Microwave-Assisted Ring Opening of Epoxides: A General Route to the Synthesis of 1-Aminopropan-2-ols with Anti Malaria Parasite Activities

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A series of 1-aminopropan-2-ols were synthesized and evaluated against two strains of malaria, *Plasmodium falciparum* FCR3 (chloroquine-resistant) and 3D7 (chloroquine-sensitive). Microwave-assisted ring opening of epoxides (aryl and alkyl glycidyl ethers, glycidol, epichlorohydrin) with various amines without catalysts generated the desired library of β-amino alcohols rapidly and efficiently. Most of the compounds showed micromolar potency against malaria, with seven of them having IC_{50} values between 1 and 10 μM against both *Plasmodium falciparum* strains.

Introduction

Malaria is one of the three major infectious diseases, and despite years of continual efforts, it is still one of the major causes of morbidity and mortality affecting more than 40% of the world's population mainly in the developing world. There are 300 to 500 million clinical cases each year, with up to two million deaths predominantly among young children in Sub-Saharan Africa. Rapidly increasing resistance to antimalarial drugs, such as chloroquine and the synergistic combination of sulfadoxine and pyrimethamine used as first line treatment, calls for novel focused strategies for combating malaria.[1,2]

The causative agent of malaria, *Plasmodium falciparum*, faces the highly complex problem of obtaining nutrients and disposing of waste products, while at the same time growing and multiplying within a cell, which is merely a container for hemeoglobin. The delivery of substrates and disposal of metabolites to the parasite depends therefore upon parasite-encoded transport proteins that facilitate exchange across the parasite plasma membrane. Identifying participating molecules and mechanisms responsible for transport processes is of potential importance because they may become new drug targets. The attractiveness of transporters as potential drug targets lies in their unique essential function for parasite growth. One of the potential targets is PfAQP[a], a single copy gene in *P. falciparum*.

Aquaporins, such as PfAQP, are integral membrane channel proteins that selectively and efficiently facilitate the passage of water (orthodox aquaporins) and/or small uncharged molecules (aquaglyceroporins) across cell membranes. Their functions are as diverse as water homeostasis in the human body, regulation of cellular osmolarity in yeast, uptake of nitrogen sources, such as ammonia, in plant nodules, or involvement in lipid metabolism via glycerol facilitation. The latter function may be of particular importance for *Plasmodium* parasites, which were shown to excessively use glycerol from the host serum for the rapid synthesis of membrane glycerolipids (see review by Beitz[3] and references therein).

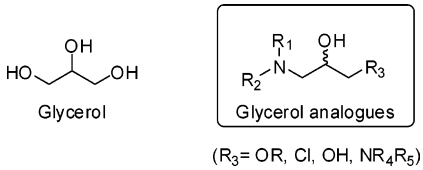

Figure 1. Libraries of 1-aminopropan-2-ols.

In our efforts to target the aquaglyceroporin channel in *Plasmodium* for chemotherapy[3−6] we were interested in generating libraries of 1-aminopropan-2-ols (Figure 1) as glycerol analogues that might block the channel. It was proposed that a robust and efficient route toward these compounds could be developed from the ring opening of epoxides, versatile starting materials or intermediates in organic synthesis.

Ring opening of epoxides is well-documented in the literature: the inherent polarity and strain of the three membered ring allows them to react with a wide number of reagents such as amines, alcohols, and thiols.[7−10] For the aminolysis of epoxides, a large variety of activators have been employed, including metal salts.[11−18] Some of the reported methods suffer from disadvantages such as moisture sensitivity, inconvenient handling procedures, expensive costs, or long reaction times. Previous studies have suggested that epoxide opening reactions can be conducted under microwave irradiation.[19−22] We report here the successful use of microwave irradiation to drive nucleophilic ring-opening reactions of epoxide intermediates without the need for any catalyst. The methodology was used for the rapid synthesis of a library of β-amino alcohols with antimalarial activities.

Results and Discussion

Ring opening of epoxides such as benzyl glycidyl ether can be achieved using Lewis acid catalysis (zinc chloride), but the reaction times were long (24 h) and required lengthy column purification. The ring opening of (±)-benzyl glycidyl ether with diethylamine (Table 1, product **1a**) was therefore studied using a variety of conditions (acidic, basic, and neutral) under microwave irradiation. It was found that neutral conditions were optimal for ring opening. The reaction proceeded cleanly with 1.5 equiv of amine in 4 min at 140 °C (80 W power), with no trace of byproducts. This strategy was then applied to a broad range of primary and secondary amines (Scheme 1, Table 1).

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[a] Abbreviations: PfAQP, *Plasmodium falciparum* aquaglyceroporin.

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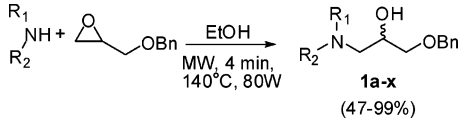
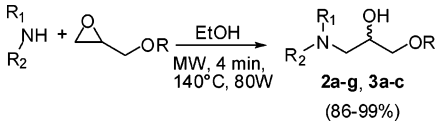
Table 1. Synthesis of β-Amino Alcohols **1a**−**x**

R_1R_2NH	Yields (product)	R_1R_2NH	Yields (product)
Et_2NH	96% (**1a**)	$PhCH_2NH_2$	95% (**1b**)
	62% (**1c**)		92% (**1d**)
	94% (**1e**)		85% (**1f**)
	92% (**1g**)		89% (**1h**)
	47% (**1i**)		82% (**1j**)
	57% (**1k**)		96% (**1l**)
	87% (**1m**)		81% (**1n**)
	59% (**1o**)		99% (**1p**)
	79% (**1q**)		58% (**1r**)
	73% (**1s**)		84% (**1t**)
	99% (**1u**)		99% (**1v**)
	57% (**1w**)		95% (**1x**)

Scheme 1. Ring Opening of Benzyl Glycidyl Ether with Amines under Microwave Conditions



Scheme 2. Ring Opening of Alkyl/aryl Glycidyl Ethers or Glycidol (R = H) with Amines under Microwave Conditions



Products **1a**−**x** were isolated in good yields by simple evaporation of the reaction solvent or, if necessary, purification *via* Kugelrohr bulb to bulb distillation.

Apart from benzyl ethers, a large number of β-amino alcohols could also be obtained depending on the amines and the epoxides used as starting materials (Scheme 2). The method was adapted to use various alkyl/aryl glycidyl ethers or glycidol itself for the synthesis of 1-amino-3-alkoxy/aryloxypropan-2-ols **2a**−**g** or 3-aminopropan-1,2-diols **3a**−**c**, respectively, with good yields (Table 2).

