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Synthesis and antimicrobial activity of 3-arylamino-1-chloropropan-2-ols

Ashok K. Prasad,[a,*] Pankaj Kumar,[a,b] Ashish Dhawan,[a] Anil K. Chhillar,[c] Deepti Sharma,[a] Vibha Yadav,[c] Manish Kumar,[c] Hirday N. Jha,[b] Carl E. Olsen,[d] Gainda L. Sharma[c] and Virinder S. Parmar[a]

[a]*Bioorganic Laboratory, Department of Chemistry, University of Delhi (North Campus), Mall Road, Delhi 110 007, India*
[b]*Department of Chemistry, M.M.H. College, C.C.S. University, Meerut 250 002, India*
[c]*Institute of Genomics & Integrative Biology, Mall Road, Delhi 110 007, India*
[d]*University of Copenhagen, Faculty of Life Sciences, Department of Natural Sciences, DK-1871 Frederiksberg C, Denmark*

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Abstract—A series of nine 3-arylamino-1-chloropropan-2-ols **2a**–**2i** were synthesized and their anti-fungal activity against pathogenic strains of *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger* and *Candida albicans*, and antibacterial activity against four pathogenic bacterial strains of *Salmonella typhi*, *Pseudomonas aeruginosa*, *Streptococcus pneumonae* and *Staphylococcus aureus* were evaluated using different assay systems. 1-Chloro-3-(4′-chlorophenylamino)-propan-2-ol was found to be the most active anti-fungal compound against three pathogenic strains under study, i.e., *A. fumigatus*, *A. flavus* and *A. niger*; the compound showed more than 90% inhibition of growth of *A. fumigatus* at a concentration of 5.85 μg/ml in disc diffusion assay. Interestingly, 1-chloro-3-(4′-chlorophenylamino)-propan-2-ol did not show any toxicity up to a concentration of 4000 μg/ml. Although 1-chloro-3-(4′-chlorophenylamino)-propan-2-ol was about 8 times less active than the standard compound amphotericin B, its toxicity was many more fold less than the toxicity of amphotericin B. Further, 1-chloro-3-(2′,6′-dichlorophenylamino)-propan-2-ol and 1-chloro-3-(3′,5′-dichlorophenylamino)-propan-2-ol were found to be the most active compounds against *C. albicans*. In the anti-microbial assay, 1-chloro-3-(2′,4′-dichlorophenylamino)-propan-2-ol and 1-chloro-3-(3′,5′-dichlorophenylamino)-propan-2-ol were found to be the most active compounds against *Salmonella typhi* and 1-chloro-3-(3′,4′-dichlorophenylamino)-propan-2-ol was found to be the most active compound against *P. aeruginosa*. Although, the activities of 1-chloro-3-(2′,4′-dichlorophenylamino)-propan-2-ol and 1-chloro-3-(3′,5′-dichlorophenylamino)-propan-2-ol are about half the activity of the standard anti-bacterial compound tetracycline, these compounds also were many fold less toxic than the standard drug.

The increasing number of pathogenic bacteria and fungi which are resistant to commonly used therapies has been a major worldwide health problem. The mortality caused by aspergillosis, tuberculosis, etc. needs a very systematic and focused approach to find out newer and safer drugs to deal with the menace. Therefore it is imperative to search for new antimicrobial agents with novel modes of action. There are several groups of researchers around the world who are engaged in synthesizing molecules with different moieties and functionalities, and are evaluating them for their antimicrobial activities. Some of these synthetic molecules have been derived from series of quinolines,[1] imidazoles,[2] quinaldines,[3] demethoxyviridins,[4] dihydropyridines,[5] *etc*.

β-Amino alcohols are an important class of organic compounds which have found much use in medicinal chemistry.[6] These compounds have been well recognized as versatile intermediates in the synthesis of a vast range of biologically active natural and synthetic products,[7] unnatural amino acids[8] and chiral auxiliaries.[9] β-Amino alcohols, like 3-arylamino-1-chloropropan-2-ols, have been used as important intermediates, for the synthesis of 1-[4,4-bis-(4-fluorophenyl)butyl]-4-[2-hydroxy-3-(phenylamino)propyl]piperazine, which is a potent dopamine uptake inhibitor[10] and is present as a key functional group in natural products, such as sphingosine, which exhibits a wide range of physiological activities.[11] Some of the β-amino alcohols have also been

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* Corresponding author. Tel.: +91 11 27666555; fax: +91 11 27667206; e-mail: ashokenzyme@yahoo.com

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used as starting materials for the preparation of oxazolines,[12] insecticidal agents and as chiral ligands in asymmetric synthesis.[13] In view of this, the current study was undertaken to synthesize a series of β-amino alcohol derivatives and investigate their antimicrobial potential against pathogenic fungi and bacteria.

