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Synthesis, antibacterial activity and QSAR studies of 1,2-disubstituted-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines

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Abstract

Some new substituted-tetrahydroisoquinoline derivatives were synthesized and evaluated for their in vitro antimicrobial activities against the standard Gram positive and Gram negative strains: *Staphylococcus aureus* (ATCC 25923), *S. epidermidis* (WHO-6), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **4a–c** proved to be effective with MIC 3.5–20 (μg ml^{-1}). Quantitative structure activity relationship (QSAR) studies with multiple linear regression analysis were applied to find correlation between different calculated molecular descriptors of the synthesized compounds and biological activity.

Keywords: 1,2,3,4-Tetrahydroisoquinolines; Antibacterial activity; Linear free energy relationship (LFER); QSAR

1. Introduction

Isoquinoline alkaloids represent one of the largest groups of alkaloids and have attracted a great deal of interest over the decades due to their potent biological activities [1–3]. Several plants and mammalian species contain simple 1,2,3,4-tetrahydroisoquinoline (THIQs). THIQs are the constituents of several drugs and as they exhibit antitumor [4], cardiovascular to β-adrenergeic receptor antagonism [5], antibacterial [6], antiplasmodial activity [7], antitubercular [8], antimicrobial [9–11], antifungal agents [12] and noncompetitive AMPA receptor antagonist [13].

The wide range of biological activities of isoquinoline mentioned above promoted us to prepare new derivatives of isoquinoline with simple and efficient method. In prior literature, a wide variety of methods have been reported for the synthesis of THIQs [14]. A widely used method is the Pictet–Spengler reaction in which the condensation proceeds easily if the aromatic ring possess some electron donating group whereas the synthesis of those with electron withdrawing substituents is more challenging due to decreased activity of the aromatic ring.

In the present work, we report the synthesis of new substituted THIQs via iminium cation intermediate using a previously reported method [13,15]. 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **4a–c,** which has free NH group were substituted by benzotriazolyl moiety (CH_2Bt) to generate series of new compounds and were characterized by IR, NMR, LCMS and elemental analysis. This series of compounds were then subjected to in vitro antibacterial activities against some standard Gram positive and Gram negative strains. The quantitative structure activity relationship (QSAR) of biological activity with various calculated molecular descriptors have also been discussed in order to reach a better understanding of different physico-chemical parameters.

2. Chemistry

Reaction of 2-(3′,4′-dimethoxypheny1)ethylamine **1** and aromatic aldehydes **2a–c** in anhydrous toluene generate intermediate azomethines **3a–c** which underwent intramolecular cyclization effected by trifluoroacetic acid to give corresponding racemic mixture of 1-ary1-6,7-dimethoxy-1,2,3,4-tetrahydroi-

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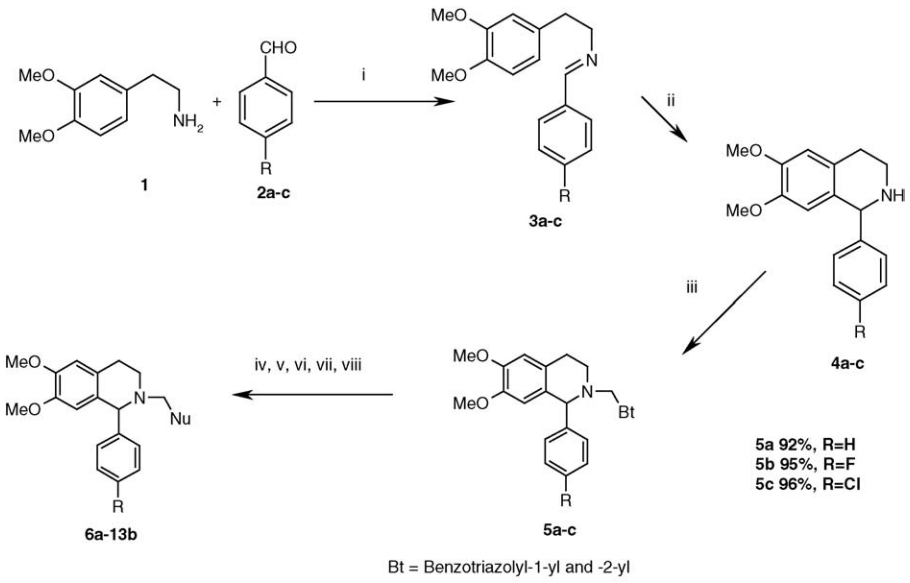


Scheme 1. Synthesis of compound **6a–13b**. Reagents: (i) Toluene reflux; (ii) CF_3COOH; (iii) CH_2O, BtH in CH_3OH:H_2O(9:1) stirred for 2–5 h; (iv) R^1MgX, (R^1 = Ph, cyclo-C_6H_{11}, *n*-C_3H_7, *n*-C_5H_{11}, CH_2=CH-CH_2, $(CH_3)_2CH$) THF, 0 °C, then reflux; (v) $P(OEt)_3$, $ZnBr_2$, DCM, 0 °C to 25 °C, 24 h; (vi) NaCN, DMSO, 25 °C, 36 h; (vi) $NaBH_4$, THF, reflux, 12 h; (vii) CH_2=CH CH_2(TMS), $BF_3.Et_2O$, DCM, 0 °C, 3 h; (viii) CH_2=C(OTMS)Ph, $BF_3.Et_2O$, DCM, 0 °C, 3 h.

soquinolines **4a–c** [13] in good yields without isolating azomethines **3a–c** (Scheme 1). Benzotriazolyl intermediates **5a–c** was obtained by condensation of equimolar amount of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **4a–c,** benzotriazole and formaldehyde (37% aqueous solution) in methanol–water at 25 °C. ^{1}H NMR spectral analysis showed that compound **5a–c** were obtained as mixture of 1-benzotriazolyl (Bt^1) and 2-benzotriazolyl (Bt^2) isomers. Bt^1 intermediate was obtained as a major product, it is difficult to distinguish the proton and carbon NMR peaks of the minor Bt^2 isomer due to their overlap with each other, and therefore we report only the ^{1}H and ^{13}C NMR data for the major Bt^1 isomers. The reactive C–N bonds of *N*-substituted benzotriazoles allow easy replacement of the benzotriazolyl group with other functionalities via nucleophilic substitutions, elimination, reduction and cyclization. Nucleophilic substitution of **5a–c** with various Grignard reagents such as phenyl magnesium bromide, cyclohexyl magnesium chloride, propyl magnesium bromide, *n*-pentyl magnesium bromide, allyl magnesium bromide and isopropyl magnesium bromide in dry THF furnished the novel 1,2-disubstituted-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **6a–c, 7a–b, 8a–b** in 65–73% yields [15] (Table 1). The structures of substituted compound **6a–c, 7a–b** and **8a–b** were clearly supported by their ^{1}H, ^{13}C spectra, LC-MS, IR and elemental analysis.

