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Original article

Synthesis and QSAR modeling of 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridines as potential antibacterial agents

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Abstract

The present communication deals with the synthesis of a series of 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridines. The compounds were synthesized in excellent yields (70–80%) and the structures were established on the basis of consistent IR, ^{1}H NMR and elemental analysis data. The purity has been ascertained by chromatographic resolution using acetic acid–toluene (6:4 v/v) as binary eluent. All the compounds have been tested for their antimicrobial activity against a representative panel of bacteria i.e. *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas diminuta* and *Staphylococcus aureus* using azinomycin as reference drug. All the synthesized compounds were found to exhibit profound antimicrobial activity.

Keywords: Quantitative structure–activity relationship (QSAR); 2-Acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridines; Antibacterial; Molar refractivity

1. Introduction

The highly strained three-membered [1–3] aziridines have been the synthetic targets as well as useful building blocks for the synthesis of wide range of nitrogen containing heterocycles due to their high regio- and stereoselective [4–8] properties. A systematic perusal of literature reveals that a variety of methods have been developed for the synthesis of aziridines, including ring formation of amino alcohols, ring opening of epoxides with metal azides, addition of α-halo ester to imines [9–11], transfer of nitrene group to olefin, etc. The clinical activity of aziridine is very much included in the DNA modification. Armstrong and co-workers reported that azinomycin B containing aziridine nucleus interacts with duplex DNA in the major groove. Aziridine nucleus forms a covalent interstrand cross-link via the N7 positions of suitably disposed purine bases in the duplex DNA sequence 5′-d (PuNPy)-3′, via the electrophilic C10 and C21 carbons, which make these compounds to act as antitumour agents. Also, antibiotic and antitumour activities [12–17] exhibited by Mitomycin C are attributed to the presence of aziridine ring in it. Similarly Azicemicins A and B possess significant antimicrobial and antibacterial activities owing to the presence of aziridine moiety. Various *N*-substituted aziridines are versatile intermediates for the synthesis of many biologically active compounds that are valuable for new drug development. Buoyed from these findings vis-a-vis keeping in view the unique reactivity feature of the three-membered ring and in continuation of our previous work on various heterocyclic systems [18–21], herein, we document a new route to synthesize analogues of biologically active aziridine carboxylate viz., 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridine. These synthesized compounds were screened for their antibacterial activities against a panel of Gram-positive and Gram-negative bacteria and can be envisaged as the new lead compounds for future perspectives.

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2. Chemistry

An important preparative methodology for the synthesis of 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridine is described incorporating ethyl acetoacetate and *N*,*N*-dimethyl amino benzaldehyde as the substrates. In this strategy, ethyl acetoacetate was stirred with *N*,*N*-dimethyl amino benzaldehyde under Knoevenagel reaction conditions to give (**6**) in initial mechanistic steps. The key compound (**6**) was further treated with freshly prepared *p*-amino azobenzene under the oxidative influence of lead tetraacetate in the presence of dichloromethane/pentane. Upon gentle stirring for 10 min a solidified mass of 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridine appeared in excellent (75–80%) yield. A mechanistic overview of the synthetic pathway is depicted in Scheme 1.

Conclusively, the most prominent cyclization step involves nucleophilic attack of $-NH_2$ fragment of *p*-amino azobenzene on −C═C− olefinic moiety of *N*,*N*-dimethyl amino-1-phenyl-2-ethoxy carbonyl but-2-en-1-one (**6**) to form cyclized C−C−N fraction of aziridine nucleus. Here, oxidative addition of lead tetraacetate plays a very promising role in the ring closure. IR, ^{1}H NMR and mass spectral data corroborated towards the structure of the synthesized aziridines.

3. Biological studies

All the newly synthesized derivatives were screened for their antibacterial activities against *Escherichia coli* ATCC 13067, *Pseudomonas diminuta* MTCC 3361, *Staphylococcus aureus* ATCC 2943, and *Bacillus subtilis* ATCC 6633.

Nutrient agar media were prepared for bacterial growth. Stock solution was prepared in DMF and suspension containing approximately 10^7 CFU/ml of bacteria was prepared from broth culture in log phase growth. Bacterial plates were prepared in triplicate and incubated at 37 °C within 16–24 h for bacteria. Also azinomycin was tested under similar conditions as a control drug. Minimal inhibitory concentration (MIC) was determined by means of standard twofolds serial dilution method using agar media and reported in Table 1, where MIC is defined as the lowest concentration of compound that inhibited visible growth.

All the reported compounds exhibited remarkable in vitro activity against the tested bacterial strains compared to reference drug. A systematic perusal of data depicted in Table 1 reveals significant antibacterial activities. In general antibacterial profile of the tested compounds follows the pattern:

B. subtilis > *P. diminuta* > *S. aureus* > *E. coli*

Further, a close inspection of screening results reveals that the substitution in aromatic ring attached with azo moiety of aziridine 2-carboxylate exerted significant influence on the antibacterial armament. It is deduced from the data presented in Table 1 that the in vitro antibacterial activity is found to be increased with the derivatives bearing $-NO_2$ (**8j**), −COOH (**8f**), −OH (**8i**), and −Cl (**8b**) substituents in the *meta* position of the phenyl ring (Fig. 1).

3.1. QSAR analysis

To obtain a significant correlation between structural features and biological activities, QSAR studies were performed using the linear free energy relationship (LFER) model of Hansch and Fujita [46]. Biological activity data were reported as −log MIC on molar basis and used as dependent variable to get the linear relationship in the QSAR model. The physicochemical parameters taken from the list of Skagerberg et al. [22] were then correlated with varied molecular descriptors like log of octanol–water partition coefficient (log *p*), energy of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), molar refractivity (M_R) and Connolly accessible area (CAA), Connolly molecular area (CMA), dipole–dipole energy (DDENE), Van der Waals volume (VDW) and non-Van der Waals volume (NVDW).

