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Research Article

Synthesis and Antibacterial Activity Evaluation of Unsymmetrically Substituted Cyclohexane-1,2-diamine Derivatives

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Abstract: A series of unsymmetrically substituted cyclohexane-1,2-diamine derivatives with different substitution pattern on the aromatic ring have been prepared and evaluated for their antibacterial activity against Gram-positive and Gram-negative bacterial strains. Some of the compounds showed good activity against *P. aeruginosa*, *S. epidermidis* and *S. aureus* while compounds **18m** and **19k** showed antibacterial activity against all three bacterial strains with MIC 0.065 µg/mL.

Introduction

Among the infectious diseases, bacteria have been responsible for the most deadly diseases and widespread epidemics of human civilization [1-4]. From 1940 to 2004 about 335 new infectious diseases were identified and among them more than 50% were associated with bacteria [5]. The problem of drug resistance is so serious that incidences of bacterial resistance have been reported against different classes of antibacterial agents such as *β*-lactams, quinolones, vancomycin, glycopeptides, macrolides etc. In many cases resistance was even reported soon after or even before their introduction into the clinical market [6-9]. The multidrug resistance due to methicillin resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* and vancomycin-resistant *Enterococci* (VRE) have been the leading cause of high casualties worldwide [10-15]. To make the situation worse, the problem of multidrug resistance has been continuously increasing and no new class of antibacterial has been introduced in the market until the discovery of linezolid in 2000 [16]. Unfortunately within a year this compound also became resistant and recently some linezolid resistant clinical isolates of vancomycin resistant *Enterococcus faecium* (VREF) and *S. aureus* have been reported [17,18]. In order to overcome the increasing resistance problems and to develop a better therapeutic agent, there is an urgent need to develop a novel antibacterial agent with distinct mode of action which would not be affected by resistance mechanism.

As a part of our ongoing work towards the synthesis of novel antibacterial agent [19-22], we recently reported the synthesis and antimicrobial activity of cyclohexane

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diamine derivatives [23-25]. These compounds have been developed as synthetic analogues of bromhexine (**1**), a well known secretolytic or mucolytic agent [26-28]. The structure activity relationship (SAR) revealed that the introduction of alkyl chain at *para* position of benzene ring led to the discovery of potent antimicrobial agents (**2** and **3**). Encouraged by these observations, we decided to synthesize unsymmetrically substituted cyclohexane-1,2-diamine derivatives in which one of the benzene ring was replaced by some heterocyclic moieties and to study the effect of benzyl group on the antimicrobial activity. A number of structurally diverse compounds were synthesized using cyclohexene oxide (**4**) as starting material as shown in scheme 1.

Chemistry

In order to synthesize title compounds, we started with cyclohexene oxide (**4**) as starting material. The three membered ring of cyclohexene oxide (**4**) was opened with different secondary amines (**5-8**) to give (±)-*trans*-2-aminocyclohexanols (**9-12**). In the second step, the hydroxyl group of (±)-*trans*-2-aminocyclohexanols was converted into amino group by one pot procedure reported in the literature [29]. The resulting products (**13-16**) were then used as a starting material for the synthesis of the titled compounds (**18a-18n, 19a-19n, 20a-20n, 21a-21n**) by the literature method [30].

Biological Activity

***In vitro* antibacterial activity**:
Antimicrobial susceptibility testing was carried out using National Committee for Clinical Laboratory Standards (NCCLS) micro dilution assay. Briefly, the bacterial strains were grown in standard media until exponential growth was achieved. Tests were performed in the 96-well microliter plate in a final volume of 100 µL. Test compounds were dissolved in 5% DMSO at an initial concentration of 500 µg/mL and serially diluted in plate. Each well was then inoculated with ~2-5 x 10^5 bacterial cells and incubated at 37 ^oC for 24 h with shaking at 200 rpm. One well containing bacterial cells (~2-5 x 10^5) and 5% DMSO without any test compound (growth control), and one well containing only growth medium (sterility control) were used as controls. Growth of bacteria was determined using Power wave 200 microplate scanning spectrophotometer (Bio-Tek Instruments, Winooski, VT, USA). Percent survival was calculated using growth without any compound as 100% survival. The MIC values were calculated using Grafit 4.0 software (Erithacus Software Ltd., Horley, Surrey, UK).

Results and Discussion

All the compounds were evaluated against Gram-negative (*E. coli* and *P. aeruginosa*) and Gram-positive (*S. aureus* and *S. epidermidis*) bacterial strains using tetracycline as a standard drug. The MIC values are shown in table 1. Out of the four different series (**18a-18n, 19a-19n, 20a-20n, 21a-21n**), only two series (**18a-18n** and **19a-19n**) were found to be active. All the compounds were inactive against *E. coli*. Among the series (**18a-18n**), seven compounds (**18f**, **18h**, **18j-18n**) showed mild to potent activity against all the three bacterial strains. Compound **18a** with unsubstituted benzene ring showed poor activity against *P. aeruginosa* and *S. epidermidis* with MIC of 0.5 µg/mL, which is in good agreement with our earlier observation [25]. Remarkable effect on antibacterial activity was observed when chloro, bromo or fluoro groups were present at *para* position rather than at *meta* position of the benzene ring (**18b**, **18d**, **18f** *vs* **18c**, **18e**, **18g**). Compound **18b** with chloro group at *para* position of benzene ring showed good activity against *P.*

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aeruginosa and *S. epidermidis* with MIC of 0.125 µg/mL, whereas compounds **18d** and **18f** with bromo and fluoro substituent at *para* position were found to be active against all the three bacterial strains with MIC values ranging from 0.125 to 1.0 µg/mL. Alkyl substituents in the benzene ring have pronounced effect on the activity (**18h**-**18n**). Compound **18h** with methyl group at *para* position of benzene ring showed significant activity against all the three bacterial strains (*P. aeruginosa*, *S. aureus* and *S. epidermidis*) with MICs of 0.25, 1.0, 0.5 µg/mL, respectively, While compound **18k** with methyl group at *meta* position showed slight less activity against two bacterial strains (*P. aeruginosa* and *S. epidermidis*) with MIC of 0.25 µg/mL. On increasing the chain length of the alkyl substituent at *para* position of benzene ring from methyl to butyl, the activity gets improved. For example compounds **18m** and **18n** with *n*-butyl and *t*-butyl groups at *para* position of the benzene ring showed better activity than the other analogues in which ethyl (**18j**), *n*-propyl (**18k**) and *iso*-propyl (**18l**) groups were present in the benzene ring. Out of these 14 compounds, compound **18n** was found to be the most potent (MIC = 0.065 µg/mL) and showed comparable activity to the reference compound tetracycline.

In the series **19a**-**19n**, only compounds with alkyl substituents at *para* position (**19j**-**19n**) in the benzene ring were found to be active and rest of the compounds with chloro, bromo or fluoro subtituents did not show any activity. Compound **19j** with ethyl group at *para* position showed mild activity (MIC = 0.25 µg/mL) against all the three bacterial strains (*P. aeruginosa*, *S. aureus* and *S. epidermidis*). On introduction of *n*-propyl and *iso*-propyl groups at *para* position (**19k** and **19l**), the activity is enhanced and compound **19k** showed very good activity against all the three bacterial strains with MIC of 0.065 µg/mL. Compounds **19m** and **19n** with *n*-butyl and *t*-butyl groups at *para* position of the benzene ring also showed promising activity with MIC value 0.125 µg/mL against all the three bacterial strains.

In series (**20a**-**20n**), only one compound (**20m**) with *n*-butyl group at *para* position of the benzene ring showed activity against *P. aeruginosa* with MIC of 1.0 µg/mL. Similarly in series (**21a**-**21n**), only one compound (**21m**) with *n*-butyl group at *para* position of the benzene ring showed activity against *S. epidermidis* with MIC of 0.25 µg/mL.

Conclusion

We synthesised 56 new unsymmetrically substituted cyclohexane-1,2-diamine derivatives and evaluated their antibacterial activity. Some of the compounds exhibited mild to potent activity against *P. aeruginosa, S. aureus and S. epidermidis* bacterial strains. Two compounds **18m** and **19k** showed comparable activity to reference drug tetracycline which could be considered as a lead for the development of new antibacterial drug.

Experimental protocols

All the chemicals used were purchased from Sigma-Aldrich and used as such. ^{1}H NMR and ^{13}C NMR spectral data were recorded on Jeol ECX spectrospin instrument at 400 and 100 MHz, respectively using $CDCl_3$ as solvent and TMS as internal reference. The chemical shift values were expressed on δ scale and the coupling constant (*J*) in Hz. IR (film in chloroform) spectra were recorded on Perkin-elmer FT-IR spectrophotometer and the values were expressed in cm^{-1}. Mass Spectra were recorded on a THERMO finnigan LCQ Advantage max ion trap mass spectrometer.

Synthesis of 2-(pyrrolidin-1-yl)cyclohexanol (9) and related compounds (10-12) [29]

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The secondary amine, pyrrolidine (**5**, 2.17 g, 0.03 mol) was added to a solution of cyclohexene oxide (**4**, 2.0 g, 0.02 mol) in ethanol and the resulting mixture was heated under reflux for 24 hrs. After cooling, the solvent was evaporated and the crude 2-(pyrrolidin-1-yl)cyclohexanol (**9**) was purified by column chromatography using 20% EtAc/hexane as eluent.

Synthesis of 2-(pyrrolidin-1-yl)cyclohexanamine (13) and related compounds (13-16) [29]

The 2-(pyrrolidin-1-yl)cyclohexanol (**9**, 2.0 g, 0.011 mol) was dissolved in anhydrous diethyl ether, and triethylamine (1.90 g, 0.018 mol) was added. The resulting solution was cooled to 0 ^{o}C and to this, methane sulfonyl chloride (1.6 g, 0.14 mol) was added drop wise. A white precipitate was formed. After 1 hr, triethylamine (2.26 g, 0.02 mol) was added and then the reaction mixture was allowed to warm to room temperature. When the temperature reached to room temperature, 30% aq. ammonia solution was added and the resulting two phase mixture was vigorously stirred for 16 hrs. After completion of the reaction two layers were separated and the light yellow aq. layer was extracted with diethyl ether. The combined organic layer was washed with brine solution, and organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give the crude product (**13**), which was purified by column chromatography.