The benzotriazolyl group of **5a–c** was replaced by triethyl phosphite (1.2 equivalent) in the presence of $ZnBr_2$ to produce diethyl (6,7-dimethoxy-1-aryl-3,4-dihydroisoqinolin-2(1H)-yl) methyl phosphonate **9a–c** in 76–88% yields. The benzotriazolyl group in **5a–c** is substituted by a cyano anion to afford **10a–c** in 85–89% yields. Treatment of **5c** with 2 equivalent of sodium borohydride in refluxing THF replaced the benzotriazole group with hydrogen to give 1-(4-chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoqinoline **11c** in 65% yield. (Table 1) The benzotriazolyl group of **5b** was also replaced by allyltrimethylsilane and 1-phenylvinyl trimethylsilyl ether to afford 2-but-3-enyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline **12b** and 3-[1-(4-fluorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2yl]-1-phenyl-propane-1-one **13b** in 61%, and 65% yields, respectively. The Lewis acids $ZnBr_2$ or $BF_3.Et_2O$ facilitate the loss of benzotriazolyl anion to form an iminium cation, which is then attacked by a nucleophile.

Table 1
Reagents and yields of the synthesized compounds

Compound	Reagent	Nu	*Y* [a] (%)
6a	PhMgBr	Ph	72
7a	Cyclo-$C_6H_{11}MgCl$	Cyclo-C_6H_{11}	67
8a	$CH_3CH_2CH_2MgBr$	*n*-C_3H_7	65
6b	*n*-C_5H_{11} MgBr	*n*-C_5H_{11}	73
7b	CH_2=CH–CH_2 MgBr	CH_2=CH–CH_2	66
8b	$(CH_3)_2CH$ MgBr	$(CH_3)_2CH$	70
6c	Ph MgBr	Ph	71
9a	$(C_2H_5O)_3P$	$(C_2H_5O)_2P$=O	84
9b	$(C_2H_5O)_3P$	$(C_2H_5O)_2P$=O	88
9c	$(C_2H_5O)_3P$	$(C_2H_5O)_2P$=O	76
10a	NaCN	CN	85
10b	NaCN	CN	89
10c	NaCN	CN	87
11c	$NaBH_4$	H	65
12b	CH_2=CH–CH_2TMS	CH_2CH=CH_2	61
13b	CH_2=C(OTMS)Ph	CH_2COPh	65

[a] Isolated yield.

3. Results and discussions

3.1. In vitro antibacterial activity

Antibacterial activity was investigated in vitro on Gram positive and Gram negative bacteria. The standard strains used in

Table 2
The in vitro antimicrobial activity of the synthesized 1,2-disubsitituted-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives

Compound	MIC (μg ml^{-1})							
	Gram positive bacteria				Gram negative bacteria			
	S. aureus ATCC25923		*S. epidermidis* WHO-6		*E. coli* ATCC 25922		*P. aeruginosa* ATCC 27853	
	MIC	–log MIC	MIC	–log MIC	MIC	–log MIC	MIC	–log MIC
4a	3.5	4.465	3.5	4.465	7	4.83	3.5	4.465
4b	3.5	4.565	7	4.611	20	4.155	3.5	4.565
4c	12.5	4.384	7	4.636	20	4.181	12.5	4.384
5a	250	3.188	250	3.188	250	3.188	250	3.188
5b	250	3.208	250	3.208	250	3.208	250	3.208
5c	250	3.226	250	3.226	250	3.226	250	3.226
6a	100	3.555	125	3.458	100	3.555	100	3.555
6b	62.5	3.773	90	3.615	200	3.268	100	3.569
6c	31.2	3.716	31.2	3.716	125	3.498	31.2	3.497
7a	75	3.863	100	3.562	100	3.562	62.5	3.533
7b	31.5	3.716	31.5	3.716	15.5	4.321	31.5	3.716
8a	70	3.643	70	3.643	90	3.543	70	3.643
8b	12.5	4.417	25	4.115	25	4.115	100	3.509
10a	32.2	4.026	50	3.826	25	4.115	12.5	4.392
10b	100	3.532	100	3.532	125	3.436	70	3.669
10c	250	3.224	250	3.224	250	3.224	250	3.224
A [b]	30	–	16	–	12.5	–	16	–

[b] A = ampicillin.

these tests: *S. aureus* (ATCC 25923), *S. epidermidis* (WHO-6), *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853). A logarithmic phase culture of each bacterial strain was diluted with nutrient broth in order to obtain a density of 10^6 CFU ml^{-1}. Nutrient broth (pH 6.9) and Hinton agar (pH 7.4) were purchased from the Hi media Laboratory Pvt. Ltd. The test was performed in a 96-well microtiter plate in a final volume of 100 μl. Test compounds were dissolved in dimethyl sulfoxide (DMSO) at an initial concentration of 1000 μg ml^{-1} and serially diluted in the plate (500–3.25 μg ml^{-1}) using the nutrient broth. Each well was then inoculated with the standardized bacterial suspension (10^6 CFU ml^{-1}) and incubated at 37.0 °C for 18–24 h. One well containing bacteria without sample (growth control), and one well only containing broth (sterility control) were also used. After the incubation, the growth (or its lack) of the bacteria was determined visually both in wells containing test compound and in the control wells. The lowest concentration at which there was no visible growth (turbidity) was taken as the MIC. In addition, 5 μl of suspension from each well were inoculated in a Muller Hinton agar plate to control bacterial viability.

The listed MIC values in Table 2 show that the compound (**4a–c**) with free NH group in the isoquinoline moiety showed 3.5–20 μg ml^{-1} against all the standard strains and the compounds **5a–c** showed moderate MIC values, revealing that the moiety with free NH group had significant biological activity. Further, the compounds replaced with different nucleophiles also showed moderate MIC values. But the compound **7b** showed significant activity (15.5 μg ml^{-1}) against *E. coli* and compound **8b** showed activity (12.5 μg ml^{-1}) against *S. aureus*. These values suggested that the alkyl chain attached to the moiety might have increased the activities of these compounds. There is an important role of the phenyl ring at the 1-position of the isoquinoline moiety while compound **9a–c**, **11c**, **12b**, and **13b** showed no activity.

3.2. QSAR analysis

The QSAR investigations were carried out by the linear free energy relationship (LFER) model proposed by Hansch and Leo [16]. $\log 1/C$ was considered as dependent variable, where C is molar dose that produces or prevents certain biological response.

$$\log 1/C = k_1 a + k_2 b + k_3$$

where a and b are the molecular descriptors to be investigated and k_1, k_2, k_3 are the constant.

The selection of parameters is the first step in any QSAR study. In the present study, parameters that were considered relevant to the activity of substituted-tetrahydroisoquinoline series (electronic, hydrophobic and steric) were selected and considered as consistent, which included molar refractivity (MR), Van der Waals volume (VDW), Connolly accessible area (CAA), Connolly molecular area (CMA), Connolly solvent excluded area (CSEV), dipole–dipole energy (DD), partition coefficient (log$P$), HOMO and LUMO energies. The above-mentioned parameters were calculated by MM2 studies using Chem 3D 6.0 software [17]. Geometries of all compounds were completely optimized by the same software package.

