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Design, synthesis, antibacterial and QSAR studies of benzimidazole and imidazole chloroaryloxyalkyl derivatives

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Abstract—In view of obtaining some potential antibacterial compounds, we have described synthesis of some chloroaryloxyalkyl imidazole and benzimidazole derivatives. The relevant step in the synthetic sequence was the initial condensation of 4-chloro or 2,4-dichlorophenol with 1, *n*-dibromoalkanes ($n = 2, 4, 5$) to provide compounds **3a**–**f** in sufficient yields. The subsequent condensation of **3a**–**f** with some imidazole derivatives and benzimidazole afforded products **4a**–**l** and **5a**–**e** in good yields. Some of compounds **4a**–**l** as well as **5a**–**e** were tested in vitro against *Salmonella typhi O-901* and *Staphylococcus aureus A 15091*. Compounds **4a** and **4c** showed considerable bactericidal activities against tested bacteria. Compound **4b** showed significant activity against *S. aureus A 15091* but was inactive against *S. typhi O-901*. Other compounds showed intermediate activities against *S. aureus A 15091* but most of them were inactive against *S. typhi O-901*. Semiempirical AM1 calculations showed that negative electrostatic potentials around oxygen of the phenoxy and nitrogen of the imidazole moieties have direct effect on the antibacterial activity towards *S. aureus A 15091*. In QSAR analysis, different electronic, topologic, functional groups and physicochemical descriptors were calculated for each molecule and a three parametric equation was found between the log MIC and HOMO energy, hydration energy and number of primary carbon atoms of the molecules.

1. Introduction

The incorporation of the imidazole and benzimidazole nuclei is an important synthetic strategy in drug discovery.[1] The high therapeutic properties of the related drugs have encouraged the medicinal chemists to synthesize the large number of novel chemotherapeutic agents. Imidazole and benzimidazole drugs have broaden scope in remedying various dispositions in clinical medicine.[2] Pharmaceutical properties including; antifungal and antimycotic,[3] antiprotozoal and trichomonas infection;[4] antineoplastic;[5] antiulcer;[6] antihistaminic and antiallergic;[7] anesthetic and hypnotic;[8] antihypertensive;[9] anthelmintic;[10] neuroleptic and antipsychotic[11] and thromboxane synthetase inhibitor,[12] all are unique characteristics known from imidazole and benzimidazole derivatives. The resistance of common pathogens to standard antibiotic therapies is rapidly becoming a major public health problem throughout the world. The incidence of multidrug-resistant gram-positive and gram-negative bacteria is increasing, and infections caused by *Staphylococcus aureus and Salmonella typhi* are particularly problematic.[13]

There is real perceived need for the discovery of new compounds endowed with antibacterial activity, possibly acting through mechanisms of action, which are distinct from those of well-known classes of antibacterial agents to which may clinically relevant pathogens are now resistant. Through the various molecules designed and synthesized for this aim, it was demonstrated that *N*-alkyl imidazoles could be considered as future antibacterial candidate.[14] Recently, we have reported that *N*-alkylimidazole with the most simple structure possess inhibitory effects on several pathogenic bacteria.[15] In this context, we would like to report synthesis of some imidazole and benzimidazole chloroaryloxyalkyl derivatives, which are longer carbon chain analogs of our previously synthesized imidazole and benzimidazole acycloaromatic nucleosides **1**,**2**.[16] Then, antibacterial effects of title compounds on gram-positive (*S. aureus A 15091*) and

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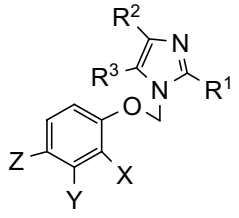
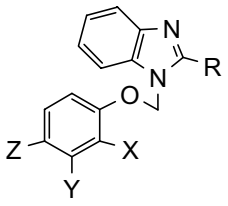
gram-negative (*S. typhi O-901*) were investigated. Finally, a quantitative structure–activity relationship (QSAR) analysis was conducted to investigate the quantitative effect of structural properties of the molecules on their antibacterial activity.[17–23] QSAR as one of the most important areas in chemistry gives information that is useful for drug design and medicinal chemistry. These are mathematical equations relating chemical structure to a wide variety of physical, chemical, biological and technological properties. The derived relationship between molecular descriptors and activity are used to estimate the property of other molecules and/or to find the parameters affecting the biological activity.