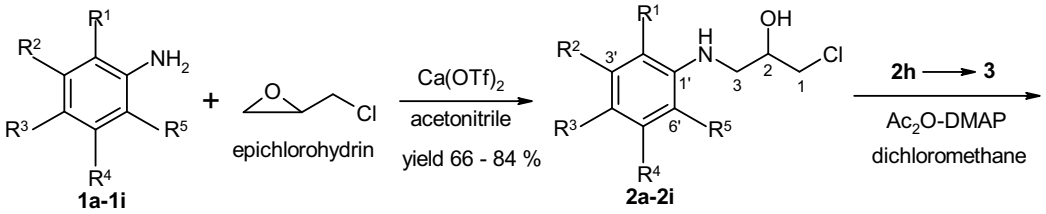
Epoxides are versatile intermediates in organic chemistry and their reactions with different nucleophiles have been the subject of extensive studies. Although transition metal salts typically catalyze aminolysis reactions of epoxides, new catalytic systems are continuously being explored in the search for improved efficiencies and cost effectiveness. In this context, Lewis acids such as calcium trifluoromethanesulfonate (calcium triflate), alumina, zirconium sulfophenyl phosphonate, cerium(III) chloride, diisopropoxyaluminium trifluoroacetate, tantalum(V) chloride ($TaCl_5$) and lithium triflate (LiOTf) have been reported as catalysts.[14] Regioselective ring opening of epoxides can also be accomplished by using aminolead compounds; the reagent attacks the less hindered carbon of the epoxide ring to give the corresponding amino alcohols in good yields.[15] Various metal salts like $LiClO_4$, $CaCl_2$, $ZnCl_2$, $NaClO_4$, $Mg(ClO_4)_2$ and $Zn(OTf)_2$ have also emerged as efficient catalysts[16] for selective aminolysis of 1,2-epoxides even with amines of low nucleophilicity. The reaction proceeds under mild conditions and in aprotic solvents, like acetonitrile.

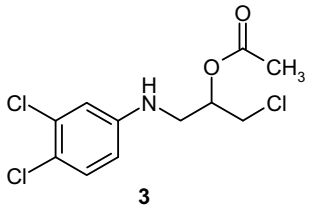
Although different kinds of catalysts are available for the nucleophilic opening of epoxide ring, calcium trifluoromethanesulfonate [$Ca(OTf)_2$] is the most sought after reagent because it is inexpensive, can easily be prepared and also because it performs reactions in a highly regioselective manner.[17] Calcium triflate is easily prepared by reaction of two equivalents of trifluoromethanesulfonic acid with calcium carbonate suspended in toluene at room temperature.[17]

All nine β-amino-alcohols, i.e., 1-chloro-3-(2′-chlorophenylamino)-propan-2-ol (**2a**), 1-chloro-3-(3′-chlorophenylamino)-propan-2-ol (**2b**), 1-chloro-3-(4′-chlorophenylamino)-propan-2-ol (**2c**), 1-chloro-3-(2′,3′-dichlorophenylamino)-propan-2-ol (**2d**), 1-chloro-3-(2′,4′-dichlorophenylamino)-propan-2-ol (**2e**), 1-chloro-3-(2′,5′-dichlorophenylamino)-propan-2-ol (**2f**), 1-chloro-3-(2′,6′-dichlorophenylamino)-propan-2-ol (**2g**), 1-chloro-3-(3′,4′-dichlorophenylamino)-propan-2-ol (**2h**) and 1-chloro-3-(3′,5′-dichlorophenylamino)-propan-2-ol (**2i**) were prepared by aminolysis of the racemic epichlorohydrin with the corresponding aromatic amines (**1a**–**1i**) in acetonitrile in the presence of calcium triflate following the procedure of Cepanec[17] et al. in 66–84% yields (Scheme 1). The structures of **2a**–**2i** were unambiguously established from the analysis of their spectral data (IR, ^1H, ^{13}C NMR and mass spectra). The structures of known compounds **2a**, **2c**, **2e** and **2h** were further confirmed by comparison of their melting points and/or spectral data with those reported in the literature.[10,18–20] The spectral data of the unknown compounds **2b**, **2d**, **2f**, **2g** and **2i** are given in the References and Notes section. [21–25] Compound **2h** has earlier been obtained as oil, however we isolated the compound as light brown solid. Spectral data of the known compound **2h** have been given in the References and Notes section.[26]