The use of epichlorohydrin as starting material was also investigated in order to facilitate further glycerol modifications, such as nucleophile substitution of the chlorine. Reaction of epichlorohydrin with morpholine using solvent free conditions with montmorillonite K10 clay has been reported by Saidi et al.[21] The yield was 54% because of the formation of a byproduct resulting from the nucleophilic attack at the more substituted carbon of the epoxide. We investigated the reaction of epichlorohydrin with diethylamine using the conditions developed previously. Upon analysis by mass spectrometry, the desired product and the expected chlorine isotope peak were not

Table 2. Synthesis of β-Amino Alcohols **2a**−**g** and **3a**−**c**

R_1R_2NH	OR	Yields (product)
		99% (**2a**)
		86% (**2b**)
		88% (**2c**)
		99% (**2d**)
		99% (**2e**)
		97% (**2f**)
		99% (**2g**)
	OH	99% (**3a**)
	OH	99% (**3b**)
	OH	99% (**3c**)

Scheme 3. Proposed Route for Formation of Unwanted Side Products

Scheme 4. Ring Opening of Epichlorohydrin with Amines under Microwave Conditions

observed. However, an intense molecular ion peak at *m*/*z* 203 (100%) and a smaller peak at *m*/*z* 130 (50%) were evident, and a further peak at *m*/*z* 332 was also observed. It was postulated that the microwave conditions used for this reaction could have promoted further reaction of unwanted side products as shown in Scheme 3 (product *m*/*z* 203 was isolated in 75% yield). Optimization of the experimental conditions was conducted. Altering the number of amine equivalent (0.9 equiv), the temperature (20 °C), and the reaction time (1 min) prevented formation of byproducts. Using these new conditions, a small library of 1-chloro-3-aminopropan-2-ol was synthesized (Scheme 4, Table 3). Purification was achieved by removing the solvent under reduced pressure using a low-temperature bath (keeping

Table 3. Synthesis of β-Amino Alcohols **4a**−**h**

R_1R_2NH	Yields (product)	R_1R_2NH	Yields (product)
	68% (**4a**)		12% (**4b**)
	65% (**4c**)		72% (**4d**)
	70% (**4e**)		61% (**4f**)
	55% (**4g**)		76% (**4h**)

Table 4. Results of Biological Tests against *Plasmodium falciparum* FCR3 and 3D7

compd	IC_{50} FCR3 (μM)	IC_{50} 3D7 (μM)	compd	IC_{50} FCR3 (μM)	IC_{50} 3D7 (μM)
1a	28.1	NE[a]	**1t**	5.8	9.7
1b	12.5	NE	**1w**	15.8	32.5
1c	20.2	NE	**4f**	38.5	66
1f	12.5	NE	**4g**	23.8	NE
1h	8.4	NE	**4h**	31.0	15.6
1j	31.1	NE	**6a**	41.6	15.4
1k	0.7	NE	**6b**	43.9	43.5
1l	2.0	47	**6c**	7.7	3.7
1n	12.7	NE	**7**	16.3	9.3
1o	15.2	NE	**8a**	5.9	5.1
1p	10.3	15.1	**8b**	5.3	2.9
1q	7.7	NE	**9a**	4.6	3.9
1r	3.4	NE	**9b**	2.4	1.4
1s	1.2	NE			

[a] NE: noneffective.

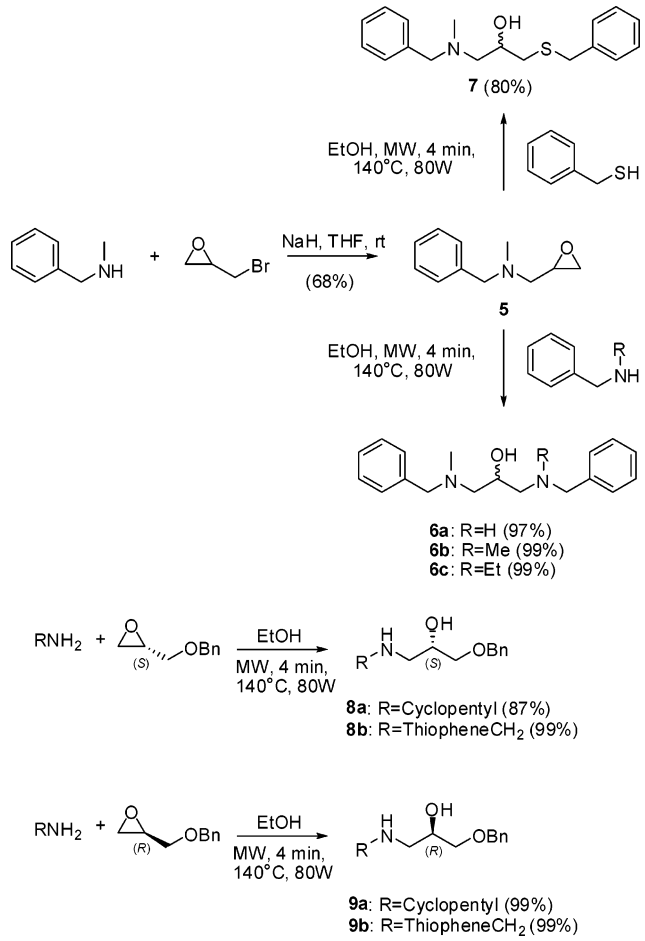
water bath temperature under 20 °C), and products **4a**−**h** were obtained in good yields.

All the compounds generated have been tested *in vitro* against two strains of *Plasmodium falciparum*: FCR3 (chloroquine-resistant) and 3D7 (chloroquine-sensitive) (Table 4). Compounds were first tested against the FCR3-resistant strain. Since the objective is to find compounds with a broad antimalarial spectrum, only those compounds showing activity against FCR3 were subsequently tested against the 3D7 strain.

Of this first generation of compounds, all active compounds included a benzyloxy or a chloro group in their structure and had an IC_{50} under 50 μM against the FCR3 strain. Six compounds (**1l**, **1p**, **1t**, **1w**, **4f**, and **4h**) had inhibitory effects for both strains, with **1l** having the lowest IC_{50} among these compounds for the FCR3 strain. Therefore, some derivatives of **1l** were synthesized in order to replace the benzyloxy group with its sulfur (**7**) and nitrogen (**6a**−**c**) analogues. Compounds **6a**−**c** and **7** were obtained under microwaves conditions by ring opening of epoxide **5** (Scheme 5.). The most interesting biological result was obtained with **6c**. In fact, compared to **1l**, compound **6c** showed a similar IC_{50} against FCR3 but a better IC_{50} against 3D7 (3.7 μM). Enantiopure synthesis of two of the most interesting compounds generated by the library (**1p** and **1t**) were also realized in order to know if one of the two enantiomers could be more effective. The synthesis was achieved by reacting the commercially available enantiopure benzylglycidyl ethers (*R*) or (*S*) with the appropriate amine to generate **8a**,**b** and **9a**,**b** (Scheme 5). The results of the biological tests showed that both enantiomers have the same inhibitory effect, similar to that of the racemic mixtures.

Compounds **1b**, **1h**, **1k**, **1l**, **1t**, and **6c** were tested as inhibitors of *Plasmodium falciparum* aquaglyceroporin function in a yeast-based assay at concentrations up to 100 μM. None of the compounds affected aquaglyceroporin function.

Scheme 5. Synthesis of Analogues of **1l** and Enantiopure Analogues of **1p** (**8a** and **9a**) and **1t** (**8b** and **9b**)



Five of the most interesting compounds with inhibition of both *Plasmodium* strains (**4f, 4h**, **1t**, **6c**, and **7**) were also tested in toxicity assays. The effect of these compounds on cell viability (NALM-6, MONO-MAC-6, and Jurkat cell lines) was measured in 96-well plates after 24 h (1 cell cycle) of exposure of the cell suspension (25 cells/μL) to 100 μM compound concentration at 37 °C. The experiments were done in duplicate, and cell growth was monitored by incorporating the vital dye Trypan Blue. None of the compounds showed any toxicity at concentrations of 100 μM.