1

X,Y,Z=Me,Cl,allyl,H,Ph
R^1,R^2,R^3=Me,NO_2,H

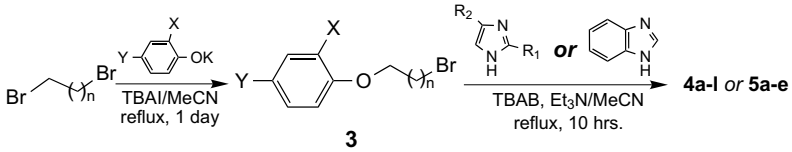


2

X,Y,Z=Me,MeO,H
R=Me,H

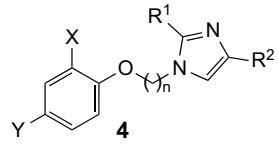
2. Chemistry

The synthesis of compounds **4a**–**l** and **5a**–**e** followed the general pathway illustrated in Scheme 1. Compounds **3a**–**f** are the key intermediates for synthesis of title compounds. They can normally be prepared from alkylation of phenols by using 1, *n*-dihaloalkanes in the presence of bases such as NaOH or K_2CO_3 in anhydrous ketones as the solvent.[24] However, in our experience, application of potassium salt of phenols instead of phenols gave better yields.[16] Therefore, we condensed the potassium salts of both *p*-chlorophenol and 2,4-dichlorophenol with manifolds (4 equiv) of 1,2-dibromoethane, 1,4-dibromobutane and 1,5-dibromopentane in the presence of catalytic amount of tetrabutylammonium iodide (TBAI), as phase transfer catalyst (PTC), in anhydrous acetonitrile (MeCN) to afford mainly compounds **3a**–**f** with 50%, 52%, 60%, 65%, 72%, 76% yields, respectively. The *p*-chloro and 2,4-dichlorophenols were designated as aryloxy moieties owing to the fact that, their free phenols show apparent bactericidal properties.[25] The methods for *N*-alkylation of imidazole are well-documented and fully established.[26] The literature survey indicated that, method reported by Liu et al.[27] is appropriate for *N*-alkylation of imidazole, since the formation of quaternary imidazolium salts, as unwanted side product, was usually limited. In this method, we used triethylamine (TEA) (Scheme 1) instead of K_2CO_3 employed by Liu et al. The equimolar reaction of compounds **3a**–**f** with imidazoles or benzimidazole and dry TEA, in the presence of catalytic amount of tetrabutylammonium bromide (TBAB) in refluxing anhydrous MeCN, afforded compounds **4a**–**l** in 70–90% and compounds **5a**–**e** in 50–70% yields. The *N*-alkylation of 2-methyl-4(5)-nitroimidazole usually provides mixture of two regio-isomers owing to the reversible tautomeric conversion (1,3-shift of *N*H) of 2-methyl-4-nitroimidazole to 2-methyl-5-nitroimidazole. The alkylation of 2-methyl-4(5)-nitroimidazole by alkyl halides, under alkaline conditions, yields *N*-alkyl-2-methyl-4-nitro rather than *N*-alkyl-2-methyl-5-nitro isomer[28] while; under acidic media formation of *N*-alkyl-2-methyl-5-nitro derivatives is more satisfactory. Principally, in alkaline conditions *N*-alkyl-2-



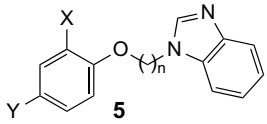
3

n=1, X=Y=Cl (**3a**)
n=1, X=H,Y=Cl (**3b**)
n=3, X=Y=Cl (**3c**)
n=3, X=H,Y=Cl (**3d**)
n=4, X=Y=Cl (**3e**)
n=4, X=H,Y=Cl (**3f**)



4

n=2, X=Y=Cl, R^1=R^2=H (**4a**)
n=4, X =Y=Cl, R^1=R^2=H (**4b**)
n=4, X=H,Y=Cl, R^1=R^2=H (**4c**)
n=4, X=H,Y=Cl, R^1=C_2H_5,R^2=H (**4d**)
n=4, X=Y=Cl, R^1=CH_3,R^2=NO_2 (**4e**)
n=4, X=H,Y=Cl,R^1=CH_3,R^2=NO_2 (**4f**)
n=5, X=Y=Cl, R^1=R^2=H (**4g**)
n=5, X=Y=Cl, R^1=C_2H_5,R^2=H (**4h**)
n=5, X=H,Y=Cl, R^1=R^2=H (**4i**)
n=5, X=H,Y=Cl, R^1=C_2H_5,R^2=H (**4j**)
n=5, X=Y=Cl, R^1=CH_3,R^2=NO_2 (**4k**)
n=5, X=H,Y=Cl,R^1=CH_3,R^2=NO_2 (**4l**)



5

n=2, X=H,Y=Cl (**5a**)
n=4, X =Y=Cl (**5b**)
n=4, X=H,Y=Cl (**5c**)
n=5, X=Y=Cl (**5d**)
n=5, X=H,Y=Cl (**5e**)

Scheme 1.

methyl-4-nitro derivatives is yielded, since *N*3 atom in the anion (conjugated base) of 2-methyl-4-nitroimidazole is more basic as well as more nucleophilic.[27,28] Distinction between *N*-alkyl-2-methyl-4-nitroimidazole and *N*-alkyl-2-methyl-5-nitroimidazole can be easily subtle with comparing chemical shifts of CH_2 group attached to *N*1 where the former show NMR signals measurably downfield. The other methods for recognition of *N*-alkyl-2-methyl-4-nitroimidazoles from their isomers (i.e., *N*-alkyl-2-methyl-5-nitroimidazoles) are also explained in literatures.[28] Indeed, in our experiments, compounds **4e**,**f**,**k** and **4l** were produced dominantly along with trace amounts of their 5-nitro isomers (<5%).

3. Biology

We carried out the screening experiments for antibacterial activities of compounds **4a–d**, **4g–j** and **5a–e** against a gram-positive (G^+) (*S. aureus A 15091*) and a gram-negative (G^-) (*S. typhi O-901*) bacterium in vitro, following disk diffusion method.[29] In this method, bacteria were streaked onto a series of 150 and 100 mm petri dishes containing *Muller Hinton* agar. The proper amounts of compounds were pipetted on the sterilized blank disks (6 mm in diameter) and subsequently all disks were placed on the medium incubated at 37 °C. The experiments were performed against both of the above mentioned microorganisms, with compounds concentrated up to 128 μg/mL. The results are depicted in Table 1. Chloramphenicol and hexachlorophene are two well-known bacteriostatic agents,[30] which were designated in our experiment as control drugs **1**, **2** (C.D.1, C.D.2) respectively.

The average of duplicate determinations was considered as minimum inhibitory concentration (MIC) value defines as the lowest concentration of antibiotic requires preventing visible growth of bacteria. As it is indicated in Table 1 compounds **4c** and **4a** show noteworthy antibacterial activities whereas compounds **4i**,**g** and **5c** showed intermediate antibacterial activities against both tested microorganisms. Compounds **4b**, **4d**, **4g**, **4h**, **5a**, **5b**, **5d** and **5e** were inactive against *S. typhi O-901*, but they showed favourable antibacterial activity against *S. aureus A 15091* with different intensities.