A classical Hansch multivariate regression analysis using the least-square method was chosen to derive QSAR equations for the data set (Tables 3 and 4). The level of significance of each coefficient was judged by statistical procedure such as F tests. Statistic analysis was carried out by employing the meth-

Table 3
Values of descriptors calculated for 1,2-disubstituted-6,7-dimethoxy-1, 2,3,4-tetrahydroisoquinoline

Compound	MR	CAA	CMA	CSEV	VDW	D/D	HOMO	LUMO	log*P*
4a	79.82	509.725	270.370	237.290	15.440	0.1364	–9.5460	–1.0702	3.04
4b	80.04	572.440	273.410	239.060	15.110	0.3915	–10.0386	–0.5274	3.20
4c	84.60	523.970	284.330	257.220	15.520	0.3955	–9.7640	–1.0991	3.60
5a	118.42	652.380	367.980	343.230	21.988	0.7728	–8.0578	–1.9667	4.90
5b	118.64	630.470	358.955	362.450	21.940	0.7970	–8.0757	–2.3401	5.01
5c	123.23	646.273	373.701	371.930	22.310	0.7578	–8.4270	–2.0223	5.46
6a	109.73	633.863	357.602	335.690	22.742	0.8669	–8.9290	–1.3920	5.15
6b	108.41	667.700	357.843	353.120	21.927	0.5754	–8.2953	–0.4387	5.65
6c	115.16	668.930	375.160	349.360	21.879	0.3414	–10.9224	–1.9092	7.10
7a	111.41	633.060	360.716	366.767	22.991	0.2971	–11.0922	–1.5568	7.08
7b	94.50	579.590	315.739	288.892	19.053	1.0645	–7.9361	–1.5210	4.26
8a	99.46	620.054	301.924	318.279	19.303	0.5208	–10.6430	–1.5099	6.32
8b	99.08	600.578	332.871	320.727	20.571	0.5536	–8.0482	-1.0081	4.80
10a	90.18	550.425	298.668	273.096	18.419	1.7730	–8.5924	–1.0014	3.16
10b	90.40	559.831	303.403	277.160	18.269	2.0095	–8.9185	–0.9407	3.32
10c	94.29	573.067	289.685	289.685	18.744	2.0825	–7.8975	–0.3232	3.72
12b	94.50	579.590	315.739	288.892	19.053	1.0645	–7.9361	–1.5210	4.26
13b	115.24	676.818	376.727	345.615	23.230	2.0731	–8.5523	–5.0068	4.49
A	87.43	504.330	282.091	292.349	8.9545	–1.1731	–7.7688	–1.8313	–0.20

A = ampicillin.

Table 4
Correlation matrix of calculated molecular descriptors for 4a–13b

	SA	SE	EC	PA	MR	CAA	CMA	CSEV	VDW	D/D	HOMO	LUMO	log*P*
SA	1												
SE	0.9549	1											
EC	0.8250	0.8227	1										
PA	0.8212	0.8699	0.8018	1									
MR	–0.9390	–0.9010	–0.8959	–0.9504	1								
CAA	–0.6918	–0.7517	–0.8478	–0.8393	0.8894	1							
CMA	–0.6915	–0.7644	–0.7491	–0.8596	0.9573	0.9055	1						
CSEV	–0.7464	–0.8332	–0.8406	–0.9206	0.9732	0.8957	0.9399	1					
VDW	–0.7537	–0.8680	–0.7892	–0.9065	0.9412	0.8934	0.9516	0.9565	1				
D/D	–0.4580	–0.4670	–0.2985	–0.2031	0.1048	0.0829	0.0574	0.0279	0.1933	1			
HOMO	–0.2956	–0.3092	–0.0961	–0.2541	0.0943	–0.0244	0.0693	0.0475	0.1286	0.5768	1		
LUMO	0.5726	0.5149	0.4039	0.5313	–0.5550	–0.5118	–0.5763	–0.4481	–0.5172	–0.3404	–0.0337	1	
log*P*	–0.4422	–0.5253	–0.6101	–0.6792	0.7336	0.7675	0.7209	0.8152	0.7301	–0.3353	–0.4468	–0.2093	1

SA = *S. aureus*, SE = *S. epidermidis*, EC = *E. coli*, PA = *P. aeruginosa*, MR = molar refractivity, VDW = Van der Waals volume, CAA = Connolly accessible area, CMA = Connolly molecular area, CSEV = Connolly solvent excluded area, DD = dipole–dipole energy, log*P* = partition coefficient.

od of least square using the NCSS software [18], with stepwise selection and elimination procedure. For each equation several indices of best fit were considered: the regression coefficient "*r*", the standard deviation "*s*", and the measure of level of statistical significance "*F*".

All the parameters showed significant correlation with biological activity ($r < 0.8$) (Table 4), but the molar refractivity exhibited best correlation ($r > 0.9$) of high statistical significance > 99.9%. The statistical quality of the resulting models depicted in Eqs. (1)–(4) is determined by r^2 ($r^2 > 0.9$). Calculated parameters and correlation matrix needed for MRA (Multiple Regression Analysis) are shown in Tables 3 and 4.

QSAR Model for *S. aureus*

$$-\log \mathrm{MIC} = \{\ 7.00243(\pm 0.7102)\ \} - \mathrm{MR}\ \{\ 0.03119(\pm 0.0068)\ \} \quad (1)$$

$$n = 16 \quad |r| = 0.939 \quad s = 0.175 \quad F = 98.189...$$

QSAR Model for *S. epidermidis*

$$-\log \mathrm{MIC} = \{\ 6.77927(\pm 0.8466)\ \} - \mathrm{MR}\ \{\ 0.02967(\pm 0.0081)\ \} \quad (2)$$

$$n = 16 \quad |r| = 0.901 \quad s = 0.218 \quad F = 60.645$$

QSAR Model for *E. coli*

$$-\log \mathrm{MIC} = \{\ 6.71258(\pm 0.9053)\ \} - \mathrm{MR}\ \{\ 0.02902(\pm 0.0087)\ \} \quad (3)$$

$$n = 16 \quad |r| = 0.895 \quad s = 0.223 \quad F = 52.321$$

QSAR Model for *P. aeruginosa*

$$-\log \mathrm{MIC} = [7.09664(\pm 0.6955)] - \mathrm{MR}[3.20859(\pm 0.0066)] \quad (4)$$
$$n = 16 \quad |r| = 0.9504 \quad s = 0.164 \quad F = 112.157$$

The F values obtained in Eqs. (1)–(4) were found statistically significant at 99% level.

