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Synthesis and Anticonvulsant Activity of Certain *N*-Aralkyl-*N*-(1-Substituted Cyclohexyl) Benzenamines

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Abstract

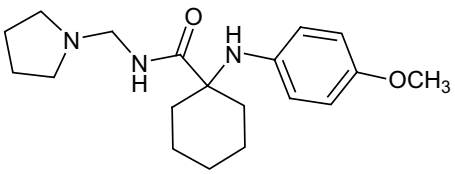
The synthesis of certain *N*-aralkyl(1-aminomethylcyclohexyl) benzenamines **6a-i**, *N*-(alkyloxymethyl or aralkyloxymethylcyclohexyl)-*N*-arylbenzenamines **9a-l** and 1-(1-(aralkylphenylamino)cyclohexyl methoxy)-3-isopropylaminopropan-2-ols **11a-c** has been accomplished. These compounds exhibited anticonvulsant activity. Compounds **9h**, **9b** and **11a** at doses 0.06, 0.075 and 0.08 mmol/kg, respectively provoked maximal anticonvulsant potential against pentylenetetrazol (PTZ) induced seizures test compared with diphenylhydantoin (0.2 mmol/kg) and valproic acid (0.24mmol/kg).

Key Words

N-aralkyl-*N*-(1-substitutedcyclohexyl)benzenamines, 1-(1-(aralkylphenyl amino)cyclohexylmethoxy)-3-isopropylaminopropan-2-ol, anticonvulsant activity.

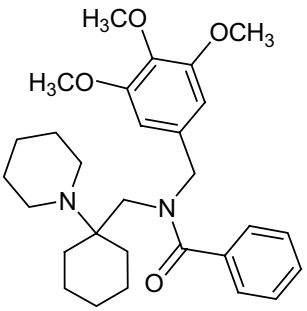
Introduction

Many 1,1-disubstituted cyclohexane amines have been reported to display anticonvulsant potential, such as 1-(4-methoxyphenylamino)-*N*-((pyrrolidin-1-yl)methyl)cyclohexane carboxamide **I** [1].



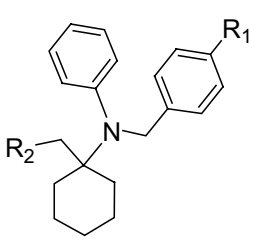
I

N-((1-(piperidin-1-yl)cyclohexyl)methyl)-*N*-(3,4,5-trimethoxybenzyl)-benzamide, **II** (5 mg, 0.01 mmol/kg) [2] has been reported to provoke maximal anticonvulsant activity in PTZ test compared with diphenylhydantoin (50 mg, 0.2mmol/kg).

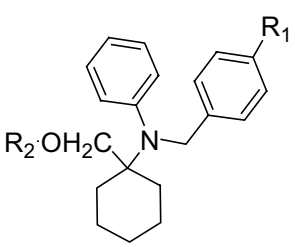


II

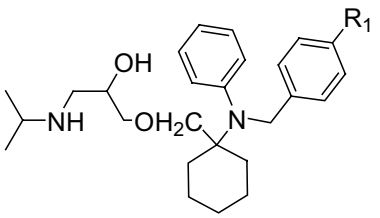
These results instigated the synthesis of three series of 1-substituted cyclohexyl benzenamines namely *N*-aralkyl(1-amino methylcyclohexyl)benzenamines **6a-i (Scheme I**, **Table 3)**, *N*-(alkyl oxymethyl or aralkyloxymethylcyclohexyl)-*N*-arylbenzenamines **9a-l**, in addition to 1-(1-(aralkylphenylamino)cyclohexylmethoxy)-3-isopropyl aminopropan-2-ols, **11a-c (Scheme II**, **Table 4**,**6)** to screen their anticonvulsant activities.



6a-i



9a-l



11a

Results and Discussion

1. Chemistry

Synthesis of *N*-aralkyl(1-aminomethylcyclohexyl)benzenamines, **6a-i** was illustrated in Scheme I, Table 3.

1-(Phenylamino)cyclohexanecarboxylic acid **(3)** was prepared from 1-(phenylamino)cyclohexanecarbonitrile **(1)** which was then hydrolyzed in two steps using conc. sulphuric acid then conc. hydrochloric acid [3].

1-(*N*-arylanilido) cyclohexane carboxylic acids **4a-c** have been prepared as described [4].

The *N*-(amidocyclohexyl)-*N*-phenylbenzamides, **5a-i** were obtained in high yields by adopting the mixed anhydride method using **4a-c** and trifluoroacetic anhydride followed by the addition of the appropriate amine. Subsequent hydride reduction of the two amidic carbonyl groups of **5a-i** gave the target compounds *N*-aralkyl(1-aminomethyl) cyclohexanebenzamines **6a-i**.

