Synthesis of certain *N*-aralkyl-*N*-(1-((cyclohexylamino) methyl)cyclohexyl)benzenamines and benzamides and their anticonvulsant and analgesic potential

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Background and objectives
Epilepsy is a central nervous system disorder, affecting about 1% of the world's population, and is mostly prevalent in developing nations. In addition, many geminally disubstituted cyclohexane derivatives have proven to have anticonvulsant and analgesic activities. The aim of this study was to synthesize a new series of *N*-aralkyl-*N*-(1-((cyclohexylamino)methyl)cyclohexyl) benzenamines, **6a–h**, and *N*-(1-((cyclohexylamino)methyl)cyclohexyl)-*N*-phenyl-substituted benzamides, **8a–g**, for the purpose of evaluating their anticonvulsant and analgesic potential. In addition, the in-silico properties of the newly synthesized compounds have been discussed.

Materials and methods
Starting from 1-(*N*-phenylbenzamido and 4-substituted benzamido)cyclohexane carboxylic acids **3a–g**, a new series of *N*-aralkyl-*N*-(1-((cyclohexylamino)methyl)cyclohexyl) benzenamines, **6a–h**, was synthesized through formation of the corresponding methyl esters **4a–g**, which underwent complete reduction of both the ester and the tertiary amidic carbonyl groups to afford the desired amino alcohols, **5a–g**. Condensation of the corresponding mesylate esters with cyclohexylamine gave the target diamines **6a–g**. Also, the alcohols **7a–g** were achieved from **3a–g** using $NaBH_4$ without affecting the amidic group, followed by preparation of the corresponding intermediate mesylate esters, which reacted with cyclohexylamine to yield the benzamidecyclohexyl amines **8a–g**. The anticonvulsant and analgesic properties of **6a–h** and **8a–h** were studied using the pentylenetetrazole screening test and the hot-plate technique, respectively.

Results and conclusion
The results of the present study revealed that the most active compounds that exhibited remarkable 100% protection in mice were **6b**, **6d**, **6e**, **8a**, **8b**, **8f** and **8h**, compared with diphenylhydantoin sodium and valproic acid, which were used as reference drugs. Both *N*-aralkyl-*N*-(1-((cyclohexyl amino)methyl)cyclohexyl)benzenamine and *N*-(1-((cyclohexylamino)methyl) cyclohexyl)-*N*-phenyl-substituted benzamide series, **6a–h** and **8a–h**, displayed significant antinociceptive effects. However, the **6a–h** series showed higher potential than the **8a–h** one. The results of the in-silico studies for the newly synthesized compounds showed that compounds **6c**, **6e**, **6h**, **8e**, **8f** and **8h** exhibit low mutagenic, tumorigenic, reproductive and medium irritant effect, as well as good drug-likeness and drug score.

Keywords:
anticonvulsants, antinociceptives, benzamides, 1,1-disubstituted cyclohexyl benzenamines

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Introduction

Epilepsy is a chronic seizure disorder characterized by excessive discharge of cortical neurons. It is prevalent in ~1% of the population worldwide with cumulative incidence at 2–5%, and about 30% of patients with partial-onset seizures cannot be adequately controlled with existing antiepileptic drugs [1–4]. This gave a great impetus to the area of medicinal chemistry to search for potential pharmacologically active anticonvulsant agents with lower undesirable side effects [5–7].

Many geminally disubstituted cyclohexane derivatives such as gabapentin have proven to have an anticonvulsant profile [8]. Aboul-Enein *et al.* [9] disclosed the synthesis of *N*-benzyl-*N*-(1-((pyrrolidin-1-yl) methyl)cyclohexyl)benzenamine (**Ia**), *N*-benzyl-*N*-(1-((piperidin-1-yl)methyl)cyclohexyl)benzenamine (**Ib**) and *N*-(4-methoxybenzyl)-*N*-(1-((piperidin-1-yl)methyl)cyclohexyl)benzenamine (**Ic**), which exhibited 100% protection against pentylenetetrazole seizures at a dose level of 0.11 mmol/kg, compared with diphenylhydantoin sodium and valproic acid as reference drugs, which reached the same protection level at dose levels of 0.20 and 0.24 mmol/kg, respectively. Furthermore, an array of 1,1-disubstituted cycloalkanes were found to exhibit potent analgesic effects [10–16].

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Accordingly, the present work is targeted towards the synthesis of certain *N*-(substituted) benzyl-*N*-(1-((cyclohexyl amino)methyl)cyclohexyl)benzenamines, **6a–h**, to study the anticonvulsant potential of replacing the heterocyclic ring (A) in **I** having an endo-N with the more lipophilic cyclohexyl amino moiety having an exo-N. This increase in lipophilicity would lead to increased crossing of the blood–brain barrier, which is a parameter for achieving anticonvulsant activity [17]. The synthesis of the corresponding benzamide cyclohexyl amines **8a–h** was considered in order to investigate their biological effects and for the purpose of comparison. In addition, both series were also screened for their antinociceptive potential, as many geminally substituted cyclohexanes exhibit such an effect.

Materials and methods

Chemistry

All melting points are uncorrected and were determined with an electrothermal capillary melting point apparatus. Infrared (IR) spectra were recorded as thin film (for oils) in NaCl discs or as KBr pellets (for solids) with a JASCO FT/IR-6100 (Milano, Italy) Spectrometer and values are presented in cm^{-1}. ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on a Jeol ECA 500 MHz Spectrophotometer (Jeol) (Tokyo, Japan) using tetramethylsilane (TMS) as the internal standard, and chemical shift values are recorded in ppm on δ scale. The ^1H NMR data were represented as follows: chemical shifts, multiplicity (s, singlet; m, multiplet; br, broad) and number of protons. The ^{13}C NMR data are presented as chemical shifts and type of carbon. The mass spectra (CI/CH_4) were run on a Finnigan Mat SSQ-7000 (USA) Spectrophotometer and Jeol JMS-AX 500 (Tokyo, Japan). Elemental analyses were carried out at the Microanalytical Unit, National Research Centre, Cairo, Egypt. Aluminium oxide 60G F_{254} neutral plates for TLC (E. Merck, Germany) were used for thin-layer chromatography. Visualization was performed by illumination with a ultraviolet light source (254 nm). Column chromatography was performed with silica gel for gravity columns. The synthesis of compounds **3–5 (a–c)** was performed by adopting the reported procedure of Aboul-Enein *et al.* [9].

General procedure for the synthesis of 1-(N-phenylbenzamido and 4-substituted benzamido) cyclohexane carboxylic acids, **3d–g**

To a solution of 10.9 g (0.05 mol) of 1-(phenylamino) cyclohexane carboxylic acid (**1**) and 15 g (0.15 mol, 21 ml) of triethylamine (TEA) in 50 ml of dry benzene was added dropwise under stirring and cooling 0.05 mol of the appropriate acid chloride **2a–g**. The reaction mixture was refluxed for 12 h and the precipitated TEA hydrochloride was filtered off; the filtrate was dried (Na_2SO_4) and evaporated under vacuum. The residual solid was crystallized from ethanol to give solid crystals of the corresponding acids **3d–g**.

*1-(4-Nitro-N-phenylbenzamido)cyclohexanecarboxylic acid (**3d**)*: Yield 67%; pale yellow solid; m.p.: 198–199°C; IR (cm^{-1}): 3350 (OH, carboxylic acid), 1720 (C = O, carboxylic acid) and 1630 (C = O, amide); ^1H NMR ($CDCl_3$): 1.12–2.34 (10H, m, H-cyclohexyl), 3.32 (1H, s, OH exchangeable), 7.25–8.38 (m, 9H, H-ar). MS *m/z* (%): 369.38, (M + H) + 100. Anal. calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.42; H, 5.61; N, 7.48.

*1-(3,4,5-Trimethoxy-N-phenylbenzamido) cyclohexanecarboxylic acid (**3e**)*: Yield 55%; pale yellow solid; m.p.: 180–181°C; IR (cm^{-1}): 3421 (OH, carboxylic acid), 1710 (C = O, carboxylic acid) and 1645 (C = O, amide); ^1H NMR ($CDCl_3$): 0.94–1.47 (10H, m, cyclohexane), 3.34 (1H, s, OH), 3.72 (9H, s, $(OCH_3)_3$), 7.06–7.72 (7H, m, H-ar). MS *m/z* (%): 414.46, (M + H) + 100. Anal. calcd. for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.72; H, 6.61; N, 3.22.

*1-(7-Methoxy-N-phenylbenzo[d][1,3]dioxole-5-carboxamido)cyclohexane carboxylic acid (**3f**)*: Yield 60%; white solid; m.p.: 200–201°C; IR (cm^{-1}): 3370 (OH, carboxylic acid), 1710 (C = O, carboxylic acid), 1640 (C = O, amide); ^1H NMR ($CDCl_3$): 1.13–1.81 (10H, m, cyclohexane), 3.23 (1H, s, OH), 3.83 (3H, s, OCH_3), 5.73 (2H, s, OCH_2O), 7.13–7.64 (7H, m, H-ar). MS *m/z* (%): 398.42, (M + H) + 100. Anal. calcd. for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.61; H, 5.79; N, 3.43.

*1-(8-Methoxy-N-phenyl-2,3-dihydrobenzo[b][1,4] dioxine-6-carboxamido)cyclohexane carboxylic acid (**3g**)*: Yield 65%; white solid; m.p.: 188–189°C; IR (cm^{-1}): 3370 (OH, carboxylic acid), 1710 (C = O, carboxylic acid), 1640 (C = O, amide); ^1H NMR ($CDCl_3$): 1.13–1.82 (10H, m, cyclohexane), 3.43 (1H, s, OH), 3.79 (3H, s, OCH_3), 4.25 (4H, s, OCH_2CH_2O), 7.20–7.74 (7H, m, H-ar). MS *m/z* (%): 412.1, (M + H) + 100. Anal. calcd. for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 66.93; H, 6.24; N, 3.29.

