COOC_2H_5$,THF, 36 h.

Condensation of **6a**–**p** with phosphors trichloride (2 equiv) in the presence of triethylamine (3 equiv.) in toluene yielded intermediate synthesis of 5-bis(dichlorophosphino)-ylidene-(3*S*)-*N*-ethoxycarbonyl-7-methyl-3-arylazo-2-oxo-1,2,3,5-tetrahydro-5*H*-1,4-benzodiazepine **9a**–**p**.[29] The initially formed mono dichlorophosphino derivative **7a**–**p** is highly activated and undergoes instantaneous substitution by phosphorus trichloride to provide the bis(dichlorophosphino) derivative **9a**–**p**. Further, the absence of any ^1H NMR signal at δ 6.00 ppm, which is characteristic of a C-5 methine proton, also supports the formation of **9a**–**p**. This was cyclized to give **10a**–**p** on heating with an additional amount of triethylamine in acetonitrile (Scheme 2).

The polarity of the solvent influences the progress of the above reaction. In non-polar solvents such as toluene and xylene, the reaction stops at stage **9a**–**p**, whereas in polar solvents, viz., acetonitrile, ethylacetate the initially formed bis(dichlorophosphino) derivative **9a**–**p** undergoes intramolecular cyclocondensation to form species**10a**–**p** and finally 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides **11a**–**p**.[30]

Structures of all the newly obtained compounds have been ascertained on the basis of their consistent IR, NMR and mass spectral assignments.[31–34]

The newly obtained derivatives were evaluated for in vitro antibacterial activity against *Escherichia coli* ATCC 6633, *Bacillus subtilis* ATCC 16404 and antifungal activity against *Aspergillus niger* ATCC 16404 and *Candida albicans* ATCC 10231. Nutrient agar and saboured dextrose agar were employed for bacterial and fungal growth, respectively. Minimum inhibitory concentrations (MIC) were determined by means of standard 2-fold serial dilution method using agar media.[35] Stock solutions of test compounds were prepared in DMSO at a concentration of 1 mg/mL. Suspension containing approximately 10^7 CFUs/mL of bacteria and 10^6 CFUs/mL of fungi was prepared from broth cultures. Bacterial and fungal plates were made in triplicate and incubated at 37 °C for 16–47 h for bacteria and 48–72 h for fungi. Ampicillin trihydrate and clotrimazole were also screened under similar conditions as



Scheme 2. Reagents and conditions: (v) $CH_2COOC_2H_5CH_3$, PCl_3, Et_3N, 4–6 h; (vi) CH_3CN, PCl_3, Et_3N, 2–4 h, $Et_3NH^+Cl^-$; (vii) PCl_3, Et_3N, 40 min.

reference drugs, respectively. The screening results reveal that reported compounds showed a remarkable effect on the bactericidal potency. However, these compounds have been found to show least to moderate activity on the growth of *C. albicans.* The deduced pattern followed by tested compounds is in the order *E. coli* > *B. subtilis* > *A. niger* > *C. albicans*.

In order to identify substituent effect on the antimicrobial activity, quantitative structure–activity relationship (QSAR)[36] studies of title compounds were preformed. Biological activity data (MIC) were calibrated to their logarithmic values (−log MIC) and are listed in Table 1. The congener series possesses the substitution on the aromatic ring system at 3′ and 4′ positions. QSAR studies were performed by multiple regression analysis (MRA) approach. The calculated parameters used in present studies include molar refractivity (MR), vander Waals volume (VDW), Connolly accessible area (CAA), Connolly molecular area (CMA), Connolly Solvent Excluded Area (CSEV), and partition coefficient (log *P*). These parameters were calculated by using Chem 3D 6.0 Software.[37] Further, electronic parameters like HOMO and LUMO energies were calculated by semiempirical PM3[38] studies using MOPAC 6.0 package.[38] Energy minimized geometry of the parent molecule **11a** is shown in Figure 1. The Hammett substituent constant (σ) values were obtained from the literature.[39]

A correlation analysis was performed on all the descriptors, depending on the inter-correlation among the independent descriptors and also their individual correlation with biological activity. Different possible combinations of parameters were subjected to multiple regression analyses. Calculated parameters and correlation matrix needed for regression analysis are elicited in Tables 2 and 3, respectively.