Table 1. Antibacterial screening summary

Compound	*S. typhi O-901* MIC[a]	*S. aureus A 15091* MIC[a]
4a	8.5	7.5
4b	>128	8.5
4c	7.5	7.5
4d	>128	23
4g	>128	30
4h	>128	42
4i	35	30
4j	50	45
5a	>128	35
5b	>128	30
5c	22	24
5d	>128	35
5e	>128	25
C.D.1[b]	16	20
C.D.2[b]	10	1

[a] MIC: Minimum inhibitory concentration (μg/mL).
[b] C.D.1: chloramphenicol; C.D.2: hexachlorophene.

4. QSAR analysis

The chemical structure of the molecules was drawn by the Hyperchem software (Hypercube Inc. version 7) into personal computer. Semiempirical AM1 calculations were used for geometry optimization of the molecules by the software. The overlaid three-dimensional structure of both types of molecules is represented in Figure 1. The molecules possess a phenoxy moiety and a imidazolyl moiety attached by $(CH_2)_n$. The stereoplots shown in Figure 1 reveals that for both types of derivatives, the conformation of the imidazolyl moiety was changed by changing substitution patterns on the molecules. However, the conformation of the phenyl moiety of the imidazole derivatives was not altered as the substitution pattern on the molecules varied. Meanwhile, the phenyl moiety of the benzimidazole derivatives adapted to more or less different conformations by variation in the substitution patterns. The three-dimensional isosurface plot of the molecular electrostatic potentials for three compounds is shown in Figure 2. As it is observed, the negative electrostatic potentials are around the oxygen of the phenoxy and nitrogen of the imidazole, and other atoms carrying the positive electrostatic potentials. As it is shown in Figure 2, the major differences between the high and the low active antibacterial molecules are the amount of distribution of the negative electrostatic potentials around the oxygen and the nitrogen atoms. There are high values of the negative electrostatic potential around the oxygen and nitrogen of **4a**, which is the most potent compound. While, **5c** with moderate activity has lower negative

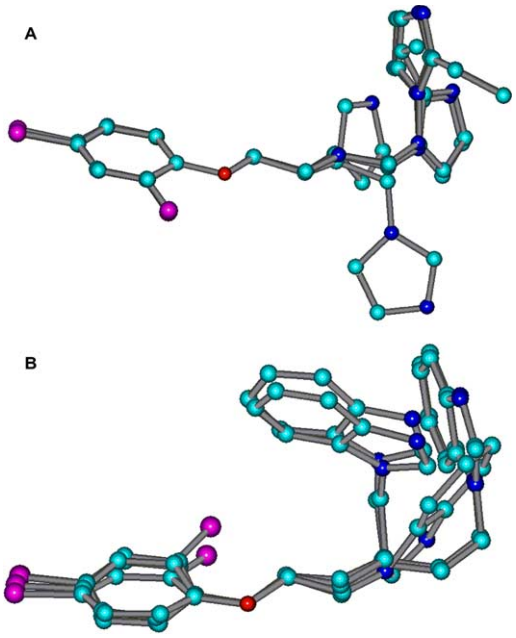


Figure 1. The overlaid three-dimensional structure of imidazole (A) and benzimidazole (B) derivatives.

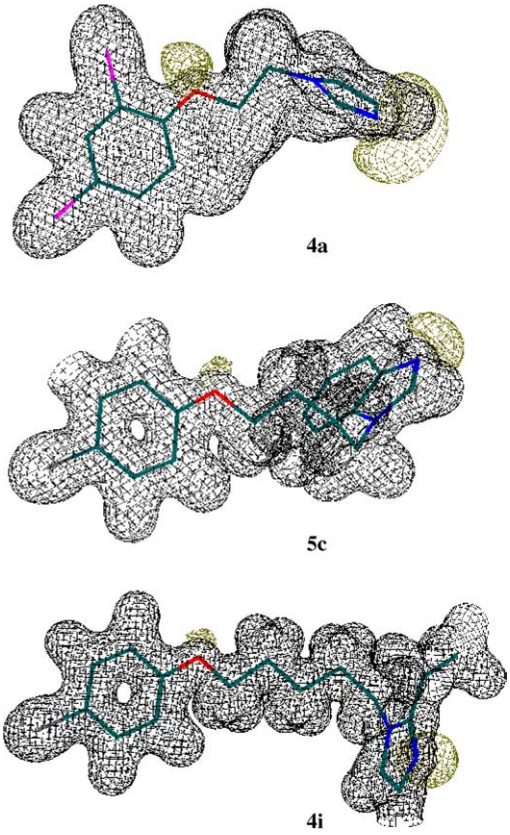


Figure 2. The 3D isosurface plots of the molecular electrostatic potential of **4a** (the most active derivative), **4i** (the least active derivative) and **5c** (moderate activity); darker surfaces: positive potentials and whiter surfaces: negative potentials.

electrostatic potential and **4i**, the least active molecules, is containing the least electrostatic potential around its oxygen and nitrogen atoms.