The synthesis of both *N*-(alkyloxymethyl or aralkyloxy methylcyclohexyl)-*N*-arylbenzenamines, **9a-l** and 1-(1-(aralkylphenyl amino)cyclohexylmethoxy)-3-isopropylaminopropan-2-ol, **11a-c** were illustrated in **Scheme II**, **Table 4**,**6**.

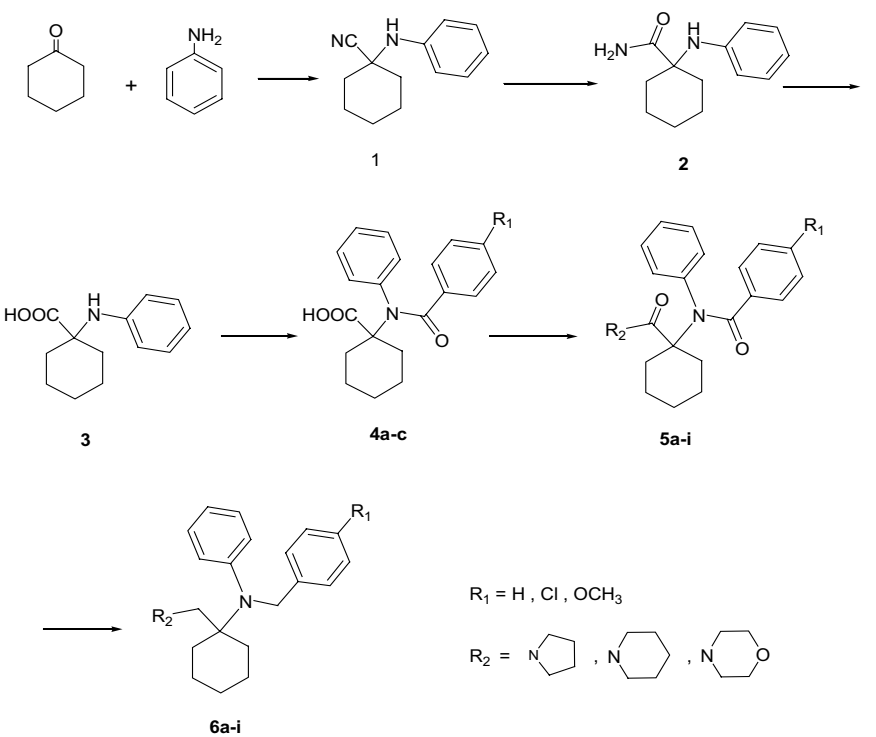
Compound **8b**, which is not reported before, has been synthesized by following our reported procedure for the preparation of **8a** and **8c** [4] through esterification of **4b** with methanol in the presence of catalytic amount of p-toulenesulphonic acid to afford the corresponding ester **7b**

and subsequent $LiAlH_4$ reduction of both the ester and the tertiary amidic groups to afford the desired amino alcohols **8a-c** in high yields.

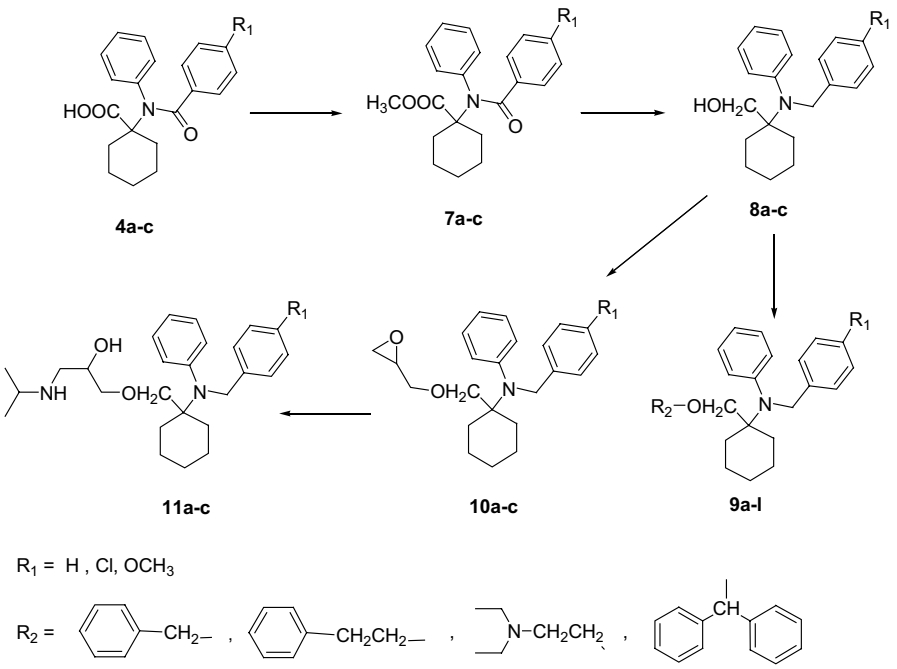
Compounds **9a-l** and **10a-c** were obtained through the etherification of the amino alcohols **8a-c** with the appropriate aralkyl, aminoalkyl halide (in case of **9a-l**) and epichlorohydrin (in case of **10a-c**) in the presence of sodium hydride in DMF (c.f. **Table 4,5**).