It has been observed that molar refractivity (MR) tends to correlate with biological activity exclusively. The statistical quality of the resulting models, as depicted in Eqs. 1–4, is determined by *r* (coefficient of correlation), *s* (standard error of estimate) and *F* (F-statistics) values. It is noteworthy that all these equations were derived using entire data set of compounds ($n = 16$) and no outliers were identified.

Table 1. The in vitro antimicrobial activity of substituted [1,3]azaphospholo-[1,5-*d*][1,4]benzodiazepin-3-ethoxycarbonyl-1-phosphorus dichlorides

Compound	R^1	−log MIC (μg/mL)			
		Gram positive bacteria	Gram negative bacteria	Fungi	
		Escherichia coli ATCC 445	*Bacillus subtilis* ATCC 6633	*Aspergillus niger* ATCC 16404	*Candida albicans* ATCC 10231
11a	H	4.05	4.05	4.12	4.10
11b	3-CH_3	4.22	4.25	4.31	4.17
11c	3-COOH	4.36	4.37	4.48	4.32
11d	4-C_2H_5	4.58	4.64	4.64	4.52
11e	3-Cl	4.54	4.46	4.68	4.47
11f	4-OC_2H_5	4.74	4.83	4.74	4.59
11g	3-NO_2	4.73	4.55	4.56	4.50
11h	3-OCH_3	4.30	4.28	4.56	4.39
11i	4-OCH_3	4.26	4.29	4.39	4.24
11j	4-Cl	4.39	4.41	4.51	4.36
11k	4-OH	4.11	4.17	4.18	4.06
11l	3-OC_2H_5	5.04	4.96	4.89	4.78
11m	3-C_2H_5	4.88	4.68	4.82	4.61
11n	4-CH_3	4.17	4.22	4.22	4.09
11o	3-OH	4.20	4.22	4.25	4.11
11p	4-NO_2	4.61	4.52	4.45	4.32
A	—	4.60	4.61	—	—
C	—	—	—	3.23	3.13

A, ampicillin; C, clotrimazole.

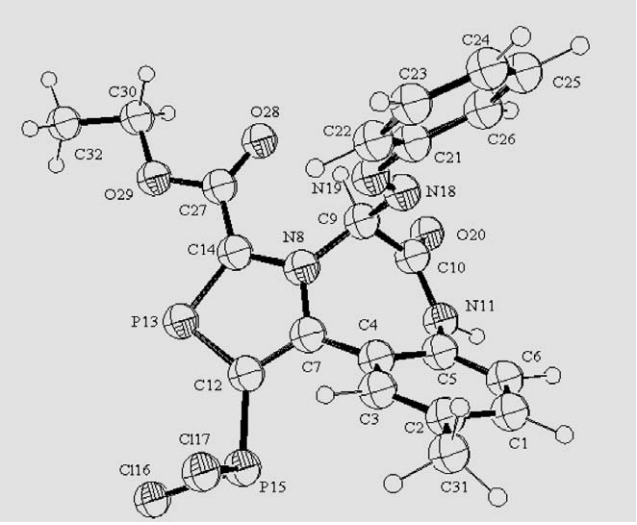


Figure 1. The ORTEP drawing (PM3 optimized geometry) of 10-methyl-6-oxo-5-phenylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*]-[1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichloride **11a** with atom numbering.

QSAR model for activity against *E. coli*

$$-\log \mathrm{BA} = [3.91423(\pm 0.217073)] + \mathrm{MR}[0.756708(\pm 0.280636)]$$
$$n = 16,\ r = 0.841,\ s = 0.163,\ F = 33.921 \quad (1)$$

QSAR model for activity against *B. subtilis*

$$-\log \mathrm{BA} = [3.93497(\pm 0.143867)] + \mathrm{MR}[0.702574(\pm 0.185994)]$$
$$n = 16,\ r = 0.908,\ s = 0.108,\ F = 66.572 \quad (2)$$

QSAR model for activity against *A. niger*

$$-\log \mathrm{BA} = 4.04209(\pm 0.148464)] + \mathrm{MR}[0.630564(\pm 0.191937)]$$
$$n = 16,\ r = 0.884, s = 0.112,\ F = 50.355 \quad (3)$$