Conclusion

In summary, we have shown that it is possible to generate focused libraries of 1-aminopropan-2-ols using microwave-assisted ring opening of epoxides. Short reaction times and simple procedures and purifications make this method applicable for library synthesis, while liberating a free alcohol group useful for further transformations. The biological tests against two strains of malaria parasites (one resistant against chloroquine) have shown some interesting results, with seven compounds having an IC_{50} between 1 and 10 μM against the two strains of *Plasmodium falciparum*. Synthesis of more analogues are therefore currently under investigation.

Experimental Section

General. Solvents and reagents were obtained from commercial sources and used as received. Proton and carbon NMR spectra were obtained using Bruker AC250 or DPX-360 instruments. Chemical shifts are reported in parts per million (ppm, δ) relative to TMS using $CDCl_3$ as solvent. The coupling constants are reported in hertz

(Hz) using the following abbreviations: s = singulet, d = doublet, t = triplet, q = quadruplet, qu = quintet and m = multiplet. High-resolution mass spectrometry fast atom bombardment (HRMS FAB) was performed using a Kratos MS50TC instrument, and electrospray (ES-MS) nominal mass spectra were recorded using a Micromass Platform II instrument. All microwave-assisted reactions were carried out in a CEM Discover Microwave Synthesizer with Explorer Carousel. Analytical HPLC was performed on an Agilent Series 1100. The methods used were (A) a normal phase system and (B) a reverse phase system (see Supporting Information).

Parasite Cultures. The *P. falciparum* chloroquine-resistant (QR) strain FCR3 and the chloroquine-sensitive (QS) strain 3D7 were maintained in continuous culture with 5% fresh O^+ erythrocytes depleted of lymphocytes obtained from the University Hospital in Tübingen. Parasites were kept according to the standard procedure in RPMI-1640 medium (Sigma, Steinheim, Germany) supplemented with 25 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (Sigma), 0.5% albumax (GIBCO, Paisley, Scotland), 2 mM L-glutamine (GIBCO), and 50 μM/mL gentamicin (GIBCO) and incubated at 37 °C in a 5% CO_2, 5% O_2, and 90% N_2 atmosphere. Parasites were maintained as highly synchronized cultures by regular treatment with 5% D-sorbitol (SIGMA) twice a week. The success of the synchronization was determined by thin blood smears stained with 10% Giemsa stain solution (SIGMA) in phosphate buffer pH 7.2.

Drug Susceptibility Assay. *P. falciparum* drug sensitivity assays were performed in 96-well plates by monitoring the accumulation of the parasite protein histidine-rich protein 2 (HRPII) in the culture supernatant after lysis of the parasite cells.[23] Ring-stage parasites were seeded at 0.05% parasitemia in 1.5% hematocrit.[24] The cultures were incubated for 72 h at 37 °C in complete culture medium containing three-fold serial dilutions of the drugs starting at 100 μM. Since compounds were dissolved in DMSO or acetonitrile, parasite viability was previously assessed. Parasites were frozen and thawed twice to obtain complete lysis, and the samples were stored at −20 °C. Parasite growth controls were obtained by culturing parasites without drug harvesting at 0 and 72 h. Growth inhibition in the presence of the test compounds is expressed as a percent of the control cultures. Chloroquine was used as a positive control for growth inhibition. The experiments were done in duplicate, and IC_{50} values were calculated from the HRPII production in the 72 h time interval. Drug sensitivities were assayed as published previously.[25]

In Vitro Toxicity Assay. Human B cell precursor leukemia NALM-6, monocytic leukaemia MONO-MAC-6, and Jurkat lymphoblastoid cell lines were routinely cultured at 37 °C in RPMI 1640 medium complemented with 1 mmol/L-glutamine and 10% fetal calf serum (GIBCO) in 5% humidified CO_2. The effect of the drugs on cell viability was measured in 96-well plates after 24 h (1 cell cycle) of exposure of 6000 cells/well to drug concentrations of 100, 50, 25, 1 μM and 500 nM at 37 °C. The experiments were done in duplicate, and cell growth was monitored by incorporating Trypan Blue (SIGMA, Taufkirchen, Germany). The results are expressed as the drug concentration resulting in 50% inhibition of the cell growth.

Yeast-Based Assay for PfAQP Inhibition. Efflux permeability of cytotoxic methylamine was used to test for the functionality of PfAQP and inhibition by the test compounds **1b**, **1h**, **1k**, **1l**, **1t**, and **6c**. BY4742Δfps1 yeast cells expressing PfAQP were grown in 1 mL of 20 mM MES-buffered (pH5.5) liquid minimal YNB medium with 3% glucose, 0.1% proline, with and without addition of 50 mM methylamine hydrochloride. The test compound concentration was 100 μM. Untreated cells were used as controls. Cultures were set up with an initial OD_{600} of 0.1 and were incubated for 48 h. A reduction in cell proliferation as determined by OD_{600} measurement would indicate PfAQP inhibition by the test compounds. All experiments were done in duplicate.

General Procedure for the Synthesis of 1a−x, 2a−g, and 3a−c. Benzyl glycidyl ether (for **1a**−**x**), alkyl/aryl glycidyl ether (for **2a**−**g**), or glycidol (for **3a**−**c**) (1 mmol) was dispensed into a microwave tube and dissolved in absolute ethanol (2.5 mL). Amine (1.5 mmol) was added to the tube and placed in the CEM Discover Microwave Synthesizer Explorer Carousel. Each sample was heated at 140 °C with stirring for 4 min (80 W, 50 psi). A period of 5 min was allowed for sample cooling. Each sample was concentrated *in vacuo*, and purification was performed if necessary, by using Kugelrohr bulb to bulb distillation apparatus to yield the desired products **1a**−**x**, **2a**−**g**, or **3a**−**c**.

1-Benzyloxy-3-diethylaminopropan-2-ol (1a). Yield 96%, oil; ^{1}H NMR($CDCl_3$); δ 1.10 (6H, t, ^3J = 7.0 Hz, 2 CH_3), 2.51−2.78 (6H, m, 2 NCH_2CH$_3$, NCH_2CH), 3.56 (2H, d, ^3J = 5.3 Hz, CHCH_2O), 3.90 (1H, qu, ^3J = 4.7 Hz, C*H*OH), 4.66 (2H, s, OCH_2Ar), 7.34−7.43 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 11.8 (2 *C*H$_3$), 46.9 (2 NCH_2CH$_3$), 55.8 (NCH_2CH), 66.4 (*C*HOH), 72.7 (CH*C*H$_2$O), 73.3 (O*C*H$_2$Ar), 127.4 (*C*H$_{ar}$), 127.5 (2 *C*H$_{ar}$), 128.2 (2 *C*H$_{ar}$), 138.1 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 238; found (HRMS FAB) [M + H]$^+$ 238.18086 $C_{14}H_{23}NO_2$ requires 238.18070.