Synthesis of *N*-(4-Chlorobenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine (18b) and related compounds (18a-n, 19a-n, 20a-n, 21a-n) [30]

The above synthesized compound (**13**, 0.5 g, 0.003 mol) was treated with *p*-Cl benzaldehyde (0.42 g, 0.003 mol) in dry methanol to give Schiff bases which were reduced with sodium borohydride *in situ* to give the reduced product which was purified using column chromatography and was converted into HCl salt (**18b**) by passing dry HCl gas in its solution in chloroform.

***N*-Benzyl-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18a):** Yield: 50%; IR (Film, cm^{-1}): 2947, 2693, 1632, 1458, 1024, 914; ^{1}H NMR (400 MHz, $CDCl_3$): 1.30-1.32 (m, 1H), 1.49-1.57 (m, 2H), 1.91-1.99 (m, 4H), 2.16-2.17 (m, 2H), 2.29-2.34 (m, 2H), 2.41-2.45 (m, 1H), 2.97 (s, 1H), 3.21 (s, 1H), 3.34 (brs, 2H), 3.76 (brs, 1H), 4.12 (d, 1H, *J* = 13.2 Hz), 4.41 (brs, 1H), 4.53 (d, 1H, *J* = 13.2 Hz), 7.41-7.45 (m, 3H, ArH), 7.73-7.75 (m, 2H, ArH), 10.19 (brs, 1H, NH^+), 11.08 (brs, 1H, NH_2^+), 11.43 (brs, 1H, NH_2^+).

***N*-(4-Chlorobenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18b):** Yield: 70%; IR (Film, cm^{-1}): 2929, 2692, 1602, 1458, 1093, 1016, 919; ^{1}H NMR (400 MHz, $CDCl_3$): 1.25-1.32 (m, 1H), 1.92 (brs, 2H), 2.01 (brs, 2H), 2.14-2.25 (m, 6H), 2.42 (brs, 1H), 3.02 (brs, 1H), 3.32 (brs, 2H), 3.47 (brs, 1H), 3.80 (brs, 1H), 4.09 (d, 1H, *J* = 13.0 Hz), 4.44 (d, 2H, *J* = 13.0 Hz), 7.39 (d, 2H, *J* = 8.0 Hz, ArH), 7.73 (d, 2H, *J* = 8.0 Hz, ArH), 10.19 (brs, 1H, NH^+), 11.26-11.37 (brs, 2H, NH_2^+).

***N*-(3-Chlorobenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18c):** Yield: 65%; IR (Film, cm^{-1}): 2931, 2683, 1575, 1455, 1213, 1171, 1083, 914; ^{1}H NMR (400 MHz, $CDCl_3$): 1.32-1.34 (m, 1H), 1.53 (brs, 2H), 1.92 (brs, 2H), 2.03 (brs, 2H), 2.14-2.17 (m, 2H), 2.27 (brs, 1H), 2.40-2.43 (m, 1H), 3.05 (brs, 1H), 3.34 (brs, 2H), 3.44-3.47 (m, 1H), 3.79 (brs, 1H), 4.11 (d, 2H, *J* = 13.2 Hz), 4.42 (s, 1H), 4.48 (d, 1H, *J* = 13.2 Hz), 7.38 (d, 2H, *J* = 4.4 Hz, ArH), 7.72 (t, 1H, *J* = 4.4 Hz, ArH), 7.76 (s, 1H, ArH), 10.37 (brs, 1H, NH^+), 11.36 (brs, 2H, NH_2^+).

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***N*-(4-Bromobenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18d):** Yield: 75%; IR (Film, cm^{-1}): 2925, 2693, 2360, 2342, 1592, 1442, 1219, 1069, 1010; ^{1}H NMR (400 MHz, $CDCl_3$): 1.29-1.31 (m, 1H), 1.51 (brs, 2H), 1.94 (brs, 2H), 2.01 (brs, 2H), 2.14-2.25 (m, 4H), 2.40-2.42 (m, 1H), 3.02 (brs, 1H), 3.32 (brs, 2H), 3.47 (brs, 1H), 3.80 (brs, 1H), 4.09 (d, 1H, *J* = 13.2 Hz), 4.44 (d, 2H, *J* = 13.2 Hz), 7.55 (d, 2H, *J* = 8.0 Hz, ArH), 7.67 (d, 2H, *J* = 8.0 Hz, ArH), 10.15 (brs, 1H, NH^+), 11.35 (brs, 2H, NH_2^+); ESI-MS (*m/z*): 337.1 $[M+1 - 2HCl]^+$.

***N*-(3-Bromobenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18e):** Yield: 65%; IR (Film, cm^{-1}): 2947, 2694, 1635, 1458, 1211, 1170, 1075; ^{1}H NMR (400 MHz, $CDCl_3$): 1.33-1.35 (m, 1H), 1.53 (brs, 2H), 1.90-1.92 (m, 2H), 2.01-2.04 (m, 2H), 2.12-2.18 (m, 3H), 2.27 (brs, 1H), 2.41-2.43 (m, 1H), 3.05 (brs, 1H), 3.35 (brs, 2H), 3.46 (brs, 1H), 3.79 (brs, 1H), 4.13 (d, 1H, *J* = 14.0 Hz), 4.39 (brs, 1H), 4.47 (d, 1H, *J* = 14.0 Hz), 7.32 (t, 1H, *J* = 8.0 Hz, ArH), 7.53 (d, 1H, *J* = 8.0 Hz, ArH), 7.77 (d, 1H, *J* = 8.0 Hz, ArH), 7.92 (s, 1H, ArH), 10.27 (brs, 1H, NH^+), 11.14 (brs, 1H, NH_2^+), 11.38 (brs, 1H, NH_2^+).

***N*-(4-Fluorobenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18f):** Yield: 60%; IR (KBr, cm^{-1}): 2877, 2609, 1600, 1567, 1510, 1218, 1027; ^{1}H NMR (400 MHz, $CDCl_3$): 1.25-1.33 (m, 1H), 1.45-1.57 (m, 2H), 1.93-2.01 (m, 3H), 2.22 (brs, 4H), 2.37 (s, 1H), 3.00 (brs, 1H), 3.27 (brs, 2H), 3.48 (brs, 1H), 3.87 (brs, 1H), 4.04 (d, 2H, *J* = 13.0 Hz), 4.49 (d, 2H, *J* = 12.8 Hz) 7.10-7.14 (m, 2H, ArH), 7.76-7.79 (m, 2H, ArH), 10.04 (brs, 1H, NH^+), 11.47 (brs, 1H, NH_2^+), 11.62 (brs, 1H, NH_2^+).

***N*-(3-Fluorobenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18g):** Yield: 60%; IR (Film, cm^{-1}): 2930, 2681, 2209, 1590, 1455, 1256, 1153, 1011, 921; ^{1}H NMR (400 MHz, $CDCl_3$): 1.27-1.32 (m, 1H), 1.54 (brs, 2H), 1.91 (brs, 3H), 2.05-2.17 (m, 5H), 2.27 (brs, 1H), 2.43 (brs, 1H), 3.29 (brs, 2H), 3.39 (brs, 2H), 4.10 (d, 1H, *J* = 13.2 Hz), 4.42 (brs, 1H), 4.49 (d, 1H, *J* = 13.2 Hz), 7.08-7.12 (m, 1H, ArH), 7.38-7.44 (m, 1H, ArH), 7.52-7.57 (m, 2H, ArH), 10.88 (br, 3H, NH^+, NH_2^+).

***N*-(4-Methylbenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18h)** Yield: 65%; IR (Film, cm^{-1}): 2946, 2691, 2614, 2496, 1617, 1457, 1171, 1024; ^{1}H NMR (400 MHz, $CDCl_3$): 1.25-1.28 (m, 1H), 1.46-1.58 (m, 2H), 1.90-1.93 (m, 2H), 1.99 (brs, 2H), 2.14-2.24 (m, 5H), 2.35 (s, 3H), 2.96 (brs, 1H), 3.15 (brs, 1H), 3.32 (brs, 1H), 3.38 (brs, 2H), 3.80 (brs, 1H), 4.05 (brs, 1H), 4.44-4.50 (m, 2H), 7.22 (d, 2H, *J* = 8.0 Hz, ArH), 7.60 (d, 2H, *J* = 8.0 Hz, ArH), 10.09 (brs, 1H, NH^+), 11.18 (brs, 1H, NH_2^+), 11.49 (brs, 1H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 20.93, 21.09, 23.09, 23.30, 23.56, 23.97, 29.36, 48.08, 49.70, 52.95, 53.93, 61.57, 126.75, 129.55, 130.37, 140.33; ESI-MS (*m/z*): 273.2 $[M+1 - 2HCl]^+$.

***N*-(3-Methylbenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18i):** Yield: 65%; IR (Film, cm^{-1}): 2929, 2687, 1617, 1458, 913; ^{1}H NMR (400 MHz, $CDCl_3$): 1.25-1.29 (m, 1H), 1.47-1.59 (m, 2H), 1.90-1.93 (m, 2H), 1.99 (brs, 2H), 2.18 (brs, 5H), 2.38 (s, 3H), 2.96 (brs, 1H), 3.16 (brs, 1H), 3.34 (brs, 2H), 3.80 (brs, 1H), 4.04 (d, 1H, *J* = 12.5 Hz), 4.45 (brs, 1H), 4.50 (d, 1H, *J* = 12.5 Hz), 7.21 (d, 1H, *J* = 7.3 Hz, ArH), 7.32 (t, 1H, *J* = 8.0 Hz, ArH), 7.50 (s, 1H, ArH), 7.56 (d, 1H, *J* = 7.3 Hz, ArH), 10.13 (brs, 1H, NH^+), 11.19 (brs, 1H, NH_2^+), 11.52 (brs, 1H, NH_2^+).