QSAR model for activity against *C. albicans*

$$-\log \mathrm{BA} = [3.94185(\pm 0.141714)] + \mathrm{MR}[0.580462(\pm 0.18321)]$$
$$n = 16,\ r = 0.877,\ s = 0.106,\ F = 46.833 \quad (4)$$

The *F*-value obtained in Eqs. 1–4 is found statistically significant at 99% level since all the calculated *F* values are higher as compared to tabulated values. Similarly, cross validation of the obtained equations was subsequently checked by employing the leave-one-out (LOO) method[40] and on the basis of related cross-validation parameters viz. PRESS (predicted residual sum of squares), 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 2 and 3.

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. Thus, in view of this, 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 lesser than 0.4. The data presented in Table 4 indicate that for all the four proposed models this ratio is <0.38 there by suggesting all of them to be good models. Moreover, the values of bootstrapping r^2 are

Table 2. Physicochemical parameters data for the compounds **11a**–**p**

Compound	HOMO	LUMO	VDW	σ	log P	CSEV	CMA	CAA	MR
11a	−9.238	−1.223	12.468	0	2.868	379.232	413.253	722.538	0.103
11b	−9.237	−1.118	12.485	−0.07	6.090	404.848	433.343	743.104	0.565
11c	−9.408	−1.225	11.219	0.37	2.867	393.415	427.675	745.492	0.693
11d	−9.234	−1.148	11.219	−0.15	2.867	417.372	447.339	769.975	1.030
11e	−9.266	−1.273	11.860	0.37	3.152	398.187	423.807	730.163	0.603
11f	−9.292	−0.873	11.219	−0.24	2.867	424.025	458.399	794.785	1.247
11g	−11.256	−5.006	10.009	0.71	−0.234	254.775	306.438	578.755	0.736
11h	−9.263	−1.243	15.086	0.12	3.152	403.284	439.247	753.337	0.787
11i	−9.205	−1.203	13.366	−0.27	3.152	401.887	439.183	753.337	0.787
11j	−9.292	−1.271	12.468	0.23	2.868	393.397	427.66	745.483	0.603
11k	−9.228	−1.215	11.219	−0.37	2.868	393.415	427.675	745.492	0.285
11l	−9.275	−1.177	11.219	0.1	2.867	382.741	418.023	731.697	1.247
11m	−9.243	−1.154	11.219	−0.07	2.867	415.268	446.336	743.104	1.03
11n	−9.228	−1.110	11.219	−0.17	2.868	404.503	433.523	740.377	0.565
11o	−9.284	−1.260	11.219	0.12	2.868	379.232	413.253	722.538	0.285
11p	−11.095	−4.870	16.520	0.78	−0.423	392.361	426.51	744.605	0.736

Table 3. Correlation matrix of molecular descriptors calculated for **11a**–**p**

	EC	BS	AN	CA	HOMO	LUMO	VDW	σ	LOGP	CSEV	CMA	CAA	MR
EC	1												
BS	0.962	1											
AN	0.921	0.915	1										
CA	0.946	0.938	0.980	1									
HOMO	0.309	0.174	0.049	0.126	1								
LUMO	0.271	0.126	0.012	0.087	0.995	1							
VDW	0.174	0.204	0.13	0.168	0.226	0.268	1						
σ	0.303	0.147	0.179	0.211	0.790	0.787	0.274	1					
log P	0.352	0.244	0.126	0.201	0.835	0.834	0.158	0.658	1				
CSEV	0.138	0.013	0.066	0.049	0.707	0.704	0.284	0.581	0.570	1			
CMA	0.123	0.033	0.081	0.031	0.696	0.695	0.302	0.595	0.546	0.996	1		
CAA	0.130	0.055	0.065	0.032	0.661	0.667	0.312	0.570	0.502	0.975	0.985	1	
MR	0.841	0.909	0.885	0.877	0.044	0.005	0.065	0.026	0.090	0.181	0.216	0.221	1