Subsequent treatment of **10a-c** with isopropylamine adopting the procedure of Osa *et al.* [5] resulted in the corresponding 1-(1-(aralkyl phenylamino)cyclohexylmethoxy)-3-isopropylaminopropan-2-ols, **11a-c** in high yields (c.f. **Table 6**).

SCHEME I



SCHEME II



2. Pharmacology

The data presented in **Table 1** illustrates the anticonvulsant potential of the **6a-i**, **9a-l** and **11a-c series** compared with diphenylhydantoin and valproic acid used as reference drugs.

In the **6a-i series** the *N*-benzyl-*N*-(1-((pyrrolidin-1-yl)methyl) cyclohexyl)benzenamine **(6a)**, the *N*-benzyl-*N*-(1-((piperidin-1-yl)methyl)cyclohexyl)benzenamine **(6b)** and the *N*-(4-methoxybenzyl)-*N*-(1-((piperidin-1-yl)methyl)cyclohexyl)benzenamine **(6h)**, exhibited 100% protection against pentylenetetrazol seizures at a dose level of 0.11 mmol/kg, while diphenylhydantoin sodium and valproic acid, used as reference drugs, reached the same protection level at dose levels of 0.20 and 0.24 mmol/kg, respectively. Moreover, the *N*-benzyl-*N*-(1-(morpholinomethyl)cyclohexyl)benzenamine **(6c)** and the (4-chloro-benzyl)-*N*-(1-(morpholinomethyl)cyclohexyl)benzenamine **(6f)** exhibited

an equipotent protection potential of 87.50% at the tested dose level (0.11 mmol/kg). Regarding the structure-activity relationship, the different congeners of the **6a-i series** showed a decrease in the anticonvulsant potential in the following order **6a = 6b = 6h > 6c = 6f > 6d = 6i > 6e = 6g**.

Concerning the **9a-l** and **11a-c series** (c.f. **Table 1**), compounds **9h** (0.06 mmol/kg), **9b** (0.075 mmol/kg), **11a** (0.08 mmol/kg) and **9k** (0.11 mmol/kg) displayed 100% protection compared with diphenylhydantoin (0.2 mmol/kg) and valproic acid (0.24 mmol/kg) used as reference drugs. Whereas, compounds **9d, 9e, 9g, 9i, 9j, 9l** and **11c** exhibited equipotent protection potential of 75% at a dose level 0.11 mmol/kg. Regarding the structure-activity relationship, the anticonvulsant activity was arranged in the following decreasing order:

9h >9b > 11a > 9k > 9d = 9e = 9g = 9i = 9j = 9l = 11c > 9c = 9f > 11b.

Moreover, compounds **6a, 6b, 6h, 9b, 9h 9k** and **11a** which displayed 100% protection were assayed in a dose up to 10 times the tested dose (1.1 mmol/kg) and did not prove to be toxic, since neither mortality nor toxic manifestations were observed up to 24 hours after compound administration. The ED_{50} for compound **9h** was 0.034 mmol/kg with 95% confidence limits of 0.023 and 0.05 mmol/kg.

In conclusion, the results of the present study revealed that the maximal potential in the **6a-li series** was achieved with the compounds having the pyrrolidine **6a** and the piperidine **6b** and **6h** heterocyclic moieties in their side chains at dose of 0.11 mmol/kg. Meanwhile, regarding the **9a-l** and **11a-c series**, compound **9h** (0.06 mmol/kg), **9b** (0.075 mmol/kg), and **11c** (0.08 mmol/kg) exhibited the 100% protection at dose level lower than that exerted by the **6a-i series**.

Table 1: Anticonvulsant activity of compounds 6a-i, 9a-l and 11a-c against lethal effect of pentylenetertazol induced seizers in adult male albino mice arranged in decreasing order according to the percentage of protection.