All the calculations to figure out molecular descriptors were done at SCF level using AM1 [23] Hamiltonian incorporated in MOPAC 6.0 [24] package. Geometries were optimized at minimum gradient level using CHEM 3D-6.0 [25] software. In order to perform correlation studies for various descriptors, intercorrelated parameters were discarded depending upon their individual correlation with biological activities. Using the stepwise selection and elimination procedures the resultant parameters were subjected to MLR analysis with the help of Valstat [26] software.

The best fit between −log MIC and these explaining parameters was obtained through multiple regression analysis (MRA) using least square method as shown in Tables 2 and 3.

Out of a number of parametric evaluations, the best correlation ($r^2 > 0.93$) was found to exist between molar refractivity and biological activity. The resulting mono-parametric models are displayed in Eqs. (1)–(4) (Table 4) with statistical parameters of regression. No outliers have been detected and these Eqs. (1)–(4) were derived using entire training data set ($n = 11$).

The overall quality of the models is indicated by coefficient of determination (r^2), standard error of estimate (s), and Fisher statistics (F).

QSAR model for activity against *B. subtilis*:

$$-\log \mathrm{MIC} = [4.0362(\pm 0.0904)] + \mathrm{MR}[0.7230(\pm 0.1522)] \quad (1)$$

$n = 11,\ r = 0.96,\ r^2 = 0.93,\ \text{variance} = 0.0022,\ \text{std} = 0.0472,\ F_{(1,9)} = 119.96.$

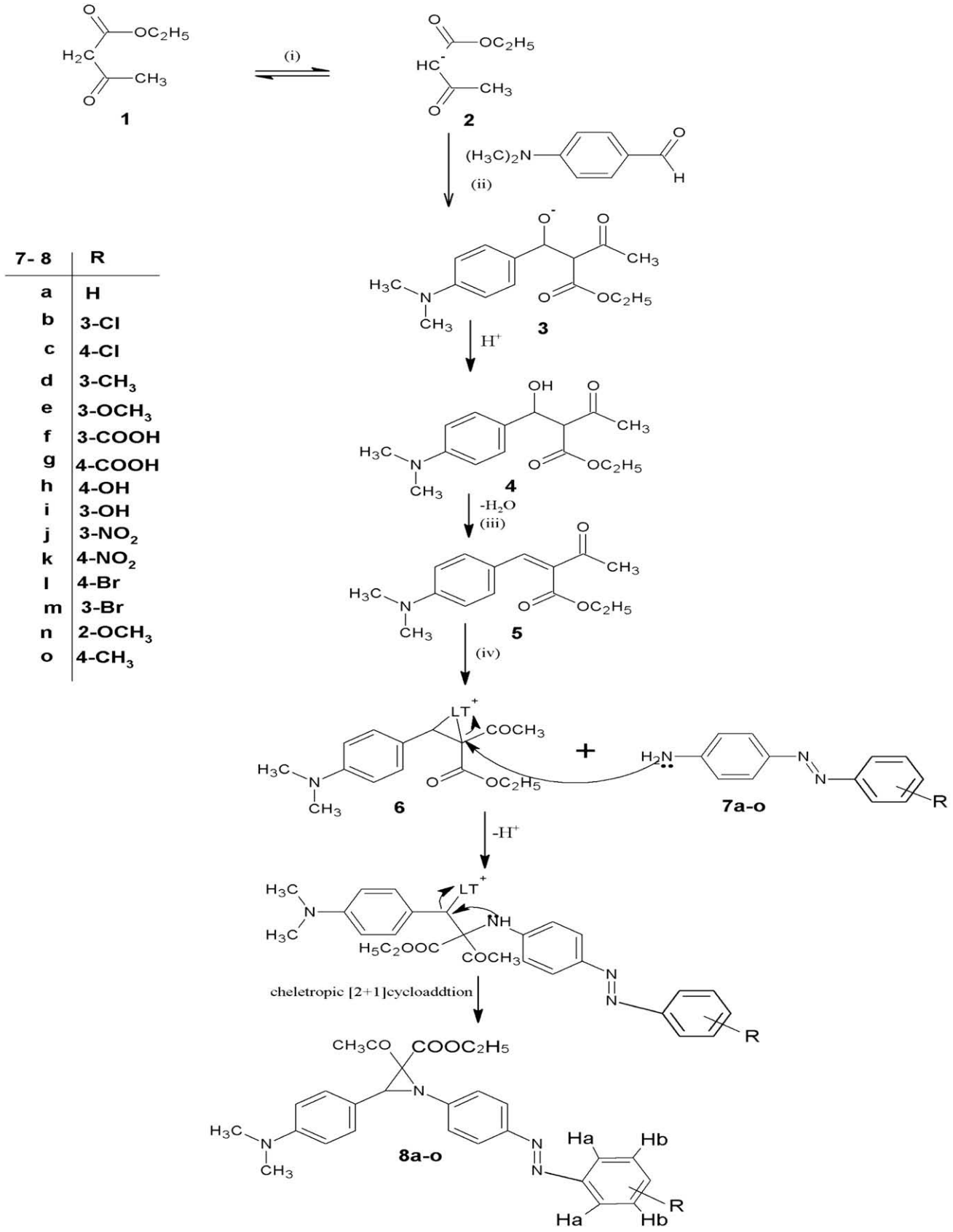
QSAR model for activity against *P. diminuta*:

$$-\log \mathrm{MIC} = [4.0209(\pm 0.0803)] + \mathrm{MR}[0.6591(\pm 0.1352)] \quad (2)$$

$n = 11,\ r = 0.97,\ r^2 = 0.93,\ \text{variance} = 0.0018,\ \text{std} = 0.0420,\ F_{(1,9)} = 126.34.$

QSAR model for activity against *E. coli*:

$$-\log \mathrm{MIC} = [3.9657(\pm 0.0585)] + \mathrm{MR}[0.5188(\pm 0.0984)] \quad (3)$$



7- 8	R
a	H
b	3-Cl
c	4-Cl
d	3-CH_3
e	3-OCH_3
f	3-COOH
g	4-COOH
h	4-OH
i	3-OH
j	3-NO_2
k	4-NO_2
l	4-Br
m	3-Br
n	2-OCH_3
o	4-CH_3

Scheme 1. Reagents and conditions: (i) $(C_2H_5)_2NH$/0 °C, (ii) stirring for 50 min, (iii) H_2SO_4 (2 M), (iv) $(COOCH_3)_4Pb/CH_2Cl_2$/pentane/stirring for 30 min at 25 °C.