The graphs between observed –log MIC and calculated –log MIC and observed –log MIC and predicted –log MIC are shown in Figs. 1–4. The calculated –log MIC have been calculated by putting the MR values in the equations and the predicted –log MIC have been calculated by the NCSS software taking all the values between the upper limits and lower limits.

Since, MR is a "corrected" form of the molar volume, it reflects the effect of size and polarizability, as indicated by Eqs. (1)–(4), suggesting that MR plays a significant role towards the expressed biological activities, which is probably due to steric interactions occurring in the polar spaces. It has generally been assumed that a positive coefficient with an MR term in a correlation equation suggests a binding action via dispersion forces. Such binding could produce a concomitant conformational change in a macromolecular binding site; however, if the conformational are detrimental, a negative coefficient could result for the MR term. Negative coefficients with MR have also been assumed to reflect steric hindrance of one kind or another.

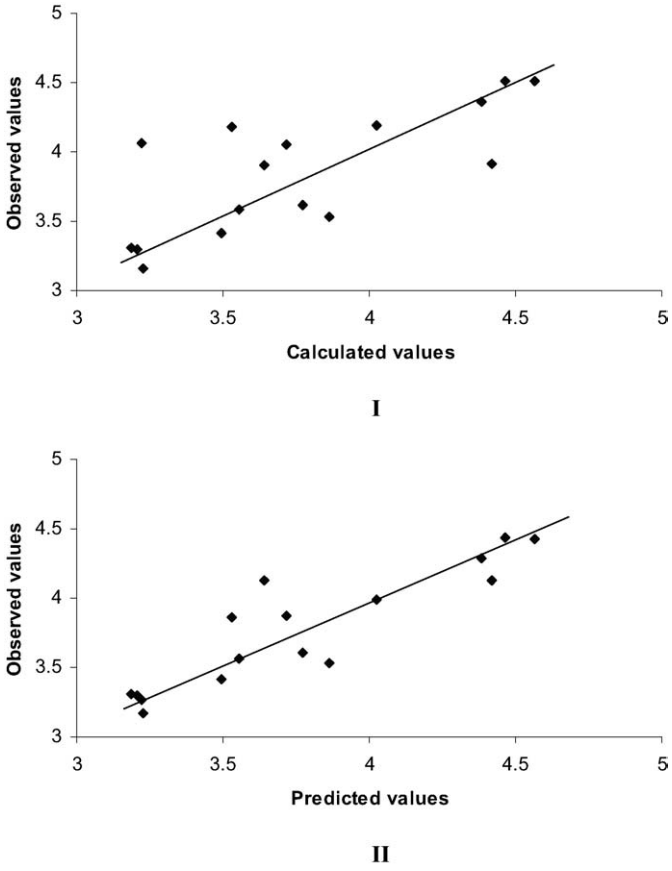


Fig. 1. Relationship between experimental vs. calculated (Graph I) and

4. Experimental

4.1. Chemistry

All reagents used were AR grade. THF was distilled from sodium/benzophenone prior to use. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 300 NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as internal references) unless otherwise stated. MS were recorded on Agluent 1100 ES-MS, Karlsruhe, Germany. Infrared spectra (υ_{max}) were recorded on Perkin Elmer FTIR spectrophotometer as thin films on KBr plates (for oils) or KBr discs (for solids). Column chromatography was performed on silica gel (230–400 mesh). Microanalyses were obtained with an Elemental Analysensysteme GmbH VarioEL V3.00 element analyzer. The reactions were monitored by thin layer chromatography (TLC) using aluminum sheets with silica gel 60 F_{254} (Merck). All the reactions were carried out under nitrogen atmosphere.

4.1.1. Preparation of 1-aryl-6, 7-dimethoxy-1, 2,3,4-tetrahydroisoquinolines *4a–c*

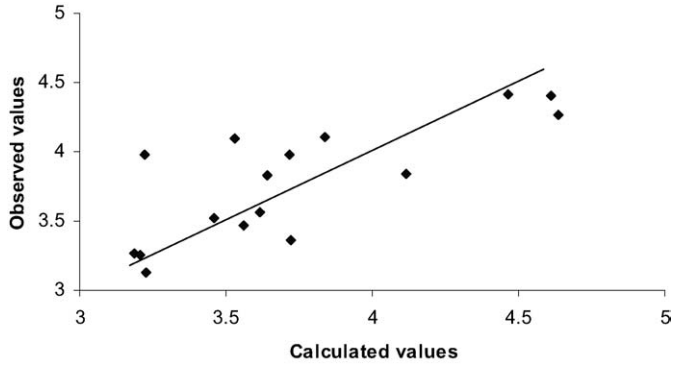
A mixture of 2-(3′,4′-dimethoxypheny1)ethy1amine **1** (0.500 g, 2.76 mmol) and appropriate aldehydes **2a–c** (2.76 mmol) in toluene (40 ml) was refluxed for 2 h and the mixture was allowed to attain room temperature; then TFA (20 ml) was added and refluxed for another 2 h. The reaction mixture was quenched by adding water, and the mixture was basified (pH ~ 8–9) with sodium hydroxide to give the isoquinoline derivatives as a solid. The crude product was collected by filtration and purified by crystallization with MeOH to afford compounds **4a–c.**

Compounds **4a–c** were obtained, fully characterized and their analytical data were found to be in accordance with the reported values. [16]

4.1.2. Synthesis of 2-benzotriazol-1-ylmethyl-6,7-dimethoxy-1-aryl-1,2,3,4-tetrahydroisoquinolines *5a–c*

1-Aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **4a–c** (3.5 g, 13 mmol), benzotriazole (1.54 g, 13 mmol) were stirred in MeOH (36 ml)/H_2O (4 ml) at 25 °C for 20 min. Formaldehyde (37% aqueous solution, 1.05 g, 13 mmol) was added to vigorously stirred mixture. After 4 h, a thick suspension was filtered and the precipitate was washed with cold MeOH to give the desired product **5a–c**.

The benzotriazolyl intermediates **5a–c** was used for the subsequent nucleophilic substitution without further purification. For microanalysis purpose, the solid formed was recrystallized from appropriate solvents or was purified by column chromatography.



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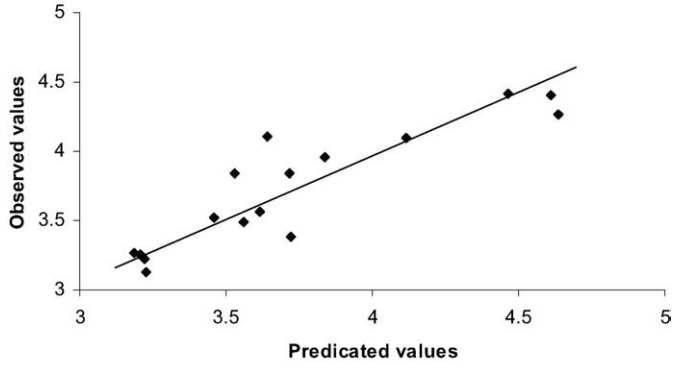


II

Fig. 2. Relationship between experimental vs. calculated (Graph I) and observed vs. predicted (Graph II) biological activity (–log MIC) for *S. epidermidis*.