General procedure for the synthesis of methyl-1-(benzamido and 4-substituted benzamido)N-phenyl cyclohexanecarboxylate, **4d–g**

A solution of 0.01 mol of the acid **3a–g**, 1.62 ml (0.04 mol) of dry methanol and *P*-toluene sulphonic acid 0.002 g (0.01 mmol) in 30 ml of dry toluene was refluxed under stirring for 24 h. The solvent

was evaporated under vacuum and the residue was dissolved in dichloromethane (DCM). The organic phase was washed with 10% aqueous Na_2CO_3 solution and water, then dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give residual solid, which was crystallized from methanol to afford **4d–g** in 55–75% yield.

*Methyl 1-(4-nitro-N-phenylbenzamido) cyclohexanecarboxylate (**4d**)*: Yield 75%; white solid; m.p.: 116–117°C; IR (cm^{-1}): 1740 (C = O, ester), 1630 (C = O, amide); ^1H NMR ($CDCl_3$): 1.22–2.13 (10H, m, H-cyclohexyl), 3.62 (3H, s, CH_3OOC), 7.28–8.31 (9H, m, H-ar). MS *m/z* (%): 383.1, (M + H) + 100. Anal. calcd. for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 66.12; H, 5.73; N, 7.17.

*Methyl 1-(3,4,5-trimethoxy-N-phenylbenzamido) cyclohexanecarboxylate (**4e**)*: Yield 55%; white solid; m.p.: 106–108°C; IR (cm^{-1}): 1740 (C = O, ester), 1640 (C = O, amide); ^1H NMR ($CDCl_3$): 1.41–2.12 (10H, m, H-cyclohexyl), 3.66 (9H, s, $(OCH_3)_3$), 3.81 (3H, s, CH_3OOC), 7.13–7.62 (7H, m, H-ar). MS *m/z* (%): 428.2, (M + H) + 100. Anal. calcd. for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.22; H, 6.87; N, 3.26.

*Methyl 1-(7-methoxy-N-phenylbenzo[d][1,3]dioxole-5-carboxamido)cyclohexane-carboxylate(**4f**)*: Yield 60%; white solid; m.p.: 112–113°C; IR (cm^{-1}): 1735 (C = O, ester), 1630 (C = O, amide); ^1H NMR ($CDCl_3$): 1.12–1.63 (10H, m, H-cyclohexyl), 3.72 (3H, s, OCH_3), 3.79 (3H, s, CH_3OOC), 5.91 (2H, s, OCH_2O protons), 7.13–7.65 (7H, m, H-ar). MS *m/z* (%): 412.2, (M + H) + 100. Anal. calcd. for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.25; H, 6.18; N, 3.42.

*Methyl 1-(8-methoxy-N-phenyl-2,3-dihydrobenzo[b] [1,4]dioxine-6-carboxamido) cyclohexanecarboxylate (**4g**)*: Yield 65%; white solid; m.p.: 107–109°C; IR (cm^{-1}): 1740 (C = O, ester), 1635(C = O, amide); ^1H NMR ($CDCl_3$): 1.12–1.84 (10H, m, H-cyclohexyl), 3.71 (3H, s,OCH_3), 3.82 (3H, s, CH_3OOC), 4.32 (4H, s, OCH_2CH_2O), 7.13–7.63 (7H, m, H-ar). MS *m/z* (%): 426.1, (M + H) + 100. Anal. calcd. for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.64; H, 6.45; N, 3.31.

General procedure for the synthesis of 1-(aralkylphenylamino)cyclohexylmethanols, **5d–g**

A solution of 0.1 mol of the ester **4a–g** in dry tetrahydrofuran (THF) was added to a slurry of 5.7 g (0.15 mol) $LiAlH_4$ in dry THF at 0°C. The temperature of the reaction mixture was increased gradually to room temperature and left for 5 h, and then refluxed for a further 3 h. The complex was decomposed using a saturated solution of Na_2SO_4 and filtered over celite. The filtrate was dried and evaporated under reduced pressure to give the alcohols **5a–g** as viscous oils, which were purified through column chromatography using petroleum ether (40–60°C) : ethylacetate (1 : 1) to yield **5a–g** at a yield of 71–78%.

IR (cm^{-1}) of compounds **5d–g** showed bands at 3200–3400 (OH) and absence of the ester and amide carbonyl bands.

*(1-((4-Nitrobenzyl)(phenyl)amino)cyclohexyl)methanol (**5d**)*: Yield 78%; pale yellow viscous oil; ^1H NMR ($CDCl_3$): 1.42–1.73 (10H, m, H-cyclohexyl), 3.66 (2H, s, CH_2OH), 4.59 (2H, s, CH_2N), 4.83 (1H, br, s, OH), 6.62–8.20 (9H, m, H-ar). MS *m/z* (%): 341.1, (M + H) + 100. Anal. calcd. for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.63; H, 7.15; N, 8.29.

(1-(Phenyl(3,4,5-trimethoxybenzyl)amino)cyclohexyl) methanol (5e): Yield 71%; pale yellow viscous oil; ^1H NMR ($CDCl_3$): 1.34–1.74 (10H, m, H-cyclohexyl), 3.67 (2H, s, CH_2N), 3.70 (s, 3H, OCH_3), 3.74(6H, s, $(OCH_3)_2$), 4.62 (2H, s, CH_2OH), 4.77 (1H, br, s, OH), 6.64–7.31(7H, m, H-ar). MS *m/z* (%): 386.2, (M + H) + 100. Anal. calcd. for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.59; H, 7.99; N, 3.65.

*(1-(((7-Methoxybenzo[d][1,3]dioxol-5-yl)methyl) (phenyl)amino)cyclohexyl)methanol (**5f**)*: Yield 74%; pale yellow viscous oil; ^1H NMR ($CDCl_3$): 1.04–1.62 (10H, m, H-cyclohexyl), 3.69 (2H, s, CH_2N), 3.71 (3H, OCH_3), 4.60 (2H, s, CH_2OH), 4.80 (1H, br, s, OH), 5.89 (2H, s, OCH_2O), 6.61–7.22 (7H, m, H-ar). MS *m/z* (%): 370.19, (M + H) + 100. Anal. calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.49; H, 7.28; N, 3.71.

(1-(((8-Methoxy-2,3-dihydrobenzo[b][1,4]dioxin-6-yl) methyl)(phenyl)amino)cyclohexyl)methanol (5g): Yield 72%; pale yellow viscous oil; ^1H NMR ($CDCl_3$): 1.42–1.73 (10H, m, H-cyclohexyl), 3.67 (2H, s, CH_2N), 3.71 (3H, OCH_3), 4.62 (2H, s, CH_2OH), 4.75 (1H, br, s, OH), 4.28 (4H, s, OCH_2CH_2O), 6.59–7.24 (7H, m, H-ar). MS *m/z* (%): 384.21, (M + H) + 100. Anal. calcd. for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.93; H, 7.45; N, 3.70.

General procedure for the synthesis of N-benzyl and substituted benzyl-N-(1-((cyclohexyl amino)methyl) cyclohexyl)benzenamines, **6a–g**

To a solution of 1.5 g TEA (15 mmol, 2.07 ml) in dry DCM (100 ml) was added 10 mmol of alcohol (**5a–g**). The resulting mixture was cooled to 0°C and methanesulphonyl chloride 1.44 g (0.99 ml, 12.7 mmol) was added under stirring for 1 h and the

solvent was evaporated. The formed mesylate in dry dimethylformamide (DMF) (30 ml) was added to a mixture of 0.99 g cyclohexylamine (10 mmol, 0.8 ml) and 3.3 g anhydrous K_2CO_3 (23.8 mmol) in dry DMF (100 ml). The mixture was stirred at 80°C overnight. The solvent was evaporated and the residual substance was dissolved in ethyl acetate and washed with water (3´50 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated to yield the corresponding amine (**6a–g**) at yields of 60–80%.

*N-benzyl-N-(1-((cyclohexylamino)methyl)cyclohexyl) benzenamine (**6a**)*: Yield 80%; white crystals; m.p.: 91–93°C (ethyl acetate); IR (cm^{-1}): 3200–3400 (NH); ^{1}H NMR (DMSO-d_6) δ ppm: 1.12–2.50 (22H, m, H-cyclohexyl and NH), 3.02 (2H, s, CH_2NH), 4.78 (2H, s, CH_2N), 7.00–7.30 (10H, m, H-ar). ^{13}C NMR (DMSO-d_6): 22.36 (2CH_2-cyclohexane), 31.2 (2CH_2-cyclohexane), 33.00 (CH_2-cyclohexane), 33.30 (CH_2-cyclohexyl), 39.31 (2CH_2-cyclohexyl), 39.71 (2CH_2-cyclohexyl), 39.97 (CH_2-aliphatic), 42.12 (CH_2-aliphatic), 62.23, 65.07 (CH-cyclohexyl, C-cyclohexyl), 127.3 (2CH-ar), 127.5 (CH-ar), 127.9 (CH-ar), 131.21 (2CH-ar), 137.19 (2CH-ar), 139.15 (2CH-ar), 142.76 (C-ar), 145.26 (C-ar). MS *m/z* (%): 377.1, (M + H) + 100. Anal. calcd. for $C_{26}H_{36}N_2$: C, 82.93; H, 9.64; N, 7.44. Found: C, 83.09; H, 9.54; N, 7.29.

*N-(4-chlorobenzyl)-N-(1-((cyclohexylamino)methyl) cyclohexyl)benzenamine (**6b**)*: Yield 69%; white crystals; m.p.: 108–109°C (ethyl acetate : *n*-hexane); IR (cm^{-1}): 3200–3400 (NH); ^{1}H NMR (DMSO-d_6) δ ppm: 0.98–2.12 (22H, m, H-cyclohexyl and NH), 2.77 (2H, s, CH_2NH), 4.62 (2H, s, CH_2N), 6.70–7.41 (9H, m, H-ar). ^{13}C NMR (DMSO-d_6): 21.87 (2CH_2-cyclohexyl), 29.54 (2CH_2-cyclohexane), 32.27 (CH_2-cyclohexyl), 32.63 (CH_2-cyclohexyl), 37.96 (2CH_2-cyclohexyl), 38.34 (2CH_2-cyclohexyl), 40.64 (CH_2-aliphatic), 44.32 (CH_2-aliphatic), 61.75 (CH-cyclohexyl), 64.89 (C-cyclohexyl), 122.36 (2CH-ar), 123.64 (CH-ar), 123.96 (2CH-ar), 128.86 (2CH-ar), 132.53 (2CH-ar), 134.32 (C-ar), 141.69 (C-ar), 144.78 (C-ar). MS *m/z* (%): 412.3, (M + H) + 100. Anal. calcd. for $C_{26}H_{35}ClN_2$: C, 75.98; H, 8.58; N, 6.82. Found: C, 75.77; H, 8.65; N, 6.91.