To obtain the quantitative effects of the structural parameters of the imidazole and benzimidazole derivatives on their antibacterial activity, QSAR analysis with three types of molecular descriptors including electronic, physicochemical and topological parameters was operated.[22] HOMO and LUMO energies, dipole moments (DM), electronegativity (χ), electrophilicity (ω), softness (S) and hardness (η) were used to account the electronic feature of the molecules. Molecular surface area (MSA), molar volume (MV), molar refractivity (MR), lipophilicity (log P) and hydration energy (HE) are the physicochemical properties that calculated for each molecule. Electronic and physicochemical descriptors were calculated by Hyperchem software. The Dragon software[23] were used for calculation of topological indices such as total structure connectivity index (Xt), average connectivity index (X1A), average valence connectivity index (X2Av), sum of topological distance between N and Cl atoms (TN-Cl) and path/walk-3 randic shape index (PW3), and functional group indices including number of total primary carbons (nCp) and number of total secondary carbons (nCs). As it was shown in Table 1, the molecules have valuable MIC values towards gram-positive (G^+) (*S. aureus*) bacterium. Therefore, these data were used to find QSAR models. First the correlation of each one of the descriptors with each other and with log MIC was calculated. The resulted correlation matrix is represented in Table 2 for some descriptors that had high correlation with log MIC. As it is indicated, HOMO, LOMO, HE, Xt and MR had significant correlation with log MIC. However, there was observed some colinearity between the calculated descriptors. Examples of some collinear pairs are HOMO–LUMO, Log P-MR, Xt-MR, X1A-X2Av and Xt-HOMO. Among the collinear descriptors, one of them, which had the highest correlation with log MIC was retained and the others were removed. The remaining descriptors were used to find a multilinear equation of the form $\log \mathrm{MIC} = b_0 + b_1\mathrm{DES}_1 + b_2\mathrm{DES}_2 + \ldots$ between activity and structural parameters. A multilinear equation of the form $\log \mathrm{MIC} = b_0 + b_1\mathrm{DES}_1 + b_2\mathrm{DES}_2 + \ldots$ was build. The stepwise selection and elimination of variable procedure of SPSS software was used to find the best set of descriptors. The resulted QSAR models are as following:

$$\log \mathrm{MIC} = 16.77(\pm 1.50) + 1.70(\pm 0.17)\mathrm{HOMO} + 0.06(\pm 0.01)\mathrm{HE}$$
$$N = 13 \; R = 0.979 \; \mathrm{Se} = 0.062 \; F = 113.45 \quad (1)$$

$$\log \mathrm{MIC} = 17.37(\pm 1.22) + 1.73(\pm 0.14)\mathrm{HOMO} + 0.07(\pm 0.01)\mathrm{HE} - 0.11(\pm 0.04)\mathrm{nCp}$$
$$N = 13 \; R = 0.988 \; \mathrm{Se} = 0.048 \; F = 121.26 \quad (2)$$

Table 2. Correlation (R^2) matrix for some of descriptors used in this study

	log MIC	HOMO	LUMO	DM	MR	Log P	HE	Xt	X1A	X2Av	PW3	TN-Cl	nCp	nCs
log MIC	1.00	0.89	0.70	0.04	0.49	0.39	0.55	0.45	0.02	0.00	0.18	0.01	0.15	0.27
HOMO		1.00	0.75	0.04	0.66	0.53	0.31	0.68	0.04	0.00	0.23	0.00	0.18	0.34
LUMO				0.17	0.36	0.19	0.31	0.29	0.02	0.05	0.02	0.02	0.31	0.53
DM				1.00	0.12	0.01	0.00	0.03	0.11	0.40	0.09	0.17	0.00	0.43
MR					1.00	0.88	0.04	0.85	0.16	0.00	0.38	0.12	0.02	0.29
Log P						1.00	0.02	0.85	0.48	0.13	0.59	0.05	0.00	0.05
HE							1.00	0.01	0.03	0.04	0.05	0.01	0.32	0.12
Xt								1.00	0.27	0.07	0.37	0.01	0.00	0.14
X1A									1.00	0.74	0.50	0.00	0.30	0.30
X2Av										1.00	0.30	0.23	0.17	0.54
PW3											1.00	0.05	0.02	0.03
T(N..Cl)												1.00	0.00	0.07
nCp													1.00	0.34
nCs														1.00

Table 3. Data of the selected descriptors used in this study and the experimental and predicted values of log MIC

Compound	Descriptors			Log MIC (*S. aureus A 15091*)		
	HOMO (eV)	HE (kcal/mol)	nCp	Experimental	Predicted by Eq. 1	Predicted by Eq. 2
4a	−9.32	−6.07	0	0.875	0.880	0.880
4b	−9.26	−7.77	0	0.929	0.890	0.870
4c	−9.23	−7.29	0	0.875	0.967	0.955
4d	−9.01	−4.98	1	1.362	1.456	1.384
4g	−9.06	−4.76	0	1.477	1.387	1.419
4h	−8.94	−2.91	1	1.623	1.676	1.637
4i	−9.05	−4.54	0	1.477	1.417	1.453
4j	−8.93	−3.61	1	1.653	1.666	1.617
5a	−9.02	−3.74	0	1.544	1.499	1.548
5b	−8.96	−6.59	0	1.477	1.442	1.455
5c	−8.98	−6.84	0	1.380	1.405	1.414
5d	−8.97	−4.29	0	1.544	1.564	1.609
5e	−9	−6.87	0	1.398	1.367	1.374

In these equations the values in the parenthesis represent the standard deviation of the coefficients. *N*, *R*, Se and *F* are number of components, correlation coefficient, standard error of regression and Fisher's *F*-ratio, respectively. Eq. 1 reveals that the antibacterial activity of the studied compounds is affected by the electronic (HOMO energy) and hydrophobicity (HE) of the molecules. The positive sign of the coefficients of these parameters indicates that the log MIC increases (or antibacterial activity decreases) as HOMO and HE change to more positive values. Addition of the number of primary carbon atoms (nCp), a functional group descriptor, enhanced the quality of the resulted QSAR model. As it is shown in Table 2, the value of nCp descriptor is 1 for **4d**,**h** and **4j**, whose R^1 is ethyl, and is zero for the other molecules. The negative sign of the coefficient of this parameter confirms the lowering effect of the primary carbon atoms on the antibacterial activity of the molecules that means the presence of the ethyl substituent lowers the antibacterial activity. According to the discussion made above, the nCp, HE and HOMO of the more active molecules must be lower than those of the less active derivatives. As it is indicated in Table 3, least negative values of HE and HOMO are obtained for compounds **4a**,**b** and **4c**, which have the highest activity. For example, a comparison between **4a** and **4g**, which are only different in the number of CH_2 group, reveals that addition of three methylene groups to the imidazolyl, changes the respective values of HOMO and HE from −9.32 to −9.06 and from −6.07 to −4.76, where change in HE is more significant. The overall effect of both parameters is a significant increasing in log MIC (or decreasing in the antibacterial activity).