Comp.	Dose mmol/kg	No. of Survival*	% protection	Comp.	Dose mmol/kg	No. of Survival*	% protection
Control	-	0	0	**9a**	0.11	7	87.50
Diphenyl hydantoin	0.06	4	50.00	**9d**	0.11	6	75.00
	0.10	5	62.50	**9e**	0.11	6	75.00
	0.20	8	100	**9g**	0.11	6	75.00
Valproic acid	0.17	6	75.00	**9i**	0.11	6	75.00
	0.24	8	100	**9j**	0.11	6	75.00
9h	0.06	8	100	**9l**	0.11	6	75.00
9b	0.75	8	100	**11c**	0.11	6	75.00
11a	0.08	8	100	**9c**	0.11	5	62.50
6a	0.11	8	100	**9f**	0.11	5	62.50
6b	0.11	8	100	**6d**	0.11	4	50.00
6h	0.11	8	100	**6i**	0.11	4	50.00
9k	0.11	8	100	**6e**	0.11	3	37.50
6c	0.11	7	87.50	**6g**	0.11	3	37.50
6f	0.11	7	87.50	**11b**	0.11	1	12.50

* out of eight animals

Experimental

1. Chemistry

All melting points were uncorrected and determined with Electrothermal Capillary melting point apparatus.

Infrared (IR) spectra were recorded as thin film (for oils) in KBr discs or in KBr pellets (for solids) with Philips PU 9712 IR and Schimadzu IR 435 spectrometer and values are reported in cm^{-1}.

^{1}H NMR and ^{13}C NMR spectra were carried out on Varian Mercury VX 300 MHz Spectrophotometer using TMS as an internal standard. Chemical shift values are recorded in ppm δ scale.

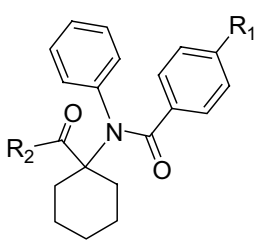
Mass spectral data were recorded as chemical ionization (CI/CH_4) from a Finnigan Mat SSQ-7000 Spectrophotometer.

Elemental analyses were carried out in Microanalytical Unit, National Research Centre.

***General procedure for the preparation of N-(amidocyclohexyl)-N-phenylbenzamides,* 5a-i**

To a stirred solution of 0.01 mol of the acids **4a-c** [4] in 20 mL of dry THF, 0.01 mol (2.1 g, 1.4 mL) of trifluoroacetic anhydride was added dropwise at 5°C and stirred for 5 min. at 5°C. The appropriate amine (0.01 mol) was added in one portion. The mixture was left over night under continuous stirring, evaporated under vacuum and the resulted oils were dissolved in methylene chloride, washed with sodium carbonate, dilute HCl and finally with distilled water (20 mL each). The organic layer was dried over anhydrous $MgSO_4$ and evaporated under vacuum**,** the residual solids were crystallized from isopropanol to give the corresponding amides **5a-i** (c.f. **Table 2**).

Table 2: Physical and analytical data of *N*-(amidocyclohexyl)-*N*-phenylarylamides, **5a-i**



5a-i

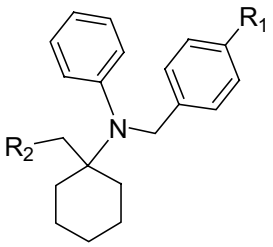
No.	R_1	R_2	Yield (%)	m.p. °C	Formula Mol.Wt.	Cl/CH_4, m/z $(M+H)^+$	Microanalysis %			
								C	H	N
5a	H		85	188-9	$C_{24}H_{28}N_2O_2$ 376.49	377.5	Calc. F.	76.56 76.75	7.50 7.39	7.44 7.54
5b	H		95	182-3	$C_{25}H_{30}N_2O_2$ 390.52	391.5	Calc. F.	76.89 76.53	7.74 7.81	7.17 7.26
5c	H		92	174-5	$C_{24}H_{28}N_2O_3$ 392.49	393.5	Calc. F.	73.44 73.16	7.19 7.05	7.14 7.23
5d	Cl		95	170-1	$C_{24}H_{27}ClN_2O_2$ 410.94	412	Calc. F.	70.15 69.85	6.62 6.49	6.68 6.55
5e	Cl		91	168-9	$C_{25}H_{29}ClN_2O_2$ 424.96	425.9	Calc. F.	70.66 70.82	6.88 6.63	6.59 6.62
5f	Cl		90	186-7	$C_{24}H_{27}ClN_2O_3$ 426.94	427.9	Calc. F.	67.52 67.27	6.37 6.22	6.56 6.44
5g	OCH_3		83	198-9	$C_{24}H_{29}N_2O_3$ 393.50	394.5	Calc. F.	73.25 73.05	7.43 7.53	7.12 6.95
5h	OCH_3		94	169-70	$C_{26}H_{32}N_2O_3$ 420.54	421.5	Calc. F.	74.26 73.99	7.67 7.41	6.66 6.49
5i	OCH_3		93	195-6	$C_{25}H_{30}N_2O_4$ 422.52	423.5	Calc. F.	71.07 70.77	7.16 6.97	6.63 6.68

IR revealed the presence of anilido C=O band 1680 and the other amidic C=O at 1648.