*N-(1-((cyclohexylamino)methyl)cyclohexyl)-N-(4-methoxybenzyl)benzenamine (**6c**)*: Yield 72%; pale white crystals; m.p.: 104–105°C (ethyl acetate : *n*-hexane); IR (cm^{-1}): 3210–3400 (NH); ^{1}H NMR (DMSO-d_6) δ ppm: 1.11–2.24 (22H, m, H-cyclohexyl and NH), 2.65 (2H, s, CH_2NH), 3.73 (3H, s, OCH_3), 4.58 (2H, s, CH_2N), 6.65–7.34 (9H, m, H-ar). ^{13}C NMR (DMSO-d_6): 22.68 (2CH_2-cyclohexyl), 26.43 (2CH_2-cyclohexyl), 32.88 (CH_2-cyclohexyl), 33.21 (CH_2-cyclohexyl), 38.36 (2CH_2-cyclohexyl), 38.64 (2CH_2-cyclohexyl), 42.74 (CH_2-aliphatic), 47.11 (CH_2-aliphatic), 58.54 (OCH_3), 60.66, 63.74 (CH-cyclohexyl, C-cyclohexyl), 118.97 (2CH-ar), 120.74 (2CH-ar), 123.04 (CH-ar), 128.38 (C-ar), 129.23 (2CH-ar), 131.79 (2CH-ar), 148.49 (C-ar), 156.21 (C-ar). MS *m/z* (%): 407.3, (M + H) + 100. Anal. calcd. for $C_{27}H_{38}N_2O$: C, 79.76; H, 9.42; N, 6.89. Found: C, 79.59; H, 9.63; N, 6.71.

*N-(1-((cyclohexylamino)methyl)cyclohexyl)-N-(4-nitrobenzyl)benzenamine (**6d**)*: Yield 65%; yellow crystals; m.p.: 100–102°C (ethyl acetate). IR (cm^{-1}): 3200–3400 (NH); ^{1}H NMR (DMSO-d_6) δ ppm: 0.85–2.20 (22H, m, H-cyclohexyl and NH), 2.56 (2H, s, CH_2NH), 4.52 (2H, s, CH_2N); 6.61–8.10 (9H, m, H-ar). ^{13}C NMR (DMSO-d_6): 22.12 (2CH_2-cyclohexyl); 24.76 (2CH_2-cyclohexyl), 30.11 (CH_2-cyclohexyl), 30.85 (CH_2-cyclohexyl), 34.14 (2CH_2-cyclohexyl), 34.55 (2CH_2-cyclohexyl), 49.53 (CH_2-aliphatic), 55.64 (CH_2-aliphatic), 56.89, 57.14 (CH-cyclohexyl, C-cyclohexyl), 114.97 (2CH-ar), 118.77 (CH-ar), 124.34 (2CH-ar), 129.23 (2C-ar), 130.58 (2CH-ar), 143.72 (C-ar), 147.00 (C-ar), 150.19 (C-ar). MS *m/z* (%): 422.2, (M + H) + 100. Anal. calcd. for $C_{26}H_{35}N_3O_2$: C, 74.07; H, 8.37; N, 9.97. Found: C, 74.21; H, 8.24; N, 9.86.

*N-(1-((cyclohexylamino)methyl)cyclohexyl)-N-(3,4,5-trimethoxybenzyl) benzenamine (**6e**)*: Yield 62%; viscous oil purified by column chromatography; IR (cm^{-1}): 3200–3400 (NH); ^{1}H NMR (DMSO-d_6) δ ppm: 1.06–1.74 (22H, m, H-cyclohexyl and NH), 2.73 (2H, s, CH_2NH), 3.75 (9H, s, $(OCH_3)_3$), 4.64 (2H, s, CH_2N), 6.67–7.52 (7H, m, H-ar). ^{13}C NMR (DMSO-d_6): 21.22 (2CH_2-cyclohexyl), 23.48 (2CH_2-cyclohexyl), 28.32 (CH_2-cyclohexyl), 28.58 (CH_2-cyclohexyl), 34.41 (2CH_2-cyclohexyl), 34.63 (2CH_2-cyclohexyl), 49.74 (CH_2-aliphatic), 55.68 (CH_2-aliphatic), 56.13, 56.51, 56.97, 57.23 (2(OCH_3), OCH_3, CH-cyclohexyl, C-cyclohexyl), 105.67 (2CH-ar), 115.12 (2CH-ar), 118.76 (CH-ar), 129.80 (2C-ar), 131.23 (C-ar), 138.11(C-ar), 149.89 (C-ar), 151.77 (2C-ar). MS *m/z* (%): 467.1, (M + H) + 100. Anal. calcd. for $C_{29}H_{42}N_2O_3$,: C, 74.64; H, 9.07; N, 6.00. Found: C, 74.51; H, 9.15; N, 6.12.

*N-(1-((cyclohexylamino)methyl)cyclohexyl)-N-((7-methoxybenzo[d][1,3]dioxol-5-yl)methyl)benzenamine (**6f**)*: Yield 60%; buff powder; m.p.: 104–106°C (ethyl acetate); IR (cm^{-1}): 3200–3400 (NH); ^{1}H NMR (DMSO-d_6) δ ppm: 1.08–2.32 (22H, m, H-cyclohexyl and NH), 2.71 (2H, s, CH_2NH), 3.73 (3H, s, OCH_3), 4.62 (2H, s, CH_2N), 5.88 (2H, s, OCH_2O), 6.60–7.32 (7H, m, H-ar). ^{13}C NMR (DMSO-d_6): 21.12 (2CH_2-cyclohexyl), 23.32 (2CH_2-cyclohexyl), 28.11 (CH_2-cyclohexyl), 28.42 (CH_2-cyclohexyl), 34.40 (2CH_2-cyclohexyl), 34.57 (2CH_2-cyclohexyl), 49.62

(CH_2-aliphatic), 55.89 (CH_2-aliphatic), 56.02, 56.13, 56.75 (OCH_3, CH-cyclohexyl, C-cyclohexyl), 101.70 (OCH_2O), 105.35 (2CH-ar), 114.83 (2CH-ar), 118.81 (CH-ar), 129.78 (2CH-ar), 131.31 (C-ar), 135.21 (C-ar), 149.69 (2C-ar), 150.72 (C-ar). MS *m/z* (%): 451.2, (M + H) + 100. Anal. calcd. for $C_{28}H_{38}N_2O_3$: C, 74.63; H, 8.50; N, 6.22. Found: C, 74.81; H, 8.39; N, 6.36.

*7-N-(1-((cyclohexylamino)methyl)cyclohexyl)-N-((8-methoxy-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl) benzenamine (**6g**)*: Yield 65%; buff powder; m.p.: 90–92°C (ethyl acetate : *n*-hexane); IR (cm^{-1}): 3200–3400 (NH); ^{1}H NMR (DMSO-d_6) δ ppm: 1.12–2.13 (22H, m, H-cyclohexyl and NH), 2.72 (2H, s, CH_2NH), 3.71 (3H, s, OCH_3), 4.32 (4H, s, CH_2N), 4.62 (2H, s, OCH_2CH_2O), 6.61–7.31 (7H, m, H-ar). ^{13}C NMR (DMSO-d_6): 21.02 ($2CH_2$-cyclohexyl), 23.30 ($2CH_2$-cyclohexyl), 28.22 (CH_2-cyclohexyl), 28.35 (CH_2-cyclohexyl), 34.42 ($2CH_2$-cyclohexyl), 34.59 ($2CH_2$-cyclohexyl), 49.59 (CH_2-aliphatic), 55.88 (CH_2-aliphatic), 56.10, 56.22, 56.68 (OCH_3, CH-cyclohexyl, C-cyclohexyl), 64.25 and 64.56 (OCH_2CH_2O), 105.42 (2CH-ar), 114.51 (2CH-ar), 118.67 (CH-ar), 129.57 (C-ar), 129.68 (2CH-ar), 134.21 (C-ar), 147.67 (C-ar), 149.89 (C-ar), 150.73 (C-ar). MS *m/z* (%): 465.3, (M + H) + 100. Anal. calcd. for $C_{29}H_{40}N_2O_3$: C, 74.96; H, 8.68; N, 6.03. Found: C, 74.85; H, 8.79; N, 5.98.

General procedure for the synthesis of N-(1-(hydroxymethyl)cyclohexyl)-N-phenylbenzamide and 4-substituted N-(1-(hydroxymethyl)cyclohexyl)-N-phenylbenzamide, **7a–g**

A solution of 5.4 g (0.05 mol, 4.7 ml) of ethoxy carbonyl chloride in 5 ml dry THF was added slowly under stirring to a cold solution (10°C) of 0.05 mol of acids **3a–g** and 5.05 g (0.05 mol, 7 ml) of TEA in 50 ml THF. A precipitate was formed in 30 min, which was filtered off. The filtrate was added dropwise under stirring to a cold (10°C) solution of 3.7 g (0.1 mol) of sodium borohydride in 25 ml water and stirred at room temperature for 12 h; the solvent was then removed and 50 ml of water was added and extracted with DCM (3 × 50 ml). The organic layer was dried, filtered and evaporated to give viscous oils, which were purified by column chromatography using petroleum ether (40–60°C) : ethyl acetate (1 : 1) to afford **7a–g** at 65–85%, which were used as such in the next step.

*N-(1-(hydroxymethyl)cyclohexyl)-N-phenylbenzamide (**7a**)*: Yield 73%; pale yellow viscous oil; IR (cm^{-1}): 3250 (OH), 1630 (C = O amide); ^{1}H NMR ($CDCl_3$): 1.38–1.80 (10H, m, cyclohexane), 3.76 (2H, s, CH_2OH), 4.85 (1H, br, s, OH), 7.32–7.71 (10H, m, H-ar). MS *m/z* (%): 310.18, (M + H) + 100. Anal. calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.60; H, 7.34; N, 4.33.