The opening of epoxide ring in epichlorohydrin with aromatic amines **1a**–**1i** under these conditions proceeds in a completely regioselective manner and results in the exclusive formation of the secondary alcohol. The secondary nature of hydroxyl group in aminoalcohols **2a**–**2i** was confirmed by acetylation of one of the compounds, 1-chloro-3-(3′,4′-dichlorophenylamino)-propan-2-ol (**2h**), and comparison of the chemical shift value of the C-2H in the ^1H NMR spectrum of alcohol **2h** with the chemical shift value of the C-2H in the ^1H NMR spectrum of the resultant acetate **3**. In the ^1H NMR spectrum of **2h**, the C-2H resonated at δ 4.06, however the same proton in the corresponding acetate **3** resonated at δ 5.17.[27] The chemical shift values of other protons in the ^1H NMR spectra of the alcohol **2h** and the acetate **3** remained almost at the same positions. The shift of 1.11 ppm in the chemical shift value of C-2H of acetate with respect to the alcohol indicates that the hydroxyl group in **2h** is at the C-2 and thus secondary in nature. This was further confirmed by the observation of a similar downfield shift in the chemical shift value of the C-2 of the acetate **3** with respect to that in the alcohol **2h** in their ^{13}C NMR spectra. The formation of *O*-acetylated compound **3** over *N*-acetylated compound during acetylation of compound **2h** may be because of the secondary nature of the amino function, which is also attached to a 3,4-dichlorophenyl ring.

The anti-*Aspergillus* activity of the 3-arylamino-1-chloropropan-2-ols **2a**–**2i** was evaluated against pathogenic strains of *Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus niger* using disc diffusion (DDA), microbroth dilution (MDA) and percentage spore germination inhibition (PSGI) assays.[28] The results are shown in Table 1. The analysis of results revealed that the anti-*Aspergillus* activity of 1-chloro-3-(4′-chlorophenylamino)-propan-2-ol (**2c**) was the maximum in all three assay systems, i.e., DDA, MDA and PSGI against all three test pathogens, except in the case of inhibition of *A. niger*, where the activity of **2c** equals the activity of compound **2a** in DDA assay. Thus, there was more than 90% inhibition of the growth of *A. fumigatus* at the concentration of 5.85 μg/ml. Among the three mono-chlorophenylamino alcohols, 1-chloro-3-(2′-chlorophenylamino)-propan-2-ol (**2a**) was the second highest active compound, followed by 1-chloro-3-(3′-chlorophenylamino)-propan-2-ol (**2b**). The structure-activity relationship among the three mono-chlorophenylamino alcohols revealed that the presence of a chloro substituent at the *para* position with respect to the amino group makes the compound most active as in case of **2c**. The activity decreases almost 2 and 4 times, when chlorine occupies *ortho* and *meta* positions with respect to the amino group as in the case of compounds **2a** and **2b**, respectively. In general, the anti-*Aspergillus* activities of dichlorophenylamino alcohols were less than those of the monochlorophenylamino alcohols, except in case of 1-chloro-3-(3′,4′-dichlorophenylamino)-propan-2-ol (**2h**) which exhibited almost the same order of activity as