***General procedure for the preparation of N-aralkyl(1-amino-methylcyclohexyl)benzenamines*, 6a-i**

A solution of 0.02 mol of the amides **5a-i** in dry THF was added dropwise to a cold (5-10 °C) slurry of 0.04 mol (1.52 g) of $LiAlH_4$ in THF. The reaction mixture was stirred and refluxed for 24h. After cooling, the excess $LiAlH_4$ was decomposed by slow addition of a saturated solution of Na_2SO_4. The precipitate was filtered off and washed with THF. The filtrate and washings were evaporated under vacuum to give viscous oils which were then purified through column chromatography using neutral alumina as a stationary phase and n-hexane : ethylacetate (8 : 2) as a mobile phase to give oils of the corresponding amines **6a-i** (c.f. **Table 3**).

Table 3: Analytical data of *N*-aralkyl(1-aminomethylcyclohexyl) Benzenamines, **6a-i**



6a-i

No.	R_1	R_2	Yield (%)	Formula Mol.Wt.	Cl/CH_4, m/z $(M+H)^+$	Microanalysis %			
							C	H	N
6a	H		95	$C_{24}H_{32}N_2$ 348.52	349.5	Calc. F.	82.71 82.39	9.25 9.31	8.04 7.88
6b	H		90	$C_{25}H_{34}N_2$ 362.55	363.5	Calc. F.	82.82 82.55	9.45 9.49	7.73 7.65
6c	H		82	$C_{24}H_{32}N_2O$ 364.52	365.5	Calc. F.	79.08 79.14	8.85 8.61	7.68 7.52
6d	Cl		83	$C_{24}H_{31}ClN_2$ 382.97	383, M^+	Calc. F.	75.27 74.91	8.16 7.99	7.31 7.35
6e	Cl		92	$C_{25}H_{33}ClN_2$ 397.00	398	Calc. F.	75.63 75.88	8.38 8.21	7.06 6.82
6f	Cl		85	$C_{24}H_{31}ClN_2O$ 398.97	400	Calc. F.	72.25 71.96	7.83 7.61	7.02 6.87
6g	OCH_3		81	$C_{25}H_{34}N_2O$ 378.55	379.5	Calc. F.	79.32 79.04	9.05 8.86	7.40 7.49
6h	OCH_3		88	$C_{26}H_{36}N_2O$ 392.58	393.6	Calc. F.	79.55 79.71	9.24 9.01	7.14 6.94
6i	OCH_3		90	$C_{24}H_{34}N_2O_2$ 394.55	395.5	Calc. F.	76.10 75.75	8.69 8.78	7.10 6.98

***Methyl 1-(4-chloro-N-phenylbenzamido)cyclohexanecarboxylate* (7b)**

A solution of 0.01 mol of the acid **4b**, 0.04 mol (1.28 gm, 1.62 mL) of dry methanol and 0.002 g of p-toluenesulphonic acid in 30 mL of dry benzene was refluxed under stirring for 12h. The solvent was evaporated under vacuum and the residue was dissolved in chloroform. The chloroformic solution was washed with aqueous Na_2CO_3 solution then with water (20 mL each). The organic phase was dried over anhydrous $MgSO_4$. The chloroform was driven off under vacuum and

the residual solid was crystallized from ether-cyclohexane m.p. = 105-106 ^{0}C, analysis calculated for $C_{21}H_{22}ClNO_3$: C: 67.83, H:5.96, N: 3.77; Found: C: 67.98, H: 5.89, N: 3.85. IR revealed the presence of an ester band at 1735 and amide band at 1687 and EI/MS, m/z (%): 371, M^+, $C_{21}H_{22}ClNO_3^+$ (40); 298 (100).

***(1-((4-Chlorobenzyl)phenylamino)cyclohexyl)methanol* (8b)**

A solution of 0.1 mol of the esters **7b** in dry THF was added to a slurry of 0.15 mol (5.7g) of $LiAlH_4$ in dry THF at 0^{0}C. The temperature of the reaction was raised gradually to room temperature and left for 5h, then refluxed for further 3h. The complex was decomposed using a saturated solution of Na_2SO_4 and filtered over celite. The filtrate was dried over anhydrous Na_2SO_4 and evaporated under vacuum to give the alcohol **8b** as viscous oil.