The values of the descriptors used by Eqs. 1 and 2 together with the experimental and predicted log MIC are listed in Table 3. Obviously, there is a close agreement between the experimental and predicted activity values.

5. Conclusion

In approach of preparing new antibacterial compounds, we have synthesized some chloroaryloxyalkyl benzimidazole and imidazole derivatives. In view of realizing potential antibacterial activities of synthesized compounds, screening experiments were performed for two significant pathogenic bacteria, that is, *S. typhi O-901* and *S. aureus A 15091*. Compounds **4a**,**c** showed considerable in vitro antibacterial activities against both bacteria. In general, these synthesized compounds were shown to be more effective for inhibiting growth of *S. aureus A 15091* rather than *S. typhi O-901*. Molecular modeling and QSAR analysis were performed to find the quantitative effects of the molecular structure of the molecules on their antibacterial activity. Semiempirical AM1 calculations showed that negative electrostatic potentials around oxygen of the phenoxy and nitrogen of the imidazole moieties have direct effect on the antibacterial activity towards *S. aureus*. In QSAR analysis, different electronic, topologic, functional groups and physicochemical descriptors were calculated for each molecule and a three parametric equation was found between the log MIC and HOMO energy, hydration energy and number of primary carbon atoms of the molecules.

6. Experimental

General. All chemicals were obtained from *Fluka* or *Merck*. Solvents were purified according to reported methods and stored over molecular sieves. With TLC using Silica gel *SILG/UV 254* plates the progress of reaction was followed. IR spectra were run on a *Shimadzu FTIR-8300* spectrophotometer; in cm^{-1}. ^1H NMR spectra were run on *a Bruker Avance DPX-250, FTNMR* spectrometer; δ in ppm, *J* in Hz. Mass spectra were recorded on a *Shimadzu GC MS-QP 1000EX* apparatus. Microanalyses were performed on a *Perkin–Elmer 240-B* microanalyzer. Melting points were recorded on a *Büchi* 510 apparatus in open capillary tubes and are uncorrected.

6.1. General procedure for preparation of compounds 3a–f

To mixture of potassium aryloxide (0.001 mol), 1, *n*-dibromoalkane ($n = 2, 4, 5$) (0.004 mol) and catalytic amount of TBAI (0.1 g) in a round bottomed flask was added anhydrous MeCN (40 mL) and the mixture was refluxed for 1 day. When TLC monitoring indicated

no further progress in reaction, the solvent was evaporated and the crude mixture was suspended in water (200 mL). The organic materials were extracted with $CHCl_3$ (2 × 100 mL) and dried over Na_2SO_4 (15 g). Filtration and evaporation of the solvent gave the crude product, which was purified by column chromatography on silica gel with EtOAc/*n*-hexane (2:8).

6.2. General procedure for the preparation of compounds 4a–l and 5a–e

To solution of **3** (0.01 mol), imidazole (0.015 mol) or benzimidazole (0.015 mol) and catalytic amount of TBAB (0.1 g) in anhydrous MeCN (40 mL) was added Et_3N (1.01 g, 0.01 mol) and then solution was refluxed. After 10 h, when TLC monitoring indicated disappearance of the starting compound **3**, the solvent was evaporated and the crude mixture was suspended in water (200 mL). The organic materials were extracted with $CHCl_3$ (2 × 150 mL) and dried over Na_2SO_4 (20 g). Filtration and evaporation of the solvent gave the crude product, which was purified by column chromatography on silica gel with EtOAc.

6.2.1. 1-[2-(2,4-Dichlorophenoxy)ethyl]-1*H*-imidazole (4a). Brown oil (2.1 g, 80%). R_f (EtOAc) 0.51. IR (liquid film) 3200m, 2900m, 2850m, 1680m, 1600s, 1430s, 1260s, 1100s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.62 (s, 1H, C(2)-H, imid.); 7.25–6.62 (m, 5H, aryl, C(4)-H, C(5)-H, imid.); 4.32–4.28 (t, J = 4.4, 2H, OCH_2); 4.12–4.09 (t, J = 4.4, 2H, NCH_2). MS [*m*/*z* (%)]: 257 (12.2). Anal. Calcd for $C_{11}H_{10}Cl_2N_2O$: C 51.38, H 3.92, Cl 27.58, N 10.90. Found: C 51.43, H 3.96, Cl 27.62, N 10.85.

6.2.2. 1-[4-(2,4-Dichlorophenoxy)butyl]-1*H*-imidazole (4b). Brown oil (1.99 g, 70%). R_f (EtOAc) 0.33. IR (liquid film) 3200m, 2950m, 2868m, 1670m, 1600s, 1430s, 1270s, 1150s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.86 (s, 1H, C(2)-H, imid.); 7.29–6.71 (m, 5H, aryl, C(4)-H, C(5)-H, imid.); 4.03–3.97 (t, J = 6.9, 2H, OCH_2); 3.95–3.90 (t, J = 5.8, 2H, NCH_2); 2.02–1.90 (m, 2H, CH_2); 1.79–1.69 (m, 2H, CH_2). MS [*m*/*z* (%)]: 285 (15). Anal. Calcd for $C_{13}H_{14}Cl_2N_2O$: C 54.75, H 4.95, Cl 24.86, N 9.82. Found: C 54.73, H 5.01, Cl 24.85, N 9.80.