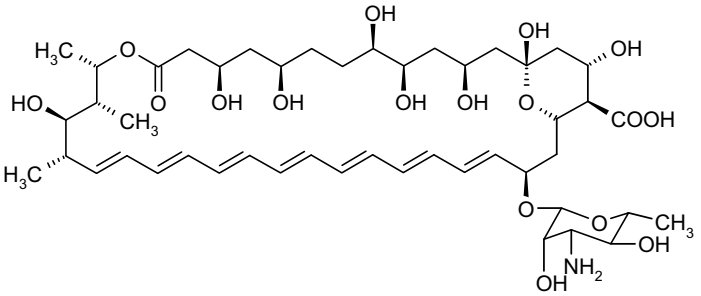


3
yield 91 %

Compds. 1 and 2	a	b	c	d	e	f	g	h	i
R^1	Cl	H	H	Cl	Cl	Cl	Cl	H	H
R^2	H	Cl	H	Cl	H	H	H	Cl	Cl
R^3	H	H	Cl	H	Cl	H	H	Cl	H
R^4	H	H	H	H	H	Cl	H	H	Cl
R^5	H	H	H	H	H	H	Cl	H	H

Scheme 1.

Table 1. In vitro antifungal activity of 3-arylamino-1-chloropropan-2-ols **2a**–**2i** against *A. fumigatus*, *A. flavus* and *A. niger* using disc diffusion (DDA), microbroth dilution (MDA) and percentage spore germination inhibition (PSGI), and against *C. albicans* using percent growth inhibition assay (PGI)



Amphotericin B (**4**)

Compound	MIC[a] (μg/disc)									
	A. fumigatus			*A. flavus*			*A. niger*			*C. albicans*
	DDA	MDA	PSGI	DDA	MDA	PSGI	DDA	MDA	PSGI	PGI
2a	11.71	31.25	31.25	23.43	63.50	31.25	23.43	62.50	62.50	250.00
2b	23.43	62.50	62.50	46.87	62.50	62.50	46.87	62.50	62.50	125.00
2c	5.85	15.62	15.62	11.71	31.25	15.62	23.43	31.25	31.25	62.50
2d	46.87	125.00	62.50	46.87	125.00	125.00	93.75	125.00	125.00	62.50
2e	23.43	62.50	62.50	46.87	125.00	62.50	93.75	125.00	125.00	62.50
2f	46.87	125.00	125.00	93.75	125.00	62.50	93.75	125.00	125.00	62.50
2g	46.87	125.00	125.00	46.87	125.00	62.50	93.75	250.00	125.00	31.25
2h	11.71	31.25	31.25	23.43	62.50	31.25	46.87	62.50	62.50	125.00
2i	46.87	125.00	125.00	46.87	125.00	125.00	93.75	250.00	250.00	31.25
Amphotericin B[b]	0.73	1.95	1.95	0.73	1.95	1.95	0.73	1.95	1.95	—

[a] Minimum inhibitory concentration.
[b] Amphotericin B (**4**) has been used as a standard drug.

1-chloro-3-(2′-chlorophenylamino)-propan-2-ol (**2a**). Among the dichlorophenylamino alcohols, compound **2h** was the most active compound, followed by 1-chloro-3-(2′,4′-dichlorophenylamino)-propan-2-ol (**2e**). The other four dichlorophenylamino alcohols **2d**, **2f**, **2g** and **2i** had almost the same order of activity and it was not significant. The placement of chlorine at *para*-position with respect to the amino group in amino alcohol **2c** efficiently attracts the lone pair of electrons on the N-atom, which may be one of the reasons of enhancement of activity of the compound. Further, there is chlorine at the *para*-position in dichlorophenylamino alcohols **2e** and **2h** together with the other chlorine atom at *ortho*- and *meta*-position with respect to the amino group, respectively, and as expected these compounds exhibited better anti-*Aspergillus* activity among six experimental di-chlorosubstituted compounds **2d**–**2i**. Among these two di-chlorosubstituted amino alcohols **2e** and **2h**, the latter one with *meta*, *para*-di-chlorosubstitution is more active than the former one with *ortho*-,

para-di-chlorosubstitution. The anti-*Aspergillus* activity of the most active compound **2c** is less than the activity of the standard compound amphotericin B (**4**).