IR showed OH band at 3450. CI/CH_4, m/z **8b**: 326.4, $(M+H)^+$, Analysis calculated for $C_{20}H_{24}ClNO$: C: 72,82, H: 7.33, N: 4.25; Found: C: 75.53, H: 4.18

***General procedure for the preparation of N-(alkyloxy or aralkyloxy methylcyclohexyl)-N-arylbenzenamines,* 9a-l**

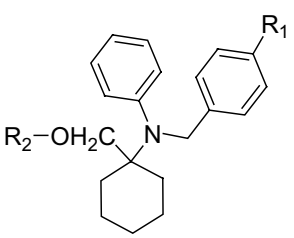
To a stirred mixture of 5 mmol of the alcohols **8a-c**, and 8 mmol (0.19 g) of sodium hydride in DMF (15 mL) was added dropwise 6 mmol of the appropriate aralkyl halide or 2-diethylaminoethyl chloride HCl in DMF (5 mL). The reaction mixture was stirred at room temperature for 30 min., then heated at 80^{0}C for 4h. The mixture was cooled to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (15 mL x 3). For compounds **9a**,**b**,**d**,**e**,**f**,**h**,**l**,**j** and **l** the organic extracts were dried over $MgSO_4$, filtered and evaporated under vacuum to give viscous oils of the corresponding ethers, which were then purified through column chromatography using neutral alumina as a stationary phase and n-hexane : ethyl acetate (9.5 : 0.5) as a mobile phase to give pale yellow oils of the corresponding ethers **9a**,**b**,**e**,**f**,**i** and **j** and

white solids for compounds **9d**,**h** and **l**. For compounds **9c**,**g** and **k** the ethyl acetate was driven off and the residual oil was acidified with 10 mL of 2N HCl, then washed with ether (3x15 mL). The acidic layer was separated and rendered alkaline with 10% sodium hydroxide solution and extracted with ethyl acetate (3x25 mL). The organic layer was separated and dried over anhydrous $MgSO_4$ and evaporated under vacuum to give viscous oils of the target compounds (c.f. **Table 4)**.

***General procedure for the preparation of N-(1-(((oxiran-2-yl) methoxy) methyl)cyclohexyl)-N-aralkylbezeneamine*, 10a-c :**

To a stirred mixture of 5 mmol of the alcohols **8a-c**, and 8 mmol (0.19 g) of sodium hydride in DMF (15 mL) was added dropwise 6 mmol of epichlorohydrin (0.55 g, 0.47 mL) in DMF (5 mL). The reaction mixture was stirred at room temperature for 30 min., then heated at 80^0C for 4h. The mixture was cooled to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (15 mL x 3). The organic extracts were dried over $MgSO_4$, filtered and evaporated under vacuum to give viscous oils of the corresponding ether which were then purified through column chromatography using neutral alumina as a stationary phase and n-hexane : ethyl acetate (9.5 : 0.5) as a mobile phase to give pale yellow oils of the corresponding ethers **10a-c** (c.f. **Table 5**).

Table 4: *N*-(alkyloxy or aralkyloxy methylcyclohexyl)-*N*-aryl benzen amines, **9a-l**



9a-l

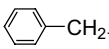
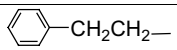
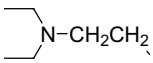
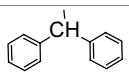
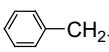
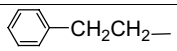
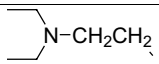
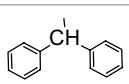
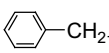
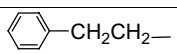
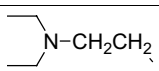
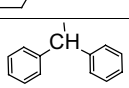
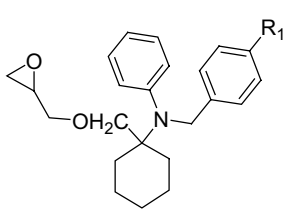
No.	R_1	R_2	Yield (%)	m.p ^0C	Formula Mol.Wt.	Cl/CH_4, m/z $(M+H)^+$	Microanalysis %			
								C	H	N
9a	H		80	oil	$C_{27}H_{31}NO$ 385.54	386.5	Calc. F.	84.11 83.80	8.10 7.94	3.63 3.70
9b	H		82	oil	$C_{28}H_{33}NO$ 399.57	400.6	Calc. F.	84.17 84.41	8.32 8.15	3.51 3.31
9c	H		79	oil	$C_{26}H_{38}N_2O$ 394.59	395.5	Calc. F.	79.14 78.85	9.71 9.45	7.10 6.97
9d	H		75	170	$C_{33}H_{35}NO$ 461.64	462.6	Calc. F.	85.86 86.21	7.64 7.41	3.03 2.75
9e	Cl		85	oil	$C_{27}H_{33}ClNO$ 419.99	421	Calc. F.	77.21 77.01	7.20 6.99	3.34 3.21
9f	Cl		84	oil	$C_{28}H_{32}ClNO$ 434.01	435	Calc. F.	77.49 77.20	7.43 7.34	3.23 3.11
9g	Cl		77	oil	$C_{26}H_{37}ClN_2O$ 429.04	430	Calc. F.	72.79 72.54	8.69 8.48	6.53 6.32
9h	Cl		78	165	$C_{33}H_{34}ClNO$ 496.08	497	Calc. F.	79.90 80.12	6.91 6.77	2.82 2.68
9i	OCH_3		80	oil	$C_{28}H_{33}NO_2$ 415.57	415, M^+	Calc. F.	80.93 80.25	8.00 7.88	3.37 3.24
9j	OCH_3		78	oil	$C_{29}H_{35}NO_2$ 429.59	30.6	Calc. F.	81.08 80.74	8.21 8.09	3.26 3.12
9k	OCH_3		85	oil	$C_{27}H_{40}N_2O_2$ 424.62	424.6, M^+	Calc. F.	76.37 76.04	9.50 9.35	6.60 6.72
9l	OCH_3		73	190	$C_{34}H_{37}NO_2$ 491.66	492.6	Calc. F.	93.06 92.69	7.59 7.68	2.85 2.69