1-Benzylamino-3-benzyloxypropan-2-ol (1b). Yield 95%; oil; ^{1}H NMR($CDCl_3$); δ 2.02 (1H, s, N*H*), 2.62−2.82 (2H, m, NCH_2CH), 3.42−3.56 (2H, m, CHCH_2O), 3.79 (2H, s, ArCH_2N), 3.84−4.12 (1H, m, C*H*OH), 4.55 (2H, s, OCH_2Ar), 7.52−7.65 (10H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 52.1 (NCH_2CH), 54.3 (ArCH_2N), 68.8 (*C*HOH), 73.3 (CH*C*H$_2$O), 73.8 (O*C*H$_2$Ar), 127.4−129.6 (10 *C*H$_{ar}$), 138.5 (C_{ar}), 140.4 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 272; found (HRMS FAB) [M + H]$^+$ 272.15723 $C_{17}H_{21}NO_2$ requires 272.15730. HPLC 98% purity (A), 95% purity (B).

1-Benzyloxy-3-pyrrolidin-1-ylpropan-2-ol (1c). Yield 62%; oil; ^{1}H NMR($CDCl_3$); δ 1.62−1.68 (4H, m, 2 CH_2 pyrrolidine), 2.24−2.62 (6H, m, 2 NCH_2 pyrrolidine, NCH_2CH), 3.21−3.39 (2H, m, CHCH_2O), 3.79 (1H, qu, ^3J = 4.6 Hz, C*H*OH), 4.45 (2H, s, OCH_2Ar), 7.15−7.24 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 23.6 (2 *C*H$_2$ pyrrolidine), 54.3 (2 NCH_2 pyrrolidine), 58.8 (NCH_2CH), 68.1 (*C*HOH), 73.0 (CH*C*H$_2$O), 73.5 (O*C*H$_2$Ar), 127.7 (*C*H$_{ar}$), 127.8 (2 *C*H$_{ar}$), 128.4 (2 *C*H$_{ar}$), 138.2 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 236; found (HRMS FAB) [M + H]$^+$ 236.16572 $C_{14}H_{21}NO_2$ requires 236.16505.

1-Benzyloxy-3-morpholin-4-ylpropan-2-ol (1e). Yield 94%; oil; ^{1}H NMR($CDCl_3$); δ 2.30−2.36 (4H, m, 2 NCH_2 morpholine), 2.47−2.55 (2H, m, NCH_2CH), 3.37−3.41 (2H, m, CHCH_2O), 3.55−3.62 (4H, m, 2 OCH_2 morpholine), 3.84 (1H, qu, ^3J = 4.6 Hz, C*H*OH), 4.47 (2H, s, OCH_2Ar), 7.15−7.25 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 53.3 (NCH_2CH), 57.7 (2 NCH_2 morpholine), 65.6 (*C*HOH), 66.5 (2 OCH_2 morpholine), 72.1 (CH*C*H$_2$O), 73.1 (O*C*H$_2$Ar), 127.2 (*C*H$_{ar}$), 127.3 (2 *C*H$_{ar}$), 128.0 (2 *C*H$_{ar}$), 137.6 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 252; found (HRMS FAB) [M + H]$^+$ 252.15970 $C_{14}H_{21}NO_3$ requires 252.15997.

1-Benzyloxy-3-piperazin-1-ylpropan-2-ol (1f). Yield 85%, oil; ^{1}H NMR($CDCl_3$); δ 2.28−2.33 (4H, m, 2 CH_2 piperazine), 2.42−2.48 (2H, m, NCH_2CH), 2.73−2.77 (4H, m, 2 CH_2 piperazine), 3.36−3.42 (2H, m, CHCH_2O), 3.84 (1H, qu, ^3J = 4.6 Hz, C*H*OH), 4.46 (2H, s, OCH_2Ar), 7.15−7.25 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 46.1 (2 *C*H$_2$ piperazine), 47.1 (2 *C*H$_2$ piperazine), 54.6 (NCH_2CH), 66.0 (*C*HOH), 72.7 (CH*C*H$_2$O), 73.5 (O*C*H$_2$Ar), 127.7 (*C*H$_{ar}$), 127.8 (2 *C*H$_{ar}$), 128.4 (2 *C*H$_{ar}$), 138.1 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 251; found (HRMS FAB) [M + H]$^+$ 251.17590 $C_{14}H_{22}N_2O_2$ requires 251.17595.

1-Benzyloxy-3-(cyclopropylmethylamino)propan-2-ol (1h). Yield 89%, oil, ^{1}H NMR($CDCl_3$); δ 0.09−0.13 (2H, m, CH_2 cyclopropane), 0.36−0.41 (CH_2 cyclopropane), 0.78−0.87 (C*H* cyclopropane), 1.89 (1H, s, N*H*), 2.32−2.41 (2H, m, cyclopropane CH_2NH), 2.54−2.66 (2H, m, NCH_2CH), 3.34−3.41 (2H, m, CHCH_2O), 3.77−3.81 (1H, m, C*H*OH), 4.47 (2H, s, OCH_2Ar), 7.19−7.29 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 3.8 (2 *C*H$_2$ cyclopropane), 11.6 (*C*H cyclopropane), 52.2 (NCH_2CH), 55.3 (cyclopropane*C*H$_2$N), 68.8 (*C*HOH), 73.0 (CH*C*H$_2$O), 73.8 (O*C*H$_2$Ar), 127.9 (*C*H$_{ar}$), 128.1 (2 *C*H$_{ar}$), 128.8 (2 *C*H$_{ar}$), 138.4 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 236; found (HRMS FAB) [M + H]$^+$ 236.16450 $C_{14}H_{21}NO_2$ requires 236.16505.

1-Benzyloxy-3-(pyridin-2-ylamino)propan-2-ol (1j). Yield 82%, oil, ^{1}H NMR($CDCl_3$); δ 2.01 (1H, s, N*H*), 3.38−3.56 (4H, m, NCH_2CH, CHCH_2O), 3.90−4.12 (1H, m, C*H*OH), 4.44 (2H, s, OCH_2Ar), 6.51 (1H, m, C*H* pyridine), 6.59 (1H, d, ^3J = 9.0 Hz,

C*H* pyridine), 7.23−7.35 (5H, m, H_{ar}), 7.46 (1H, d, ^3J = 5.5 Hz, C*H* pyridine), 7.81−7.89 (1H, m, C*H* pyridine); ^{13}C NMR($CDCl_3$) δ 54.5 (NCH_2CH), 68.0 (*C*HOH), 73.8 (CHCH_2O), 74.0 (OCH_2Ar), 107.1 (*C*H pyridine), 114.2 (*C*H pyridine), 128.3−128.9 (5 *C*H_{ar}), 138.1 (*C*H pyridine), 139.6 (C_{ar}), 148.3 (*C*H pyridine) 158.9 (*C* pyridine); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 259; found (HRMS FAB) $[M + H]^+$ 259.14411 $C_{15}H_{18}N_2O_2$ requires 259.14465.