4.1.3. 2-Benzotriazol-1-ylmethyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ***5a***

Colorless needles (from EtOAc/hexanes), (4.78 g, 92%); m.p. 133–135 °C; (Bt^1). ^{1}H NMR ($CDCl_3$) δ: 2.66–2.72 (m, 2 H), 2.79–2.86 (m, 2 H), 3.56 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.60 (s, 2 H, NCH_2), 4.84 (s, 1 H), 5.02 (s, 1 H), 6.16 (s, 1 H), 7.10 (s, 5 H, Ph), 7.28 (dd, J = 7.2, 7.2 Hz, 1 H, bt), 7.34 (dd, J = 7.6, 7.6 Hz, 1 H, bt), 7.53 (d, J = 6.0 Hz, 1 H, bt), 8.04 (d, J = 9.0 Hz, 1 H, bt). ^{13}C NMR ($CDCl_3$) δ: 28.8, 47.7, 55.7, 62.8, 66.0, 110.7, 111.2, 123.8, 124.4, 128.3, 129.0, 130.0, 131.3, 132.2, 133.4, 143.0, 145.3, 146.0 LCMS *m/z*: 401.7(M + 1, 60%). Anal Calcd. for $C_{24}H_{24}O_2N_4$: C, 71.98; H, 6.04; N, 13.99; Found: C, 71.58; H, 6.44; N, 13.69%.

4.1.4. 2-Benzotriazol-1-ylmethyl-1-(4-fluoro-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ***5b***

Colorless needles (from EtOAc/hexanes); (5.16 g, 95%); m.p. 110–111 °C; (Bt^1) ^{1}H NMR ($CDCl_3$) δ: 2.66–2.70 (m, 2 H), 2.79–2.86 (m, 2 H), 3.56 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.60 (s, 2 H, NCH_2), 4.84 (s, 1 H), 5.02 (s, 1 H), 6.16 (s, 1 H), 6.90–7.10 (m, 4 H, C_6H_4), 7.28 (dd, J = 7.2, 7.2 Hz, 1 H, bt), 7.34 (dd, J = 7.6, 7.6 Hz, 1 H, bt), 7.53 (d, J = 6.0 Hz, 1 H, bt), 8.04 (d, J = 9.0 Hz, 1 H, bt); ^{13}C NMR ($CDCl_3$) δ: 28.8, 47.7, 55.7, 62.8, 66.0, 110.7, 111.2, 123.8, 124.4, 128.3, 129.0, 130.0, 132.2, 133.4, 138.0, 145.3, 146.0, 162.9. Anal Calcd. for $C_{24}H_{23}N_4O_2F$: C, 68.88; H, 5.54; N, 13.39 Found: C, 68.54; H, 5.33; N, 13.69%; LCMS *m/z*: 419.5(M + 1, 70%).

4.1.5. 2-Benzotriazol–1-ylmethyl-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ***5c***

Colorless needles (from EtOAc/hexanes); (5.25 g, 93%); m.p. 113–116 °C; (Bt^1) ^{1}H NMR ($CDCl_3$) δ: 2.66–2.72 (m, 2 H), 2.79–2.86 (m, 2 H), 3.56 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.60 (s, 2 H, NCH_2), 4.84 (s, 1 H), 5.02 (s, 1 H), 6.16 (s, 1 H), 7.10 (s, 4H, C_6H_4), 7.28 (dd, J = 7.0, 7.0 Hz, 1 H, bt), 7.34 (dd, J = 7.6, 7.6 Hz, 1 H, bt), 7.53 (d, J = 6.0 Hz, 1 H, bt), 8.04 (d, J = 9.0 Hz, 1 H, bt). ^{13}C NMR ($CDCl_3$) δ: 28.8, 47.7, 55.7, 62.8, 66.0, 110.7, 111.2, 123.8, 124.4, 128.3, 129.0, 130.0, 131.3, 132.2, 133.4, 140.0, 145.3, 146.0. Anal Calcd. for $C_{24}H_{23}N_4O_2Cl$: C, 66.28; H, 5.33; N, 12.88; Found: C, 66.32; H, 5.29; N, 12.92%; LCMS *m/z*: 436.0(M + 1, 54%).

4.1.6. General procedure for the nucleophilic substitutions of ***5a–c*** *with Grignard reagents*

To a solution of 2-benzotriazol–1-ylmethyl-1-aryl-6-7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **5a–c** (1.0 mmol) in dry THF (10 ml) at 0 °C was added drop wise a solution of

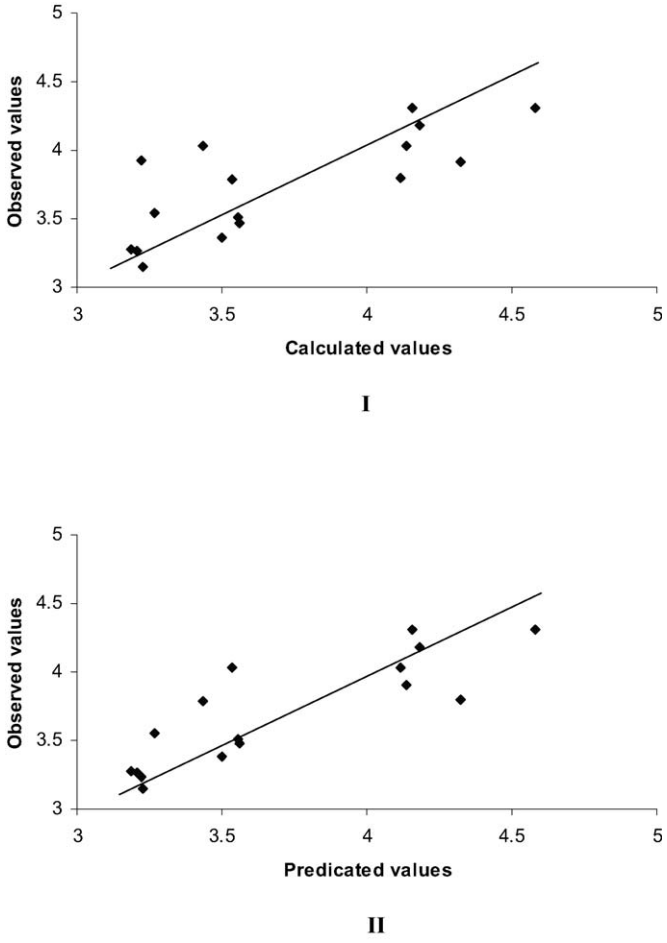


Fig. 3. Relationship between experimental vs. calculated (Graph I) and observed vs. predicted (Graph II) biological activity (–log MIC) for *E. coli*.

an appropriate Grignard reagent (1.2 mmol). The reaction mixture was allowed to warm to 25 °C and stirred for 0.5 h. Then, the mixture was refluxed for 2 h. After the mixture was cooled, the reaction was quenched with water and the mixture was extracted with ether. The combined extracts were washed with 1 N NaOH, brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (6:1 to 3:1) as an eluent to give **6a–c, 7a–b,** and **8a–b** in 65–73% yields.