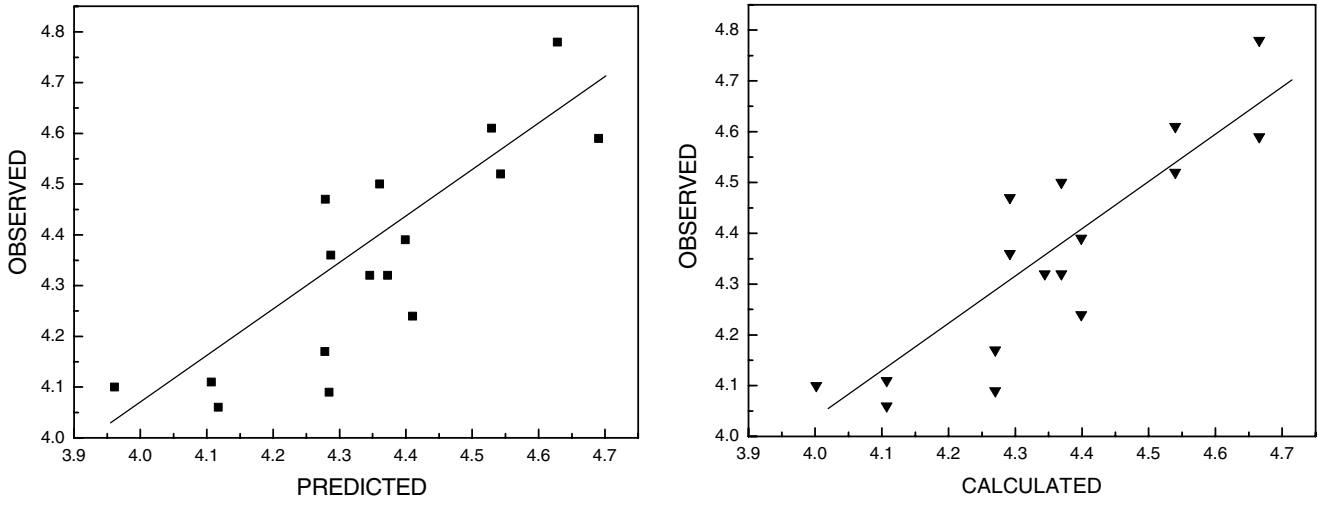


Figure 2. Plots of observed versus calculated and observed versus predicted activity of compounds **11a**–**p** screened against *Escherichia coli* (Eq. 1).

further in support of the predictive power of these explaining models (Eqs. 1–4).

Biological activity was found to have a good correlation with molar refractivity (MR). The positive contribution of molar refractivity towards the activity is possible due to steric interaction in polar spaces. All the synthesized compounds bearing substituents 3′-NO_2, 3′-Cl and 3′-OH have been found to be more active than 4′-NO_2, 4′-Cl, indicating that compounds having electron-attracting groups on the para position of the ring decrease the activity, whereas, if they are present on the meta