***N*-(4-Ethylbenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18j):** Yield: 60%; IR (Film, cm^{-1}): 2933,

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2689, 1625, 1458, 913; ^{1}H NMR (400 MHz, $CDCl_3$): 1.23 (t, 3H, *J* = 8.0 Hz), 1.27-1.31 (m, 1H), 1.49-1.59 (m, 2H), 1.90-1.98 (m, 4H), 2.15-2.18 (m, 3H), 2.28 (brs, 2H), 2.41-2.44 (m, 1H), 2.65 (q, 2H, *J* = 7.3 Hz), 2.96 (s, 1H), 3.17 (brs, 1H), 3.35 (brs, 1H), 3.77 (s, 1H), 4.04-4.07 (m, 1H), 4.42-4.51 (m, 2H), 7.25 (d, 2H, *J* = 8.0 Hz, ArH), 7.63 (d, 2H, *J* = 8.0 Hz, ArH), 10.11 (brs, 1H, NH^+), 11.13 (brs, 1H, NH_2^+), 11.50 (brs, 1H, NH_2^+); ESI-MS (*m/z*): 287.2 $[M+1 - 2HCl]^+$.

***N*-(4-Propylbenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18k):** Yield: 55 %; IR (Film, cm^{-1}): 2958, 2695, 2213, 1637, 1457, 1170, 1023, 913; ^{1}H NMR (400 MHz, $CDCl_3$): 0.93 (t, 3H, *J* = 7.3 Hz), 1.25-1.32 (m, 1H), 1.49-1.56 (m, 1H), 1.58-1.67 (m, 2H), 1.91-1.98 (m, 4H), 2.20 (brs, 5H), 2.41-2.44 (m, 1H), 2.58 (t, 2H, *J* = 7.7 Hz), 2.94 (brs, 1H), 3.17 (brs, 1H), 3.31 (brs, 2H), 3.77 (brs, 1H), 4.08 (d, *J* = 13.2 Hz, 1H), 4.42 (brs, 1H), 4.49 (d, *J* = 13.2 Hz, 1H), 7.23 (d, 2H, *J* = 8.0 Hz, ArH), 7.62 (d, 2H, *J* = 8.0 Hz, ArH), 10.10 (brs, 1H, NH^+), 11.07 (brs, 1H, NH_2^+), 11.47 (brs, 1H, NH_2^+).

***N*-(4-Isopropylbenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18l):** Yield: 55%; IR (Film, cm^{-1}): 2958, 2870, 2686, 2491, 2211, 1587, 1516, 1455, 1171, 1056; ^{1}H NMR (400 MHz, $CDCl_3$): 1.23 (d, 6H, *J* = 6.6 Hz), 1.33-1.38 (m, 1H), 1.52-1.59 (m, 2H), 1.91-1.98 (m, 4H), 2.18 (brs, 3H), 2.29-2.31 (m, 1H), 2.43-2.46 (m, 1H), 2.89-2.94 (m, 2H), 3.20 (brs, 1H), 3.30 (brs, 2H), 3.74 (brs, 1H), 4.07 (d, *J* = 13.2 Hz, 1H), 4.40 (brs, 1H), 4.49 (d, *J* = 13.2 Hz, 1H), 7.28 (d, 2H, *J* = 8.0 Hz, ArH), 7.64 (d, 2H, *J* = 7.8 Hz, ArH), 10.12 (s, 1H, NH^+), 11.01 (s, 1H, NH_2^+), 11.47 (s, 1H, NH_2^+); ESI-MS (*m/z*): 301.2 $[M+1 - 2HCl]^+$.

***N*-(4-Butylbenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18m):** Yield: 55%; IR (Film, cm^{-1}): 2932, 2859, 2691, 1630, 1458, 1171, 1022; ^{1}H NMR (400 MHz, $CDCl_3$): 0.92 (t, 3H, *J* = 7.32 Hz), 1.31-1.36 (m, 3H), 1.56-1.59 (m, 4H), 1.92-1.98 (m, 4H), 2.17 (s, 3H), 2.42 (brs, 3H), 2.60 (t, 2H, *J* = 7.32 Hz), 2.95 (s, 1H), 3.18 (s, 1H), 3.32 (brs, 1H), 3.76 (s, 1H), 4.06-4.08 (m, 1H), 4.40 (s, 1H), 4.47-4.50 (m, 1H), 7.23 (d, 2H, *J* = 7.32 Hz, ArH), 7.62 (d, 2H, *J* = 7.32 Hz, ArH), 10.11 (br, 1H, NH^+), 11.02 (br, 1H, NH_2^+), 11.45 (br, 1H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 19.89, 21.15, 22.91, 22.97, 23.67, 27.41, 45.92, 46.69, 51.76, 54.33, 63.01, 63.11, 65.59, 125.70, 127.10, 131.73, 131.92, 137.86, 139.64.

***N*-(4-*Tert*-butylbenzyl)-2-(pyrrolidin-1-yl)cyclohexanamine dihydrochloride (18n):** Yield: 50%; IR (Film, cm^{-1}): 2958, 2869, 2681, 2490, 1587, 1458, 1419, 1269, 1108, 922; ^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (s, 9H), 1.51-1.54 (m, 1H), 1.88-1.95 (m, 4H), 2.15 (brs, 3H), 2.27 (brs, 3H), 2.39-2.42 (m, 1H), 2.92 (brs, 1H), 3.18 (brs, 1H), 3.28 (brs, 2H), 3.74 (brs, 1H), 4.04 (brs, 1H), 4.39-4.47 (m, 2H), 7.41 (d, 2H, *J* = 8.0 Hz, ArH), 7.62 (d, 2H, *J* = 8.0 Hz, ArH), 10.06 (brs, 1H, NH^+), 11.09 (brs, 1H, NH_2^+), 11.47 (brs, 1H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 19.0, 20.36, 22.48, 22.56, 23.22, 26.90, 45.55, 46.28, 51.26, 53.81, 62.26, 62.66, 65.09, 128.03, 130.02, 130.43, 132.19, 134.31, 135.54; ESI-MS (*m/z*): 315.2 $[M+1 - 2HCl]^+$.

***N*-benzyl-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19a): Yield:** 60%; ^{1}H NMR (400 MHz, DMSO-d_6): 1.26-1.28 (m, 1H), 1.39-1.48 (m, 2H), 1.92-1.95 (m, 3H), 2.11-2.14 (m, 4H), 2.31-2.38 (m, 3H), 2.87-2.91 (m, 2H), 3.22 (s, 1H), 3.36 (s, 1H), 3.72 (s, 1H), 3.82 (s, 1H), 4.06 (d, 1H, *J* = 12.9 Hz), 4.32 (s, 1H), 4.45 (d, 1H, *J* = 12.8 Hz), 7.21-7.24 (m, 2H), 7.46-7.49 (m, 3H), 10.26 (s, 1H, NH^+), 11.26 (brs, 2H, NH_2^+).

***N*-(4-Chlorobenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride**

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(19b): Yield: 80%; IR (Nujol, cm^{-1}): 2921, 2853, 1593, 1462, 1455, 1377, 1093, 1014; ^{1}H NMR (400 MHz, DMSO-d_6): 1.17-1.25 (m, 2H), 1.32-1.39 (m, 1H), 1.48-1.53 (m, 1H), 1.63-1.72 (m, 6H), 2.12-2.15 (m, 3H), 2.36-2.39 (m, 1H), 2.88-2.90 (m, 1H), 3.22-3.26 (m, 3H), 3.62 (brs, 1H), 3.72-3.74 (m, 1H), 4.17 (d, 1H, *J* = 12.8 Hz), 4.34 (d, 1H, *J* = 12.5 Hz), 7.45 (d, 2H, *J* = 8.2 Hz, ArH), 7.70 (d, 2H, *J* = 8.24 Hz, ArH), 10.27 (br, 3H, NH^+, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 21.64, 22.22, 22.56, 23.17, 23.23, 26.73, 47.17, 47.80, 53.21, 53.96, 65.49, 128.88, 131.0, 133.05, 134.14; ESI-MS (*m/z*): 307.1 [M+1 - 2HCl]$^+$.

***N*-(3-Chlorobenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19c):** Yield: 65%; IR (Film, cm^{-1}): 2945, 2678, 2398, 1578, 1457, 1212, 1083, 1007; ^{1}H NMR (400 MHz, $CDCl_3$): 1.22-1.25 (m, 1H), 1.39-1.42 (m, 1H), 1.52 (brs, 2H), 1.84-1.91 (m, 4H), 2.20 (brs, 3H), 2.35-2.38 (m, 2H), 2.60 (brs, 1H), 2.81 (brs, 1H), 3.10 (brs, 1H), 3.24 (brs, 1H), 3.43 (brs, 1H), 3.83 (brs, 1H), 4.09 (brs, 1H), 4.46-4.51 (m, 2H), 7.37 (s, 2H, ArH), 7.74-7.78 (m, 2H, ArH), 10.75 (brs, 2H, NH_2^+), 11.53 (brs, 1H, NH^+).

***N*-(4-Bromobenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19d):** Yield: 70%; IR (Nujol, cm^{-1}): 2921, 2853, 2727, 1591, 1455, 1377, 1067, 1011; ^{1}H NMR (400 MHz, DMSO-d_6): 1.16-1.24 (m, 2H), 1.32-1.38 (m, 1H), 1.45-1.53 (m, 1H), 1.61-1.76 (m, 6H), 2.13 (brs, 3H), 2.35-2.38 (m, 1H), 2.88-2.90 (m, 1H), 3.26 (brs, 3H), 3.64 (brs, 1H), 3.74-3.79 (m, 1H), 4.15 (d, 1H, *J* = 12.8 Hz), 4.31 (d, 1H, J=12.4 Hz), 7.56 (d, 2H, *J* = 8.4 Hz, ArH), 7.63 (d, 2H, *J* = 8.2 Hz, ArH), 10.26 (brs, 2H, NH_2^+), 10.44 (brs, 1H, NH^+); ^{13}C NMR (100 MHz, $CDCl_3$): 21.17, 21.74, 22.08, 22.70, 26.30, 46.70, 47.20, 52.72, 53.44, 65.05, 122.41, 130.90, 131.38, 132.83.