Table 1
Antibacterial screening data for 2-acetyl-2-ethoxycarbonyl-1-[4-(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenylaziridines

Compound	MIC in μg/ml							
	Gram-negative bacteria				Gram-positive bacteria			
	E. coli		*P. diminuta*		*S. aureus*		*B. subtilis*	
	MIC $\times 10^{-5}$	−log MIC	MIC $\times 10^{-5}$	−log MIC	MIC $\times 10^{-5}$	−log MIC	MIC $\times 10^{-5}$	−log MIC
8a	8.995	4.046	7.447	4.128	8.337	4.079	7.014	4.154
8b	5.297	4.276	3.872	4.412	4.688	4.329	3.467	4.460
8c	5.916	4.228	4.487	4.348	5.297	4.276	4.074	4.390
8d	5.741	4.241	4.256	4.371	5.105	4.292	3.614	4.442
8e	4.325	4.364	2.884	4.540	3.707	4.431	2.472	4.607
8f	4.602	4.337	3.199	4.495	3.999	4.398	2.799	4.553
8g	5.000	4.301	3.597	4.444	4.395	4.357	3.199	4.495
8h	8.054	4.094	6.561	4.183	7.413	4.130	6.138	4.212
8i	7.621	4.118	6.138	4.212	6.998	4.155	5.715	4.243
8j	3.990	4.399	2.594	4.586	3.396	4.469	2.198	4.658
8k	4.188	4.378	2.992	4.524	3.589	4.445	2.594	4.586

Table 2
Values of selected descriptors with correlation $r > 0.45$

	MR[a]	HOMO (eV)	DDENE	VDW	NVDW
8a	0.103	−7.823	3.176	33.530	9.561
8b	0.603	−8.606	3.599	28.101	11.082
8c	0.603	−8.737	3.185	19.988	9.801
8d	0.565	−8.516	3.011	20.159	9.941
8e	0.787	−8.486	2.081	22.249	14.852
8f	0.693	−8.214	2.812	1.165	1.121
8g	0.693	−8.775	4.209	28.760	7.288
8h	0.285	−8.369	3.298	132.442	13.851
8i	0.285	−8.482	2.003	18.285	11.061
8j	0.736	−10.791	3.747	25.159	5.762
8k	0.736	−10.484	2.443	22.563	10.521

[a] MR is scaled by factor 0.1.

$$-\log \mathrm{MIC} = [4.1781(\pm 0.1610)] + \mathrm{MR}[0.6843(\pm 0.1329)] + \log p[-0.0206(\pm 0.0207)] \quad (5)$$

$n = 11,\ r = 0.98,\ r^2 = 0.94,\ \text{variance} = 0.0009,\ \text{std} = 0.0305,\ F_{(1,9)} = 147.65.$

QSAR model for activity against *S. aureus*:

$$-\log \mathrm{MIC} = [3.9880(\pm 0.0669)] + \mathrm{MR}[0.5736(\pm 0.1126)] \quad (4)$$

$n = 11,\ r = 0.97,\ r^2 = 0.94,\ \text{variance} = 0.0012,\ \text{std} = 0.0349,\ F_{(1,9)} = 138.09.$

The F value obtained in Eqs. (1)–(4) is found to be statistically significant at 99% level.

Moreover, we have also tried to test bi- and tri-parametric correlation statistically but we have not found any significant result as can be illustrated in Eq. (5) which represents a biparametric model for *B. subtilis*.

QSAR model (biparametric model) for activity against *B. subtilis*:

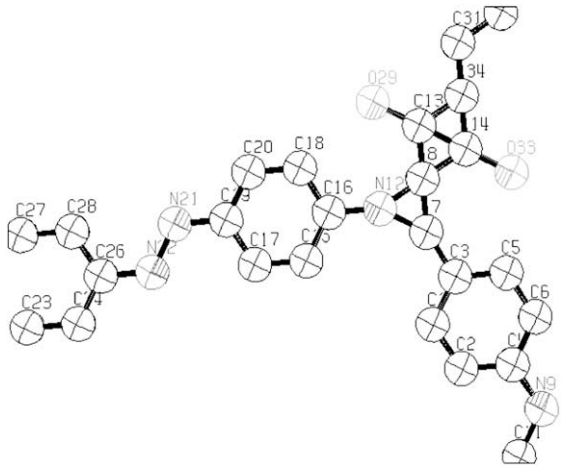


Fig. 1. ORTEP diagram of **8a** (PM3 optimized geometry) with atom numbering. Thermal ellipsoids are scaled to the 50% probability level. The atom numbering is arbitrary and has nothing to do with the IUPAC nomenclature.

$n = 11,\ r = 0.98,\ r^2 = 0.96,\ \text{variance} = 0.0015,\ \text{std} = 0.0385,\ F_{(1,9)} = 93.$

However, the results obtained from Eq. (5) are not statistically allowed which revealed the need of mono-parametric model over bi- and tri-parametric models.

The predictive power of these equations was also checked by leave one out (LOO) cross-validated r^2_{CV} values (>0.88). The observed biological activities are also in accordance with calculated and predictive activities as depicted in Fig. 2, Tables 5 and 6.

To further validate our results, four compounds (entries T1–T4) have been chosen as the test set molecules whose −log MIC values range between 4.021 and 4.686 (which were not included in the training set). Predicted and actual biological activities of test set molecules are summarized in Table 7. Predicted −log MIC values agree well with the experimental ones, which suggests that our model is good for prediction of the biological activity of related compounds.