All the nine 3-arylamino-1-chloropropan-2-ols **2a**–**2i** were also evaluated for their in vitro antifungal activity against pathogenic strain of *C. albicans* by percent growth inhibition assay (PGI) following the method of Iijima et al.[29] (Table 1). 1-Chloro-3-(2′,6′-dichlorophenylamino)-propan-2-ol (**2g**) and 1-chloro-3-(3′,5′-dichlorophenylamino)-propan-2-ol (**2i**) were found to be the most active compounds among the nine amino alcohols evaluated for their anti-*candidal* activity. It was observed that there was more than 90% inhibition of growth of *C. albicans* cells in wells treated with 31.25 μg/ml of compounds **2g** and **2i** in PGI assay.[28] The other three di-chlorosubstituted amino alcohols **2d**, **2e** and **2f**, and one mono-chlorosubstituted amino alcohol **2c** exhibited almost half the activity of the most active compounds **2g** and **2i**. 3-Arylamino-1-chloropropan-2-ols **2a**,**2b** and **2h** were the least active compounds. Among these three amino alcohols, the anti-candidal activity of **2b** and **2h** was double than the activity of 1-chloro-3-(2′-chlorophenylamino)-propan-2-ol (**2a**). It is noteworthy to see that the anti-candidal activity of dichlorosubstituted amino alcohols is better than that of the mono-chlorosubstituted amino alcohols. However the trend is in the other way in case of anti-*Aspergillus* activity. In general, 3-arylamino-1-chloropropan-2-ols **2a**–**2i** exhibited better anti-*Aspergillus* activity than anti-candidal activity.

Table 2. In vitro antibacterial activity of 3-arylamino-1-chloropropan-2-ols **2a**–**2i** against pathogenic bacterial strains of *S. typhi*, *P. aeruginosa*, *S. pneumonae* and *S. aureus* using microbroth dilution assay (MDA)

Compounds	MIC (μg/ml)			
	S. typhi	*P. aeruginosa*	*S. pneumonae*	*S. aureus*
2a	250.0	62.5	250.0	500.0
2b	500.0	250.0	500.0	1000.0
2c	62.5	125.0	500.0	1000.0
2d	62.5	62.5	62.5	500.0
2e	31.3	62.5	125.0	500.0
2f	250.0	62.5	500.0	250.0
2g	500.0	125.0	500.0	500.0
2h	62.5	31.3	125.0	62.50
2i	31.3	62.5	250.0	125.0
Tetracycline[a]	15.6	7.9	7.9	7.9

[a] Tetracycline has been used as a standard drug.

Antibacterial activity of the chloropropanols **2a**–**2i** was evaluated against four pathogenic bacterial strains, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Streptococcus pneumonae* and *Staphylococcus aureus* using microbroth dilution assay (MDA). Tetracycline was used as the reference drug. The percentage of inhibition of tested compounds against pathogenic bacterial strains is shown in Table 2. In general, amino alcohols **2a**–**2i** were found more active against *S. typhi* and *P. aeruginosa* than against *S. pneumonae* and *S. aureus*. 3-Arylamino-1-chloropropan-2-ols **2e** and **2i** were found most active against *S. typhi* and amino alcohol **2h** was found most active against *P. aeruginosa*. Thus, there was more than 90% inhibition of growth of *S. typhi* cells in wells treated with 31.25 μg/ml of compounds **2e** and **2i**, which is about half the activity of the standard compound tetracycline.[28] Compound **2h** showed more than 90% inhibition of growth of *P. aeruginosa* cells in wells treated with 31.25 μg/ml of the compound, but its activity is only about one-fourth of the activity of the standard compound tetracycline. The most active compounds against *S. pneumonae* and *S. aureus* were 1-chloro-3-(2′,3′-dichlorophenylamino)-propan-2-ol (**2d**) and 1-chloro-3-(3′,4′-dichloro-phenylamino)-propan-2-ol (**2h**). However their activity is eight fold less than the activity of standard compound tetracycline. The remaining compounds did not show any appreciable activity against any of the tested bacteria. It is interesting that all active compounds against the bacterial strains are dichlorosubstituted amino alcohols.