***N*-(3-Bromobenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19e):** Yield: 60%; IR (Film, cm^{-1}): 2946, 2676, 2391, 1590, 1455, 1307, 1259, 1214, 1075, 1030, 1009; ^{1}H NMR (400 MHz, $CDCl_3$): 1.17-1.25 (m, 1H), 1.31-1.37 (m, 1H), 1.45-1.54 (m, 2H), 1.80-1.84 (m, 2H), 1.88-1.91 (m, 3H), 2.17-2.19 (m, 1H), 2.27-2.33 (m, 2H), 2.39-2.46 (m, 1H), 2.56-2.66 (m, 1H), 2.80 (t, 1H, *J* = 11.72 Hz), 3.07 (t, 1H, *J* = 11.72 Hz), 3.23-3.26 (m, 1H), 3.42 (brs, 1H), 3.83-3.85 (m, 1H), 4.04 (d, 1H, *J* = 13.1 Hz), 4.46 (d, 1H, *J* = 12.4 Hz), 4.53 (brs, 1H), 7.31 (t, 1H, *J* = 8.05 Hz, ArH), 7.53 (d, 1H, *J* = 8.05 Hz, ArH), 7.79 (d, 1H, *J* = 7.3 Hz, ArH), 7.93 (s, 1H, ArH), 10.79 (brs, 2H, NH_2^+), 11.69 (brs, 1H, NH^+).

***N*-(4-Fluorobenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19f):** Yield: 60%; IR (Film, cm^{-1}): 2945, 2870, 2678, 2396, 1604, 1513, 1457, 1226, 1163, 1009; ^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (brs, 1H), 1.37 (brs, 1H), 1.52 (brs, 2H), 1.83-1.91 (m, 5H), 2.19 (brs, 1H), 2.28 (brs, 1H), 2.37 (brs, 2H), 2.57 (brs, 1H), 2.80 (brs, 1H), 3.08 (brs, 1H), 3.25 (brs, 1H), 3.44 (brs, 1H), 3.82 (brs, 1H), 4.04-4.06 (m, 1H), 4.44-4.46 (m, 1H), 4.52 (brs, 1H), 7.01-7.10 (m, 2H, ArH), 7.79 (m, 2H, ArH), 10.65 (brs, 2H, NH_2^+), 11.50 (brs, 1H, NH^+).

***N*-(3-Fluorobenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19g):** Yield: 55%; IR (Film, cm^{-1}): 2947, 2679, 2394, 1591, 1457, 1306, 1258, 1152, 1030, 1008; ^{1}H NMR (400 MHz, $CDCl_3$): 1.14-1.25 (m, 1H), 1.31-1.37 (m, 1H), 1.45-1.55 (m, 2H), 1.80-1.83 (m, 2H), 1.88-1.91 (m, 3H), 2.17-2.20 (m, 1H), 2.27-2.30 (m, 1H), 2.34-2.45 (m, 2H), 2.56-2.66 (m, 1H), 2.80 (t, 1H, *J* = 12.4 Hz), 3.07 (t, 1H, *J* = 11.0 Hz), 3.26 (d, 1H, *J* = 11.0 Hz), 3.42-3.43 (m, 1H), 3.85 (d, 1H, *J* = 11.7 Hz), 4.06 (d, 1H, *J* = 13.2 Hz), 4.48 (d, 1H, *J* = 13.2 Hz), 4.53-4.55 (m, 1H), 7.07-7.11 (m, 1H, ArH), 7.38-

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7.43 (m, 1H, ArH), 7.54-7.56 (m, 1H, ArH), 7.59 (d, 1H, *J* = 7.3 Hz, ArH), 10.78 (brs, 2H, NH_2^+), 11.66 (brs, 1H, NH^+).

_N_-(4-Methylbenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19h): Yield: 60%; IR (Film, cm^{-1}): 2945, 2869, 2679, 1590, 1457, 1307, 1136, 1031; ^{1}H NMR (400 MHz, $CDCl_3$): 1.15-1.20 (m, 1H), 1.35-1.44 (m, 2H), 1.47-1.54 (m, 1H), 1.73-1.77 (m, 1H), 1.86-1.89 (m, 4H), 2.19-2.21 (m, 3H), 2.25-2.28 (m, 1H), 2.35 (s, 3H), 2.39-2.43 (m, 1H), 2.47-2.54 (m, 1H), 2.75-2.80 (m, 1H), 2.99-3.01 (m, 1H), 3.07-3.13 (m, 1H), 3.29 (brs, 1H), 3.78-3.81 (m, 1H), 4.04 (d, 1H, *J* = 13.1 Hz), 4.48 (d, 1H, *J* = 12.4 Hz), 7.22 (d, 2H, *J* = 8.0 Hz, ArH), 7.63 (d, 2H, *J* = 8.0 Hz, ArH), 10.63 (brs, 2H, NH_2^+), 11.25 (brs, 1H, NH^+); ^{13}C NMR (100 MHz, $CDCl_3$): 21.17, 21.72, 22.09, 22.43, 22.92, 23.0, 23.43, 26.76, 47.60, 47.87, 52.87, 54.05, 65.84, 126.57, 129.80, 130.57, 139.68.

_N_-(3-Methylbenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19i): Yield: 55%; IR (Film, cm^{-1}): 2946, 2869, 2678, 2540, 1590, 1457, 1245, 1008; ^{1}H NMR (400 MHz, $CDCl_3$): 1.15-1.21 (m, 1H), 1.37-1.44 (m, 2H), 1.47-1.53 (m, 1H), 1.73-1.77 (d, 1H, *J* = 13.91 Hz), 1.82-1.88 (m, 4H), 2.18-2.22 (m, 3H), 2.25-2.31 (m, 1H), 2.38 (s, 3H), 2.45-2.52 (m, 1H), 2.78 (t, 1H, *J* = 11.0 Hz), 2.92-2.94 (m, 1H), 3.11 (t, 1H, *J* = 11.7 Hz), 3.26-3.27 (m, 1H), 3.76-3.79 (m,1H), 4.04 (d, 1H, *J* = 13.18 Hz), 4.43 (brs, 1H), 4.50 (d, 1H, *J* = 13.91 Hz), 7.21 (d, 1H, *J* = 7.3 Hz, ArH), 7.31 (t, 1H, *J* = 7.3 Hz, ArH), 7.53-7.56 (m, 2H, ArH), 10.69 (brs, 2H, NH_2^+), 11.27 (brs, 1H, NH^+).

_N_-(4-Ethylbenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19j): Yield: 50%; IR (Film, cm^{-1}): 2934, 2871, 2677, 1589, 1455, 1307, 1136, 1008, 922; ^{1}H NMR (400 MHz, $CDCl_3$): 1.23 (brs, 4H), 1.42 (brs, 1H), 1.54 (brs, 1H), 1.75 (brs, 1H), 1.87 (brs, 4H), 2.26 (brs, 3H), 2.41 (brs, 4H), 2.65-2.66 (m, 2H), 2.95 (brs, 1H), 3.13 (brs, 1H), 3.30 (brs, 1H), 3.78 (brs, 1H), 4.05 (brs, 1H), 4.48 (brs, 2H), 7.27 (s, 2H, ArH), 7.66 (s, 2H, ArH), 10.67 (brs, 2H, NH_2^+), 11.24 (brs, 1H, NH^+); ESI-MS (*m/z*): 301.2 [M+1 - 2HCl]$^+$.

2-(Piperidin-1-yl)-_N_-(4-propylbenzyl)cyclohexanamine dihydrochloride (19k): Yield: 50%; IR (Film, cm^{-1}): 2949, 2870, 2680, 1614, 1588, 1454, 1378, 1008; ^{1}H NMR (400 MHz, $CDCl_3$): 0.93 (t, 3H, *J* = 7.32 Hz), 1.17 (brs, 1H), 1.36 (brs, 2H), 1.52 (brs, 1H), 1.60-1.65 (m, 2H), 1.71-1.74 (m, 1H), 1.85-1.89 (m, 6H), 2.17 (brs, 2H), 2.36 (brs, 2H), 2.58 (t, 2H, *J* = 7.32 Hz), 2.70 (brs, 1H), 3.04 (brs, 2H), 3.25 (brs, 1H), 3.76 (brs, 1H), 4.02 (d, 1H, *J* = 13.1 Hz), 4.48 (d, 1H, *J* = 12.5 Hz), 7.23 (d, 2H, *J* = 7.3 Hz, ArH), 7.63 (d, 2H, *J* = 7.0 Hz, ArH), 10.80 (brs, 2H, NH_2^+), 11.42 (brs, 1H, NH^+); ^{13}C NMR (100 MHz, $CDCl_3$): 13.72, 21.84, 22.23, 22.53, 23.04, 24.22, 26.74, 37.62, 47.78, 47.95, 53.01, 54.19, 65.86, 126.87, 129.22, 130.63, 144.44.

_N_-(4-Isopropylbenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19l): Yield: 55%; IR (Film, cm^{-1}): 2932, 2869, 2677, 1615, 1458, 825; ^{1}H NMR (400 MHz, $CDCl_3$): 1.23 (d, 7H, *J* = 6.8 Hz), 1.39-1.45 (m, 3H), 1.65-1.68 (m, 1H), 1.80-1.83 (m, 2H), 1.87-1.89 (m, 2H), 2.20 (brs, 4H), 2.38-2.41 (m, 1H), 2.71 (brs, 2H), 2.87-2.94 (m, 1H), 3.09 (brs, 1H), 3.23 (brs, 1H), 3.61 (brs, 1H), 4.04 (d, 1H, *J* = 13.2 Hz), 4.19 (brs, 1H), 4.49 (d, 1H, *J* = 12.8 Hz), 7.28 (d, 2H, *J* = 7.3 Hz, ArH), 7.62 (d, 2H, *J* = 7.3 Hz, ArH), 10.48 (brs, 3H, NH^+, NH_2^+).