PRESS (predicted residual sum of squares) is a cross-validation parameter whose value less than SSY (sum of the squares of response value) points out that the model predicts better than chance and can be considered statistically important. Table 4 suggests that all the proposed models have PRESS ≪ SSY demonstrating them to be statistically significant. Further, to be a reasonable QSAR model PRESS/SSY ratio should be smaller than 0.4 and its value smaller than 0.11 indicates an excellent model. The data pertaining to Table 4 indicate that for all the four proposed models this ratio is ≅0.1 suggesting all of them to be excellent models. 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, size and polarity of groups as displayed through Eqs. (1)–(4) suggest that molar refractivity is a key factor to express biological activities, which may be possible due to steric interaction occurring in polar species.

Table 3
Correlation matrix of biological activity[a] with molecular descriptors

	MR	HOMO	log *p*	CAA	CMA	DDENE	LUMO	VDW	NVDW	BS	PD	EC	SA
MR	1.00												
HOMO	0.54	1.00											
log *p*	0.29	0.37	1.00										
CAA	0.25	0.23	0.32	1.00									
CMA	0.41	0.33	0.30	0.85	1.00								
DDENE	0.07	0.06	0.01	0.13	0.19	1.00							
LUMO	0.10	0.59	0.50	0.51	0.55	0.18	1.00						
VDW	0.45	0.89	0.07	0.54	0.53	0.21	0.82	1.00					
NVDW	0.27	0.10	0.12	0.49	0.19	0.44	0.13	0.28	1.00				
BS	0.64	0.05	0.09	0.10	0.09	0.05	0.16	0.02	0.60	1.00			
PD	0.07	0.14	0.07	0.04	0.07	0.02	0.13	0.08	0.52	0.48	1.00		
EC	0.24	0.15	0.03	0.07	0.04	0.02	0.07	0.09	0.60	0.67	0.97	1.00	
AS	0.07	0.15	0.09	0.07	0.10	0.03	0.18	0.09	0.43	0.29	0.98	0.90	1.00

[a] EC = *E. coli*, PD = *P. diminuta*, SA = *S. aureus*, BS = *B. subtilis*.

4. Experimental

All the chemicals used were of AR-grade purity. IR spectra were recorded on Perkin Elmer model 377 spectrophotometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DRX300 instrument. The FAB mass spectra were recorded on a JEOLSX102/DA-6000 Mass Spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Analytical thin layer chromatography was performed using E. Merck silica gel G, 0.50 mm plates, (Merck No. 5700). The melting points were determined on an electric melting point apparatus in open capillaries and are uncorrected.

*4.1. Synthesis of N,N-dimethyl amino-1-phenyl-2-ethoxycarbonyl but-1-en-2-one (**5**)*

The compound (**5**) was prepared by condensing together *N*,*N*-dimethyl amino benzaldehyde (4.5 g, 0.03 M) and 1-ethoxy butane-1,3-dione (2.6 ml, 0.02 M) in the presence of catalytic amount of diethyl amine and allowed to undergo stirring at 0 °C for 50 min followed by the addition of sulfuric acid (50 ml, 2 M). On cooling the precipitate so obtained was filtered, thoroughly washed with water and dried. As a result *N*,*N*-dimethyl amino-1-phenyl-2-ethoxycarbonyl but-1-en-2-one was obtained in good yield (80%) as a yellowish crystalline product. It was recrystallized from a mixture of ethanol and DMF.

*4.2. Synthesis of p-aminoarylazo benzene (**7a–o**)*

Preparation of this compound (**7a–o**) was accomplished [27] in two steps viz., A and B as follows.

Table 4
Cross-validation parameters

Equation	Number of compound used	PRESS	SSY	PRESS/SSY	S_{PRESS}	SDEP	r^2_{CV}	r^2_{bsp}
(1)	11	0.032	0.288	0.111	0.059	0.054	0.889	0.922
(2)	11	0.025	0.238	0.105	0.053	0.048	0.895	0.925
(3)	11	0.013	0.146	0.089	0.038	0.035	0.911	0.931
(4)	11	0.017	0.179	0.095	0.044	0.040	0.905	0.934

4.2.1. Synthesis of diazoaminobenzene (A)

The mixture of 6.5 ml (0.07 M) of aniline, 10.0 ml of conc. hydrochloric acid and 40.0 ml of water was taken in a 250 ml Erlenmeyer flask and stirred to make a homogeneous solution followed by the addition of 25 g of crushed ice. Now, 2.6 g (0.037 M) of sodium nitrite solution in 6 ml of water was added slowly with constant shaking during a period of 10–15 min. The contents were allowed to stand for 10 min and 10.5 g (0.128 M) of sodium acetate dissolved in 20 ml of water was added. A yellow precipitate of diazoaminobenzene commences to appear which was kept at 20 °C with occasional shaking for 40 min. The yellow solid thus formed was filtered on a Buchner funnel, washed with 100 ml of cold water and recrystallized from light petroleum.

4.2.2. Conversion of diazoaminobenzene to p-aminoarylazo benzene (B)

In an Erlenmeyer flask, a mixture of 2.5 g (0.0125 M) of diazoaminobenzene and 6.9 ml (0.07 M) of aniline was taken. To the solution 1.3 g of finely powdered aniline hydrochloride was added and the mixture was allowed to warm at 40–45 °C for 1 h on a water bath with occasional shaking. The reaction mixture was permitted to stand for 15 min at room temperature. Now 15 ml of 1:1 glacial acetic acid was added and shaken thoroughly to remove excess aniline as aniline acetate. It was then allowed to stand for 15 min. The solid product thus obtained was filtered on a Buchner funnel, washed with water, recrystallized from carbon tetrachloride, and resulted in appreciable yield.