*4-Chloro-N-(1-(hydroxymethyl)cyclohexyl)-N-phenylbenzamide (**7b**)*: Yield 65%; pale yellow viscous oil; IR (cm^{-1}): 3245 (OH), 1642 (C = O amide); ^{1}H NMR ($CDCl_3$): 1.35–1.86 (10H, m, H-cyclohexyl), 3.74 (2H, s, CH_2OH), 4.82 (1H, br, s, OH), 7.37–8.21 (9H, m, H-ar). MS *m/z* (%): 344.13, (M + H) + 100. Anal. calcd. for $C_{20}H_{22}ClNO_2$: C, 69.86; H, 6.45; N, 4.53. Found: C, 69.78; H, 6.37; N, 4.46.

*N-(1-(hydroxymethyl)cyclohexyl)-4-methoxy-N-phenylbenzamide (**7c**)*: Yield 85%; pale yellow viscous oil; IR (cm^{-1}): 3247 (OH), 1635 (C = O amide); ^{1}H NMR ($CDCl_3$): 1.33–1.81 (10H, m, H-cyclohexyl), 3.73 (2H, s, CH_2OH), 3.82(3H, s, OCH_3), 4.77 (1H, br, s, OH), 6.99–8.03 (9H, m, H-ar). MS *m/z* (%): 340.18, (M + H) + 100. Anal. calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.37; H, 7.45; N, 4.08.

*N-(1-(hydroxymethyl)cyclohexyl)-4-nitro-N-phenylbenzamide (**7d**)*: Yield 81%; yellow viscous oil; IR (cm^{-1}): 3248 (OH), 1640 (C = O amide); ^{1}H NMR ($CDCl_3$): 1.39–1.82 (10H, m, H-cyclohexyl), 3.75 (2H, s, CH_2OH), 4.75 (1H, br, s, OH), 7.15–8.47 (9H, m, H-ar). MS *m/z* (%): 355.16, (M + H) + 100. Anal. calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.83; H, 6.30; N, 7.88.

*N-(1-(hydroxymethyl)cyclohexyl)-3,4,5-trimethoxy-N-phenylbenzamide (**7e**)*: Yield 67%; yellow viscous oil; IR (cm^{-1}): 3245 (OH), 1637 (C = O amide); ^{1}H NMR ($CDCl_3$): 1.38–1.79 (10H, m, H-cyclohexyl), 3.77 (2H, s, CH_2OH), 3.84 (9H, s, $(OCH_3)_3$), 4.79 (1H, br, s, OH), 7.20–7.72 (7H, m, H-ar). MS *m/z* (%): 400.20, (M + H) + 100. Anal. calcd. for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.23; H, 7.22; N, 3.56.

*N-(1-(hydroxymethyl)cyclohexyl)-7-methoxy-N-phenylbenzo[d][1,3]dioxole-5-carboxamide (**7f**)*: Yield 78%; yellow viscous oil; IR (cm^{-1}): 3245 (OH), 1635 (C = O amide); ^{1}H NMR ($CDCl_3$): 1.00–1.64 (10H, m, H-cyclohexyl), 3.74 (2H, s, CH_2OH), 3.82 (3H, s, OCH_3), 4.77 (1H, br, s, OH), 5.91(2H, s, OCH_2O), 7.14–7.70 (7H, m, H-ar). MS *m/z* (%): 384.17, (M + H) + 100. Anal. calcd. for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: 68.97; H, 6.64; N, 3.56.

*N-(1-(hydroxymethyl)cyclohexyl)-8-methoxy-N-phenyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide (**7g**)*: Yield 71%; yellow viscous oil; IR (cm^{-1}): 3250 (OH), 1635 (C = O amide); ^{1}H NMR ($CDCl_3$): 1.34–1.88 (10H, m, H-cyclohexyl), 3.75 (2H, s, CH_2OH), 3.85 (3H, s, OCH_3), 4.33 (4H, s, CH_2CH_2), 4.79 (1H, br, s, OH), 7.16–7.69 (7H, m, H-ar). MS *m/z* (%): 398.19,

(M + H) + 100. Anal. calcd. for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.48; H, 6.87; N, 3.55.

General procedure for the synthesis of N-(1-((cyclohexylamino)methyl)cyclohexyl)-N-phenyl-substituted benzamides, **8a–g**

To a solution of 1.5 g TEA (15 mmol, 2.07 ml) in 100 ml dry DCM was added 10 mmol of the appropriate alcohol **7a–g**, which was then cooled (0°C); 1.44 g methanesulphonyl chloride (12.7 mmol) was introduced and stirred for 1 h, and the solvent was evaporated. The formed mesylate dissolved in dry DMF (30 ml) was added to a mixture of 0.99 g cyclohexylamine (10 mmol) in dry DMF (100 ml) and anhydrous K_2CO_3 (3.3 g, 23.8 mmol). The reaction mixture was stirred at 80°C overnight and the solvent was removed; the residual substance was dissolved in ethyl acetate (75 ml) and washed with water (3 × 50 ml). The organic layer was dried, filtered and evaporated to give a solid substance, which was crystallized from ethyl acetate : *n*-hexane to afford **8a–g** at 54–69% yield.

*N-(1-((cyclohexylamino)methyl)cyclohexyl)-N-phenylbenzamide (**8a**)*: Yield 65%; white crystals; m.p.: 108–109°C; IR (cm^{-1}): 3350 (NH), 1638 (C = O, amide); ^{1}H NMR ($CDCl_3$) δ ppm: 0.98–2.30 (22H, m, H-cyclohexyl and NH), 2.72 (2H, s, CH_2NH), 6.76–7.54 (10H, m, H-ar). ^{13}C NMR ($CDCl_3$) δ ppm: 20.87 ($2CH_2$-cyclohexyl), 23.21 ($2CH_2$-cyclohexyl), 28.10 (CH_2-cyclohexyl), 28.51 (CH_2-cyclohexyl), 33.10 ($2CH_2$-cyclohexyl), 35.21 ($2CH_2$-cyclohexyl), 50.56 (C-cyclohexyl), 55.56(CH_2-aliphatic), 60.67(CH-cyclohexyl), 121.21 (2CH-ar), 124.43 (CH-ar), 127.23 (2CH-ar), 129.12 (2CH-ar), 130.32 (2CH-ar), 132.76 (CH-ar), 134.45 (C-ar), 139.52 (C-ar), 170.31 (C-carbonyl). MS *m/z* (%): 391.2, (M + H) + 100. Anal. calcd. for $C_{26}H_{34}N_2O$: C, 79.96; H, 8.77; N, 7.17. Found: C, 80.10; H, 8.65; N, 7.32.

*4-Chloro-N-(1-((cyclohexylamino)methyl)cyclohexyl)-N-phenylbenzamide (**8b**)*: Yield 60%; white crystal; m.p.: 116–118°C; IR (cm^{-1}): 3350 (NH), 1637 (C = O, amide); ^{1}H NMR ($CDCl_3$) δ ppm: 1.08–2.21 (22H, m, H-cyclohexyl and NH), 2.75 (2H, s, CH_2NH), 7.14–7.88 (9H, m, H-ar). ^{13}C NMR ($CDCl_3$) δ ppm: 20.74 ($2CH_2$-cyclohexyl), 23.32 ($2CH_2$-cyclohexyl), 28.21 (CH_2-cyclohexyl), 28.48 (CH_2-cyclohexyl), 34.15 ($2CH_2$-cyclohexyl), 35.16 ($2CH_2$-cyclohexyl), 50.49, 57.42 (C-cyclohexyl, CH-cyclohexyl), 54.74 (CH_2-aliphatic), 121.57 (2CH-ar), 124.52 (CH-ar), 128.87 (4CH-ar), 129.11 (2CH-ar), 132.26 (C-ar), 137.58 (C-ar), 139.31(C-ar), 169.22 (C-carbonyl). MS *m/z* (%): 391.2, (M + H) + 100. Anal. calcd. for $C_{26}H_{33}ClN_2O$: C, 73.48; H, 7.83; N, 6.59. Found: C, 73.65; H, 7.59; N, 6.71.

*N-(1-((cyclohexylamino)methyl)cyclohexyl)-4-methoxy-N-phenylbenzamide (**8c**)*: Yield 69%; white crystals; m.p.: 94–95°C; IR (cm^{-1}): 3350 (NH), 1638 (C = O, amide); ^{1}H NMR ($CDCl_3$) δ ppm: 1.02–2.18 (22H, m, H-cyclohexyl and NH), 2.78 (2H, s, CH_2NH), 3.87 (3H, s, OCH_3), 7.06–7.95 (9H, H-ar). ^{13}C NMR ($CDCl_3$) δ ppm: 20.68 ($2CH_2$-cyclohexyl), 23.25 ($2CH_2$-cyclohexyl), 28.07 (CH_2-cyclohexyl), 28.32 (CH_2-cyclohexyl), 33.89 ($2CH_2$-cyclohexyl), 34.29 ($2CH_2$-cyclohexyl), 50.52, 54.35, 55.91, 56.83 (CH-cyclohexyl, CH_2-aliphatic, OCH_3, C-cyclohexyl), 115.32 (2CH-ar), 121.73 (2CH-ar), 124.48 (CH-ar), 127.10 (C-ar), 128.48 (2CH-ar), 129.22 (2CH-ar), 138.88 (C-ar), 163.72 (C-ar), 169.14 (C-carbonyl). MS *m/z* (%): 421.2, (M + H) + 100. Anal. calcd. for $C_{27}H_{36}N_2O_2$: C, 77.10; H, 8.63; N, 6.66. Found: C, 77.25; H, 8.49; N, 6.53.