1-(Benzyl(ethyl)amino)-3-(benzyloxy)propan-2-ol (1k). Yield 57%, oil, ^{1}H NMR($CDCl_3$); δ 0.94 (3H, t, ^3J = 7.1 Hz, CH_3), 2.42−2.59 (4H, m, NCH_2CH, CH_3CH_2), 3.33−3.40 (3H, m, CHCH_2O, ArCH_2N), 3.64 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 3.75−3.81 (1H, m, C*H*OH), 4.44 (2H, s, OCH_2Ar), 7.19−7.35 (10H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 12.0 (CH_3), 47.8 (CH_2CH_3), 56.4 (NCH_2CH), 58.5 (ArCH_2N), 67.1 (*C*HOH), 73.0 (CHCH_2O), 73.8 (OCH_2Ar), 127.4−129.2 (10 *C*H_{ar}), 138.6 (C_{ar}), 139.3 (C_{ar}); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 300. HPLC 96% purity (A), 95% purity (B).

1-(Benzyl(methyl)amino)-3-(benzyloxy)propan-2-ol (1l). Yield 96%, oil, ^{1}H NMR($CDCl_3$); δ 2.24 (3H, s, NCH_3), 2.41−2.63 (2H, m, NCH_2CH), 3.46−3.57 (2H, m, CHCH_2O), 3.52 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 3.67 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 3.92−3.99 (1H, m, C*H*OH), 4.57 (2H, s, OCH_2Ar), 7.25−7.37 (10H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 42.2 (NCH_3), 59.9 (NCH_2CH), 62.6 (ArCH_2N), 66.9 (*C*HOH), 72.7 (CHCH_2O), 73.6 (OCH_2Ar), 127.0−129.1 (10 *C*H_{ar}), 138.5 (C_{ar}), 140.2 (C_{ar}); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 286; found (HRMS FAB) $[M + H]^+$ 286.18044 $C_{18}H_{23}NO_2$ requires 286.18070. HPLC 99% purity (A), 97% purity (B).

1-Benzyloxy-3-(ethyl(isopropyl)amino)propan-2-ol (1m). Yield 87%, oil, ^{1}H NMR($CDCl_3$); δ 0.79−0.92 (9H, m, CH_3CH_2, $(CH_3)_2$CH), 2.24−2.41 (4H, m, CH_3CH_2, NCH_2CH), 2.83 (1H, septet, ^3J = 6.6 Hz, $(CH_3)_2$C*H*), 3.34−3.37 (2H, m, CHCH_2O), 3.60−3.65 (1H, m, C*H*OH), 4.44 (2H, s, OCH_2Ar), 7.11−7.24 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 14.6 (CH_3CH_2), 20.4 ((CH_3)$_2$CH), 44.2 (CH_3CH_2), 50.4 ((CH_3)$_2$*C*H), 52.0 (NCH_2CH), 66.6 (*C*HOH), 73.1 (CHCH_2O), 73.6 (OCH_2Ar), 127.7 (*C*H_{ar}), 127.8 (2 *C*H_{ar}), 128.4 (2 *C*H_{ar}), 138.4 (C_{ar}); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 252; found (HRMS FAB) $[M + H]^+$ 252.19624 $C_{15}H_{25}NO_2$ requires 252.19635.

1-Benzyloxy-3-(*tert*-butylamino)propan-2-ol (1n). Yield 81%, oil, ^{1}H NMR($CDCl_3$); δ 0.99 (9H, s, $(CH_3)_3$), 2.44−2.60 (2H, m, NCH_2CH), 3.34−3.41 (2H, m, CHCH_2O), 3.65−3.72 (1H, m, C*H*OH), 4.44 (2H, s, OCH_2Ar), 7.17−7.28 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 27.2 ((CH_3)$_3$), 44.9 (NCH_2CH), 54.0 (*C*$(CH_3)_3$), 69.3 (*C*HOH), 72.8 (CHCH_2O), 73.5 (OCH_2Ar), 127.6 (*C*H_{ar}), 127.8 (2 *C*H_{ar}), 128.4 (2 *C*H_{ar}), 138.2 (C_{ar}); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 238; found (HRMS FAB) $[M + H]^+$ 238.18058 $C_{14}H_{23}NO_2$ requires 236.18070.

1-Benzyloxy-3-(cyclobutylamino)propan-2-ol (1o). Yield 59%, oil; ^{1}H NMR($CDCl_3$); δ 1.51−1.62 (4H, m, CH_2 cyclobutane), 2.07−2.12 (2H, m, CH_2 cyclobutane), 2.50−2.58 (2H, m, NCH_2CH), 3.09−3.17 (1H, m, C*H* cyclobutane), 3.33−3.43 (2H, m, CHCH_2O), 3.73−3.79 (1H, m, C*H*OH), 4.47 (2H, s, OCH_2Ar), 7.18−7.26 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 14.6 (*C*H_2 cyclobutane), 30.9 (2 *C*H_2 cyclobutane), 49.1 (NCH_2CH), 54.0 (*C*H cyclobutane), 68.9 (*C*HOH), 72.9 (CHCH_2O), 73.3 (OCH_2Ar), 127.6−128.3 (5 *C*H_{ar}), 138.0 (C_{ar}); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 236.

1-Benzyloxy-3-(cyclopentylamino)propan-2-ol (1p). Yield 99%, oil; ^{1}H NMR($CDCl_3$); δ 1.21−1.93 (8H, 4 m, CH_2 cyclopentane), 2.59−2.78 (3H, m, NCH_2CH, N*H*), 3.07 (1H, qu, ^3J = 6.9 Hz, C*H* cyclopentane), 3.48−3.52 (2H, m, CHCH_2O), 3.87−3.93 (1H, m, C*H*OH), 4.59 (2H, s, OCH_2Ar), 7.23−7.36 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 23.8 (2 *C*H_2 cyclopentane), 32.9 (2 *C*H_2 cyclopentane), 50.8 (NCH_2CH), 59.7 (*C*H cyclopentane), 68.9 (*C*HOH), 72.9 (CHCH_2O), 73.3 (OCH_2Ar), 127.5−128.3 (5 *C*H_{ar}), 138.0 (C_{ar}); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 250. HPLC 95% purity (A), 98% purity (B).

1-Benzyloxy-3-[(tetrahydrofuran-2ylmethyl)amino]propan-2-ol (1q). Yield 79%, oil; ^{1}H NMR($CDCl_3$); δ 1.44−1.51 (1H, m, CH_2 tetrahydrofuran), 1.76−1.91 (3H, m, CH_2 tetrahydrofuran), 2.57−2.72 (4H, m, NCH_2CH, tetrahydrofuran CH_2NH), 3.37−3.45 (2H, m, CHCH_2O), 3.66−3.77 (2H, 2 m, CH_2 tetrahydrofuran), 3.78−3.82 (1H, m, C*H* tetrahydrofuran), 3.88−3.93 (1H, m, C*H*OH), 4.48 (2H, s, OCH_2Ar), 7.23−7.28 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 25.8 (*C*H_2 tetrahydrofuran), 29.1 (*C*H_2 tetrahydrofuran), 52.0 (NCH_2CH), 54.0 (tetrahydrofuran *C*H_2), 67.9 (*C*H_2 tetrahydrofuran), 68.8 (*C*HOH), 72.8 (CHCH_2O), 73.4 (OCH_2Ar), 78.2 (*C*H tetrahydrofuran), 127.7−128.4 (5 *C*H_{ar}), 138.1 (C_{ar}); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 266.