The in vitro cell cytotoxicity of 3-arylamino-1-chloropropan-2-ols **2a**–**2i** was investigated using haemolytic assay.[30,31] Interestingly, in dose dependent study, tested compounds which showed antimicrobial activity against

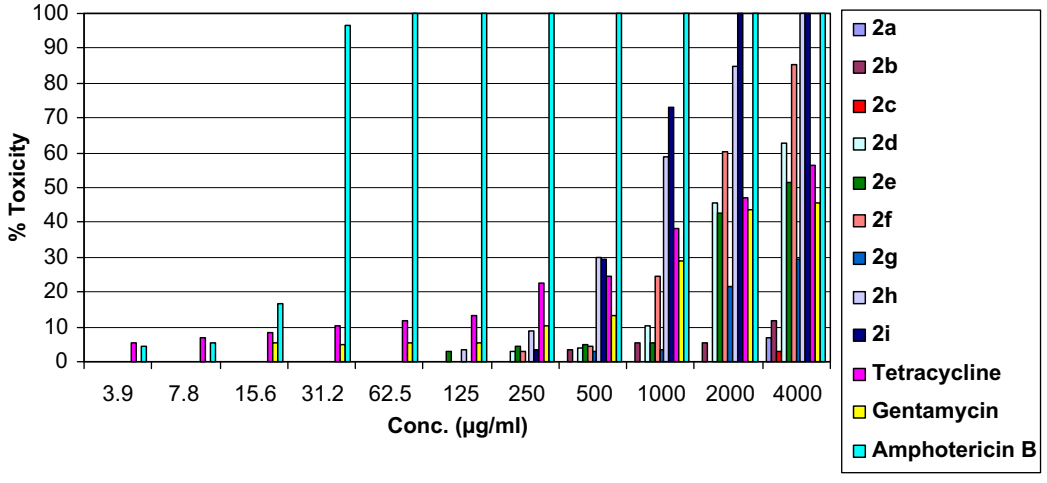


Figure 1. Cytotoxicity of compounds **2a**–**2i** against erythrocytes using haemolytic assay.

pathogenic fungal and bacterial strains were found to be almost non-toxic up to concentrations of 250 μg/ml (Fig. 1). The most interesting observation was that **2c** having strong activity against *Aspergillus* species did not show any toxicity up to a concentration of 4000 μg/ml. The well-known drugs amphotericin B, tetracycline, and gentamycin lysed 100%, 11.68%, and 5.22% erythrocytes, respectively, at a concentration of 62.5 μg/ml. At a very low concentration (3.91 μg/ml), the well-known drug gentamycin did not show any toxicity while amphotericin B and tetracycline lysed 5.52% and 4.26% erythrocytes. Our results are in accordance with the results of Cybulska et al.,[32] who have reported that 1.70 μg/ml of amphotericin B caused 50% haemoglobin loss from erythrocytes.

1-Chloro-3-(4′-chlorophenylamino)-propan-2-ol (**2c**) was identified as the most active anti-fungal compound, which exhibits more than 90% inhibition of *A. fumigatus* in DDA assay at a concentration of 5.85 μg/ml per disc. Compounds **2g** and **2i** were found to be the most active against *C. albicans*; the MIC being 31.25 μg/ml. Compounds **2e** and **2i** exhibited strong activity against *S. typhi* whereas compound **2h** was found to be the most active against *P. aeruginosa*. Compound **2c** emerged as a potential lead for the development of anti-fungal drug candidate even though its activity was less than that of amphotericin B, but it was many fold less toxic than the standard anti-fungal agent. Further, compounds **2e** and **2i** having about half the activity of the standard anti-bacterial compound tetracycline and less toxicity than this standard compound may be potential candidates for the development as anti-bacterial drug candidate/hit compound.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.01.080.