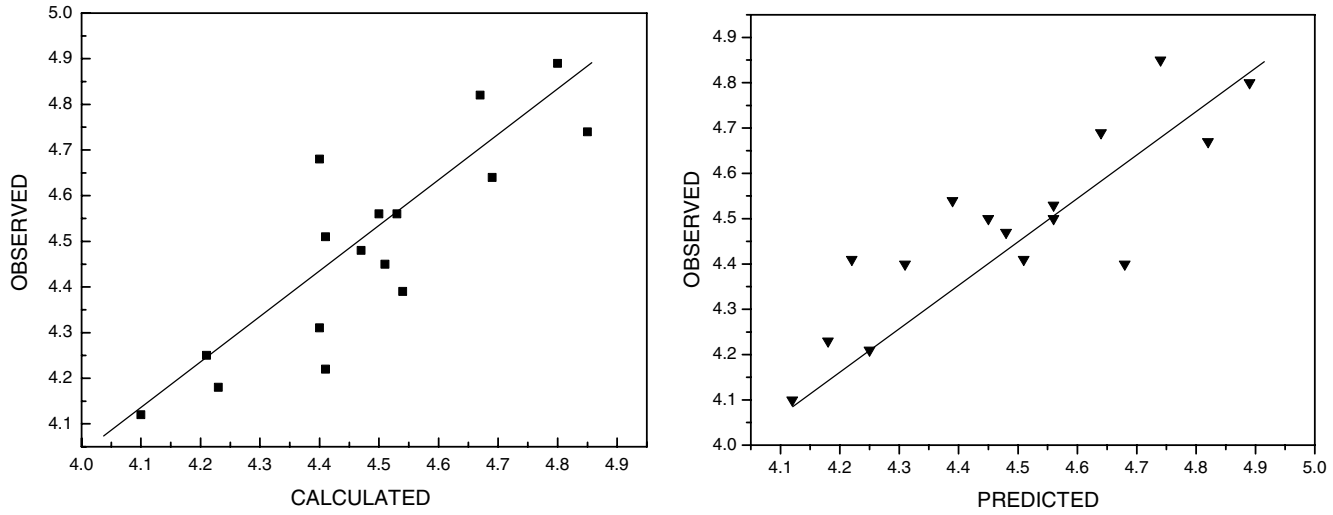


Figure 3. Plots of observed versus calculated and observed versus predicted activity of compounds **11a**–**p** screened against *Aspergillus niger* (Eq. 3).

Table 4. Cross-validation parameters

Equation	Compound	PRESS	SSY	PRESS/SSY	S_{PRESS}	SDEP	r^2_{bsp}
Eq. 1	**16**	0.273	0.909	0.300	0.184	0.172	0.700
Eq. 2	**16**	0.208	0.785	0.264	0.122	0.114	0.814
Eq. 3	**16**	0.214	0.632	0.338	0.124	0.116	0.765
Eq. 4	**16**	0.206	0.535	0.385	0.121	0.113	0.768

position they tend to increase the activity to a greater extent. In general, it has been concluded that the antimicrobial results follow the pattern:

11l > 11m > 11g > 11e > 11h > 11c > 11b > 11o > 11a > 11f > 11d > 11p > 11j > 11i > 11n > 11k

Thus, we have successfully constructed a tricyclic heterocyclic system comprising of benzodiazepine and heterophosphole nuclei in an unprecedented manner. All the synthesized compounds have shown the remarkable in vitro inhibitory activity on the growth of tested bacterial and fungal strains. Further, the QSAR studies using the conventional Hansch approach have revealed that the antimicrobial activity exhibited by these molecules is mainly governed by the polarizability parameter, that is, MR. Since molar refractive index represents the influence of size and polarity of the group, the compounds with different substituent in the newly generated nucleus will be designed, synthesized and will subsequently be tested for their potential as antimicrobial agents.