1-Benzyloxy-3-[(2-furylmethyl)amino]propan-2-ol (1r). Yield 58%, oil; ^{1}H NMR($CDCl_3$); 2.51−2.65 (3H, m, NCH_2CH, N*H*), 3.34−3.44 (2H, m, CHCH_2O), 3.68 (2H, s, furanCH_2NH), 3.77−3.82 (1H, m, C*H*OH), 4.45 (2H, s, OCH_2Ar), 6.07 (1H, d, ^3J = 1.1 Hz, C*H* furan), 6.21 (1H, d, ^3J = 1.1 Hz, C*H* furan), 7.20−7.25 (6H, m, 5 H_{ar}, C*H* furan); ^{13}C NMR($CDCl_3$) δ 45.9 (furanCH_2-NH), 51.1 (NCH_2CH), 68.8 (*C*HOH), 72.7 (CHCH_2O), 73.3 (OCH_2Ar), 106.9 (*C*H furan), 110.0 (*C*H furan), 127.6−128.3 (5 *C*H_{ar}), 137.9 (C_{ar}), 141.7 (*C*H furan), 153.5 (*C* furan); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 262.

1-Benzyloxy-3-[2-(2-thienylethyl)amino]propan-2-ol (1s). Yield 73%, oil; ^{1}H NMR($CDCl_3$); 2.47−2.64 (2H, m, NCH_2CH), 2.73−2.89 (4H, m, CH_2CH_2NH, thiophene CH_2CH_2), 3.33−3.40 (2H, m, CHCH_2O), 3.74−3.78 (1H, m, C*H*OH), 4.43 (2H, s, OCH_2Ar), 6.70 (1H, d, ^3J = 2.1 Hz, C*H* thiophene), 6.81 (1H, dd, ^3J = 2.1 Hz, ^3J = 3.0 Hz, C*H* thiophene), 7.02 (1H, d, ^3J = 3.0 Hz, C*H* thiophene), 7.19−7.24 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 30.2 (thiophene CH_2CH_2), 50.9 (CH_2CH_2NH), 51.5 (NCH_2CH), 68.7 (*C*HOH), 72.7 (CHCH_2O), 73.2 (OCH_2Ar), 123.4 (*C*H thiophene), 124.8 (*C*H thiophene), 126.7 (*C*H thiophene), 127.6−128.2 (5 *C*H_{ar}), 137.9 (C_{ar}), 142.2 (*C* thiophene); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 292.

1-Benzyloxy-3-[(2-thienylmethyl)amino]propan-2-ol (1t). Yield 84%, oil; ^{1}H NMR($CDCl_3$); 2.55−2.70 (3H, m, NCH_2CH, N*H*), 3.36−3.43 (2H, m, CHCH_2O), 3.79−3.84 (1H, m, C*H*OH), 3.90 (2H, s, thiophene CH_2NH), 4.46 (2H, s, OCH_2Ar), 6.80−6.86 (2H, m, C*H* thiophene), 7.11 (1H, d, ^3J = 3.0 Hz, C*H* thiophene), 7.20−7.26 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 48.6 (thiopheneCH_2NH), 51.5 (NCH_2CH), 69.3 (*C*HOH), 73.1 (CHCH_2O), 73.7 (OCH_2Ar), 124.8 (*C*H thiophene), 125.3 (*C*H thiophene), 126.9 (*C*H thiophene), 128.0−128.8 (5 *C*H_{ar}), 138.3 (C_{ar}), 144.1 (*C* thiophene); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 278. HPLC 97% purity (A), 92% purity (B).

1-Benzyloxy-3-(bicyclo[2.2.1]hept-2-ylamino)propan-2-ol (1x). Yield 95%; oil; ^{1}H NMR($CDCl_3$); δ 1.04−1.10 (4H, m, CH_2 bicycle), 1.41−1.60 (4H, m, CH_2 bicycle, 2 C*H* bicycle), 2.13−2.20 (2H, m, CH_2 bicycle), 2.53−2.75 (3H, m, NCH_2CH, C*H* bicycle), 2.97 (1H, s, N*H*), 3.45−3.49 (2H, m, CHCH_2OH), 3.87−3.92 (1H, m, C*H*OH), 4.56 (2H, s, OCH_2Ar), 7.30−7.35 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 27.4 (*C*H_2 bicycle), 28.9 (*C*H_2 bicycle), 35.2 (*C*H_2 bicycle), 36.0 (*C*H bicycle), 40.5 (*C*H_2 bicycle), 41.4 (*C*H bicycle), 50.6 (NCH_2CH), 62.4 (*C*H bicycle), 69.2 (*C*HOH), 73.5 (CHCH_2O), 73.8 (OCH_2Ar), 128.1−128.8 (5 *C*H_{ar}), 138.5 (C_{ar}); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 276.

1-[Benzyl(methyl)amino]-3-phenoxypropan-2-ol (2a). Yield 99%, oil, ^{1}H NMR($CDCl_3$); δ 2.31 (3H, s, NCH_3), 2.55−2.73 (2H, m, NCH_2CH), 3.57 (1H, d, ^2J = 12.9 Hz, ArCH_2N), 3.72 (1H, d, ^2J = 12.9 Hz, ArCH_2N), 4.00 (2H, d, ^3J = 4.8 Hz, CHCH_2O), 4.12−4.18 (1H, m, C*H*OH), 6.92−6.98 (3H, m, H_{ar}), 7.32−7.37 (7H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 42.1 (NCH_3), 59.6 (NCH_2CH), 62.6 (ArCH_2N), 66.1 (*C*HOH), 70.2 (CHCH_2O), 114.4 (2 *C*H_{ar}), 120.8 (*C*H_{ar}), 127.2−129.4 (7 *C*H_{ar}), 138.2 (C_{ar}), 158.7 (C_{ar}); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 272.

3-[Benzyl(ethyl)amino]propan-1,2-diol (3a). Yield 99%, oil, ^{1}H NMR($CDCl_3$); δ 0.89 (3H, t, ^3J = 7.1 Hz, CH_3), 2.29−2.49 (4H, m, NCH_2CH, CH_3CH_2), 3.34−3.61 (6H, m, CH_2OH, ArCH_2N, C*H*OH), 7.08−7.17 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 11.3 (CH_3), 47.4 (CH_2CH_3), 55.4 (NCH_2CH), 58.0 (ArCH_2N), 64.5 (*C*H_2OH), 67.2 (*C*HOH), 126.9−128.7 (5 *C*H_{ar}), 138.3 (C_{ar}); *m/z*; found (ES-MS$^+$) $[M + H]^+$ 210.

General procedure for the synthesis of 4a-h. To a microwave tube containing epichlorohydrin (1 mmol) dissolved in absolute ethanol (2.5 mL) was added the amine (0.9 mmol). The reaction was placed in the CEM Discover microwave for 1 min at 20 °C (80 W, 50 psi). The crude product was allowed to cool and concentrated *in vacuo* (keeping water bath temperature <20 °C) to yield the desired products **4a**−**h**. Purification was achieved by

placing the product under high vacuum for 1 h to remove any residual solvent.