4.1.7. 2-Benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4–tetrahydroisoquinolines ***6a***

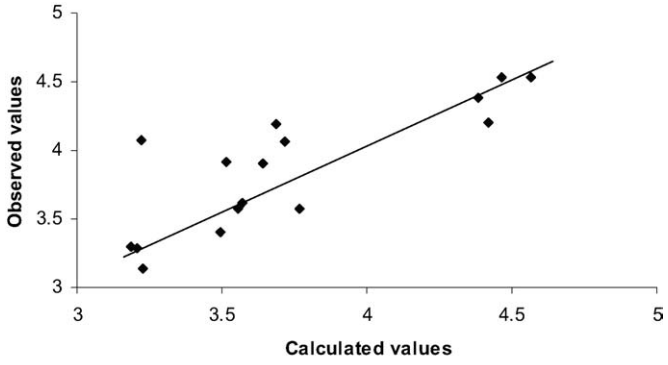
Colorless needles (from EtOAc/hexanes); (0.258 g, 72%); m.p. 114–115 °C, IR (KBr): 3027, 1610, 1515, 1446, 1331 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.66–2.71 (m, 2 H), 2.91–2.94 (m, 2 H), 3.20 (s, 2 H, N–CH_2), 3.58 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.53 (s, 1 H), 6.20 (s, 1 H), 6.58 (s, 1 H), 7.21–7.34 (m, 10 H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ: 28.3, 46.9, 55.6, 58.6, 68.0, 110.8, 111.7, 126.7, 127.1, 128.1, 128.6, 129.0, 129.4, 137.7, 139.4, 144.2, 146.9, 147.3. LCMS (*m*/*z*) 360.5 (M + 1, 45%). Anal Calcd. for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90%; Found C, 80.32; H, 7.22; N, 3.78.

4.1.8. 1-(4-Fluoro-phenyl)–2-hexyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ***6b***

Colorless oil; (0.271 g, 73%) IR (KBr): 2948, 2915, 2865, 1230 cm^{-1}.^1H NMR ($CDCl_3$) δ: 0.83 (t, $J = 6.0$ Hz, 3 H), 1.18–1.25 (m, 8 H), 2.48–2.52 (m, 2 H, N–CH_2), 3.12-3.16 (m, 2 H), 3.46–3.49 (m, 2 H), 3.58 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.49 (s, 1 H), 6.25 (s, 1 H), 6.60 (s, 1 H), 7.25–7.29 (m, 4 H, C_6H_4); ^{13}C NMR ($CDCl_3$) δ: 14.5, 24.8, 29.6, 35.6, 38.2, 42.0, 54.0, 56.0, 60.0, 65.0, 119.5, 120.0, 122.0, 132.4, 135.4, 138.0, 140.0, 145.0, 145.3, 162.0. LCMS (*m*/*z*) 372.5 (M + 1, 60%).

4.1.9. 2-Benzyl-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ***6c***

Colorless needles (from EtOAc/hexanes); (0.279 g, 71%) m.p. 131–133 °C; IR (KBr): 3010, 1609, 1518, 1420, 1332, 1252, 1089, 1018, 703 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.90–3.10 (m, 2 H), 3.20–3.30 (m, 2 H), 3.60 (s, 2 H, N–CH_2), 3.70 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.53 (s, 1 H), 6.20 (s, 1 H), 6.60 (s, 1 H), 7.20–7.50 (m, 9 H, aromatic protons). ^{13}C NMR ($CDCl_3$) δ: 28.3, 46.9, 55.6, 58.6, 68.0, 110.8, 111.7, 126.7, 127.1, 128.6, 129.0, 129.4, 129.8, 136.3, 139.4, 144.2, 146.9, 147.3; LCMS (*m*/*z*) 395.0 (M + 1, 48%). Anal Calcd. for



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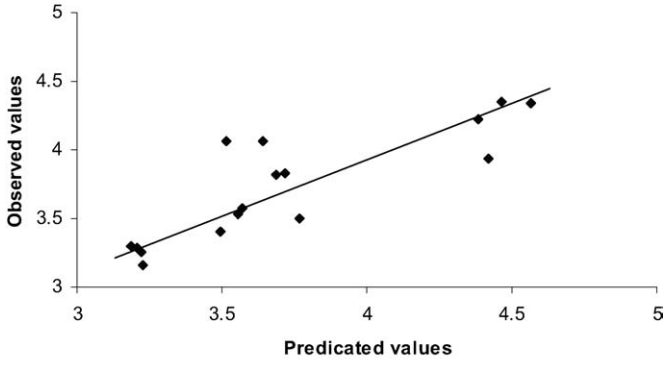

II

Fig. 4. Relationship between experimental vs. calculated (Graph I) and observed vs. predicted (Graph II) biological activity (–log MIC) for *P. aeruginosa*.

$C_{24}H_{24}NO_2Cl$: C, 73.18; H, 6.14; N, 3.56; Found C, 73.33; H, 6.43; N, 3.78%.

4.1.10. 2-(Cyclohexylmethyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ***7a***

Colorless oil; (0.244 g, 67%); IR (KBr): 3088, 1451, 1336, 1253 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.40–1.67 (m, 11H, cyclom.p. exyl), 2.41 (s, 2 H, N–CH_2), 2.66–2.72 (m, 2 H), 2.79–2.86 (m, 2 H), 3.58 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.66 (s, 1 H), 6.15 (s, 1 H), 6.60 (s, 1 H), 7.08 (s, 5 H, Ph). ^{13}C NMR ($CDCl_3$) δ: 24.6, 27.4, 29.5, 30.8, 32.3, 53.3, 54.2, 56.3, 59.3, 114.9, 115.0, 126.0, 128.4, 129.0, 133.4, 135.7, 143.0, 145.0, 145.3; LCMS (*m*/*z*) 366.5 (M + 1, 30%).

4.1.11. 2-But-3-enyl-1-(4-fluoro-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ***7b***

Colorless oil; (0.246 g, 66%), IR (KBr): 2940, 2855, 1644, 1252, 1230, 1022 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.06–2.15 (m, 2 H), 2.40–2.49 (m, 2 H, N–CH_2), 2.66–2.72 (m, 2 H), 2.79–2.89 (m, 2 H), 3.59 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.80 (d, J = 8.0 Hz, 1 H), 5.03 (d, J = 9.0 Hz, 1 H), 5.19 (s, 1 H), 5.58 (d, J = 9.0 Hz, 1 H), 6.25 (s, 1 H), 6.60 (s, 1 H), 6.90–7.04 (m, 4 H, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 40.2, 45.8, 54.0, 56.0, 60.0, 65.0, 114.9, 119.5, 120.0, 122.0, 132.4, 134.3, 135.4, 138.0, 140.0, 145.0, 145.3, 159.6; LCMS (*m*/*z*) 342.4 (M + 1, 56%).