Table 5: Analytical data of *N*-(1-(((oxiran-2-yl) methoxy) methyl) cyclohexyl)-*N*-aralkylbezeneamine, **10a-c**



10a-c

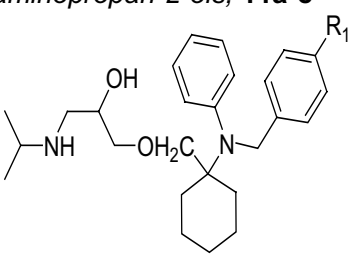
No.	R_1	Yield (%)	Formula Mol.Wt.	Cl/CH, m/z $(M+H)^+$	Microanalysis %			
						C	H	N
10a	H	75	$C_{23}H_{29}NO_2$ 351.48	352.48	Calc. F.	78.59 78.22	8.32 8.18	3.99 2.84
10b	Cl	80	$C_{23}H_{28}ClNO_2$ 385.93	387	Calc. F.	71.58 71.84	7.31 7.21	3.63 3.52
10c	OCH_3	78	$C_{24}H_{31}NO_3$ 381.51	381.5, M^+	Calc. F.	75.56 75.24	8.19 8.27	3.67 3.58

***General procedure for the preparation of 1-(1-(aralkylphenyl amino) cyclohexylmethoxy)-3- isopropylaminopropan-2-ols,* 11a-c**

A mixture of 0.01 mol of the epoxy compounds **10a-c** and 0.05 mol (3 g, 4.3 mL) of isopropylamine was stirred at room temperature in the presence of 0.01 mol (1 g, 0.9 mL) of triethylamine for 24h in isopropylamine (25 mL). The reaction mixture was evaporated to dryness and the residue was acidified with 10 mL of 2N HCl, and then extracted with ether (3x10 mL). The acidic layer was separated and rendered alkaline with 10% sodium hydroxide solution, extracted with ethyl acetate (3x25 mL), dried over anhydrous $MgSO_4$ and evaporated under vacuum to give viscous oils which was then purified through column chromatography using neutral alumina as a stationary phase and n-hexane : ethyl acetate (9 : 1) as a mobile phase to give clear colourless oils of the corresponding alcohols **11a-c** which were converted to the corresponding monohydrochloride salts by treating with methanolic-HCl solution (c.f. **Table 6**).

IR showed of NH band at 3330 and alcoholic OH bands at 3550

Table 6: Physical data of *of 1-(1-(aralkylphenyl amino)cyclohexyl-methoxy)-3-isopropylaminopropan-2-ols,* **11a-c**

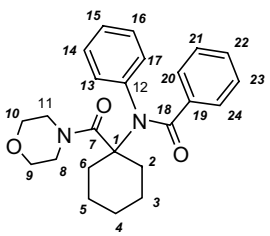


11a-c

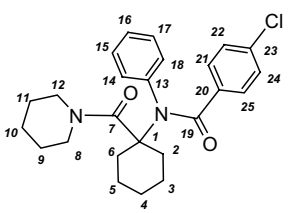
No.	R_1	Yield (%)	m.p ^0C	Formula Mol.Wt.	Cl/CH_4, m/z $(M+H)^+$	Microanalysis %			
							C	H	N
11a	H	82	Oil 130-1*	$C_{26}H_{38}N_2O_2$ 410.59	411.6	Calc. F.	76.06 75.74	9.33 9.39	6.82 6.74
11b	Cl	85	Oil 142.3*	$C_{26}H_{37}ClN_2O_2$ 445.04	446	Calc. F.	70.17 69.85	8.38 8.24	9.29 9.36
11c	OCH_3	80	Oil 122-3*	$C_{27}H_{40}N_2O_3$ 440.62	441.5	Calc. F.	73.60 73.91	9.15 9.04	6.36 6.28