1-Chloro-3-diethylaminopropan-2-ol (4a). Yield 68%, oil, ^{1}H NMR($CDCl_3$); δ 1.03 (6H, t, ^3J = 7.2 Hz, 2 CH_3), 2.40−2.68 (6H, m, 2 NCH_2CH$_3$, NCH_2CH**)**, 3.50−3.61 (2H, m, CH_2Cl), 3.80 (1H, qu, ^3J = 5.1 Hz, C*H*OH); ^{13}C NMR($CDCl_3$) δ 11.8 (2 *C*H$_3$), 47.1 (*C*H$_2$Cl), 56.2 (2 NCH$_2$CH$_3$, NCH$_2$CH), 66.8 (*C*HOH); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 166; found (HRMS FAB) [M + H]$^+$ 166.09204 C_7H_{16}NOCl requires 166.09211.

1-Chloro-3-[ethyl(isopropyl)amino]propan-2-ol (4b). Yield 12%, oil, ^{1}H NMR($CDCl_3$); δ 0.82−0.95 (9H, m, CH_3CH$_2$, (CH_3)$_2$CH), 2.20−2.38 (4H, m, CH$_3$CH_2, NCH_2CH), 2.79 (1H, septet, ^3J = 6.6 Hz, (CH$_3$)$_2$C*H*), 3.51−3.60 (2H, m, CH_2Cl), 3.89 (1H, qu, ^3J = 5.2 Hz, C*H*OH); ^{13}C NMR($CDCl_3$) δ 15.1 (*C*H$_3$CH$_2$), 21.1 ((*C*H$_3$)$_2$CH), 44.2 (CH$_3$*C*H$_2$), 46.5 (*C*H$_2$Cl), 50.4 (*C*H(CH$_3$)$_2$), 51.7 (N*C*H$_2$CH), 66.3 (*C*HOH); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 180; found (HRMS FAB) [M + H]$^+$ 180.11503 C_8H_{18}NOCl requires 180.11560.

1-Chloro-3-pyrrolidin-1-ylpropan-2-ol (4c). Yield 65%, oil, ^{1}H NMR($CDCl_3$); δ 1.73−1.78 (4H, m, 2 CH_2 pyrrolidine), 2.42−2.50 (4H, m, 2 CH_2 pyrrolidine), 2.63−2.74 (2H, m, NCH_2**)**, 3.51−3.60 (2H, m, CH_2Cl), 3.88 (1H, qu, ^3J = 5.1 Hz, C*H*OH); ^{13}C NMR($CDCl_3$) δ 23.5 (2 *C*H$_2$ pyrrolidine), 47.2 (*C*H$_2$Cl), 54.5 (2 *C*H$_2$ pyrrolidine), 56.2 (N*C*H$_2$), 68.2 (*C*HOH); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 164; found (HRMS FAB) [M + H]$^+$ 164.05937 C_7H_{14}NOCl requires 164.06562.

1-Chloro-3-piperidin-1-ylpropan-2-ol (4d). Yield 72%, oil, ^{1}H NMR($CDCl_3$); δ 1.43−1.47 (2H, m, CH_2 piperidine), 1.52−1.61 (4H, m, 2 CH_2 piperidine), 2.31−2.46 (4H, m, 2 CH_2 piperidine), 2.53−2.57 (2H, m, NCH_2**)**, 3.50−3.61 (2H, m, CH_2Cl), 3.91 (1H, qu, ^3J = 5.1 Hz, C*H*OH); ^{13}C NMR($CDCl_3$) δ 24.0 (*C*H$_2$ piperidine), 25.9 (2 *C*H$_2$ piperidine), 47.2 (*C*H$_2$Cl), 54.6 (2 *C*H$_2$ piperidine), 61.5 (N*C*H$_2$), 66.3 (*C*HOH); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 178; found (HRMS FAB) [M + H]$^+$ 178.09204 C_8H_{16}NOCl requires 178.09214.

1-Chloro-3-morpholin-4-ylpropan-2-ol (4e). Yield 70%, oil; ^{1}H NMR($CDCl_3$); δ 2.40−2.47 (4H, m, 2 NCH_2 morpholine), 2.57−2.65 (2H, m, NCH_2), 3.51−3.60 (2H, m, CH_2Cl), 3.67−3.71 (4H, m, 2 OCH_2 morpholine), 3.92 (1H, qu, ^3J = 5.1 Hz, C*H*OH); ^{13}C NMR($CDCl_3$) δ 46.9 (*C*H$_2$Cl), 53.6 (2 NCH_2 morpholine), 61.3 (N*C*H$_2$), 66.3 (*C*HOH), 66.7 (2 OCH_2 morpholine); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 180; found (HRMS FAB) [M + H]$^+$ 180.07932 $C_7H_{14}NO_2Cl$ requires 180.07913.

1-Chloro-3-piperazin-1-ylpropan-2-ol (4f). Yield 61%, oil, ^{1}H NMR($CDCl_3$); δ 2.39−2.48 (4H, m, 2 CH_2 piperazine), 2.55−2.62 (2H, m, NCH_2), 2.86−2.92 (4H, m, 2 CH_2 piperazine), 3.51−3.69 (2H, m, CH_2Cl), 3.92 (1H, qu, ^3J = 5.1 Hz, C*H*OH); ^{13}C NMR($CDCl_3$) δ 45.5 (2 *C*H$_2$ piperazine), 46.4 (*C*H$_2$Cl), 47.0 (2 *C*H$_2$ piperazine), 61.4 (N*C*H$_2$), 66.5 (*C*HOH); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 179; found (HRMS FAB) [M + H]$^+$ 179.08711 $C_7H_{15}N_2OCl$ requires 179.08705.

1-Allylamino-3-chloropropan-2-ol (4g). Yield 55%, oil, ^{1}H NMR($CDCl_3$); δ 2.56 (1H, s, N*H*), 2.65−2.83 (2H, m, NCH_2CH), 3.28 (2H, m, CH$_2$=CHCH_2), 3.50−3.62 (2H, m, CH_2Cl), 3.90 (1H, qu, ^3J = 5.1 Hz, C*H*OH), 5.10−5.23 (2H, m, CH_2=CHCH$_2$), 5.82−5.95 (1H, m, CH$_2$=C*H*CH$_2$); ^{13}C NMR($CDCl_3$) δ 47.3 (*C*H$_2$Cl), 51.2 (N*C*H$_2$CH), 52.0 (CH$_2$=CH*C*H$_2$), 69.3 (*C*HOH), 116.5 (*C*H$_2$=CH), 136.0 (CH$_2$=*C*H); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 150; found (HRMS FAB) [M + H]$^+$ 150.06865 C_6H_{12}NOCl requires 150.06857.