*4.3. Synthesis of 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-N,N-dimethylaminophenyl aziridines (**8a–o**)*

A 500 cc, three-necked round-bottomed flask equipped with an efficient mechanical stirrer was charged with a mixture of a *p*-amino azobenzene (**7a–o**) (2.3 g, 0.12 M), *N*,*N*-dimethyl amino-1-phenyl-2-ethoxycarbonyl but-1-en-2-one (**5**) (1.4 g, 0.60 M) and 30 ml of dichloromethane. To the

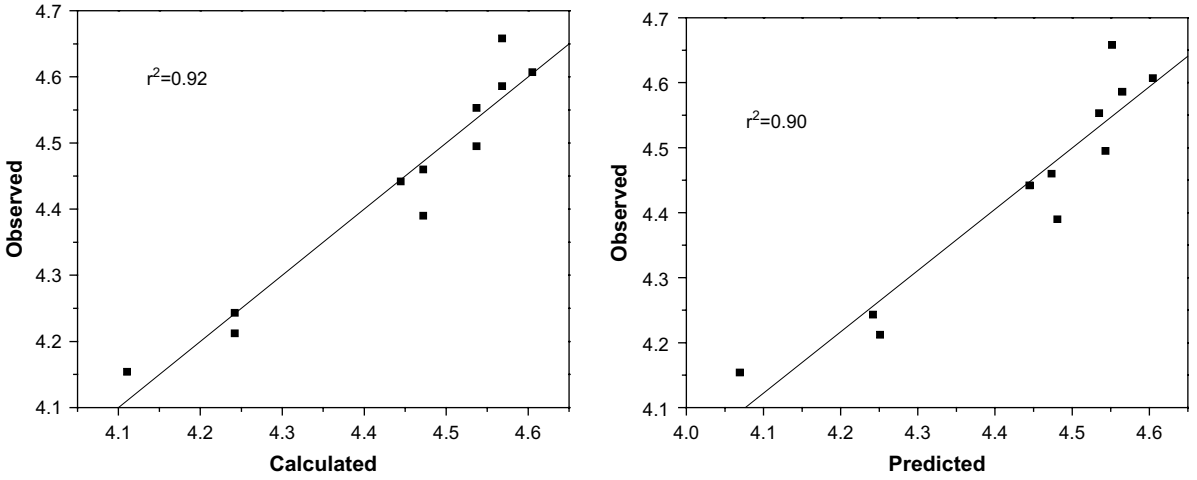


Fig. 2. Plots of observed versus calculated and observed versus predicted activities of 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylamino-phenyl aziridine derivatives (**8a**–**k**) against *B. subtilis*.

resulting suspension was added 6.0 g (0.012 M) of lead tetraacetate over a period of 10 min at room temperature with vigorous stirring. Stirring was continued for an additional 30 min, after which time the mixture was filtered through celite, which was washed twice with 25 ml partitions of dichloromethane. The combined filtrates were transferred to a 1-l beaker and 500 ml of pentane was added with gentle stirring and cooling in an ice bath. The yellow precipitate that formed after 15 min was suction filtered and redissolved in 200 ml of dichloromethane. The solution obtained was swirled for 5 min with 10 g of silica gel and filtered through celite, which was washed twice with 50 ml portions of dichloromethane. To this dichloromethane solution was added 50.0 ml of pentane with cooling. The precipitate thus formed after 30 min was dried under vacuum at room temperature for 2 h, yielding appreciable percentage of 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridines (**8a**–**o**). An overview of the synthetic scheme is delineated in Scheme 1. Structures of the synthesized compounds have been ascertained on the basis of spectroanalytical data.

4.3.1. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(2″-phenyl)azo]-phenyl}-3-N,N-dimethylaminophenyl aziridine [8a]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3110 (C–H three-membered ring), 3051 (=C–H, sp^2), 2936 (C–H, sp^3), 2371 (overtone, CO), 1763 (C=O ester), 1715 (C=O, acetyl), 1650 (C=C), 1575 (N=N), 1601, 1414, 1320 (C⋯C ring str.), 1261 (C–N), 1100 (C–O•), 819,668 (sub. phenyl); ^{1}H NMR (δ ppm) 1.30 (t, 3H, CH_3CH_2, $J = 7.1$ Hz), 1.93 (s, 6H, $(CH_3)_2N$), 2.11 (s, 3H, CH_3CO), 3.06 (s, CH, aziridine ring), 4.06 (q, 2H, CH_3CH_2, $J = 7.1$ Hz), 7.45–7.99 (m, 5H, Ar–H attached to N=N moiety), 7.81 (m, 8H, $2 \times N$-phenyl); mp (°C) 102–104, yield 71%. Anal. Calcd for $C_{27}H_{28}N_4O_3$: C, 71.03; H, 6.18; N, 12.27. Found: C, 70.92; H, 6.11; N, 12.20.

4.3.2. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(3″-chlorophenyl)-azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8b]

Prepared according to the general procedure as in Section 4.3.

Table 5
Observed versus calculated activity of 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridine derivatives (**8a**–**k**) against *B. subtilis*

Entry	Observed	Calculated
8a	4.154	4.111
8b	4.460	4.472
8c	4.390	4.472
8d	4.442	4.445
8e	4.607	4.605
8f	4.553	4.537
8g	4.495	4.537
8h	4.212	4.242
8i	4.243	4.242
8j	4.658	4.568
8k	4.586	4.568

Table 6
Observed versus predicted activity of 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridine derivatives (**8a**–**k**) against *B. subtilis*

Entry	Observed	Predicted
8a	4.154	4.069
8b	4.460	4.473
8c	4.390	4.481
8d	4.442	4.445
8e	4.607	4.605
8f	4.553	4.535
8g	4.495	4.543
8h	4.212	4.251
8i	4.243	4.242
8j	4.658	4.552
8k	4.586	4.565

Table 7
Observed versus predicted activity of 2-acetyl-2-ethoxycarbonyl-1-[4(4′-arylazo)-phenyl]-*N*,*N*-dimethylaminophenyl aziridine derivatives (T1–T4) for test set

	Entry	Compound	Observed	Predicted	Residuals
B. subtilis	T1	**8l**	4.079	4.111	−0.032
	T2	**8m**	4.329	4.472	−0.143
	T3	**8n**	4.686	4.472	0.214
	T4	**8o**	4.481	4.445	0.036
P. diminuta	T1	**8l**	4.121	4.089	0.032
	T2	**8m**	4.378	4.418	−0.04
	T3	**8n**	4.421	4.418	0.003
	T4	**8o**	4.591	4.393	0.198
E. coli	T1	**8l**	4.021	4.019	0.002
	T2	**8m**	4.379	4.278	0.101
	T3	**8n**	4.221	4.278	−0.057
	T4	**8o**	4.281	4.259	0.022
S. aureus	T1	**8l**	4.078	4.047	0.031
	T2	**8m**	4.358	4.334	0.024
	T3	**8n**	4.421	4.334	0.087
	T4	**8o**	4.492	4.312	0.180