_N_-(4-Butylbenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19m): Yield: 45%; IR (Film, cm^{-1}): 2952, 2869, 2674, 2569, 1589, 1455, 1418, 1365, 1245, 1009; ^{1}H NMR (400 MHz, $CDCl_3$): 1.15-1.20 (m, 1H), 1.30 (s, 9H), 1.54-1.56

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(m, 1H), 1.72-1.76 (m, 1H), 1.82-1.91 (m, 4H), 2.20 (brs, 1H), 2.28 (s, 3H), 2.38 (brs, 2H), 2.53-2.56 (m, 1H), 2.76 (brs, 1H), 2.99 (brs, 1H), 3.08 (brs, 1H), 3.32 (brs, 1H), 3.82-3.84 (m, 1H), 4.02 (d, 1H, *J* = 12.4 Hz), 4.48 (d, 1H, *J* = 12.4 Hz), 4.55 (brs, 1H), 7.44 (d, 2H, *J* = 8.0 Hz, ArH), 7.68 (d, 2H, *J* = 8.0 Hz, ArH), 10.60 (brs, 1H, NH_2^+), 10.80 (brs, 1H, NH_2^+), 11.37 (s, 1H, NH^+); ^{13}C NMR (100 MHz, $CDCl_3$): 21.73, 22.30, 22.45, 23.09, 23.99, 27.18, 31.15, 34.68, 48.0, 53.06, 54.10, 65.76, 126.18, 126.57, 130.61, 153.0; ESI-MS (*m/z*): 329.2 $[M+1 - 2HCl]^+$.

***N*-(4-*Tert*-butylbenzyl)-2-(piperidin-1-yl)cyclohexanamine dihydrochloride (19n):** Yield: 40%; IR (Film, cm^{-1}): 2934, 2856, 2807, 1591, 1458, 1269, 1109, 1160, 1036, ^{1}H NMR (400 MHz, $CDCl_3$): 1.01-1.07 (m, 1H), 1.11-1.18 (m, 2H), 1.31 (s, 10H), 1.34-1.36 (m, 1H), 1.63 (brs, 2H), 1.78-1.81 (m, 2H),1.86-1.90 (m, 3H), 2.02-2.10 (m, 1H), 2.26-2.29 (m, 1H), 2.46 (brs, 1H), 2.64-2.71 (m, 3H), 3.85 (d, 1H, *J* = 13.9 Hz), 4.42 (d, 1H, *J* = 13.9 Hz), 7.30 (d, 2H, *J* = 8.0 Hz, ArH),7.45 (d, 2H, *J* = 8.0 Hz, ArH), 10.78 (br, 3H, NH^+, NH_2^+).

***N*-Benzyl-2-morpholinocyclohexanamine dihydrochloride** (**20a**): Yield: 70%; IR (Film, cm^{-1}): 2924, 2854, 2420, 1596, 1454, 1260, 1112, 1045, 986; ^{1}H NMR (400 MHz, $CDCl_3$): 1.16-1.21 (m, 1H), 1.44-1.46 (m, 2H), 1.85-1.88 (m, 2H), 2.15-2.17 (m, 3H), 2.37-2.40 (m, 1H), 2.92-2.98 (m, 2H), 3.26 (brs, 1H), 3.39 (brs, 1H), 3.68-3.70 (m, 1H), 3.86 (t, 2H, *J* = 13.74 Hz), 4.04 (d, 1H, *J* = 12.82 Hz), 4.27-4.33 (m, 1H), 4.43 (d, 2H, *J* = 12.82 Hz), 7.16 (d, 1H, *J* = 7.79 Hz, ArH), 7.26 (d, 1H, *J* = 7.33 Hz, ArH), 7.49 (s, 3H, ArH), 10.42 (br, 1H, NH^+), 11.15 (br, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 21.21, 22.70, 22.81, 23.75, 26.48, 46.73, 48.25, 51.96, 53.12, 62.99, 63.21, 65.75, 127.55, 128.91, 129.65, 130.32, 131.22, 138.90.

***N*-(4-Chlorobenzyl)-2-morpholinocyclohexanamine dihydrochloride (20b**): Yield: 75%; IR (Film, cm^{-1}): 2932, 2680, 2363, 1605, 1458, 1114, 1093, 1051; ^{1}H NMR (400 MHz, $CDCl_3$): 1.25-1.28 (m, 1H), 1.45-1.52 (m, 2H), 1.92 (brs, 2H), 2.11-2.14 (m, 1H), 2.19 (brs, 1H), 2.39-2.42 (m, 1H), 3.07 (brs, 1H), 3.30 (brs, 2H), 3.64-3.70 (m, 2H), 3.93 (brs, 2H), 4.16 (d, 1H, *J* = 12.8 Hz), 4.30 (brs, 2H), 4.41 (d, 2H, *J* = 12.8 Hz), 7.37 (d, 2H, *J* = 8.2 Hz, ArH), 7.72 (d, 2H, *J* = 8.2 Hz, ArH), 10.0 (brs, 1H, NH^+), 11.24 (brs, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 23.16, 24.42, 26.59, 47.71, 54.22, 63.79, 66.36, 128.35, 129.24, 132.31, 135.79.

***N*-(3-Chlorobenzyl)-2-morpholinocyclohexanamine dihydrochloride (20c):** Yield: 60%; IR (Film, cm^{-1}): 2942, 2867, 2709, 1637, 1456, 1211, 1113; ^{1}H NMR (400 MHz, $CDCl_3$): 1.22-1.25 (m, 1H), 1.48-1.50 (m, 2H), 1.92-1.95 (m, 3H), 2.20 (brs, 2H), 2.36-2.39 (m, 1H), 3.05 (brs, 1H), 3.26 (brs, 2H), 3.47 (brs, 1H), 3.78 (brs, 1H), 3.93 (brs, 2H), 4.06 (d, 1H, *J* = 12.4 Hz), 4.30 (brs, 1H), 4.45 (d, 1H, *J* = 11.7 Hz), 4.54 (brs, 1H), 7.37-7.38 (m, 2H, ArH), 7.70-7.74 (m, 2H, ArH), 10.51 (brs, 1H, NH^+), 11.66 (brs, 2H, NH_2^+).

***N*-(4-Bromobenzyl)-2-morpholinocyclohexanamine dihydrochloride** (**20d)**: Yield: 65%; IR (Film, cm^{-1}): 2937, 2866, 2679, 2362, 1597, 1452, 1114, 1070, 1013; ^{1}H NMR (400 MHz, $CDCl_3$): 1.25-1.27 (m, 1H), 1.46-1.51 (m, 2H), 1.91-1.93 (m, 2H), 2.12-2.19 (m, 2H), 2.38-2.41 (m, 1H), 3.06 (brs, 1H), 3.29 (brs, 2H), 3.60 (brs, 1H), 3.71 (brs, 1H), 3.94 (brs, 2H), 4.12 (d, 1H, *J* = 12.8 Hz), 4.29 (brs, 2H), 4.39 (d, 2H, *J* = 12.4 Hz), 7.53 (d, 2H, *J* = 8.2 Hz, ArH),

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7.66 (d, 2H, *J* = 8.2 Hz, ArH), 11.22 (brs, 3H, NH^+, NH_2^+).

***N*-(3-Bromobenzyl)-2-morpholinocyclohexanamine dihydrochloride (20e):** Yield: 60%; IR (Film, cm^{-1}): 2924, 2854, 2537, 1570, 1460, 1377, 1113, 1075; ^1H NMR (400 MHz, $CDCl_3$): 1.05-1.11 (m, 1H), 1.22-1.37 (m, 2H), 1.72 (brs, 2H), 1.93-1.99 (m, 2H), 2.20-2.22 (m, 1H), 2.86 (brs, 1H), 3.15 (brs, 2H), 3.34 (brs, 1H), 3.46 (brs, 1H), 3.75 (brs, 3H), 3.95 (d, 1H, *J* = 12.8 Hz), 4.06 (brs, 2H), 4.20 (d, 1H, *J* = 12.8 Hz), 7.11 (t, 1H, *J* = 7.7 Hz, ArH), 7.32 (d, 1H, *J* = 7.4 Hz, ArH), 7.57 (d, 1H, *J* = 7.7 Hz, ArH), 7.76 (s, 1H, ArH), 10.53 (brs, 3H, NH^+, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 20.96, 21.31, 21.41, 24.75, 45.72, 52.42, 62.02, 63.79, 120.55, 128.0, 128.86, 130.49, 131.71, 132.06.

***N*-(4-Fluorobenzyl)-2-morpholinocyclohexanamine dihydrochloride (20f):** Yield: 65%; IR (Film, cm^{-1}): 2927, 2786, 2735, 2588, 1605, 1519, 1229, 1114, 1048; ^1H NMR (400 MHz, $CDCl_3$): 1.05-1.07 (m, 1H), 1.28 (brs, 2H), 1.71 (brs, 2H), 1.93-1.96 (m, 2H), 2.19 (brs, 1H), 2.87 (brs, 1H), 3.12 (brs, 3H), 3.40 (brs, 2H), 3.73 (brs, 2H), 3.90 (d, 1H, *J* = 12.4 Hz), 4.03 (brs, 2H), 4.18 (d, 1H, *J* = 12.4 Hz), 6.88 (m, 2H, ArH), 7.59 (m, 2H, ArH), 10.49 (brs, 3H, NH^+, NH_2^+).

***N*-(3-Fluorobenzyl)-2-morpholinocyclohexanamine dihydrochloride (20g):** Yield: 60%; ^1H NMR (400 MHz, $CDCl_3$): 1.06-1.13 (m, 1H), 1.27-1.35 (m, 2H), 1.73 (s, 2H), 1.92-2.0 (m, 2H), 2.21-2.24 (m, 1H), 2.88 (s, 1H), 3.16 (s, 2H), 3.25 (s, 1H), 3.54 (s, 1H), 3.77 (brs, 3H), 3.97 (d, 1H, *J* = 12.91 Hz), 4.08 (brs, 2H), 4.22 (d, 1H, *J* = 12.82 Hz), 7.13 (t, 1H, *J* = 7.32 Hz, ArH), 7.34 (d, 1H, *J* = 7.39 Hz, ArH), 7.59 (d, 1H, *J* = 7.8 Hz, ArH), 7.79 (s, 1H, ArH), 10.55 (br, 3H, NH^+, NH_2^+).