1-[Benzyl(methyl)amino]-3-chloropropan-2-ol (4h). Yield 76%, oil, ^{1}H NMR($CDCl_3$); δ 2.21 (3H, s, NCH_3), 2.43−2.57 (2H, m, NCH_2CH), 3.50−3.62 (2H, m, CH_2Cl), 3.78 (2H, s, ArCH_2N), 3.92 (1H, qu, ^3J = 5.1 Hz, C*H*OH), 7.19−7.33 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 42.1 (N*C*H$_3$), 47.0 (*C*H$_2$Cl), 58.2 (N*C*H$_2$CH), 62.4 (Ar*C*H$_2$N), 67.1 (*C*HOH), 127.5 (*C*H$_{ar}$), 128.3 (2 *C*H$_{ar}$), 128.7 (2 *C*H$_{ar}$), 137.9 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 214; found (HRMS FAB) [M + H]$^+$ 212.08390 $C_{11}H_{16}$NOCl requires 212.08422. HPLC 98% purity (A), 86% purity (B).

Synthesis of *N*-benzyl-*N*-methyl-1-oxiran-2-ylmethanamine (5).[26] NaH (60% in mineral oil, 0.51 g, 12.9 mmol) was added to a solution of *N*-methylbenzylamine (1.52 mL, 11.7 mmol) in THF (50 mL) at 0 °C, and the mixture was stirred for 15 min. To the mixture was added dropwise at 0 °C a solution of epibromohydrin (1 mL, 11.7 mmol) in THF (5 mL) over a period of 15 min. The solution was then stirred at reflux overnight. Under ice bath cooling, 30 mL of water was added. The aqueous phase was extracted with dichloromethane (3 × 30 mL), and the organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate as eluent) to give **5** (1.40 g, 68%) as a pale yellow oil. ^{1}H NMR($CDCl_3$); δ 2.33 (3H, s, NCH_3), 2.33−2.48 (2H, m, NCH_2CH), 2.74−2.78 (2H, m, CH_2O), 3.13 (1H, m, C*H*O), 3.52 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 3.66 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 7.32−7.36 (5H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 43.4 (N*C*H$_3$), 45.4 (*C*H$_2$O), 51.2 (*C*HO), 60.1 (N*C*H$_2$CH), 63.0 (Ar*C*H$_2$N), 127.5−129.4 (5 *C*H$_{ar}$), 139.1 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 178.

General Procedure for the Synthesis of 6a-c and 7. Epoxide **5** (1 mmol) was dispensed into a microwave tube and dissolved in absolute ethanol (2.5 mL). Amine (1.5 mmol) for **6a**−**c** or benzylmercaptan (1.1 mmol) and NaOH (2 pellets) for **7** were added to the tube and placed in the CEM Discover Microwave Synthesizer Explorer Carousel. Each sample was heated at 140 °C with stirring for 4 min (80 W, 50 psi). A period of 5 min was allowed for sample cooling. For **6a**−**c**, each sample was concentrated *in vacuo*, and purification was performed using Kugelrohr bulb to bulb distillation apparatus to yield the desired products. For **7**, the solution was dissolved with dichloromethane (10 mL) and washed with water (2 × 10 mL). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel chromatography column to yield **7** as a colorless oil.

1-(Benzylamino)-3-[benzyl(methyl)amino]propan-2-ol (6a). Yield 97%, oil, ^{1}H NMR($CDCl_3$); δ 2.27 (3H, s, NCH_3), 2.34−2.77 (4H, m, 2 × NCH_2CH), 3.52 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 3.66 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 3.84 (2H, s, ArCH_2N), 3.88−3.97 (1H, m, C*H*OH), 7.53 (10H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 42.7 (N*C*H$_3$), 53.5 (N*C*H$_2$CH), 54.4 (N*C*H$_2$CH), 61.5 (Ar*C*H$_2$N), 63.0 (Ar*C*H$_2$N), 67.1 (*C*HOH), 127.4−129.5 (10 *C*H$_{ar}$), 138.9 (C_{ar}), 140.6 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 285.

1,3-Bis[benzyl(methyl)amino]propan-2-ol (6b). Yield 99%, oil, ^{1}H NMR($CDCl_3$); δ 2.28 (6H, s, 2 × NCH_3), 2.42−2.52 (4H, m, 2 × NCH_2CH), 3.54−3.66 (4H, m, 2 × ArCH_2N), 3.90−3.99 (1H, m, C*H*OH), 7.33 (10H, s, H_{ar}); ^{13}C NMR($CDCl_3$) δ 43.0 (2 × N*C*H$_3$), 62.0 (2 × N*C*H$_2$CH), 63.1 (2 × Ar*C*H$_2$N), 65.7 (*C*HOH), 127.5−129.5 (10 *C*H$_{ar}$), 139.0 (2 × C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 299.

1-(Benzylamino)-3-[benzyl(ethyl)amino]propan-2-ol (6c). Yield 99%, oil, ^{1}H NMR($CDCl_3$); δ 1.07 (3H, t, ^3J = 7.2 Hz, CH_3CH$_2$), 2.26 (3H, s, NCH_3), 2.44−2.67 (6H, m, 2 × NCH_2CH and CH$_3$CH_2), 3.58 (2H, s, ArCH_2N), 3.60 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 3.74 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 3.85−3.91 (1H, m, C*H*OH), 7.27−7.33 (10H, m, H_{ar}); ^{13}C NMR($CDCl_3$) δ 12.2 (*C*H$_3$CH$_2$), 43.1 (N*C*H$_3$), 48.3 (*C*H$_2$CH$_3$), 58.3 (N*C*H$_2$CH), 59.0 (N*C*H$_2$CH), 62.1 (Ar*C*H$_2$N), 63.1 (Ar*C*H$_2$N), 65.9 (*C*HOH), 127.4−129.5 (10 *C*H$_{ar}$), 139.2 (C_{ar}), 139.7 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 313. HPLC 95% purity (A), 93% purity (B).

1-[Benzyl(methyl)amino]-3-(benzylthio)propan-2-ol (7). Yield 80%, oil, ^{1}H NMR($CDCl_3$); δ 2.28 (3H, s, NCH_3), 2.49−2.56 (4H, m, NCH_2CH and SCH_2CH), 3.56 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 3.72 (1H, d, ^2J = 13.5 Hz, ArCH_2N), 3.78 (2H, s, SCH_2Ar), 3.83−3.90 (1H, m, C*H*OH),7.33 (10H, s, H_{ar}); ^{13}C NMR($CDCl_3$) δ 37.0 and 37.4 (ArCH_2S and S*C*H$_2$CH), 42.4 (N*C*H$_3$), 62.3 and 62.7 (Ar*C*H$_2$N and NCH$_2$CH), 67.1 (*C*HOH), 127.5−129.7 (10 *C*H$_{ar}$), 137.4 (C_{ar}), 138.8 (C_{ar}); *m/z*; found (ES-MS$^+$) [M + H]$^+$ 302.

General Procedure for the Synthesis of 8a,b and 9a,b. See the general procedure for the synthesis of **1a**−**x**. See **1p** for chemical data of **8a** (enantiomeric excess >99% based on chiral HPLC) and **9a** (enantiomeric excess >99% based on chiral HPLC). See **1t** for chemical data of **8b** (enantiomeric excess >99% based on chiral HPLC) and **9b** (enantiomeric excess >99% based on chiral HPLC).

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Supporting Information Available: Analytical data for **1d**,**e**, **g**,**i**,**u**,**v**,**w**, **2b**−**g**, and **3b,c**; HPLC data for selected compounds **1b**,**k**,**l**,**p**,**t**, **4h**, **6c**, **8a**,**b**, and **9a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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