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27. *Experimental:* Analytical grade chemicals and solvents were always employed. Solvents were distilled under nitrogen atmosphere prior to use. Standard syringe and separation techniques were used for transferring the reactants and the product mixture. All reactions were carried out under nitrogen atmosphere. The product mixtures were analyzed by thin-layer chromatography (TLC) on silica gel sheets (Merck silica gel-G). IR spectra (in cm^{-1}) were recorded on Perkin Elmer 377 spectrophotometer. ^{1}H NMR and ^{31}P NMR spectra were recorded on JEOL EX400 and on Bruker DRX 300 MHz spectrometers, respectively in DMSO-d_6 or $CDCl_3$ chemical shifts are given in δ ppm using TMS (for ^{1}H NMR) as an internal standard and 85% H_3PO_4 (for ^{31}P NMR) as an external standard. Mass spectral analysis was performed using FAB technique. General procedure for the synthesis of (3*S*)-3-arylazo-5,7-dimethyl-1,3-dihydro-2*H*-1, 4-benzodiazepin-2-one (**5a**–**p**): To a stirred, cooled (10 °C) solution of 0.1 M of the 2-aminoacetophenone in 40 mL of 1,4-dioxan, 0.13 M of chloroacetylchloride and an equivalent amount of 3 N sodium hydroxide solution was added in small portions. The reactants were introduced alternatively at such a rate as to keep the temperature below 10 °C and the mixture neutral or slightly alkaline. The reaction was completed after 30 min. The neutral mixture was diluted with ice and water, and extracted with methylene chloride. The extract was washed with water, filtered, dried concentrated in vacuum, and the residue crystallized. Thus, obtained chloroacetamidoacetophenone **2** (0.01 M) in 200 mL of a 20% (w/v) solution of ammonia in methanol was stirred for 24 h at room temperature. The methanolic ammonia filtrate obtained after the separation of **3** was concentrated to dryness in vacuum, and residue recrystallized to give cyclized benzodiazepin-2-one nucleus **4**, which was further, allowed to react with benzene diazonium chloride (0.01 M) under thorough stirring for 3–4 h to obtain **5a**–**p**.
28. General procedure for the synthesis of *N*-ethoxycarbonyl-5,7-dimethyl-2-oxo-3-arylazo-2,3-dihydro-1*H*-1,4-benzodiazepinium chlorides (**6a**–**p**): In a 250 mL round bottom flask to a solution of alkyl halide (0.1 M) in tetrahydrofuron (50 mL), (3*S*)-3-arylazo-5,7-dimethyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **5a**–**p** (0.01 M) was added and reaction mixture was stirred for 24–48 h at room temperature. The white precipitate obtained was filtered, washed with diethyl ether (30 mL), dried in vacuum and were used without further purification.
29. General procedure for the synthesis of 5-bis(dichlorophosphino)-ylidene-(3*S*)-*N*-ethoxycarbonyl-7-methyl-3-arylazo-2-oxo-1,2,3,5-tetrahydro-5*H*-1,4-benzodiazepine (**9a**–**p**): In a closed vessel containing compound **6a**–**p** (0.01 M) in 40 mL toluene, triethylamine (2.02 mL) was added at room temperature and the reaction mixture was stirred for 1–2 h. To this mixture a solution of PCl_3 (1.37 g, 0.01 M) was added slowly and allowed to stir further for 24 h. The solvent was thereafter removed in vacuum and residue was concentrated to 25 mL and left in refrigerator overnight, when yellow to reddish yellow coloured solid was deposited which was filtered and dried in vacuum.