*N-(1-((cyclohexylamino)methyl)cyclohexyl)-4-nitro-N-phenylbenzamide (**8d**)*: Yield 54%; yellow crystals; m.p.: 112–113°C; IR (cm^{-1}): 3352 (NH), 1637 (C = O, amide); ^{1}H NMR ($CDCl_3$) δ ppm: 1.12–2.32 (22H, m, H-cyclohexyl and NH), 2.73 (2H, s, CH_2NH), 7.62–8.31 (9H, m, H-ar). ^{13}C NMR ($CDCl_3$) δ ppm: 20.73 ($2CH_2$-cyclohexyl), 23.17 ($2CH_2$-cyclohexyl), 28.14 (CH_2-cyclohexyl), 28.47 (CH_2-cyclohexyl), 34.03 ($2CH_2$-cyclohexyl), 34.44 ($2CH_2$-cyclohexyl), 50.49, 54.35, 56.73 (CH-cyclohexyl, CH_2-aliphatic, C-cyclohexyl), 121.65 (2CH-ar), 123.88 (2CH-ar), 124.50 (CH-ar), 128.51 (2CH-ar), 129.23 (2CH-ar), 139.31 (C-ar), 140.42(C-ar), 152.53 (C-ar), 169.31 (C-carbonyl). MS *m/z* (%): 436.2, (M + H) + 100. Anal. calcd. for $C_{26}H_{33}N_3O_3$: C, 71.70; H, 7.64; N, 9.65. Found: C, 71.58; H, 7.71; N, 9.51.

*N-(1-((cyclohexylamino)methyl)cyclohexyl)-3,4,5-trimethoxy-N-phenylbenzamide (**8e**)*: Yield 59%; white crystals; m.p.: 142–143°C; IR (cm^{-1}): 3350 (NH), 1638 (C = O, amide); ^{1}H NMR ($CDCl_3$) δ ppm: 1.13–2.21 (22H, m, H-cyclohexyl and NH), 2.81 (2H, s, CH_2NH), 7.12–7.63 (7H, m, H-ar). ^{13}C NMR ($CDCl_3$) δ ppm: 20.72 ($2CH_2$-cyclohexyl), 23.25 ($2CH_2$-cyclohexyl), 28.13 (CH_2-cyclohexyl), 28.29 (CH_2-cyclohexyl), 33.89 ($2CH_2$-cyclohexyl), 34.37 ($2CH_2$-cyclohexyl), 50.47, 54.18, 56.08, 56.61 (CH-cyclohexyl, CH_2-aliphatic, OCH_3, C-cyclohexyl), 56.39 $(OCH_3)_2$, 104.63 (2CH-ar), 121.58 (2CH-ar), 124.37 (CH-ar), 128.02 (CH-ar), 128.98 (2CH-ar), 138.68 (C-ar), 141.97 (C-ar), 150.11 ($2C(OCH_3)_2$-ar), 168.24(C-carbonyl). MS *m/z* (%): 481.3, (M + H) + 100. Anal. calcd. for $C_{29}H_{40}N_2O_4$: C, 72.47; H, 8.39; N, 5.83. Found: C, 72.65; H, 8.25; N, 5.69.

*N-(1-((cyclohexylamino)methyl)cyclohexyl)-7-methoxy-N-phenylbenzo[d][1,3] dioxole-5-carboxamide (**8f**)*: Yield 62%; white crystals; m.p.: 148–149°C; IR (cm^{-1}):

3350 (NH), 1638 (C = O, amide); ^{1}H NMR ($CDCl_3$) δ ppm: 1.08–2.15 (22H, m, H-cyclohexyl and NH), 2.78 (2H, s, CH_2NH), 3.84 (3H, s, OCH_3), 5.92 (2H, s, OCH_2O), 7.21–7.64 (7H, m, H-ar). ^{13}C NMR ($CDCl_3$) δ ppm: 20.67 ($2CH_2$-cyclohexyl), 23.19 ($2CH_2$-cyclohexyl), 28.07 (CH_2-cyclohexyl), 28.26 (CH_2-cyclohexyl), 33.85 ($2CH_2$-cyclohexyl), 34.29 ($2CH_2$-cyclohexyl), 50.43, 54.20, 56.04, 56.58 (CH-cyclohexyl, CH_2-aliphatic, OCH_3, C-cyclohexyl), 100.98 (OCH_2O), 104.82 (2CH-ar), 121.56 (2CH-ar), 124.41 (CH-ar), 128.60 (CH-ar), 129.12 (2CH-ar), 138.90 (C-ar), 140.01 (C-ar), 150.11 (C-ar), 151.02 (C-ar), 168.68 (C-carbonyl). MS *m/z* (%): 465.2, (M + H) + 100. Anal. calcd. for $C_{28}H_{36}N_2O_4$: C, 72.77; H, 8.00; N, 5.85. Found: C, 72.22; H, 7.99, N, 5.74.

*N-(1-((cyclohexylamino)methyl)cyclohexyl)-8-methoxy-N-phenyl-2,3-dihydrobenzo[b][1,4]dioxine-6-carboxamide (**8g**)*: Yield 59%; white crystal; m.p.: 100–102°C; IR (cm^{-1}): 3350 (NH), 1637(C = O, amide); ^{1}H NMR ($CDCl_3$) δ ppm: 1.02–2.17 (22H, m, H-cyclohexyl and NH), 2.73 (2H, s, CH_2NH), 3.83 (3H, s, OCH_3), 4.29–4.38 (4H, m, OCH_2CH_2O), 7.18–7.73 (7H, m, H-ar). ^{13}C NMR ($CDCl_3$) δ ppm: 20.71 ($2CH_2$-cyclohexyl), 23.22 ($2CH_2$-cyclohexyl), 28.08 (CH_2-cyclohexyl), 28.32 (CH_2-cyclohexyl), 33.92 ($2CH_2$-cyclohexyl), 34.41 ($2CH_2$-cyclohexyl), 50.38, 54.22, 56.12, 56.64 (CH-cyclohexyl, CH_2-aliphatic, OCH_3, C-cyclohexyl), 65.45 (OCH_2CH_2O), 104.03 (CH-ar), 105.44 (CH-ar), 121.71 (2CH-ar), 124.52 (CH-ar), 127.62 (CH-ar), 129.22 (2CH-ar), 139.73 (C-ar), 148.21 (C-ar), 151.24 (C-ar), 168.81(C-carbonyl). MS *m/z* (%): 478.62, (M + H) + 100. Anal. calcd. for $C_{29}H_{38}N_2O_4$: C, 72.77; H, 8.00; N, 5.85. Found: C, 72.65; H, 8.16, N, 5.79.

*Synthesis of N-(4-aminobenzyl)-N-(1-((cyclohexylamino) methyl)cyclohexyl)benzenamine (**6h**) and 4-amino-N-(1-((cyclohexyl amino)methyl)cyclohexyl)-N-phenylbenzamide (**8h**)*

A solution of 15 mmol of **6d** or **8d** in 250 ml of ethanol (95%) was hydrogenated at room temperature and normal pressure for 48 h, using 0.34 g (1.5 mmol) of platinum IV oxide. The catalyst was filtered off, and ethanol was evaporated to give a solid substance, which was crystallized from ethyl acetate : *n*-hexane to afford the corresponding amine **6h** or **8h** at 96–98% yield.

*N-(4-Aminobenzyl)-N-(1-((cyclohexylamino)methyl) cyclohexyl)benzenamine (**6h**)*: Yield 98%; white crystals; m.p.: 88–89°C; IR (cm^{-1}): 3200–3350 (NH, NH_2); ^{1}HNMR ($CDCl_3$) δ ppm: 1.10–2.13 (22H, m, H-cyclohexyl and NH), 2.67 (2H, s, CH_2NH), 4.62 (2H, s, CH_2N), 5.68 (2H, br, s, NH_2), 6.54–7.32 (9H, m, H-ar); ^{13}C NMR ($CDCl_3$): 21.15 ($2CH_2$-cyclohexyl), 23.34 ($2CH_2$-cyclohexyl), 28.44 (CH_2-cyclohexyl), 28.92 (CH_2-cyclohexyl), 34.52 ($2CH_2$-cyclohexyl), 34.84 ($2CH_2$-cyclohexyl), 49.50 (CH_2-aliphatic), 55.02 (CH_2-aliphatic), 56.54, 57.10 (CH-cyclohexyl, C-cyclohexyl), 114.08 (2CH-ar), 115.89 (2CH-ar), 117.78 (CH-ar), 125.66 (C-ar), 127.68 (2CH-ar), 129.01 (2CH-ar), 145.97 (C-ar), 150.01 (C-ar). MS *m/z* (%): 392.2, (M + H) + 100. Anal. calcd. for $C_{26}H_{37}N_3$,: C, 79.75; H, 9.52; N, 10.73. Found: C, 79.91; H, 9.62, N, 10.51.

*4-Amino-N-(1-((cyclohexyl amino)methyl)cyclohexyl)-N-phenylbenzamide (**8h**)*: Yield 96%; off-white crystals; m.p.: 114–6°C; IR (cm^{-1}): 3253–3354 (NH, NH_2), 1635 (C = O, amide); ^{1}H NMR ($CDCl_3$) δ ppm: 1.10–2.00 (22H, m, H-cyclohexyl and NH), 2.72 (2H, s, CH_2NH), 5.65 (2H, br, s, NH2), 6.61–7.72 (9H, m, H-ar). ^{13}C NMR ($CDCl_3$) δ ppm: 20.66 ($2CH_2$-cyclohexyl), 23.14 ($2CH_2$-cyclohexyl), 27.88 (CH_2-cyclohexyl), 28.31 (CH_2-cyclohexyl), 33.57 ($2CH_2$-cyclohexyl), 34.02 ($2CH_2$-cyclohexyl), 50.14, 53.89, 56.17 (CH-cyclohexyl, CH_2-aliphatic, C-cyclohexyl), 115.97 (2CH-ar), 121.36 (2CH-ar), 123.82 (CH-ar), 124.04 (CH-ar), 128.03 (2CH-ar), 128.73 (2CH-ar), 138.72 (C-ar), 151.53(C-ar), 168.02 (C-carbonyl). MS *m/z* (%): 406.2, (M + H) + 100. Anal. calcd. for $C_{26}H_{35}N_3O$,: C, 77.00; H, 8.70; N, 10.36. Found: C, 77.23; H, 8.63, N, 10.61.

Biological evaluation

The anticonvulsant and antinociceptive profiles of the newly synthesized compounds **6a–h** and **8a–h** were evaluated.