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21. *1-Chloro-3-(3′-chlorophenylamino)-propan-2-ol (2b)*. It was obtained as brown oil (1.60 g) in 73% yield. $R_f = 0.25$ in 15% ethyl acetate in petroleum ether. IR (nujol): 3401 (NH, OH), 2923, 1599, 1504, 1251, 1091, 988 and 766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.17 (1H, dd, $J = 13.2$ and 7.2 Hz, C-3H$_\alpha$), 3.42 (1H, dd, $J = 13.2$ and 4.3 Hz, C-3H$_\beta$), 3.63 (2H, m, C-1H), 4.04 (1H, m, C-2H), 6.48 (1H, d, $J = 8.0$ Hz, C-6′H), 6.61 (1H, br s, C-2′H), 6.69 (1H, d, $J = 7.7$ Hz, C-4′H) and 7.07 (1H, t, $J = 8.1$ Hz, C-5′H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 45.82 and 46.61 (C-1 and C-3)), 68.79 (C-2), 110.60, 115.12 and 117.02 (C-2′, C-4′ and C-6′), 129.33 (C-5′), 134.12 (C-3′) and 144.05 (C-1′); HRMS (ESI positive mode): calculated for $C_9H_{11}NOCl_2$ $[M]^+$ 219.0218, observed $[M]^+$ 219.0220.
22. *1-Chloro-3-(2′,3′-dichlorophenylamino)-propan-2-ol (2d)*. It was obtained as colourless oil (2.00 g) in 79% yield. $R_f = 0.38$ in 15% ethyl acetate in petroleum ether. IR (nujol): 3415 (NH, OH), 2858, 1589, 1503, 1322, 1279, 1040 and 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.47 (1H, brs, OH), 3.32 (1H, dd, $J = 12.4$ and 6.1 Hz, C-3H$_\alpha$), 3.43 (1H, dd, $J = 13.0$ and 4.5 Hz, C-3H$_\beta$), 3.67 (2H, m, C-1H), 4.10 (1H, m, C-2H), 4.79 (1H, br s, NH), 6.60 (1H, d, $J = 8.1$ Hz, C-6′H), 6.82 (1H, d, $J = 7.9$ Hz, C-4′H) and 7.06 (1H, t, $J = 8.0$ Hz, C-5′H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 46.95 and 47.63 (C-1 and C-3)), 69.88 (C-2), 109.43 (C-5′), 118.85 (C-4′ and C-6′), 127.91 (C-3′), 135.00 (C-2′) and 145.34 (C-1′); HRMS (ESI positive mode): calculated for $C_9H_{10}NOCl_3$ $[M]^+$ 252.9828, observed $[M]^+$ 252.9815.
23. *1-Chloro-3-(2′,5′-dichlorophenylamino)-propan-2-ol (2f)*. It was obtained as reddish oil (1.75 g) in 69% yield. $R_f = 0.44$ in 15% ethyl acetate in petroleum ether. IR

(nujol): 3413 (NH, OH), 2922, 2854, 1594, 1507, 1417, 1288, 1094 and 791 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.47 (1H, brs, OH), 3.28 (1H, dd, J = 12.1 and 6.4 Hz, C-3H_α), 3.37 (1H, dd, J = 10.5 and 6.0 Hz, C-3H_β), 3.67 (2H, m, C-1H), 4.10 (1H, brs, C-2H), 4.70 (1H, br s, NH), 6.62 and 6.65 (2H, m, C-4′H and C-6′H) and 7.16 (1H, d, J = 8.2 Hz, C-3′H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 46.64 and 47.67 (C-1 and C-3)), 69.80 (C-2), 111.51 and 117.82 (C-4′ and C-6′), 130.11 (C-3′), 133.81 (C-2′) 144.63 (C-5′) and 148.52 ′(C-1); HRMS (ESI positive mode): calculated for $C_9H_{10}NOCl_3$ $[M]^+$ 252.9828, observed $[M]^+$ 252.9818.