***N*-(4-Methylbenzyl)-2-morpholinocyclohexanamine dihydrochloride (20h)**: Yield: 55%; IR (Film, cm^{-1}): 2940, 2787, 2549, 1593, 1448, 1420, 1119, 1048; ^1H NMR (400 MHz, $CDCl_3$): 1.17-1.20 (m, 1H), 1.37-1.53 (m, 2H), 1.86-1.89 (m, 2H), 2.12-2.18 (m, 3H), 2.31 (s, 3H), 2.36-2.40 (m, 1H), 3.0 (brs, 2H), 3.25 (brs, 1H), 3.38 (brs, 1H), 3.74-3.76 (m, 1H), 3.86 (t, 2H, *J* = 12.8 Hz), 4.02 (d, 1H, *J* = 12.8 Hz), 4.27-4.33 (m, 1H), 4.42 (d, 1H, *J* = 12.8 Hz), 4.50 (brs, 1H), 7.18 (d, 2H, *J* = 7.8 Hz, ArH), 7.57 (d, 2H, *J* = 8.0 Hz, ArH), 10.43 (brs, 1H, NH^+), 11.32 (brs, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 20.68, 22.24, 22.45, 23.12, 26.01, 47.48, 52.77, 62.86, 65.40, 126.51, 129.14, 130.08, 138.06.

***N*-(3-Methylbenzyl)-2-morpholinocyclohexanamine dihydrochloride (20i)**: Yield: 55%; ^1H NMR (400 MHz, $CDCl_3$): 1.12-1.15 (m, 1H), 1.21-1.33 (m, 2H), 1.56-1.69 (m, 2H), 1.98 (brs, 3H), 2.25 (brs, 3H), 2.39-2.42 (m, 1H), 2.99 (brs, 2H), 3.11 (brs, 1H), 3.45 (brs, 1H), 3.65-3.69 (m, 1H), 3.78-3.90 (m, 2H) 4.22 (d, 1H, *J* = 12.9 Hz), 4.38-4.40 (m, 1H), 4.41 (d, 1H, *J* = 12.9 Hz), 4.48 (brs, 1H), 7.21 (t, 1H, *J* = 7.7 Hz, ArH), 7.48 (d, 1H, *J* = 7.6 Hz, ArH), 7.52 (d, 1H, *J* = 7.7 Hz), 7.63 (s, 1H), 10.56 (brs, 1H, NH^+), 11.14 (brs, 2H, NH_2^+)

***N*-(4-Ethylbenzyl)-2-morpholinocyclohexanamine dihydrochloride (20j):** Yield: 50%; IR (Film, cm^{-1}): 2937, 2785, 2538, 1590, 1578, 1428, 1109, 1046, 1025; ^1H NMR (400 MHz, $CDCl_3$): 1.13-1.17 (m, 4H), 1.43 (brs, 2H), 1.83-1.85 (m, 2H), 2.14 (brs, 3H), 2.35-2.38 (m, 1H), 2.57 (q, 2H, *J* = 7.33 Hz), 2.93 (brs, 2H), 3.22 (brs, 1H), 3.37 (brs, 1H), 3.66 (brs, 1H), 3.78-3.86 (m, 2H), 4.0 (d, 1H, *J* = 12.4 Hz), 4.25 (brs, 1H), 4.39 (d, 2H, J = 12.8 Hz), 7.17 (d, 2H, *J* = 7.8 Hz, ArH), 7.56 (d, 2H, *J* = 7.6 Hz, ArH), 10.34 (brs, 1H, NH^+),

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11.22 (brs, 2H, NH_2^+); ESI-MS (*m/z*): 303.2 $[M+1 - 2HCl]^+$.

Morpholino-*N*-(4-propylbenzyl)cyclohexanamine dihydrochloride (20k): Yield: 50%; IR (Film, cm^{-1}): 2940, 2773, 2617, 2550, 1593, 1458, 1425, 1112, 1049; ^1H NMR (400 MHz, $CDCl_3$): 0.90 (t, 3H, *J* = 7.3 Hz), 1.22 (brs, 1H), 1.48 (brs, 2H), 1.56-1.65 (m, 2H), 1.87-1.89 (m, 2H), 2.19 (brs, 2H), 2.39-2.42 (m, 1H), 2.54 (t, 2H, *J* = 7.3 Hz), 2.98 (brs, 2H), 3.28 (brs, 1H), 3.41 (brs, 1H), 3.73 (brs, 1H), 3.83-3.91 (m, 2H), 4.05 (d, 1H, *J* = 11.7 Hz), 4.28-4.34 (m, 1H), 4.44 (d, 2H, *J* = 12.4 Hz), 4.49 (brs, 1H), 7.19 (d, 2H, *J* = 7.32 Hz, ArH), 7.60 (d, 2H, *J* = 7.32 Hz, ArH), 10.41 (brs, 1H, NH^+), 11.19 (brs, 2H, NH_2^+).

***N*-(4-Isopropylbenzyl)-2-morpholinocyclohexanamine dihydrochloride (20l):** Yield: 55%; IR (Film, cm^{-1}): 2959, 2871, 2679, 1629, 1457, 1114, 1053; ^1H NMR (400 MHz, $CDCl_3$): 1.20 (d, 6H, *J* = 6.6 Hz), 1.24-1.26 (m, 1H), 1.50 (brs, 2H), 1.88 (brs, 2H), 2.20 (brs, 2H), 2.41 (brs, 1H), 2.85-2.89 (m, 1H), 3.03 (brs, 2H), 3.29 (brs, 1H), 3.46 (brs, 1H), 3.74 (brs, 1H), 3.87-3.90 (m, 2H), 4.05 (brs, 1H), 4.31 (brs, 1H), 4.43 (brs, 2H), 4.53 (brs, 1H), 7.25 (s, 2H, ArH), 7.61 (s, 2H, ArH), 10.40 (brs, 1H, NH^+), 11.21 (brs, 2H, NH_2^+).

***N*-(4-Butylbenzyl)-2-morpholinocyclohexanamine dihydrochloride (20m):** Yield: 50%; IR (Film, cm^{-1}): 2928, 2856, 2708, 1636, 1457, 1114, 1051; ^1H NMR (400 MHz, $CDCl_3$): 0.92 (t, 3H, *J* = 7.3 Hz), 1.20-1.25 (m, 1H), 1.29-1.39 (m, 2H), 1.44-1.49 (m, 1H), 1.54-1.61 (m, 3H), 1.90-1.93 (m, 2H), 2.21 (brs, 2H), 2.40-2.43 (m, 1H), 2.60 (t, 2H, *J* = 7.3 Hz), 3.01 (brs, 2H), 3.27 (brs, 1H), 3.40 (brs, 1H), 3.79 (brs, 1H), 3.85-3.93 (m, 2H), 4.02 (d, 1H, *J* = 12.4 Hz), 4.33 (brs, 1H), 4.46 (d, 2H, *J* = 13.2 Hz), 4.58 (brs, 1H), 7.27 (d, 2H, *J* = 7.8 Hz, ArH), 7.62 (d, 2H, *J* = 7.3 Hz, ArH), 10.37 (brs, 1H, NH^+), 11.50 (brs, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 13.75, 22.19, 22.65, 22.77, 23.83, 26.54, 33.18, 35.18, 46.77, 48.11, 52.03, 53.06, 62.87, 63.10, 65.86, 126.78, 129.78, 130.65, 144.58.

***N*-(4-*Tert*-butylbenzyl)-2-morpholinocyclohexanamine dihydrochloride (20n):** Yield: 45%; IR (Film, cm^{-1}): 2962, 2872, 2711, 1634, 1455, 1365, 1269, 1112, 1051; ^1H NMR (400 MHz, $CDCl_3$): 1.26 (s, 10H), 1.49 (brs, 2H), 1.87-1.91 (m, 2H), 2.15-2.21 (m, 2H), 2.40-2.43 (m, 1H), 2.89-2.91 (m, 1H), 3.03 (brs, 1H), 3.29 (t, 1H, *J* = 10.9 Hz), 3.44 (brs, 1H), 3.73 (d, 1H, *J* = 11.9 Hz), 3.82 (d, 1H, *J* = 12.3 Hz), 3.89 (d, 1H, *J* = 11.9 Hz), 4.05 (d, 1H, *J* = 12.8 Hz), 4.28-4.36 (m, 1H), 4.39-4.46 (m, 2H), 4.52 (brs, 1H), 7.39 (d, 2H, *J* = 8.2 Hz, ArH), 7.62 (d, 2H, *J* = 8.2 Hz, ArH), 10.40 (brs, 1H, NH^+), 11.17 (brs, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 22.51, 22.67, 23.66, 26.47, 30.97, 34.48, 46.62, 47.86, 51.88, 52.89, 62.79, 62.98, 65.69, 125.86, 126.52, 130.33, 152.65.

***N*-Benzyl-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21a)**: Yield: 60%; IR (Film, cm^{-1}): 2943, 2862, 2677, 2252, 2126, 1654, 1458, 1187, 1050, 1026, 1006; ^1H NMR (400 MHz, $CDCl_3$): 0.79-0.84 (m, 2H), 1.0-1.02 (m, 1H), 1.53-1.56 (m, 3H), 1.71 (brs, 1H), 1.92 (brs, 1H), 2.0 (brs, 1H), 2.35 (brs, 1H), 2.58 (s, 6H), 2.96 (brs, 1H), 3.08-3.11 (m, 2H), 3.26 (brs, 1H), 3.73 (brs, 2H), 4.34-4.38 (m, 1H), 7.17-7.19 (m, 3H, ArH), 7.50-7.51 (m, 2H, ArH), 8.57 (brs, 1H, NH^+), 9.74 (brs, 1H, NH^+), 11.59 (brs, 2H, NH_2^+) ^{13}C NMR (100 MHz, $CDCl_3$): 23.20, 23.39, 26.03, 41.47, 42.68, 46.03, 51.80, 52.0, 53.21, 63.83, 128.70, 129.19, 129.76, 130.26.

***N*-(4-Chlorobenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine**

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trihydrochloride (21b): Yield: 70%; IR (Film, cm^{-1}): 2938, 2856, 2699, 1623, 1458, 1186, 1091, 986; ^{1}H NMR (400 MHz, $CDCl_3$): 1.08-1.14 (m, 2H), 1.25-1.33 (m, 1H), 1.82-1.95 (m, 2H), 2.04-2.0 (m, 2H), 2.24-2.31 (m, 2H), 2.69 (brs, 1H), 2.84 (s, 3H), 3.02 (brs, 1H), 3.14 (brs, 2H), 3.29-3.32 (m, 1H), 3.41-3.44 (m, 2H), 3.56 (brs, 1H), 3.94 (d, 2H, *J* = 12.4 Hz), 4.49 (d, 1H, *J* = 13.1 Hz),7.40 (d, 2H, *J* = 8.0 Hz, ArH), 7.70 (d, 2H, *J* = 8.8 Hz, ArH), 9.09 (brs, 1H, NH^+), 10.54 (brs, 1H, NH^+), 12.26 (brs, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 22.68, 23.31, 24.0, 26.45, 42.93, 42.31, 52.11, 45.15, 52.40, 54.11, 63.25, 128.75, 131.25, 132.20, 133.68; ESI-MS (*m/z*): 322.2 $[M+1 - 2HCl]^+$.