IR (KBr) (cm^{-1}) 3109 (C–H three-membered ring), 3052 (=C–H, sp^2), 2930 (C–H, sp^3), 2368 (overtone, CO), 1758 (C=O ester), 1711 (C=O, acetyl), 1651 (C=C), 1571 (N=N), 1595, 1457, 1321 (C⋯C ring str.), 1260 (C–N), 1098 (C–O•), 815,667 (sub. phenyl), 550 (C–Cl); ^{1}H NMR (δ ppm) 1.29 (t, 3H, CH_3CH_2, $J = 7.7$ Hz), 1.91 (s, 6H, $(CH_3)_2N$), 2.57 (s, 3H, CH_3CO), 3.07 (s, CH, aziridine ring), 4.01 (q, 2H, CH_3CH_2, $J = 7.7$ Hz), 7.40–7.93 (m, 4H, C_6H_5 attached to N=N moiety), 7.80 (m, 8H, 2 × CH, *N*-phenyl); mp (°C) 101–102, yield 67%. Anal. Calcd for $C_{27}H_{27}ClN_4O_3$: C, 66.05; H, 5.54; N, 11.41. Found: C, 65.98; H, 5.48; N, 11.30.

4.3.3. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(4″-chlorophenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8c]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3110 (C–H three-membered ring), 3050 (=C–H, sp^2), 2932 (C–H, sp^3), 2366 (overtone, CO), 1755 (C=O ester), 1710 (C=O, acetyl), 1652 (C=C), 1570 (N=N), 1599, 1455, 1320 (C⋯C ring str.), 1261 (C–N), 1089 (C–O•), 812,665 (sub. phenyl), 556 (C–Cl); ^{1}H NMR (δ ppm) 1.31 (t, 3H, CH_3CH_2, $J = 7.9$ Hz), 1.93 (s, 6H, $(CH_3)_2N$), 2.55 (s, 3H, CH_3CO), 3.05 (s, CH, aziridine ring), 4.05 (q, 2H, CH_3CH_2, $J = 7.9$ Hz), 7.45 (d, 2H, Ar–H_b attached to N=N moiety), 7.86 (d, 2H, Ar–H_a attached to N=N moiety), 7.80 (m, 8H, 2 × *N*-phenyl); mp (°C) 122–124, yield 63%. Anal. Calcd for $C_{27}H_{27}ClN_4O_3$: C, 66.05; H, 5.54; N, 11.41. Found: C, 66.01; H, 5.47; N, 11.39.

4.3.4. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(3″-methylphenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8d]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3101 (C–H three-membered ring), 3053 (=C–H, sp^2), 2936 (C–H, sp^3), 2369 (overtone, CO), 1762 (C=O ester), 1720 (C=O, acetyl), 1657 (C=C), 1556 (N=N), 1605, 1415, 1322 (C⋯C ring str.), 1262 (C–N), 1101 (C–O•), 821,665 (sub. phenyl); ^{1}H NMR (δ ppm) 1.31 (t, 3H, CH_3CH_2, $J = 8.5$ Hz), 1.91 (s, 6H, $(CH_3)_2N$), 2.10 (s, 3H, CH_3CO), 2.34 (s, 3H, CH_3 attached to phenyl ring), 3.01 (s, CH, aziridine ring), 3.98 (q, 2H, CH_3CH_2, $J = 8.5$ Hz), 7.26–7.73 (m, 4H, Ar–H attached to N=N moiety), 7.80 (m, 8H, 2 × *N*-phenyl); mp (°C) 112–113, yield 73%. Anal. Calcd for $C_{28}H_{30}N_4O_3$: C, 71.47; H, 6.43; N, 11.91. Found: C, 71.39; H, 6.39; N, 11.90.

4.3.5. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(3″-methoxyphenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8e]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3112 (C–H three-membered ring), 3044 (=C–H, sp^2), 2932 (C–H, sp^3), 2355 (overtone, CO), 1760 (C=O ester), 1715 (C=O, acetyl), 1646 (C=C), 1548 (N=N), 1601, 1412, 1321 (C⋯C ring str.), 1258 (C–N), 1100 (C–O•), 818,662 (sub. phenyl); ^{1}H NMR (δ ppm) 1.28 (t, 3H, CH_3CH_2, $J = 9.1$ Hz), 1.89 (s, 6H, $(CH_3)_2N$), 2.11 (s, 3H, CH_3CO), 3.05 (s, CH, aziridine ring), 3.71 (s, 3H, O–CH_3 attached to phenyl ring), 3.94 (q, 2H, CH_3CH_2, $J = 9.1$ Hz), 6.97–7.50 (m, 4H, C_6H_5 attached to N=N moiety), 7.78 (m, 8H, 2 × *N*-phenyl); mp (°C) 104–105, yield 62%. Anal. Calcd for $C_{28}H_{30}N_4O_4$: C, 69.12; H, 6.21; N, 11.51. Found: C, 69.10; H, 6.18; N, 11.48.

4.3.6. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(3″-carboxyphenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8f]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3510 (–OH str.), 3114 (C–H three-membered ring), 3043 (=C–H, sp^2), 2934 (C–H, sp^3), 2370 (overtone, CO), 1755 (C=O ester), 1717 (C=O, acetyl), 1710 (C=O acid), 1652 (C=C), 1566 (N=N), 1600, 1411, 1313 (C⋯C ring str.), 1259 (C–N), 1100 (C–O•), 811,663 (sub. phenyl); ^{1}H NMR (δ ppm) 1.28 (t, 3H, CH_3CH_2, $J = 9.6$ Hz), 1.91 (s, 6H, $(CH_3)_2N$), 2.12 (s, 3H, CH_3CO), 2.99 (s, CH, aziridine ring), 4.01 (q, 2H, CH_3CH_2, $J = 9.6$ Hz), 7.67–7.99 (m, 5H, Ar–H attached to N=N moiety), 7.78 (m, 8H, 2 × *N*-phenyl) 11.0 (br s, –OH str.); mp (°C) 113–114, yield 66%. Anal. Calcd for $C_{28}H_{28}N_4O_5$: C, 67.19; H, 5.64; N, 11.19. Found: C, 67.11; H, 5.56; N, 11.13.