6.2.3. 1-[4-(4-Chlorophenoxy)butyl]-1*H*-imidazole (4c). Pale yellow oil (1.95 g, 70%). R_f (EtOAc) 0.44. IR (liquid film) 3150m, 2985m, 2895m, 1675m, 1610s, 1425s, 1285s, 1100s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.38 (s, 1H, C(2)-H, imid.); 7.09–7.05 (d, J = 8.7, 2H, aryl); 6.94–6.63 (m, 2H, C(4)-H, C(5)-H, imid.); 6.66–6.63 (d, J = 8.7, 2H, aryl); 3.89–3.84 (t, J = 6.8, 2H, OCH_2); 3.79–3.75 (t, J = 5.9, 2H, NCH_2); 1.88–1.77 (m, 2H, CH_2); 1.66–1.56 (m, 2H, CH_2). MS [*m*/*z* (%)]: 251 (78.3). Anal. Calcd for $C_{13}H_{15}ClN_2O$: C 62.28, H 6.03, Cl 14.14, N 11.17. Found: C 62.24, H 5.97, Cl 14.16, N 11.22.

6.2.4. 1-[4-(4-Chlorophenoxy)butyl]-2-ethyl-1*H*-imidazole (4d). Yellow oil (2.34 g, 84%). R_f (EtOAc) 0.40. IR (liquid film) 3150m, 2900s, 2895m, 1679m, 1610s, 1445s, 1265s, 1110s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.09–7.05 (d, J = 8.9, 2H, aryl); 6.81–6.71 (m, 2H, C(4)-H, C (5)-H, imid.); 6.67–6.63 (d, J = 8.9, 2H, aryl); 3.80–3.74 (complex, 4H, OCH_2, NCH_2); 2.59–2.50 (q, J = 7.5, 2H, C(2)-CH_2, imid.); 1.84–1.75 (m, 2H, CH_2); 1.69–1.59 (m, 2H, CH_2); 1.23–1.17 (t, J = 7.5, 3H, Me). MS [*m*/*z* (%)]: 279 (25.2). Anal. Calcd for $C_{15}H_{19}ClN_2O$: C 64.63, H 6.87, Cl 17.72, N 10.05. Found: C 64.62, H 6.91, Cl 17.76, N 10.10.

6.2.5. 1-[4-(2,4-Dichlorophenoxy)butyl]-2-methyl-4-nitro-1*H*-imidazole (4e). Pale yellow crystals (2.74 g, 81%). R_f (EtOAc) 0.79. Mp 79–81 °C. IR (KBr) 3200m, 2985m, 2850m, 1640m, 1610s, 1590s, 1420s, 1390s, 1255s, 1000s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.85 (s, 1H, C(5)-H, imid.); 7.21 (s, 1H, aryl); 7.12–7.09 (d, J = 8.8, 1H, aryl); 6.78–6.74 (d, J = 8.8,1H, aryl); 4.05–3.97 (complex, 4H, OCH_2, NCH_2); 2.73 (s, 3H, Me); 2.08–1.99 (m, 2H, CH_2); 1.88–1.80 (m, 2H, CH_2). MS [*m*/*z* (%)]: 344 (22.9). Anal. Calcd for $C_{14}H_{15}Cl_2N_3O_3$: C 48.85, H 4.39, Cl 20.60, N 12.21. Found: C 48.92, H 4.42, Cl 20.58, N 12.22.

6.2.6. 1-[4-(4-Chlorophenoxy)butyl]-2-methyl-4-nitro-1*H*-imidazole (4f). Pale yellow crystals (2.48 g, 80%). R_f (EtOAc) 0.86. Mp 51–53 °C. IR (KBr) 3100m, 2980m, 2850m, 1645m, 1605s, 1590s, 1420s, 1395s, 1260s, 1100s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.96 (s, 1H, C(5)-H, imid.); 7.15–7.12 (d, J = 7.6, 2H, aryl); 6.73–6.70 (d, J = 7.6, 2H, aryl); 3.97–3.87 (complex, 4H, OCH_2, NCH_2); 2.36 (s, 3H, Me); 1.96–1.90 (m, 2H, CH_2); 1.78–1.76 (m, 2H, CH_2). MS [*m*/*z* (%)]: 310 (71.5). Anal. Calcd for $C_{14}H_{16}ClN_3O_3$: C 54.29, H 5.21, Cl 11.45, N 13.57. Found: C 54.32, H 5.25, Cl 11.52, N 13.58.

6.2.7. 1-[5-(2,4-Dichlorophenoxy)pentyl]-1*H*-imidazole (4g). Pale yellow crystals (2.40 g, 79%). R_f (EtOAc) 0.25. Mp 48–50 °C. IR (KBr) 3150m, 2980m, 2890m, 1670m, 1610s, 1430s, 1280s, 1050s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.87 (s, 1H, C(2)-H, imid.); 7.46 (s, 1H, aryl) 7.07–7.04 (d, J = 8.8, 1H, aryl); 6.97–6.84 (m, 2H, C(4)-H, C(5)-H, imid.); 6.73–6.69 (d, J = 8.8, 1H, aryl); 3.92–3.86 (complex, 4H, OCH_2, NCH_2); 1.84–1.70 (m, 4H, $2CH_2$); 1.48–1.36 (m, 2H, CH_2). MS [*m*/*z* (%)]: 299 (7.5). Anal. Calcd for $C_{14}H_{16}Cl_2N_2O$: C 56.20, H 5.39, Cl 23.70, N 9.36. Found: C 56.23, H 5.42, Cl 23.68, N 9.42.