Materials

Animals: The anticonvulsant activity of the target compounds **6a–h** and **8a–h** was tested on adult male albino mice weighing 20–25 g. Animals were obtained from Animals House Colony of the National Research Centre, Cairo, Egypt. They were housed under standard conditions of light (12 h light/12-h dark cycle), temperature (23 ± 2°C) and relative humidity (55 ± 5%) and were allowed free access to water and maintained at a constant standard diet throughout the experimental period. All animal procedures were performed according to the protocol of the ethics committee of the National Research Center and in accordance with the recommendations for the proper care and use of laboratory animals 'Canadian Council on Animal Care Guidelines, 1984'.

Drugs and chemicals: Diphenylhydantoin sodium (Park Davis, Baltimore, USA), valproic acid (Gerot, Sanofi-Aventis, Wien, Austria), pentylenetetrazole, tween-80 (Sigma, St. Louis, Mo, USA) and tramadol hydrochloride (6th October City Pharma, Egypt) were used.

Methods

Determination of anticonvulsant activity using the maximal pentylenetetrazole seizures test [18]: Experiments were carried out on 31 groups of 6–8 mice each. The first group was the control group; rats in the next five groups received diphenylhydantoin sodium (0.06, 0.10 and 0.20 mmol/kg body weight ≡ 16.5, 27.5 and 55 mg/kg, respectively) [18] and valproic acid (0.17 and 0.24 mmol/kg ≡ 24.5 and 34.6 mg/kg, respectively) [4] individually as reference drugs. Rats in the remaining 25 groups received one of the test compounds by intraperitoneal injection at a dose of 0.08 mmol/kg for each compound in addition to 0.11 mmol/kg for some other compounds. One hour later [19] pentylenetetrazole (0.58 mmol/kg ≡ 80 mg/kg) [18] was administered (intraperitoneally). The survival rate was taken as the index for protective effect.

Evaluation of antinociceptive activity using the hot-plate technique [20]: The method depends on observing the normal response to pain stimulus in untreated animals and comparing it with the response to the same stimulus after administration of a drug at definite time intervals. The response of the animal to heat stimulus is considered a convenient parameter of this technique.

Experiments were carried out with 48 groups of 6–8 mice each. The first group was the control group and rats in the next three groups received tramadol HCl individually at doses of 0.08, 0.11 and 0.16 mmol/kg body weight ≡ 24, 33 and 50 mg/kg, respectively. Rats in each of the other 44 groups received one of the test compounds by intraperitoneal injection at a dose of 0.08 mmol/kg for each compound in addition to 0.11 mmol/kg for some other compounds.

The mice were dropped gently into a dry glass beaker of one litre capacity, maintained at 55–56°C. The normal reaction time in seconds for all animals was determined, which was the interval from the instant the mouse was placed in the hot beaker until the animal licked its feet or jumped out of the beaker. All other signs of discomfort were disregarded. The normal reaction time was determined three times at 5-min intervals and the average was calculated. Nearly all mice licked their feet within 10 s. Unaffected animals within this time were rejected. Each group of mice was injected with a dose of the test compound and the reaction time was redetermined at 10, 20, 30, 45 and 60 min intervals. Another group of mice was injected with the standard reference and the reaction time was redetermined at the previously mentioned time intervals. Thereafter, the relative potency as well as the duration of action of the test compounds was compared with the standard reference.

Data and statistical analysis [21]

Data were expressed as mean ± SEM Statistical comparison between different groups was carried out using one-way analysis of variance followed by multiple comparison *T*-test. Significance was accepted at *P* value less than 0.05.

Results and discussion

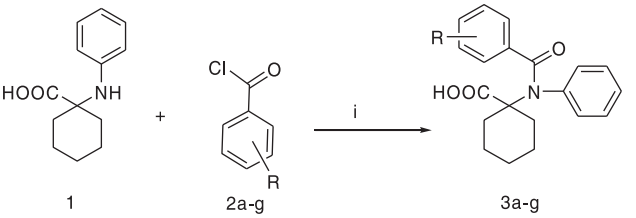
Synthesis

Scheme 1 illustrates the synthesis of 1-(*N*-phenylbenzamido and 4-substituted benzamido) cyclohexane carboxylic acids **3a–g**. By adopting the reported procedure of Aboul-Enein *et al.* [9] for the preparation of **3a–c**, compounds **3d–g** were obtained in yields of 55–67% by the reaction of 1-(phenylamino) cyclohexanecarboxylic acid (**1**) with the appropriate acid chlorides **2a–g**.

The synthesis of the designed *N*-(substituted) benzyl-*N*-(1-((cyclohexyl amino)methyl)cyclohexyl) benzenamines **6a–g** is depicted in Scheme 2. By following the previously reported procedure [9] esters **4d–g** (55–75% yields) were obtained through the reaction of **3d–g** in methanol and catalytic amount of *P*-toulene sulphonic acid. Esters **4d–g** underwent subsequent $LiAlH_4$ reduction of both the ester and the tertiary amidic carbonyl groups to afford the desired amino alcohols **5d–g** in 71–78% yields. The target diamines **6a–g** were achieved by adopting the procedure of Zhonghua *et al.* [22], in which the amino alcohols **5a–g** were reacted with methanesulphonyl chloride in the presence of TEA to form the corresponding mesylates, which were allowed to condense with cyclohexylamine to give **6a–g** in 60–80% yields.

In Scheme 3, the carboxylic acids **3a–g** were reacted with ethylchloroformate in THF, followed by reduction of the produced mixed anhydrides with sodium borohydride, to afford alcohols **7a–g**. In this procedure, the amidic group

Scheme 1



a: R= H, b: R= 4-Cl, c: R= 4-OCH_3,
d: R= 4-NO_2, e: R=3, 4, 5-$(OCH_3)_3$, f: R= 3-OCH_3 4, 5-CH_2O_2,
g: R= 3-OCH_3 4, 5-$(CH_2)_2O_2$

Reagents and conditions for the synthesis of compounds **3a–g**. (i) benzene, triethylamine, reflux 12 h.

remained intact and unaffected. This is proven through IR spectrometry, which revealed the absence of the acid carbonyl band and the presence of the amidic one at 1630 cm^{-1}, in addition to the presence of OH band at 3250 cm^{-1}. Alcohols **7a–g** were converted to the corresponding intermediate mesylates using methylsulphonyl chloride (MSC) and triethylamine (TEA), which were allowed to react with cyclohexylamine to give the target benzamidecyclohexyl amines **8a–g** in 50–80% yields. The nitro compounds **6d** (Scheme 2) and **8d** underwent reduction by hydrogenation at room temperature and normal pressure using platinum IV oxide (PtO_2) as the catalyst in ethanol to afford the corresponding amino derivatives **6h** and **8h**.

Biological evaluation

Compounds **6a–h** and **8a–h** were evaluated for their anticonvulsant potential by adopting the maximal pentylenetetrazole seizures test and diphenylhydantoin sodium and valproic acid as reference drugs (Tables 1 and 2). Antinociceptive activity was determined using the hot-plate technique and tramadol hydrochloride as the reference drug (Tables 3 and 4).

Anticonvulsant potential

The data in Tables 1 and 2 represent the anticonvulsant potential of *N*-aralkyl-*N*-(1-((cyclohexylamino) methyl)cyclohexyl)benzenamine series **6a–h** and *N*-(1-((cyclohexylamino)methyl)cyclohexyl)-*N*-phenyl-substituted benzamide series **8a–h** compared with diphenylhydantoin sodium and valproic acid as reference drugs. In the *N*-aralkyl-*N*-(1-((cyclohexylamino) methyl)cyclohexyl)benzenamine series **6a–h** (Table 1) compounds **6c**, **6d** and **6e** exhibited 100% protection at a dose level of 0.08 mmol/kg body weight, whereas **6a**, **6b**, **6f** and **6g** (Table 1) showed the same anticonvulsant potential at a dose level of 0.11 mmol/kg body weight against pentylenetetrazole seizures. Meanwhile, diphenylhydantoin sodium and valproic acid, used as reference drugs, exhibited 100% protection at dose levels of 0.20 and 0.24 mmol/kg body weight, respectively. The different congeners of this series showed a decrease in activity in the anticonvulsant potential in the following order: **6c** = **6d** = **6e** > **6a** = **6b** = **6f** = **6g** > **6h**.

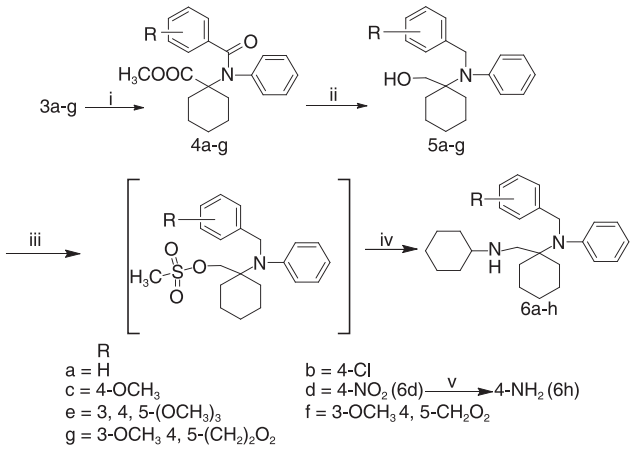
The anticonvulsant activity exhibited by the *N*-(1-((cyclohexylamino)methyl)cyclohexyl)-*N*-phenyl-

Table 1 Anticonvulsant activity of *N*-aralkyl-*N*-(1((cyclohexylamino)methyl)cyclohexyl)benzenamine series 6a–h against the lethal effect of pentylenetetrazole-induced seizures in adult male albino mice using diphenylhydantoin sodium and valproic acid as reference drugs

Compound numbers	Dose mmol/kg (mg/kg)	Number of survival	% protection
Control	0	0	0
Diphenylhydantoin sodium	0.06 (16.5)	4/8	50
	0.10 (27.5)	5/8	62.5
	0.20 (55)	8/8	100
Valproic acid	0.17 (24.5)	6/8	75
	0.24 (34.6)	8/8	100
6a	0.08 (29.3)	5/7	83.33
	0.11 (41.3)	6/6	100[a]
6b	0.08 (32.3)	7/8	87.5
	0.11 (45)	7/7	100[a]
6c	0.08 (32.8)	6/6	100[a]
6d	0.08 (33.6)	6/6	100[a]
6e	0.08 (37.2)	6/6	100[a]
6f	0.08 (36)	4/6	67
	0.11 (49.5)	6/6	100[a]
6g	0.08 (37)	6/7	86
	0.11 (51)	6/6	100[a]
6h	0.08 (31.28)	6/8	75
	0.11 (43)	5/6	84

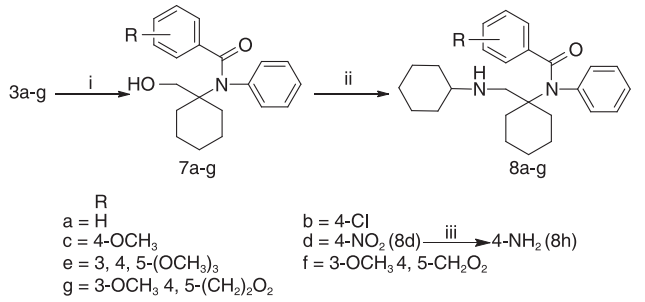
[a]Compounds with higher effect than standard drugs.