***N*-(3-Chlorobenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21c)**: Yield: 65%; IR (Film, cm^{-1}): 2939, 2852, 2702, 1634, 1457, 986; 1.04-1.09 (m, 2H), 1.25-1.30 (m, 1H), 1.78-1.88 (m, 2H), 1.95-2.01 (m, 2H), 2.08-2.11 (m, 1H), 2.21-2.24 (m, 3H), 2.55 (brs, 1H), 2.86 (s, 3H), 2.94-3.0 (m, 1H), 3.27-3.30 (m, 1H), 3.41 (brs, 3H), 3.92-3.95 (m, 2H), 4.59 (d, 1H, *J* = 13.2 Hz), 7.36-7.43 (m, 2H, ArH), 7.50 (d, 1H, *J* = 6.8 Hz, ArH), 7.95 (s, 1H, ArH), 8.97 (brs, 1H, NH^+), 10.46 (brs, 1H, NH^+), 12.0 (brs, 2H, NH_2^+).

***N*-(4-Bromobenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21d)**: Yield: 60%; IR (Film, cm^{-1}): 2918, 2850, 1735, 1462, 1052; ^{1}H NMR (400 MHz, $CDCl_3$): 1.10 (brs, 3H), 1.46-1.54 (m, 1H), 1.65 (brs, 2H), 1.73 (brs, 1H), 2.16-2.18 (m, 1H), 2.47-2.49 (m, 2H), 2.67-2.68 (m, 3H), 2.72-2.75 (m, 2H), 2.95 (brs, 1H), 3.16-3.19 (m, 2H), 3.22-3.25 (m, 2H), 3.30 (brs, 1H), 4.09-4.14 (m, 1H), 4.20-4.23 (m, 1H), 7.61-7.67 (m, 4H, ArH), 9.35 (brs, 2H, $2NH^+$), 11.04 (brs, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 22.69, 23.31, 24.01, 26.47, 41.94, 45.24, 48.65, 52.17, 54.16, 55.16, 63.26, 79.58, 122.41, 131.68, 132.50.

***N*-(3-Bromobenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21e)**: Yield: 50%; IR (Film, cm^{-1}): 2943, 2854, 2255, 1654, 1459, 1187, 1049, 1025, 1005; ^{1}H NMR (400 MHz, $CDCl_3$): 0.89-0.98 (m, 2H), 1.08-1.14 (m, 1H), 1.65-1.71 (m, 3H), 1.83-1.86 (m, 1H), 2.04-2.12 (m, 2H), 2.45 (brs, 1H), 2.71 (s, 4H), 2.79-2.84 (m, 1H), 3.13-3.16 (m, 1H), 3.20-3.23 (m, 1H), 3.27-3.30 (m, 1H), 3.38-3.40 (m, 1H), 3.83 (d, 2H, *J* = 12.4 Hz), 4.46 (d, 2H, *J* = 13.9 Hz), 7.18 (t, 1H, *J* = 8.0 Hz, ArH), 7.42 (d, 1H, *J* = 8.0 Hz, ArH), 7.48 (d, 1H, J = 6.9 Hz, ArH), 7.93 (s, 1H, ArH), 8.87 (brs, 1H, NH^+), 10.04 (brs, 1H, NH^+), 11.81 (brs, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 22.40, 22.58, 22.83, 25.39, 40.97, 41.99, 44.60, 51.46, 51.59, 53.11, 62.94, 121.63, 128.05, 129.69, 131.33, 131.69, 132.56.

***N*-(4-Fluorobenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21f)**: Yield: 50%; IR (Film, cm^{-1}): 2922, 2857, 2359, 1604, 1462, 1377, 1224, 1008; ^{1}H NMR (400 MHz, $CDCl_3$): 1.06-1.13 (m, 3H), 1.48-1.56 (m, 1H), 1.65 (brs, 2H), 1.73 (brs, 1H), 2.17-2.20 (m, 1H), 2.47-2.49 (m, 2H), 2.66-2.67 (d, 3H, *J* = 3.68 Hz), 2.74 (brs, 3H), 2.97 (brs, 1H), 3.16-3.22 (m, 2H), 3.31 (s, 2H), 4.22-4.25 (d, 1H, *J* = 13.3 Hz), 4.11-4.14 (m, 1H), 7.22-7.26 (m, 2H, ArH), 7.75-7.78 (m, 2H, ArH), 8.89 (brs, 1H, NH^+), 9.68 (brs, 1H, NH^+), 11.13 (brs, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 22.72, 23.36, 24.03, 26.49, 41.91, 42.35, 45.17, 48.67, 52.20, 52.43, 54.03, 63.26, 115.59, 115.80, 128.50, 132.61, 161.21, 163.65.

***N*-(3-Fluorobenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21g)**: Yield: 55%; IR (Film, cm^{-1}): 2923, 2853, 1612, 1455,

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1377, 1236, 1168; ^{1}H NMR (400 MHz, $CDCl_3$): 0.85-0.88 (m, 2H), 1.04-1.07 (m, 1H), 1.57-1.60 (m, 3H), 1.75-1.77 (m, 1H), 1.98-2.0 (m, 1H), 2.06-2.09 (m, 1H), 2.38-2.45 (m, 2H), 2.63(s, 4H), 2.71-2.76 (m, 1H), 3.04-3.06 (m, 1H), 3.15-3.17 (m, 2H), 3.35 (brs, 1H), 3.80-3.83 (m, 2H), 4.38-4.41 (d, 1H, *J* = 13.16 Hz), 6.91 (t, 1H, *J* = 8.0 Hz, ArH), 7.20-7.25 (m, 1H, ArH), 7.30 (d, 1H, *J* = 6.6 Hz, ArH), 7.44 (d, 1H, *J* = 8.0 Hz, ArH), 8.75 (brs, 1H, NH^+), 9.97 (brs, 1H, NH^+), 11.65 (brs, 2H, NH_2^+).

_N_-(4-Methylbenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21h): Yield: 70%; IR : 2927, 2854, 2701, 1628, 1457, 1187, 1115; ^{1}H NMR (400 MHz, $CDCl_3$): 1.18-1.37 (m, 4H), 1.85 (brs, 2H), 1.99-2.02 (m, 1H), 2.10-2.12 (m, 1H), 2.32 (brs, 1H), 2.36 (s, 3H), 2.89 (s, 3H), 3.08 (brs, 1H), 3.36 (brs, 3H), 3.51-3.53 (m, 1H), 3.71 (brs, 3H), 4.01 (brs, 2H), 4.45 (d, 1H, *J* = 12.8 Hz)), 7.21 (d, 2H, *J* = 7.8 Hz, ArH), 7.59 (d, 2H, *J* = 7.8 Hz, ArH), 9.20 (brs, 1H, NH^+), 10.44 (brs, 1H, NH^+), 12.12 (brs, 2H, NH_2^+).

_N_-(3-Methylbenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21i): Yield: 55%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.95-1.11 (m, 2H), 1.22-1.32 (m, 1H), 1.76-1.83 (m, 2H), 1.88-1.94 (m, 2H), 2.02 (brs, 4H), 2.22-2.25 (m, 1H), 2.37 (s, 3H), 2.53 (brs, 1H), 2.87 (s, 3H), 3.20 (brs, 1H), 3.28-3.34 (m, 3H), 3.88 (d, 1H, *J* = 12.5 Hz), 3.96 (brs, 1H), 4.58 (d, 1H, *J* = 12.5 Hz), 7.23 (d, 1H, *J* = 8.0 Hz, ArH), 7.31 (t, 1H, *J* = 8.0 Hz, ArH), 7.50 (s, 2H, ArH), 8.58 (brs, 1H, NH^+), 10.22 (brs, 1H, NH^+), 11.89 (brs, 2H, NH_2^+).

_N_-(4-Ethylbenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21j): Yield: 55%; IR (Film, cm^{-1}): 2940, 2863, 2719, 1634, 1456, 1187, 1115; ^{1}H NMR (400 MHz, $CDCl_3$): 1.19-1.23 (m, 4H), 1.27-1.34 (m, 2H), 1.84 (brs, 2H), 1.98-2.01 (m, 1H), 2.12 (brs, 1H), 2.32 (brs, 1H), 2.65 (q, 2H, *J* = 7.3 Hz), 2.74 (brs, 1H), 2.89 (s, 3H), 3.08 (brs, 1H), 3.37 (brs, 3H), 3.56 (brs, 2H), 3.71 (brs, 2H), 4.02 (brs, 2H), 4.47 (d, 1H, *J* = 11.5 Hz), 7.23 (d, 2H, *J* = 7.3 Hz, ArH), 7.61 (d, 2H, *J* = 7.3 Hz, ArH), 9.18 (brs, 1H, NH^+), 10.41 (brs, 1H, NH^+), 12.04 (brs, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 15.29, 23.43, 26.69, 28.39, 43.16, 47.79, 48.53, 50.92, 54.21, 65.32, 127.42, 128.34, 130.58, 145.82; ESI-MS (*m/z*): 316.2 $[M+1 - 2HCl]^+$.