4.3.7. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(4″-carboxyphenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8g]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3512 (–OH str.), 3107 (C–H three-membered ring), 3041 (=C–H, sp^2), 2935 (C–H, sp^3), 2367 (overtone, CO), 1749 (C=O ester), 1715 (C=O, acetyl), 1711

(C=O acid), 1651 (C=C), 1563 (N=N), 1600, 1421, 1311 (C⋯C ring str.), 1257 (C–N), 1108 (C–O•), 816,659 (sub. phenyl); ^{1}H NMR (δ ppm) 1.26 (t, 3H, CH_3CH_2, $J = 9.2$ Hz), 1.90 (s, 6H, $(CH_3)_2N$), 2.08 (s, 3H, CH_3CO), 2.97 (s, CH, aziridine ring), 3.99 (q, 2H, CH_3CH_2, $J = 9.2$ Hz), 8.30 (d, 2H, Ar–H_b attached to N=N moiety), 8.11 (d, 2H, Ar–H_a attached to N=N moiety), 7.82 (m, 8H, 2 × *N*-phenyl), 11.1 (br s, –OH str.); mp (°C) 134–136, yield 60%. Anal. Calcd for $C_{28}H_{28}N_4O_5$: C, 67.19; H, 5.64; N, 11.19. Found: C, 67.13; H, 5.39; N, 11.11.

4.3.8. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(4″-hydroxyphenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8h]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3445 (–OH str.), 3281 (C–H three-membered ring), 3051 (=C–H, sp^2), 2959 (C–H, sp^3), 2373 (overtone, CO), 1753 (C=O ester), 1718 (C=O, acetyl), 1622 (C=C), 1529 (N=N), 1457, 1415, 1345 (C⋯C ring str.), 1282 (C–N), 1186 (C–O•), 871,801 (sub. phenyl), 737 (–CH_2); ^{1}H NMR (δ ppm) 1.27 (t, 3H, CH_3CH_2, $J = 8.7$ Hz), 1.84 (s, 6H, $(CH_3)_2N$), 2.55 (s, 3H, CH_3CO), 3.06 (s, CH, aziridine ring), 3.39 (q, 2H, CH_3CH_2, $J = 8.7$ Hz), 6.91 (d, 2H, Ar–H_b attached to N=N moiety), 7.74 (d, 2H, Ar–H_a attached to N=N moiety), 7.238 (m, 8H, 2 × *N*-phenyl), 12.78 (br s, –OH str.); mp (°C) 112–113, yield 73%. Anal. Calcd for $C_{27}H_{28}N_4O_4$: C, 68.63; H, 5.97; N, 11.86. Found: C, 68.52; H, 5.91; N, 11.72.

4.3.9. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(3″-hydroxyphenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8i]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3441 (–OH str.), 3278 (C–H three-membered ring), 3046 (=C–H, sp^2), 2951 (C–H, sp^3), 2368 (overtone, CO), 1751 (C=O ester), 1715 (C=O, acetyl), 1621 (C=C), 1526 (N=N), 1455, 1411, 1341 (C⋯C ring str.), 1281 (C–N), 1181 (C–O•), 862,811 (sub. phenyl), 735 (–CH_2); ^{1}H NMR (δ ppm) 1.25 (t, 3H, CH_3CH_2, $J = 8.8$ Hz), 1.81 (s, 6H, $(CH_3)_2N$), 2.52 (s, 3H, CH_3CO), 2.99 (s, CH, aziridine ring), 5.34 (q, 2H, CH_3CH_2, $J = 8.8$ Hz), 6.91–7.41 (m, 5H, Ar–H attached to N=N moiety), 7.214 (m, 8H, 2 × *N*-phenyl), 12.80 (br s, –OH str.); mp (°C) 123–124, yield 75%. Anal. Calcd for $C_{27}H_{28}N_4O_4$: C, 68.63; H, 5.97; N, 11.86. Found: C, 68.49; H, 5.88; N, 11.80.

4.3.10. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(3″-nitrophenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8j]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3101 (C–H three-membered ring), 3047 (=C–H, sp^2), 2932 (C–H, sp^3), 2365 (overtone, CO), 1760 (C=O ester), 1715 (C=O, acetyl), 1646 (C=C), 1548 (N=N), 1601, 1412, 1321 (C⋯C ring str.), 1345 (NO_2), 1258 (C–N), 1100 (C–O•), 818,662 (sub. phenyl); ^{1}H NMR (δ ppm) 1.28 (t, 3H, CH_3CH_2, $J = 7.8$ Hz), 1.89 (s, 6H, $(CH_3)_2N$), 2.11 (s, 3H, CH_3CO), 3.05 (s, CH, aziridine ring), 3.94 (q, 2H, CH_3CH_2, $J = 7.8$ Hz), 7.7–8.81 (m, 4H, Ar–H attached to N=N moiety), 7.76 (m, 8H, 2 × *N*-phenyl); mp (°C) 105–106, yield 77%. Anal. Calcd for $C_{27}H_{27}N_5O_5$: C, 64.66; H, 5.43; N, 13.96. Found: C, 64.52; H, 5.39; N, 13.82.