6.2.8. 1-[5-(2,4-Dichlorophenoxy)pentyl]-2-ethyl-1*H*-imidazole (4h). White crystals (2.57 g, 79%). R_f (EtOAc) 0.44. Mp 54–56 °C. IR (KBr) 3100m, 2985s, 2890m, 1650m, 1600s, 1420s, 1250s, 1100s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.21 (s, 1H, aryl); 7.03–6.99 (d, J = 8.8, 1H, aryl); 6.90–6.79 (m, 2H, C(4)-H, C(5)-H, imid.); 6.71–6.68 (d, J = 8.8, 1H, aryl); 3.87–3.82 (t, J = 6.0, 2H, OCH_2); 3.76–3.70 (t, J = 7.1, 2H, NCH_2); 2.60–2.51 (q, J = 7.5, 2H, C(2)-CH_2, imid.); 1.77–1.63 (m, 4H, $2CH_2$); 1.46–1.34 (m, 2H, CH_2); 1.25–1.19 (t, J = 7.5, 3H, Me). MS [*m*/*z* (%)]: 327 (10). Anal. Calcd for $C_{16}H_{20}Cl_2N_2O$: C 58.72, H 6.16, Cl 21.67, N 8.56. Found: C 58.70, H 6.20, Cl 21.60, N 8.50.

6.2.9. 1-[5-(4-Chlorophenoxy)pentyl]-1*H*-imidazole (4i). White crystals (2.35 g, 88%). R_f (EtOAc) 0.31. Mp 58–60 °C. IR (KBr) 3100m, 2985m, 2850m, 1640m, 1615s, 1430s, 1285s, 1050s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.45

(s, 1H, C(2)-H, imid.); 7.13–7.09 (d, $J = 8.7$, 2H, aryl); 6.97–6.83 (m, 2H, C(4)-H, C(5)-H, imid.); 6.71–6.68 (d, $J = 8.7$, 2H, aryl); 3.89–3.83 (t, $J = 7.0$, 2H, OCH_2); 3.82–3.77 (t, $J = 6.1$, 2H, NCH_2); 1.77–1.69 (m, 4H, $2CH_2$); 1.42–1.36 (m, 2H, CH_2). MS [*m*/*z* (%)]: 265 (35.9). Anal. Calcd for $C_{14}H_{17}ClN_2O$: C 63.51, H 6.47, Cl 13.39, N 10.58. Found: C 63.47, H 6.51, Cl 13.38, N 10.60.

6.2.10. 1-[5-(4-Chlorophenoxy)pentyl]-2-ethyl-1*H*-imidazole (4j). White crystals (2.63 g, 90%). R_f (EtOAc) 0.48. Mp 62–64 °C. IR (KBr) 3120w, 2990s, 2895m, 1640m, 1620s, 1430s, 1240s, 1100s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.15–7.12 (d, $J = 7.7$, 2H, aryl); 6.88–6.75 (m, 2H, C(4)-H, C(5)-H, imid.); 6.73–6.70 (d, $J = 7.7$, 2H, aryl); 3.80–3.70 (complex, 4H, OCH_2, NCH_2); 2.65–2.57 (q, $J = 7.5$, 2H, C(2)-CH_2, imid.); 1.72–1.66 (m, 4H, $2CH_2$); 1.43–1.41 (m, 2H, CH_2); 1.30–1.24 (t, $J = 7.5$, 3H, Me). MS [*m*/*z* (%)]: 293 (22.7). Anal. Calcd for $C_{16}H_{21}ClN_2O$: C 65.63, H 7.23, Cl 12.11, N 9.57. Found: C 65.65, H 7.28, Cl 12.07, N 9.62.

6.2.11. 1-[5-(2,4-Dichlorophenoxy)pentyl]-2-methyl-4-nitro-1*H*-imidazole (4k). Pale yellow oil (2.92 g, 81%). R_f (EtOAc) 0.77. IR (liquid film) 3200m, 2980m, 2855m, 1640m, 1610s, 1580s, 1420s, 1380s, 1255s, 1100s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.67 (s, 1H, C(5)-H, imid.); 7.47 (s, 1H, aryl); 7.12–7.09 (d, $J = 8.8$, 1H, aryl); 6.77–6.73 (d, $J = 8.8$,1H, aryl); 3.97–3.89 (complex, 4H, OCH_2, NCH_2); 2.42 (s, 3H, Me); 1.61–1.47 (m, 6H, $3CH_2$). MS [*m*/*z* (%)]: 358 (46.4). Anal. Calcd for $C_{15}H_{17}Cl_2N_3O_3$: C 50.29, H 4.28, Cl 19.79, N 11.73. Found: C 50.30, H 4.25, Cl 19.82, N 11.76.

6.2.12. 1-[5-(4-Chlorophenoxy)pentyl]-2-methyl-4-nitro-1*H*-imidazole (4l). Pale yellow crystals (2.59 g, 80%). R_f (EtOAc) 0.71. Mp 98–100 °C. IR (KBr) 3150m, 2980m, 2855m, 1630m, 1615s, 1580s, 1425s, 1380s, 1255s, 1100s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.99 (s, 1H, C(5)-H, imid.); 7.15–7.13 (d, $J = 6.9$, 2H, aryl); 6.73–6.71 (d, $J = 6.9$, 2H, aryl); 3.86–3.72 (complex, 4H, OCH_2, NCH_2); 2.35 (s, 3H, Me); 1.90–1.78 (m, 4H, $2CH_2$); 1.62–1.49 (m, 2H, CH_2). MS [*m*/*z* (%)]: 323 (18.1). Anal. Calcd for $C_{15}H_{18}ClN_3O_3$: C 55.64, H 5.60, Cl 10.95, N 12.98. Found: C 55.60, H 5.60, Cl 11.00, N 13.01.