Scheme 2



Reagents and conditions for the synthesis of compounds **6a–h**. (i) methanol, *p*-toluene sulphonic acid, benzene; (ii) $LiAlH_4$, tetrahydrofuran, 0–5°C, rt, 5 h, reflux, 3 h; (iii) methanelsulphonyl chloride, triethylamine, dichloromethane, 0–5°C; iv, cyclohexylamine, K_2CO_3, DMF, 80°C, overnight; v, H_2/PtO_2, ethanol, room temperature.

Scheme 3



Reagents and conditions for the synthesis of compounds **8a–h**. (i) (a) ethylchloroformate, triethylamine (TEA), dichloromethane (DCM); (b) $NaBH_4$, H_2O, 12 h, room temperature; (ii) (a) MSC, TEA, DCM, (b) cyclohexylamine, DMF, 80°C, overnight; (iii) PtO_2, ethanol, room temperature.

substituted benzamide series **8a–h** showed that compounds **8a, 8b, 8f** and **8h** gave 100% protection at a dose level of 0.08 mmol/kg, whereas **8c** and **8g** reached the same potential at a dose level of 0.11 mmol/kg. body weight, compared with the reference drug. From these data it can be deduced that the different congeners showed the following decreasing order of anticonvulsant potential: **8a** = **8b** = **8f** = **8h** > **8c** = **8g** > **8e** > **8d** (Table 2).

Table 2 Anticonvulsant activity of *N*-(1-((cyclohexylamino) methyl)cyclohexyl)-*N*-phenyl-substituted benzamide series 8a–h against the lethal effect of pentylenetetrazole-induced seizures in adult male albino mice using diphenylhydantoin sodium and valproic acid as reference drugs

Compound numbers	Dose mmol/kg (mg/kg)	Number of survival	% protection
Control	0	0	0
Diphenylhydantoin sodium	0.06 (16.5)	4/8	50
	0.10 (27.5)	5/8	62.5
	0.20 (55.0)	8/8	100
Valproic acid	0.17 (24.5)	6/8	75
	0.24 (34.6)	8/8	100
8a	0.08 (31.2)	6/6	100[a]
8b	0.08 (33.6)	6/6	100[a]
8c	0.08 (34.0)	4/6	66.67
	0.11 (46.8)	6/6	100[a]
8d	0.08 (34.8)	4/6	66.67
	0.11 (47.8)	4/8	50
8e	0.08 (38.4)	4/8	50
	0.11 (52.8)	5/6	84
8f	0.08 (37.12)	6/6	100[a]
8g	0.08 (35.8)	4/6	67
	0.11 (49.2)	6/6	100[a]
8h	0.08 (32.6)	6/6	100[a]

[a]Compounds with higher effect than standard drugs.

Antinociceptive potential

The data presented in Tables 3 and 4 show the antinociceptive activity of the two series **6a–h** and **8a–h** compared with that of tramadol HCl as a reference drug, which gave its peak at a dose level of 0.16 mmol/kg (50 mg/kg) 20 min from administration.

In series **6a–h**, *N*-aralkyl-*N*-(1-((cyclohexylamino)methyl) cyclohexyl)benzenamine: compound **6c** at a dose level of 0.11 mmol/kg (45 mg/kg) exhibited antinociceptive activity 10–60 min from administration. In addition, **6c** at a dose level of 0.11 mmol/kg showed insignificant difference from tramadol (0.16 mmol/kg ≡ 50 mg/kg) 10–30 min after administration. Furthermore, **6c** exerted significant antinociceptive activity higher than that of the reference drug at 45–60 min and reached its peak after 60 min from administration. The antinociceptive potential of this series is arranged in the following decreasing order: **6c** > **6e** > **6f** > **6g** > **6a** = **6h** > **6b** = **6d** (Table 3).

Regarding *N*-(1-((cyclohexylamino)methyl)cyclohexyl)-*N*-phenyl-substituted benzamide series **8a–h**, compound **8g** at a dose level of 0.11 mmol/kg (49 mg/kg) showed significant antinociceptive activity at 10–60 min and peaked at 60 min after administration compared with the control value. Moreover, it exhibited insignificant difference from reference drug 20–30 min from compound administration, and a significant antinociceptive profile higher than that exhibited by the standard drug 45–60 min from administration The decreasing order of the antinociceptive activity in series **8a–h** is as follows: **8g** > **8f** > **8h** > **8d** > **8e** > **8a** = **8c** (Table 4).

Table 3 The antinociceptive activity of *N*-aralkyl-*N*-(1-((cyclohexylamino)methyl)cyclohexyl)benzenamine series 6a–h in adult male albino mice after compound administration

Compound numbers	Dose mmol/kg (mg/kg)	Time (min)[e] 0	10	20	30	45	60
Control	—	5.50 ± 0.22	5.1 ± 0.39[abc]	5.30 ± 0.24[abc]	5.20 ± 0.27[abc]	5.60 ± 0.23[c]	5.30 ± 0.26[bc]
Tramadol	0.08 (24)	5.64 ± 0.61	8.90 ± 1.80*[c]	8.08 ± 1.73*[bc]	10.08 ± 3.17*[c]	8.75 ± 2.15[c]	7.50 ± 1.14[c]
HCL	0.11 (33)	6.09 ± 0.82	11.50 ± 0.67*[c]	11.80 ± 0.97*[ac]	10.99 ± 1.08*[c]	9.10 ± 1.80[c]	8.44 ± 1.44*
	0.16 (50)	5.99 ± 0.91	14.80 ± 1.36*[ab]	19.80 ± 2.04*[ab]	17.60 ± 2.15*[ab]	16.00 ± 1.51*[ab]	14.80 ± 2.02*[ab]
6a	0.08 (29.3)	8.10 ± 1.14*[a]	8.25 ± 0.96*[c]	12.28 ± 2.77*[c]	8.41 ± 1.57*[c]	6.10 ± 0.87[c]	5.63 ± 0.82[c]
	0.11 (41.3)	7.25 ± 0.49*[a]	11.28 ± 2.80*	14.75 ± 2.00*[abc]	14.58 ± 1.49*	23.00 ± 1.5*[abc]	15.50 ± 0.73*[ab]
6b	0.08 (32.8)	8.80 ± 0.44*[abc]	12.30 ± 1.41*	17.16 ± 2.10*[ab]	20.33 ± 1.33*[ab]	21.16 ± 2.04*[ab]	20.58 ± 2.27*[abc]
6c	0.08 (32.3)	7.10 ± 1.28*[a]	13.00 ± 1.96*	14.41 ± 2.02*[ab]	13.80 ± 2.30*[c]	13.51 ± 2.61*[c]	9.32 ± 1.01*[c]
	0.11 (45)	9.1 ± 0.40*[abc]	13.00 ± 1.87*	16.20 ± 3.35*[ab]	20.8 ± 2.98*[ab]	28.60 ± 3.50*[abc]	34.40 ± 2.8*[abcd]
6d	0.08 (33.6)	7.80 ± 0.52*[a]	13.16 ± 1.09*[a]	19.66 ± 2.06*[ab]	21.33 ± 1.55 *[ab]	21.50 ± 2.70*[ab]	16.75 ± 1.63*[ab]
6e	0.08 (37.2)	7.80 ± 1.33	10.42 ± 2.05*	15.50 ± 2.03*[abc]	21.83 ± 2.45*[ab]	21.50 ± 3.00*[ab]	31.83 ± 2.89*[abc]
6f	0.08 (36)	6.62 ± 1.09	10.08 ± 2.00*[c]	11.75 ± 2.26*[c]	14.33 ± 2.68*	16.40 ± 2.90*[ab]	24.00 ± 2.51*[abc]
	0.11 (49.5)	7.48 ± 1.21	11.25 ± 2.13*	13.33 ± 2.14*[ac]	19.08 ± 2.90*[ab]	21.08 ± 1.46*[abc]	28.83 ± 2.92*[abc]
6g	0.08 (37)	6.21 ± 1.32	8.41 ± 1.16*[c]	8.71 ± 1.02*[bc]	13.14 ± 1.81*[c]	13.80 ± 1.26*[abc]	13.07 ± 1.16*[a]
	0.11 (51)	8.16 ± 1.66*[a]	12.20 ± 2.49*	13.60 ± 2.28*[ac]	18.10 ± 2.46*[ab]	21.50 ± 3.00*[ab]	27.40 ± 3.04*[abc]
6h	0.08 (31.28)	7.06 ± 0.89	11.12 ± 1.46*	12.60 ± 1.82*[c]	13.89 ± 1.09*[c]	17.33 ± 2.11*[ab]	14.32 ± 1.63*[b]
	0.11 (43)	6.90 ± 0.77	11.33 ± 1.95*	16.16 ± 2.03*[ab]	18.42 ± 2.60*[ab]	23.00 ± 2.45*[abc]	22.50 ± 2.67*[abc]

[d]Represents the most potent compound; [e]Each value represents the mean reaction time (s) ± SEM of the number of animals in each group ($n = 6$) after compound administration; [a]$P < 0.05$ compared with tramadol HCL value (0.08 mmol/kg); [b]$P < 0.05$ compared with tramadol value (0.11 mmol/kg); [c]$P < 0.05$ compared with tramadol (0.16 mmol/kg); *$P < 0.05$ compared with control value.