2-(4-Methylpiperazin-1-yl)-_N_-(4-propylbenzyl)cyclohexanamine trihydrochloride (21k): Yield: 50%; IR (Film, cm^{-1}): 2956, 2866, 2711, 1635, 1458, 1187, 1115, 985; ^{1}H NMR (400 MHz, $CDCl_3$): 0.92 (t, 3H, *J* = 7.3 Hz), 1.14 (brs, 2H), 1.31 (brs, 1H), 1.58-1.63 (m, 2H), 1.83 (brs, 2H), 1.95-1.98 (m, 1H), 2.04 (brs, 1H), 2.28-2.30 (m, 2H), 2.58 (t, 2H, *J* = 7.3 Hz), 2.87 (s, 3H), 3.12 (brs, 2H), 3.27 (brs, 2H), 3.48 (brs, 3H), 3.98 (brs, 2H), 4.49-4.52 (m, 2H), 7.21 (d, 2H, *J* = 6.6 Hz, ArH), 7.60 (d, 2H, *J* = 6.0 Hz, ArH), 8.90 (brs, 1H, NH^+), 10.30 (brs, 1H, NH^+), 11.92 (brs, 2H, NH_2^+); ^{13}C NMR (100 MHz, $CDCl_3$): 13.70, 23.60, 24.32, 26.56, 29.60, 37.55, 42.41, 43.31, 46.94, 51.75, 51.97, 53.72, 64.64, 127.59, 129.16, 130.30, 144.54.

_N_-(4-Isopropylbenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21l): Yield: 55%; IR (Film, cm^{-1}): 2930, 2855, 2678, 1618, 1452, 1187, 1115, 1054; ^{1}H NMR (400 MHz, $CDCl_3$): 1.12-1.17 (m, 1H), 1.22 (d, 6H, *J* = 7.3 Hz), 1.29-1.36 (m, 1H), 1.81-1.88 (m, 2H), 1.97-2.03 (m, 1H), 2.08-2.10 (m, 1H), 2.30-2.33 (m, 1H), 2.44 (brs, 1H), 2.86 (s, 3H), 2.89-2.94 (m, 1H), 3.27 (brs, 3H), 3.46-3.49 (m, 3H), 3.56-3.64 (m, 3H), 3.96 (brs, 2H), 4.48 (d, 1H, *J* = 12.5 Hz), 7.26 (d, 2H, *J* = 7.3 Hz, ArH), 7.61 (d, 2H, *J* = 7.3 Hz, ArH), 9.05 (brs, 1H, NH^+),

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10.43 (brs, 1H, NH^+), 12.13 (brs, 2H, NH_2^+).

***N*-(4-Butylbenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21m)**: Yield: 50%; IR (Film, cm^{-1}): 2930, 2857, 2678, 1623, 1458, 1187, 1115, 1053, 986; ^{1}H NMR (400 MHz, $CDCl_3$): 0.90-0.93 (t, 3H, *J* = 7.3 Hz), 1.25 (brs, 2H), 1.30-1.36 (m, 3H), 1.53-1.57 (m, 2H), 1.83 (brs, 2H), 1.95 (brs, 1H), 2.10 (brs, 1H), 2.29 (brs, 1H), 2.59 (brs, 3H), 2.91 (s, 3H), 3.02 (brs, 1H), 3.29 (brs, 2H), 3.41-3.47 (m, 2H), 3.58-3.62 (m, 3H), 3.95-4.01 (m, 2H), 4.45-4.48 (m, 1H), 7.20 (d, 2H, *J* = 7.3 Hz, ArH), 7.59 (d, 2H, *J* = 7.3 Hz, ArH), 9.06 (brs, 1H, NH^+), 10.28 (brs, 1H, NH^+), 11.82 (brs, 2H, NH_2^+); ESI-MS (*m/z*): 344.3 $[M+1 - 2HCl]^+$.

***N*-(4-*tert*-butylbenzyl)-2-(4-methylpiperazin-1-yl)cyclohexanamine trihydrochloride (21n)**: Yield: 40%; IR (Film, cm^{-1}): 2930, 2853, 2678, 2208, 1614, 1459, 1365, 1271, 1187, 1115, 1025; ^{1}H NMR (400 MHz, $CDCl_3$): 1.13 (brs, 2H), 1.29 (s, 9H), 1.79-1.88 (m, 2H), 1.95-2.05 (m, 2H), 2.13 (brs, 1H), 2.28-2.31 (m, 1H), 2.63 (brs, 2H), 2.74 (brs, 1H), 2.83 (s, 3H), 3.05-3.11 (m, 2H), 3.18-3.20 (m, 1H), 3.38-3.40 (m, 2H), 3.51-3.54 (m, 1H), 3.91-3.94 (m, 2H), 4.48-4.51 (d, 1H, *J* = 13.2 Hz), 7.43 (d, 2H, *J* = 8.0 Hz, ArH), 7.63 (d, 2H, *J* = 8.0 Hz, ArH), 8.86 (brs, 1H, NH^+), 10.37 (brs, 1H, NH^+), 12.16 (brs, 2H, NH_2^+).

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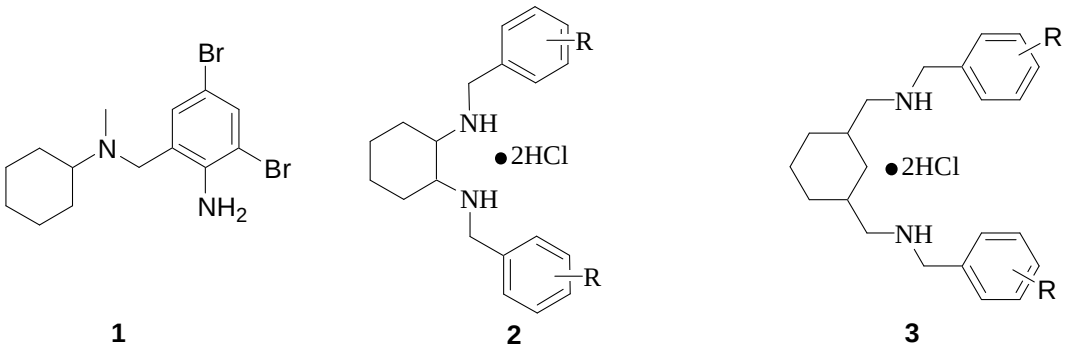

1 2 3

Figure.1 Prototype structure of cyclohexane-diamine derivatives as antibacterial agents

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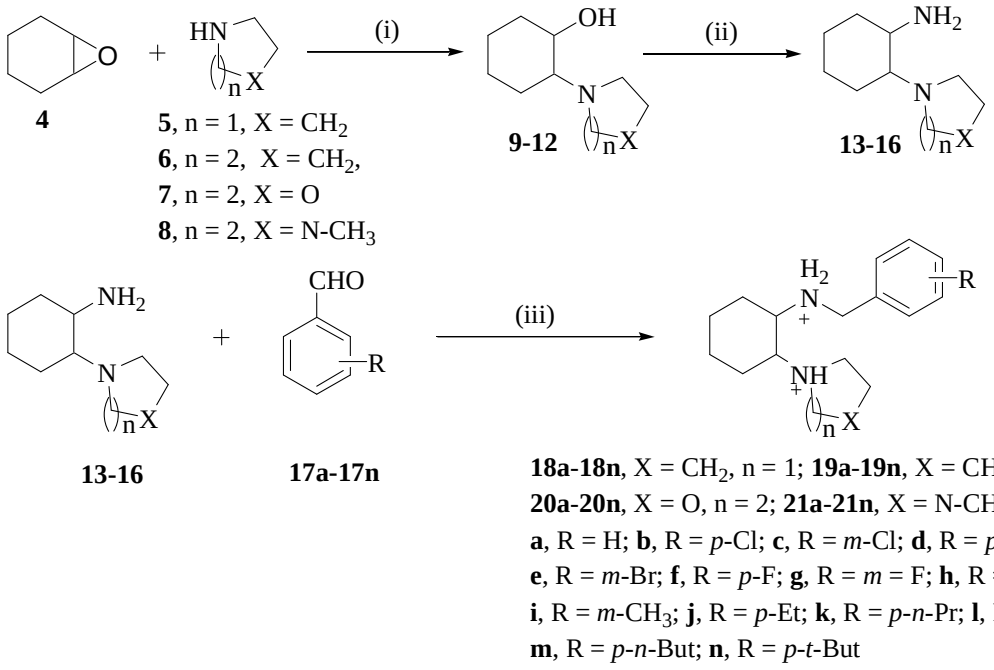

Reagents and conditions: (i) EtOH, reflux, 80-95%; (ii) (a) MsCl, Et_3N, dry THF, 0 ^oC to RT; (b) Et_3N, aq. NH_3, RT, 16 hr, 40-60%; (iii) (a) MeOH, RT, 4-5 hr; (b) $NaBH_4$, 0 ^oC to RT, 1-2 hr (c) HCl gas, $CHCl_3$, 0.5 hr, 40-80%.

Scheme 1

Table 1: Antibacterial activity of unsymmetrically substituted cyclohexane-1,2-diamine derivatives

Entry	R	X	n	MIC (µg/mL)		
				P. aeruginosa	***S. aureus***	***S. epidermidis***
18a	H	CH_2	1	0.5	NA	0.5
18b	*p*-Cl	CH_2	1	0.125	NA	0.125
18c	*m*-Cl	CH_2	1	0.25	NA	0.25
18d	*p*-Br	CH_2	1	0.125	1.0	0.125
18e	*m*-Br	CH_2	1	0.5	NA	0.5
18f	*p*-F	CH_2	1	0.25	1.0	0.5
18g	*m*-F	CH_2	1	0.125	NA	0.5
18h	*p*-CH_3	CH_2	1	0.25	1.0	0.5
18i	*m*-CH_3	CH_2	1	0.25	NA	0.25
18j	*p*-Et	CH_2	1	0.25	1.0	0.5

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18k	*p*-*n*-Pr	CH_2	1	0.25	1.0	0.5
18l	*p*-*i*-Pr	CH_2	1	0.25	NA	0.25
18m	*p*-*n*-Bu	CH_2	1	0.065	0.065	0.065
18n	*p*-*t*-Bu	CH_2	1	0.125	0.125	0.125
19j	*p*-Et	CH_2	2	0.25	0.25	0.25
19k	*p*-*n*-Pr	CH_2	2	0.065	0.065	0.065
19l	*p*-*i*-Pr	CH_2	2	0.125	0.125	0.125
19m	*p*-*n*-Bu	CH_2	2	0.125	0.125	0.125
19n	*p*-*t*-Bu	CH_2	2	0.125	0.125	0.125
Tetracycline				0.01	0.01	0.02

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