24. *1-Chloro-3-(2′,6′-dichlorophenylamino)-propan-2-ol (2g)*. It was obtained as colourless oil (1.67 g) in 66% yield. R_f = 0.50 in 15% ethyl acetate in petroleum ether. IR (nujol): 3361 (NH, OH), 2923, 1582, 1568, 1450, 1249, 1081 and 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.64 (1H, brs, OH), 3.34 (1H, dd, J = 12.9 and 7.3 Hz, C-3H_α), 3.56 (1H, dd, J = 13.2 and 3.5 Hz, C-3H_β), 3.66 (2H, m, C-1H), 4.02 (1H, brs, C-2H), 4.35 (1H, brs, NH), 6.82 (1H, t, J = 8.0 Hz, C-4′H) and 7.24 (2H, d, J = 8.0 Hz, C-3′H and C-5′H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 47.96 and 50.51 (C-1 and C-3), 71.29 (C-2), 122.89 (C-4′), 127.30 (C-3′ and C-5′), 129.30 (C-2′ and C-6′) and 142.52 (C-1′); HRMS (ESI positive mode): calculated for $C_9H_{10}NOCl_3$ $[M]^+$ 252.9828, observed $[M]^+$ 252.9797.
25. *1-Chloro-3-(3′,5′-dichlorophenylamino)-propan-2-ol (2i)*. It was obtained as colourless oil (1.82 g) in 72% yield. R_f = 0.33 in 15% ethyl acetate in petroleum ether. IR (nujol): 3414 (NH, OH), 2923, 1594, 1573, 1316, 1091 and 798 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.44 (1H, br s, OH), 3.18 (1H, dd, J = 13.1 and 7.1 Hz, C-3H_α), 3.33 (1H, dd, J = 13.1 and 4.0 Hz, C-3H_β), 3.64 (2H, m, C-1H), 4.06 (1H, brs, C-2H), 4.25 (1H, brs, NH), 6.50 (2H, d, J = 1.5 Hz, C-2′H and C-6′H) and 6.70 (1H, d, J = 1.5 Hz, C-4′H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 46.73 and 47.68 (C-1 and C-3), 69.85 (C-2), 111.53 (C-2′ and C-6′), 117.96 (C-4′), 137.01 (C-3′ and C-5′) and 149.40 (C-1′); HRMS (ESI positive mode): calculated for $C_9H_{10}NOCl_3$ $[M]^+$ 252.9828, observed $[M]^+$ 252.9818.
26. *Synthesis of 1-chloro-3-(3′,4′-dichlorophenylamino)-propan-2-ol (2h)*. It was obtained as a brownish solid (1.77 g) in 70% yield. Mp = 59–61 °C, lit.[10] reported as colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (1H, br s, OH), 3.18 (1H, dd, J = 7.1 and 13.0 Hz, C-3H_α) 3. 32 (1H, dd, J = 4.2 and 13.0 Hz, C-3H_β), 3.65 (2H, m, C-1H), 4.06 (2H, br s, C-2H and NH), 6.47 (1H, dd, J = 8.6 and 2.6 Hz, C-6′H), 6.70 (1H, d, J = 2.6 Hz, C-2′H) and 7.18 (1H, d, J = 8.6 Hz, C-5′H); ^{13}C NMR ($CDCl_3$): δ 47.03 and 47.72 (C-1 and C-3)), 69.91 (C-2), 113.15 and 114.42 (C-2′ and C-6′), 122.00 (C-5′), 130.87 (C-4′), 133.12 (C-3′), 147.49 (C-1′); HRMS(ESI positive mode): calculated for $C_9H_{10}NOCl_3$ $[M]^+$ 252.9828, observed $[M]^+$ 252.9815.
27. *Synthesis of 2-acetoxy-1-chloro-3-(3′,4′-dichlorophenylamino)-propane (3)*. To a solution of 1-chloro-3-(3′,4′-dichlorophenylamino)-propan-2-ol (**2h**, 53 mg, 0.2 mmol) and catalytic amount of dimethylaminopyridine (DMAP) in dichloromethane (20 ml), acetic anhydride (0.044 ml, 0.235 mmol) was added and the reaction mixture was stirred at room temperature for 3 h until TLC examination indicated completion of the reaction. The reaction mixture was washed with a saturated solution of sodium bicarbonate (3 × 15 ml) and brine solution (3 × 15 ml), dried over sodium sulfate and evaporated under reduced pressure to afford the crude product, which was purified by column chromatography over silica gel using petroleum ether and ethyl acetate as eluents to afford 2-acetoxy-1-chloro-3-(3′,4′-dichlorophenylamino)-propane (**3**) as yellowish oil (59 mg) in 91% yield. R_f = 0.52 in 15% ethyl acetate in petroleum ether. IR (nujol): 3406 (NH), 2929, 1740 (CO), 1599, 1499, 1374, 1232, 1045 and 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (3H, s, $OCOCH_3$), 3.43 (2H, br d, J = 5.3 Hz, C-3H), 3.69 (2H, br d, J = 4.2 Hz, C-1H), 3.96 (1H, br s, NH), 5.17 (1H, m, C-2H), 6.49 (1H, d, J = 8.4 Hz, C-6′H), 6.74 (1H, s, C-2′H) and 7.19 (1H, d, J = 8.4 Hz, C-5′H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.26 ($OCOCH_3$), 43.58 and 44.86 (C-1 and C-3), 71.80 (C-2), 113.00 (C-6′), 114.51 (C-2′), 122.40 (C-5′), 132.59 and 133.38 (C-3′ and C-4′), 147.33 (C-1′) and 170.77 ($OCOCH_3$)
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