4.1.12. 2-Butyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ***8a***

Colorless oil; (0.211 g, 65%);IR (KBr): 2962, 2931, 2852, 2834, 1610, 1515, 1465, 1446, 1336, 1249, 1026 cm^{-1}.^1H NMR ($CDCl_3$) δ: 0.74 (t, J = 9.0 Hz, 3 H, CH_3), 1.33–1.39 (m, 4 H), 2.30 (t, J = 6.0 Hz, 2 H, NCH_2), 2.62–2.68 (m, 2 H), 2.79–2.89 (m, 2 H), 3.61 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.46(s, 1 H), 6.13(s, 1 H), 6.59(s, 1 H), 6.94 (t, J = 9.0 Hz, 3 H, Aromatic protons), 7.21(d, J = 6.0 Hz, 2 H, Aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 14.0, 26.7, 29.6, 31.6, 46.8, 54.0, 55.7, 67.1, 110.8, 111.6, 113.8, 114.6, 130.0, 130.9, 140.2, 145.3, 147.0; LCMS (*m*/*z*) 326.4 (M + 1, 50%).

4.1.13. 1-(4-Fluoro-phenyl)-2-isobutyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline ***8b***

Colorless oil; (0.240 g, 70%); IR (KBr): 2999, 2966, 2828, 1455, 1450, 1231 cm^{-1}.^1H NMR ($CDCl_3$) δ: 1.34 (d, J = 8 Hz, 6 H), 2.11–2.18 (m, 1 H), 2.50–2.59 (m, 2H, N–CH_2), 2.66–2.72 (m, 2 H), 2.79–2.86 (m, 2 H), 3.59 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.49 (s, 1 H), 6.25 (s, 1 H), 6.60 (s, 1 H), 6.90–7.04 (m, 4 H, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 20.0, 35.0, 35.8, 56.0, 60.0, 62.0, 65.0, 119.5, 120.0, 122.0, 132.4, 135.4, 138.0, 140.0, 145.0, 145.3, 162.0. LCMS (*m*/*z*) 344.4 (M + 1, 35%).

*4.1.14. General procedure for the nucleophilic substitutions of **5a–c** with triethyl phosphite*

To a solution of 2-benzotriazol–1-ylmethyl-1-aryl-6-7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 5**a–c** (0.31 g, 0.69 mmol) in dry CH_2Cl_2 (20 ml) at 0 °C were successively added $ZnBr_2$ (0.186 g, 0.827 mmol) and triethyl phosphite (0.137 ml, 0.827 mmol). The reaction mixture was stirred at 0 °C for 2 h and then at 25 °C for 16 h, and the reaction was quenched with H_2O. After extraction with CH_2Cl_2, the combined organic layers were washed with 1 N NaOH, brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (4:1) as an eluent to afford **9a**–**c** with 76–88% yields.

*4.1.15. Diethyl (6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)methyl phosphonate **9a***

Yellow oil; (0.243 g, 84%); IR (KBr): 1341, 1297, 1252, 1029, 1019 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.26 (t, J= 6.0 Hz, 6 H), 2.40 (s, 2 H, N–CH_2), 2.66–2.72 (m, 2 H), 2.79-2.86 (m, 2 H), 3.58 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.05 (q, J = 6.0 Hz, 4 H), 4.67 (s, 1 H), 6.15 (s, 1H), 6.60 (s, 1 H), 7.28 (s, 5 H, Ph). ^{13}C NMR ($CDCl_3$) δ: 14.3, 29.5, 48.7, 55.6, 61.5, 62.1, 65.2, 111.7, 110.7, 126.5, 127.8, 129.6, 143.2, 145.8, 146.4, 146.9, 147.4; LCMS *m*/*z* 420.4 (M + 1, 42%.)

*4.1.16. Diethyl (6,7-dimethoxy-1-fluorophenyl-3, 4-dihydroisoquinolin-2(1H)-yl) methyl phosphonate **9b***

Yellow oil; (0.265 g, 88%);IR (KBr): 1335, 1281, 1250, 1230, 1030 1020 cm^{-1}.^1H NMR ($CDCl_3$;) δ: 1.94 (t, J = 9.0 Hz, 6 H), 2.48 (s, 2 H, NCH_2), 2.50–2.59 (m, 2 H), 2.62–2.78 (m, 2 H), 3.50 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.14 (q, J = 6.0 Hz, 4 H), 4.84 (s, 1 H), 6.51 (s, 1 H), 6.85 (s, 1H), 7.15–7.20 (m, 4 H, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 15.9, 27.1, 48.2, 58.7, 61.3, 61.6, 69.0, 110.5, 111.2, 114.3, 114.6, 130.7, 146.7, 147.2, 150.0, 159.0, 163.2; LCMS *m*/*z* 438.4 (M + 1, 55%).

*4.1.17. Diethyl (6,7-dimethoxy-1-chlorophenyl-3,4-dihydroisoquinolin-2(1H)-yl) methyl phosphonate **9c***

Yellow oil; (0.238 g, 76%); IR (KBr): 1336, 1295, 1251, 1091, 1027 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.32 (t, J = 6.0 Hz, 6 H), 2.48 (s, 2 H, NCH_2), 2.66–2.72 (m, 2 H), 2.79–2.86 (m, 2 H), 3.62 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.08 (q, J = 6.0 Hz, 4 H), 4.71 (s, 1 H), 6.13 (s, 1 H), 6.84 (s, 1 H), 7.14–7.26 (m, 4 H, C_6H_4). ^{13}C NMR ($CDCl_3$) δ: 14.3, 29.5, 48.7, 56.0, 61.5, 68.7, 70.0, 114.9, 115.8, 127.8, 129.6, 131.9, 133.8, 135.1, 143.2, 146.9, 147.4; LCMS *m*/*z* 455.0 (M + 1, 45%).

*4.1.18. General procedure for the nucleophilic substitution of **5a-c** with Sodium cyanide*

A mixture of 2-benzotriazol–1-ylmethyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 5**a–c** (0.30 g, 0.75 mmol) and NaCN (0.037 g, 0.75 mmol) in DMSO (7 ml) was stirred at room temperature for 36 h. The mixture was poured into 20 ml of water and extracted with CH_2Cl_2. The organic extract was washed with 1 N NaOH, water and brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography with hexanes/EtOAc (5:1) as an eluent to give **10a–c**.