6.2.13. 1-[2-(4-Chlorophenoxy)ethyl]-1*H*-1,3-benzimidazole (5a). Pale yellow crystals (1.69 g, 62%). R_f (EtOAc) 0.60. Mp 63–65 °C. IR (KBr) 3250m, 2989m, 2890m, 1640m, 1620s, 1450s, 1250s, 1100s. ^{1}H NMR ($CDCl_3$, 250 MHz) 8.01 (s, 1H, C(2)-H, benzimid.); 7.74–7.21 (m, 4H, benzimid.); 7.10–7.06 (d, $J = 8.7$, 2H, aryl); 6.65–6.61 (d, $J = 8.7$, 2H, aryl); 4.47–4.43 (t, $J = 4.9$, 2H, OCH_2); 4.16–4.12 (t, $J = 4.9$, 2H, NCH_2); MS [*m*/*z* (%)]: 272 (44.7). Anal. Calcd for $C_{15}H_{13}ClN_2O$: C 66.06, H 4.80, Cl 13.00, N 10.27. Found: C 66.01, H 4.78, Cl 12.98, N 10.31.

6.2.14. 1-[4-(2,4-Dichlorophenoxy)butyl]-1*H*-1,3-benzimidazole (5b). Pale brown oil (2.51 g, 75%). R_f (EtOAc) 0.44. IR (liquid film) 3240m, 2990m, 2895m, 1635m, 1620s, 1460s, 1245s, 1105s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.84 (s, 1H, C(2)-H, benzimid.); 7.54 (s, 1H, aryl); 7.28–7.15 (m, 4H, benzimid.); 7.03–6.99 (d, $J = 8.6$, 1H, aryl); 6.65–6.61 (d, $J = 8.6$, 1H, aryl); 4.20–4.14 (t, $J = 6.8$, 2H, OCH_2); 3.87–3.82 (t, $J = 5.6$, 2H, NCH_2); 2.00–1.91 (m, 2H, CH_2); 1.75–1.64 (m, 2H, CH_2). MS [*m*/*z* (%)]: 335 (43.1). Anal. Calcd for $C_{17}H_{16}Cl_2N_2O$: C 60.91, H 4.81, Cl 21.15, N 8.36. Found: C 60.90, H 4.85, Cl 21.10, N 8.40.

6.2.15. 1-[4-(4-Chlorophenoxy)butyl]-1*H*-1,3-benzimidazole (5c). Pale brown oil (1.95 g, 65%). R_f (EtOAc) 0.77.IR (liquid film) 3200m, 2950m, 2890m, 1640m, 1620s, 1465s, 1230s, 1150s. ^{1}H NMR ($CDCl_3$, 250 MHz) 8.21 (s, 1H, C(2)-H, benzimid.); 7.72–7.26 (m, 4H, benzimid.); 7.20–7.16 (d, $J = 8.6$, 2H, aryl); 6.75–6.71 (d, $J = 8.6$, 2H, aryl); 4.25–4.19 (t, $J = 6.3$, 2H, OCH_2); 3.97–3.92 (t, $J = 5.0$, 2H, NCH_2); 2.03–1.95 (m, 2H, CH_2); 1.72–1.63 (m, 2H, CH_2). MS [*m*/*z* (%)]: 300 (35.7). Anal. Calcd for $C_{17}H_{17}ClN_2O$: C 67.88, H 5.70, Cl 11.79, N 9.31. Found: C 67.93, H 5.68, Cl 11.83, N 9.33.

6.2.16. 1-[5-(2,4-Dichlorophenoxy)pentyl]-1*H*-1,3-benzimidazole (5d). Pale brown oil (1.76 g, 50%). R_f (EtOAc) 0.73. IR (liquid film) 3200m, 2980m, 2895m, 1640m, 1620 s, 1450s, 1230s, 1100s. ^{1}H NMR ($CDCl_3$, 250 MHz) 8.38 (s, 1H, C(2)-H, benzimid.); 7.82 (s, 1H, aryl); 7.45–7.28 (m, 4H, benzimid.); 7.17–7.14 (d, $J = 8.8$, 1H, aryl); 6.80–6.77 (d, $J = 8.8$, 1H, aryl); 4.28–4.22 (t, $J = 7.0$, 2H, OCH_2); 3.99–3.94 (t, $J = 6.0$, 2H, NCH_2); 2.06–1.81 (m, 4H, $2CH_2$); 1.63–1.51 (m, 2H, CH_2). MS [*m*/*z* (%)]: 349 (26.1). Anal. Calcd for $C_{18}H_{18}Cl_2N_2O$: C 61.90, H 5.19, Cl 20.30, N 8.02. Found: C 61.94, H 5.25, Cl 20.36, N 8.00.

6.2.17. 1-[5-(4-Chlorophenoxy)pentyl]-1*H*-1,3-benzimidazole (5e). White crystals (2.21 g, 70%). R_f (EtOAc) 0.65. Mp 96–98 °C. IR (KBr) 3240m, 2980m, 2850m, 1640m, 1620s, 1440s, 1240s, 1050s. ^{1}H NMR ($CDCl_3$, 250 MHz) 7.98 (s, 1H, C(2)-H, benzimid.); 7.82–7.28 (m, 4H, benzimid.); 7.19–7.16 (d, $J = 8.7$, 2H, aryl); 6.76–6.72 (d, $J = 8.7$, 2H, aryl); 4.19–4.14 (t, $J = 6.8$, 2H, OCH_2); 3.87–3.82 (t, $J = 6.0$, 2H, NCH_2); 1.95–1.86 (m, 4H, $2CH_2$); 1.50–1.49 (m, 2H, CH_2). MS [*m*/*z* (%)]: 314 (24). Anal. Calcd for $C_{18}H_{19}ClN_2O$: C 68.67, H 6.08, Cl 11.26, N 8.90. Found: C 68.72, H 6.02, Cl 11.31, N 8.95.

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