In-silico toxicities, drug-likeness and drug score

The prediction of the in-silico properties of the newly synthesized compounds was evaluated by adopting the Osiris program [23]. The Osiris program depends on the presence of some fragments responsible for mutagenic, tumorigenic, irritant or reproductive effects. The result of toxicity was promising for the new chemical entities (Table 5). Almost all compounds subjected to this study showed low mutagenic, tumorigenic and reproductive effects and moderate irritant effects, which may be due to the central mode of action and high lipophilicity exhibited by these compounds. Only two compounds **6d** and **8d** presented high mutagenic and tumorigenic as well as moderate irritant and reproductive effects, which may be due to the presence of the nitro group.

Currently, there are many approaches to assess a compound drug-likeness based on topological descriptors, fingerprint of drug-likeness keys or other properties such as molecular weight, calculated *n*-octanol/water partition coefficient (CLogP) and solubility prediction [24]. In the present work the Osiris program [23] was also used to estimate such properties and to calculate both drug-likeness and drug score for the final targeted compounds, comparing them with tramadol HCL and valproic acid as standard drugs. Concerning series **6a–h**, compounds **6a**, **6b**, **6c**, **6e** and **6h** theoretically showed drug-likeness higher than that of both tramadol HCL and valproic acid. In addition, compounds **6a**, **6c**, **6e** and **6h** gave a very good drug score in comparison with both standard drugs. In contrast, for series **8a–h** compound **8e** exhibited excellent drug-likeness (Table 5). In addition, compounds **8e**, **8f** and **8h** showed a very good drug score (Fig. 1).

The in-silico toxicity studies, drug-likeness and drug score for compounds **6a**, **6c**, **6e**, **6h**, **8e** and **8h** make these compounds promising leads for future development of antiepileptic and analgesic agents (Table 5).

Conclusion

The results of the present study revealed that the *N*-aralkyl *N*-(1-((cyclohexylamino)methyl) cyclohexyl)benzenamines **6a–h** as well as the *N*-(1-((cyclohexylamino)methyl)cyclohexyl)-*N*-phenyl-substituted benzamides **8a–c** and **8f–h** exhibited the highest anticonvulsant activity at dose levels of 0.08–0.11 mmol/kg, compared with diphenylhydantoin sodium (0.20 mmol/kg) and valproic acid (0.24 mmol/kg) used as reference drugs. Thus, it could be deduced that the substitution at the benzyl group with 4-chloro or 4-nitro substituents exhibits the highest potential as in compounds **6b**, **8b** and **6d**.

With regard to the antinociceptive profile, the *N*-aralkyl-*N*-(1-((cyclohexyl amino)methyl)cyclohexyl)benzenamine series **6a–h** showed the highest effect followed by the *N*-(1-((cyclohexylamino)methyl)cyclohexyl)-*N*-phenyl-substituted benzamide series **8a–h**.

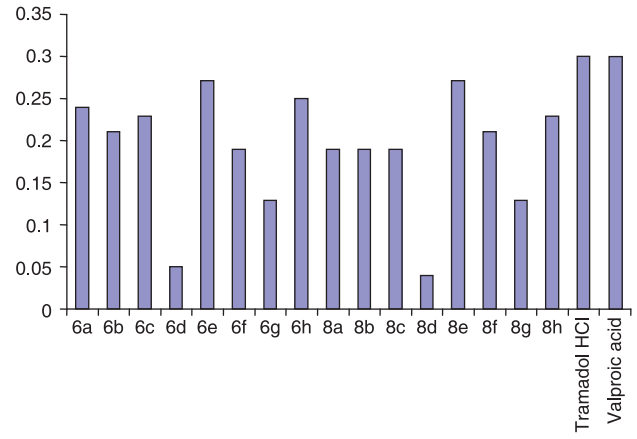
Moreover, these results revealed that replacement of endo-N in the heterocyclic ring A in **I** with exo-N in the cyclohexylaminobenzenamines **6a–h** and cyclohexylaminobenzamides **8a–h** augments the anticonvulsant potential. The in-silico studies for the newly synthesized compounds showed that compounds **6a**, **6c**, **6e**, **6h**, **8e** and **8h** are suitable for future development of antiepileptic and analgesic agents.

Table 4 The antinociceptive activity of *N*-(1-((cyclohexylamino)methyl)cyclohexyl)-*N*-phenyl-substituted benzamide series 8a–h in adult male albino mice after compound administration

		Time (min)[e]					
Compound numbers	Dose mmol/kg (mg/kg)	0	10	20	30	45	60
Control	—	5.50 ± 0.22	5.1 ± 0.39^{abc}	5.30 ± 0.24^{abc}	5.20 ± 0.27^{abc}	5.60 ± 0.23^{c}	5.30 ± 0.26^{bc}
Tramadol	0.08 (24)	5.64 ± 0.61	8.90 ± 1.80*^{c}	8.08 ± 1.73^{bc}	10.08 ± 3.17*^{c}	8.75 ± 2.15^{c}	7.50 ± 1.14^{c}
HCL	0.11 (33)	6.09 ± 0.82	11.50 ± 0.67*^{c}	11.80 ± 0.97*^{ac}	10.99 ± 1.08*^{c}	9.10 ± 1.80^{c}	8.44 ± 1.44*^{c}
	0.16 (50)	5.99 ± 0.91	14.80 ± 1.36*^{ab}	19.80 ± 2.04*^{ab}	17.60 ± 2.15*^{ab}	16.00 ± 1.51*^{ab}	14.80 ± 2.02*^{ab}
8a	0.08 (31.2)	7.00 ± 0.36	10.50 ± 1.19*^{c}	14.40 ± 2.11*^{a}	16.00 ± 2.04*^{ab}	12.60 ± 1.80*	12.80 ± 1.66*^{ab}
8c	0.08 (33.6)	7.50 ± 0.46	12.60 ± 1.07*	12.58 ± 1.40*^{ac}	16.08 ± 2.30*^{ab}	15.90 ± 2.08*^{ab}	14.16 ± 2.14*^{ab}
8d	0.08 (34.8)	7.10 ± 0.86	7.80 ± 2.10^{c}	12.40 ± 2.31*^{ac}	13.80 ± 2.07*	10.80 ± 2.00*^{c}	10.31 ± 1.13*^{c}
	0.11 (47.8)	8.30 ± 0.79	10.25 ± 1.03*^{c}	17.13 ± 1.61*^{ab}	22.00 ± 2.05*^{ab}	14.50 ± 2.10*^{ab}	14.00 ± 1.61*^{ab}
8e	0.08 (38.4)	7.03 ± 0.95	11.50 ± 1.13*	12.00 ± 1.10*^{ac}	13.20 ± 1.03*	16.60 ± 2.05*^{ab}	13.00 ± 1.06*^{ab}
	0.11 (52.8)	7.80 ± 0.63	12.75 ± 1.70*	14.50 ± 2.00*^{a}	19.25 ± 1.09*^{ab}	20.80 ± 1.74*^{abc}	15.37 ± 1.16*^{ab}
8f	0.08 (37.12)	7.28 ± 1.34	12.50 ± 2.39*	17.50 ± 2.31*^{ab}	24.58 ± 2.63*^{abc}	21.00 ± 1.94*^{abc}	15.92 ± 1.66*^{ab}
8g	0.08 (35.8)	7.55 ± 1.63	7.41 ± 1.30^{c}	9.50 ± 1.05*^{c}	9.50 ± 1.18*	16.75 ± 2.10*^{ab}	14.25 ± 2.04*^{ab}
	0.11 (49.2)	7.28 ± 1.05	9.40 ± 1.80*^{c}	15.10 ± 1.91*^{ab}	18.50 ± 1.46*^{ab}	25.10 ± 2.30*^{abc}	30.70 ± 2.61*^{abcd}
8h	0.08 (32.6)	8.30 ± 1.40	15.17 ± 2.03*^{a}	21.30 ± 2.50*^{ab}	22.30 ± 2.00*^{ab}	23.36 ± 2.10*^{abc}	17.80 ± 2.21*^{ab}

[d]Represents the most potent compound; [e]Each value represents the mean reaction time (s) ± SEM of the number of animals in each group ($n = 6$) after compound administration; [a]$P < 0.05$ compared with tramadol HCL value (0.08 mmol/kg); [b]$P < 0.05$ compared with tramadol value (0.11 mmol/kg); [c]$P < 0.05$ compared with tramadol value (0.16 mmol/kg); *$P < 0.05$ compared with control value.

Figure 1



Drug score for new synthesized compounds and standard drugs.

Table 5 In-silico toxicity, drug-likeness and lipophilicity

Compound numbers	Toxicity				Drug likeness	DS	CLogP
	M	T	I	R			
6a	Low	Low	Medium	Low	0.25	0.24	5.89
6b	Low	Low	Medium	Low	0.80	0.21	6.20
6c	Low	Low	Medium	Low	0.00	0.23	5.79
6d	High	High	Medium	Medium	−1.45	0.05	5.62
6e	Low	Low	Medium	Low	2.31	0.27	5.58
6f	Low	Low	Medium	Low	0.03	0.19	5.89
6g	Low	Low	Medium	Low	−6.99	0.13	5.87
6h	Low	Low	Medium	Low	−0.13	0.25	5.17
8a	Low	Low	Medium	Low	−0.87	0.19	6.03
8b	Low	Low	Medium	Low	0.58	0.19	6.65
8c	Low	Low	Medium	Low	−0.69	0.19	5.93
8d	High	High	Medium	Medium	−1.68	0.04	5.71
8e	Low	Low	Medium	Low	5.67	0.27	5.72
8f	Low	Low	Medium	Low	1.19	0.21	6.03
8g	Low	Low	Medium	Low	−5.8	0.13	6.02
8h	Low	Low	Medium	Low	−0.36	0.23	5.31
Tramadol HCL	Low	Low	Low	High	−1.72	0.3	2.50
Valproic acid	Low	Low	Low	High	−2.62	0.3	2.69

CLogP, calculated *n*-octanol/water partition coefficient; DS, drug score; I, irritant effect; M, mutagenic effects; R, reproductive effects; T, tumorigenic effects.

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Conflicts of interest

There are no conflicts of interest.

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