*4.1.19. 1-(Phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2(1H)-acetonitrile **10a***

Colorless needles (from EtOAc/hexanes); (0.196 g, 85%); m.p. 122–125 °C; IR (KBr): 2222, 1336, 1254, 1016 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.67–2.70 (m, 2 H), 2.72–2.98 (m, 2 H), 3.38 (s, 2 H, NCH_2), 3.48 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.57 (s, 1 H), 6.00 (s, 1 H), 6.53 (s, 1 H), 7.19–7.26 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$) δ: 28.8, 55.3, 56.2, 56.3, 59.8, 114.7, 115.9, 117.0, 125.0, 127.4, 129.0, 133.4, 135.7, 143.0, 145.3, 145.9.LCMS *m*/*z* 309.0 (M + 1, 60%). Anal Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08; Found C, 74.31; H, 6.45; N, 8.91%.

*4.1.20. 1-(4-Fluorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2(1H)-acetonitrile **10b***

Colorless needles (from EtOAc/hexanes); (0.217 g, 89%); m.p. 117–119 °C; IR (KBr): 2220, 1336, 1254, 1231, 1025 cm^{-1}.^1H NMR ($CDCl_3$) δ: 2.69–2.70 (m, 2 H), 2.72–2.94 (m, 2 H), 3.30 (s, 2H, NCH_2), 3.57 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.64 (s, 1 H), 6.05 (s, 1 H) 6.60 (s, 1 H), 7.04 (t, J = 9.0 Hz, 2 H), 7.30 (s, 2 H). ^{13}C NMR ($CDCl_3$) δ: 28.8, 43.6, 49.6, 55.7, 65.9, 111.2, 114.7, 115.0, 115.7, 118.8, 125.7, 129.0, 140.0, 147.3, 147.7, 160.8; LCMS (*m*/*z*) 327.4 (M + 1, 48%). Anal Calcd. for $C_{19}H_{19}N_2O_2F$: C, 69.92; H, 5.87; N, 8.58; Found C, 69.65; H, 6.01; N, 8.50%.

*4.1.21. 1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2 (1H)-acetonitrile **10c***

Colorless needles (from EtOAc/hexanes); (0.233 g, 87%); m.p.: 144–145.0 °C; IR (KBr): 2230, 1332, 1254, 1090, 1027 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.90–3.10 (m, 2 H), 3.35–3.50 (m, 2 H), 3.52 (s, 2 H, NCH_2), 3.58 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.64 (s, 1 H), 6.04 (s, 1 H), 6.60 (s, 1 H), 7.26–7.34 (m, 4 H, C_6H_4); ^{13}C NMR ($CDCl_3$) δ: 28.8, 43.7, 49.7, 55.8, 66.0, 110.7, 114.6, 115.2, 117.8, 128.0, 129.0, 129.5, 130.6, 140.6, 145.3, 145.8. LCMS (*m*/*z*) 344.0 (M + 1, 40%). Anal Calcd. for $C_{19}H_{19}N_2O_2Cl$: C, 66.57; H, 5.59; N, 8.17; Found C, 66.29; H, 5.50; N, 8.40%.

4.1.22. General procedure for the reduction of 5c with sodium borohydride

A mixture of 2-benzotriazol–1-ylmethyl-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **5c** (0.31 g, 1.0 mmol) and $NaBH_4$ (0.076 g, 2.0 mmol) was refluxed in dry THF (10 ml) overnight after removal of the solvent in vacuo, the residue was diluted with EtOAc. The mixture was washed with 1 N NaOH, and brine and dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded **11c**.

*4.1.23. 1-(4-Chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **11c***

Yellow oil; (0.206 g, 84%);IR (KBr): 2910, 1251, 1091, 1027,cm^{-1}.^{1}H NMR ($CDCl_3$) δ: 1.25 (s, 3 H, N–CH_3), 2.50–2.70 (m, 2 H), 3.10–3.25 (m, 2 H), 3.58 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.19 (s, 1 H), 6.04 (s, 1 H), 6.60 (s, 1 H), 7.14–7.36 (m, 4 H, C_6H_4); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.9, 36.1, 41.5, 55.6, 60.5, 110.5, 111.3, 127.0, 127.4, 130.0, 132.7, 134.2, 143.2, 147.4, 148.0. LCMS (*m*/*z*) 318.8 (M + 1, 65%)

*4.1.24. General procedure for the nucleophilic substitution of **5b** with allylsilanes and silyl enol ether*

To a solution of 2-benzotriazol–1-ylmethyl-1- (4-fluoro-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 5**b** (0.5 g, 1.18 mmol), (2-methylpropenyl) trimethylsilane, and allyltrimethylsilane or 1-phenylvinyl trimethylsilyl ether (1.18 mmol) in dry CH_2Cl_2 (10 ml) under N_2 was added $BF_3.Et_2O$ (1.18 mmol) at 0 °C. The mixture was stirred for 3 h and then warmed to room temperature and stirred for another 3 h. The mixture was washed with 5% $NaHCO_3$ and H_2O; the combined aqueous phase was extracted with EtOAc, and then combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography (silica gel) with EtOAc/hexanes (1:5) as an eluent to afford **12b** and **13b**.

*4.1.25. 2-But-3-enyl-1-(4-fluoro-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **12b***

Colorless oil; (0.245 g, 66%). IR (KBr): 2940, 2855, 1644, 1260, 1231, 1029 cm^{-1}.^{1}H NMR ($CDCl_3$) δ: 2.06–2.15 (m, 2 H), 2.40–2.48 (m, 2 H, NCH_2), 2.66–2.72 (m, 2 H), 2.79–2.86 (m, 2 H), 3.59 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.80 (d, J = 8.0 Hz, 1 H), 5.03 (d, J = 9.0 Hz, 1 H), 5.19 (s, 1 H), 5.58 (d, J = 8.2 Hz, 1 H), 6.25 (s, 1 H), 6.60 (s, 1 H), 6.90–7.04 (m, 4 H, C_6H_4); ^{13}C NMR ($CDCl_3$) δ: 40.2, 45.8, 54.8, 56.0, 60.0, 65.0, 114.9, 119.5, 120.0, 122.0, 132.4, 134.3, 135.4, 138.0, 140.0, 145.0, 145.3, 159.6.LCMS *m*/*z* 342.4 (M + 1, 36%).

*4.1.26. 3-[1-(4-Fluoro-phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-yl]-1-phenyl-propan-1-one **13b***

Colorless oil; (0.321 g, 65%); IR (KBr): 3324, 1690, 1257, 1231, 1031 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.44–2.54 (m, 4 H, NCH_2CH_2), 2.66–2.72 (m, 2 H), 2.79–2.86 (m, 2 H), 3.59 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.49 (s, 1 H), 6.25 (s, 1 H), 6.60 (s, 1 H), 7.20–7.82 (m, 9 H, Aromatic). ^{13}C NMR ($CDCl_3$) δ: 29.8, 50.0, 56.0, 60.0, 62.4, 65.0, 119.5, 120.0, 122.0, 125.4, 128.6, 130.0, 132.0, 133.4, 135.0, 137.0, 140.0, 145.0, 145.3, 197.6. LCMS (*m*/*z*) 420.4 (M + 1, 56%).

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