4.3.11. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(4″-nitrophenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8k]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3100 (C–H three-membered ring), 3052 (=C–H, sp^2), 2934 (C–H, sp^3), 2374 (overtone, CO), 1760 (C=O ester), 1719 (C=O, acetyl), 1658 (C=C), 1553 (N=N), 1600, 1412, 1320 (C⋯C ring str.), 1350 (NO_2), 1261 (C–N), 1100 (C–O•), 819,668 (sub. phenyl); ^{1}H NMR (δ ppm) 1.29 (t, 3H, CH_3CH_2, $J = 8.9$ Hz), 1.92 (s, 6H, $(CH_3)_2N$), 2.14 (s, 3H, CH_3CO), 3.05 (s, CH, aziridine ring), 4.06 (q, 2H, CH_3CH_2, $J = 7.8$ Hz), 7.71 (d, 2H, Ar–H_b attached to N=N moiety), 7.98 (d, 2H, Ar–H_a attached to N=N moiety), 7.79 (m, 8H, 2 × *N*-phenyl); mp (°C) 105–106, yield 77%. Anal. Calcd for $C_{27}H_{27}N_5O_5$: C, 64.66; H, 5.43; N, 13.96. Found: C, 64.52; H, 5.38; N, 13.84.

4.3.12. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(3″-bromophenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8l]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3110 (C–H three-membered ring), 3051 (=C–H, sp^2), 2928 (C–H, sp^3), 2361 (overtone, CO), 1754 (C=O ester), 1710 (C=O, acetyl), 1649 (C=C), 1570 (N=N), 1591, 1454, 1320 (C⋯C ring str.), 1256 (C–N), 1094 (C–O•), 811,661 (sub. phenyl), 570 (C–Br); ^{1}H NMR (δ ppm) 1.27 (t, 3H, CH_3CH_2, $J = 7.7$ Hz), 1.90 (s, 6H, $(CH_3)_2N$), 2.54 (s, 3H, CH_3CO), 3.04 (s, CH, aziridine ring), 4.01 (q, 2H, CH_3CH_2, $J = 7.6$ Hz), 7.37–7.83 (m, 4H, C_6H_5 attached to N=N moiety), 7.74 (m, 8H, 2 × CH, *N*-phenyl); mp (°C) 114–115, yield 66%. Anal. Calcd for $C_{27}H_{27}BrN_4O_3$: C, 66.57; H, 5.08; N, 10.46. Found: C, 66.51; H, 5.04; N, 10.39.

4.3.13. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(4″-bromophenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [8m]

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3112 (C–H three-membered ring), 3048 (=C–H, sp^2), 2929 (C–H, sp^3), 2364 (overtone, CO), 1753 (C=O ester), 1712 (C=O, acetyl), 1651 (C=C), 1568 (N=N), 1597, 1451, 1322 (C⋯C ring str.), 1262 (C–N), 1088 (C–O•), 814,662 (sub. phenyl), 568 (C–Br); ^{1}H NMR (δ ppm) 1.25 (t, 3H, CH_3CH_2, $J = 7.9$ Hz), 1.91 (s, 6H, $(CH_3)_2N$), 2.53 (s, 3H, CH_3CO), 3.03 (s, CH, aziridine ring), 4.01 (q, 2H, CH_3CH_2, $J = 7.9$ Hz), 7.44 (d, 2H, Ar–H_b attached to N=N moiety), 7.81 (d, 2H, Ar–H_a attached to

N=N moiety), 7.84 (m, 8H, 2 × *N*-phenyl); mp (°C) 121–122, yield 63%. Anal. Calcd for $C_{27}H_{27}BrN_4O_3$: C, 66.57; H, 5.08; N, 10.46. Found: C, 66.52; H, 5.02; N, 11.41.

*4.3.14. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(4″-methoxyphenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [**8n**]*

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3111 (C–H three-membered ring), 3041 (=C–H, sp^2), 2930 (C–H, sp^3), 2351 (overtone, CO), 1757 (C=O ester), 1711 (C=O, acetyl), 1641 (C=C), 1543 (N=N), 1600, 1411, 1321 (C⁚⁚C ring str.), 1251 (C–N), 1100 (C–O•), 813,659 (sub. phenyl); ^{1}H NMR (δ ppm) 1.26 (t, 3H, CH_3CH_2, $J = 9.1$ Hz), 1.88 (s, 6H, $(CH_3)_2N$), 2.12 (s, 3H, CH_3CO), 3.01 (s, CH, aziridine ring), 3.67 (s, 3H, O–CH_3 attached to phenyl ring), 3.92 (q, 2H, CH_3CH_2, $J = 9.1$ Hz), 6.95–7.47 (m, 4H, C_6H_5 attached to N=N moiety), 7.76 (m, 8H, 2 × *N*-phenyl); mp (°C) 101–102, yield 61%. Anal. Calcd for $C_{28}H_{30}N_4O_4$: C, 69.12; H, 6.21; N, 11.51. Found: C, 68.89; H, 6.15; N, 11.47.

*4.3.15. 2-Acetyl-2-ethoxycarbonyl-1-{4-[4′(4″-methylphenyl)azo]phenyl}-3-N,N-dimethylaminophenyl aziridine [**8o**]*

Prepared according to the general procedure as in Section 4.3.

IR (KBr) (cm^{-1}) 3100 (C–H three-membered ring), 3051 (=C–H, sp^2), 2941 (C–H, sp^3), 2362 (overtone, CO), 1761 (C=O ester), 1715 (C=O, acetyl), 1656 (C=C), 1553 (N=N), 1601, 1413, 1321 (C⁚⁚C ring str.), 1261 (C–N), 1102 (C–O•), 815,661 (sub. phenyl); ^{1}H NMR (δ ppm) 1.32 (t, 3H, CH_3CH_2, $J = 8.5$ Hz), 1.89 (s, 6H, $(CH_3)_2N$), 2.11 (s, 3H, CH_3CO), 2.31 (s, 3H, CH_3 attached to phenyl ring), 3.04 (s, CH, aziridine ring), 3.92 (q, 2H, CH_3CH_2, $J = 8.5$ Hz), 6.98 (d, 2H, Ar–H_b attached to N=N moiety), 7.47 (d, 2H, Ar–H_a attached to N=N moiety), 7.78 (m, 8H, 2 × *N*-phenyl); mp (°C) 114–115, yield 71%. Anal. Calcd for $C_{28}H_{30}N_4O_3$: C, 71.47; H, 6.43; N, 11.91. Found: C, 71.45; H, 6.38; N, 11.89.

Conclusively, a variety of aziridine 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, 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.

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