30. General procedure for the synthesis of 10-methyl-6-oxo-5-arylazo-6,7-dihydro-5*H*-[1,3]azaphospholo[1,5-*d*][1,4]benzodiazepin-2-phospha-3-ethoxycarbonyl-1-phosphorus dichlorides (**11a**–**p**): To 5-bis(dichlorophosphino)-ylidene-(3*S*)-*N*-ethoxycarbonyl-7-methyl-3-arylazo-2-oxo-1,2,3,5-tetrahydro-5*H*-1,4-benzodiazepine (0.01 M), which was cooled to 0–5 °C under stirring acetonitrile (40 mL) was added. To this a solution of triethylamine (4.04 g, 0.04 M) was also added slowly to the reaction mixture till the development of yellow colour. After stirring for 30 min a solution of PCl_3 (1.37 g, 0.01 M) was added drop wise till the reaction mixture turns pale yellow to brown. The reaction mixture was allowed to attain the room temperature and stirring was continued for 10 h. Now the solvent was evaporated in vacuum and the white shiny crystals of **11a**–**p** were obtained.
31. Analytical data of compound **5b**: mp 151–152 (°C), yield 72%; IR KBr (ν cm^{-1}) 3350 (N–H), 3050 (C–H, sp^2), 2850 (C–H, sp^3), 2020 (N=N), 1710 (C=O), 1620 (C=C/C=N), 1580, 1490, 1450 (C⋯⋯C, ring str), 920, 850, 740 (sub phenyl), ^{1}H NMR (δ) ppm 0.92 (s, 3H, CH_3, azepine ring), 1.11 (q, 2H, $-CH_2CH_3$), 2.35 (s, 3H, CH_3-φ), 2.52 (s, CH, azepine ring), 3.41 (t, 3H, $-CH_2CH_3$), 3.82 (s, 2H, CH_2–N), 7.12 (d, H_8), 7.25 (s, H_6), 7.42 (d, H_9), 7.59 (s, 5H, C_6H_5), 8.20 (s, NH), MS (FAB): $M+H^+$ peak at *m*/*z* 305. Elemental analyses, found (calcd) (%) C, 70.57 (70.66); H, 5.92 (6.05); N, 18.29 (18.32).
32. Analytical data of compound **6a**: mp 162–163 (°C), yield 78%;IR KBr (ν cm^{-1}) 3350 (N–H), 3050 (C–H, sp^2), 2850 (C–H, sp^3), 2020 (N=N), 1710 (C=O), 1620 (C=C/C=N), 1580, 1490, 1450 (C⋯⋯C, ring str), 920, 850, 740 (sub phenyl), ^{1}H NMR (δ) ppm 1.05 (s, 3H, CH_3, azepine ring), 1.21 (q, 2H, $-CH_2CH_3$), 2.25 (s, 3H, CH_3-φ), 2.63 (s, CH, azepine ring), 3.30 (t, 3H, $-CH_2CH_3$), 3.94 (s, 2H, CH_2–N), 7.09 (d, H_8), 7.30 (s, H_6), 7.46 (d, H_9), 7.75 (s, 5H, C_6H_5), 8.05 (s, NH), MS (FAB): $M+H^+$ peak at *m*/*z* 290. Elemental analyses, found (calcd) (%) C, 66.47 (66.59); H, 6.11 (6.18); N, 14.77 (14.85).
33. Analytical data of compound **9a**: mp (°C) 146–147, yield 68%; IR KBr (ν cm^{-1}) 3330 (N–H), 3050 (C–H, sp^2), 2840 (C–H, sp^3), 1980 (N=N), 1710 (C=O), 1630 (C=C/C=N), 1580, 1490, 1470 (C⋯⋯C, ring str), 1430 (C–P), 930, 820, 710 (sub. phenyl), 570 (P–Cl), ^{1}H NMR (δ) ppm 1.12 (t, 3H, $-CH_2CH_3$), 2.25 (s, 3H, CH_3-φ), 3.40 (s, CH, azepine ring), 4.05 (s, 2H, CH_2–N), 4.60 (q, 2H, $-CH_2CH_3$), 6.85 (d, H_8), 7.20 (s, 4H, C_6H_4), 7.30 (d, H_6), 7.60 (d, H_9), 9.5 (s, NH), ^{31}P NMR 145.6 (δP_A), MS (FAB): $M+H^+$ peak at *m*/*z* 595. Elemental analyses, found (calcd) (%) C, 57.01 (57.13); H, 5.47 (5.51); N, 12.66 (12.78).
34. (a) Analytical data of compound **11a**: mp (°C) 256–257, yield 72%; IR KBr (ν cm^{-1}) 3274 (N–H), 3010 (C–H, sp^2), 2118 (C–H_{asym}, sp^3), 2852 (C–H_{sym}, sp^3), 1735 (C–O, ester), 1710 (C=O), 1555 (N=N), 1500, 1464, 1377 (C⋯⋯C, ring str), 1308 (C–P), 722, 700 (sub phenyl), 550 (P–Cl),^{1}H NMR (δ) ppm 1.42 (t, 3H, CH_3), 2.30 (s, 3H, CH_3-φ), 4.76 (q, 2H, CH_2), 7.33 (m, 3H, Ar-H), 7.49 (s, 5H, C_6H_5), 9.50 (s, NH), ^{31}P NMR 36.5 (δP_A) 166.7 (δP_B), MS (FAB): $M+H^+$ peak at *m*/*z* 506. Elemental analyses, found (calcd) (%) C, 49.72 (49.85); H, 3.58 (3.60); N, 11.05 (11.13).; (b) Analytical data of compound **11b**: mp (°C) 232–233, yield 82%; IR KBr (ν cm^{-1}) 3250 (N–H), 3040 (C–H, sp^2), 2920, (C–H_{asym}, sp^3), 2852 (C–H_{sym}, sp^3), 1735 (C=O), 1620 (C=C/C=N), 1600, 1466, 1376 (C⋯⋯C, ring str), 1540 (N=N), 1118 (C–P), 909, 736 (sub phenyl), 649 (P–Cl), ^{1}H NMR (δ) ppm 1.12 (t, 3H, $-CH_2CH_3$), 2.15 (s, 3H, CH_3-φ), 3.15 (s, CH, azepine ring), 4.36 (q, 2H,

$-CH_2CH_3$), 6.90 (d, 1H, H_8), 7.35 (s, 5H, C_6H_5), 7.65 (d, H_6), 7.95 (s, H_9), 9.51 (s, NH), ^{31}P NMR 41.3 (δP_A) 173.8 (δP_B), MS (FAB): $M+H^+$ peak at *m/z* 520. Elemental analyses, found (calcd) (%) C, 50.69 (50.72); H, 3.87 (3.96); N, 10.75 (10.88).

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