* Melting point of the corresponding monohydrochloride salts

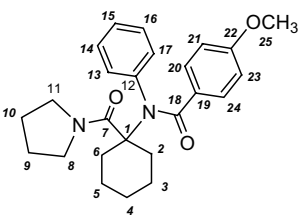
Table 7: ^{1}H NMR* Data of 5c, 5e, 5g, 6a, 6e, 6i, 9a, 9f, 9h, 9k, 10b and 11a & ^{13}CNMR* Data of 5c, 5e, 5g, 6a, 6e, 6i, 9f, 9h, and 10b.



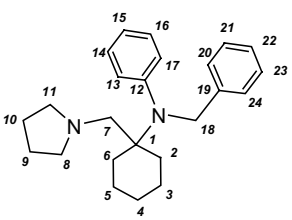
5c



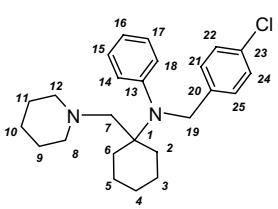
5e



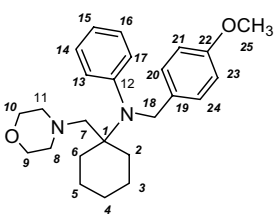
5g



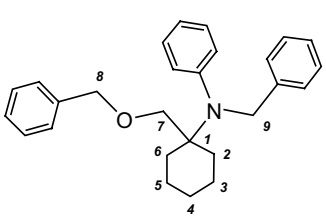
6a



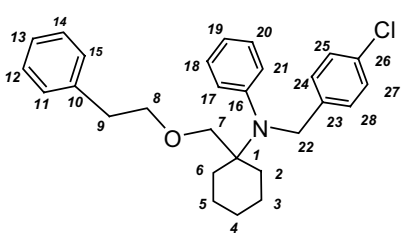
6e



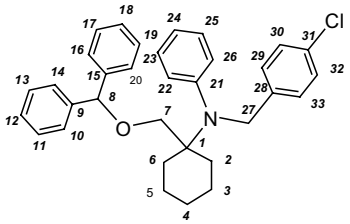
6i



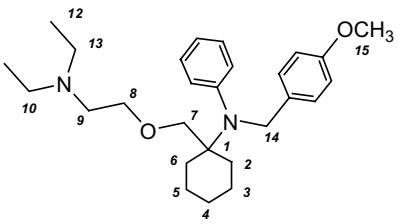
9a



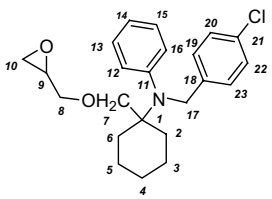
9f



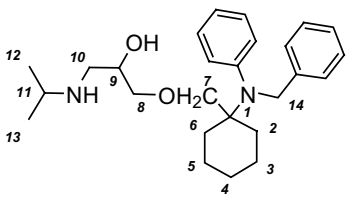
9h



9k



10b



11a

No.	Type	Data
5c	^{1}HNMR ($CDCl_3$)	1.32-2.49 (m, 10H, cyclohexane); 3.70 (t, 4H, *J* = 4.75 **H-*8,11***); 3.92 (t, 4 H, *J* = 4.77, **H-*9,10***); 7.15-7.26 (m, 10H, aromatic).
	^{13}CNMR ($CDCl_3$)	22.97 (**C-*3,5***); 25.20 (**C**-4); 33.17 (**C-*2,6***); 45.35 (**C-*8,11***); 58.33 (**C-*1***); 66.87 (**C-*9,10***); 127.81 (**C-*13,17***); 128.15 (**C-*15***); 128.36 (**C-*20-24***); 128.85 (**C-*21,23***); 129.58(**C-*14,16***); 131.72 (**C-*22***); 136.00 (**C-*19***); 139.38 (**C-*12***); 170.32 (**C-*7***); 171.21 (**C-*18***).
5e	^{1}HNMR ($CDCl_3$)	1.45-2.10 (m, 10H, cyclohexane, **H-*9,10,11***); 3.32 (t, *J* = 5.75, 4H, **H-*8,12***); 7.10-7.92 (m, 9H, aromatic).
	^{13}CNMR ($CDCl_3$)	20.82 (**C-3,5**); 27.50 (**C-4**); 30.95 (**C-2,6**); 25.52 (**C-9,11**); 25.85 (**C-10**); 45.55 (**C-8,12**); 57.96 (**C-1**); 120.86 (**C-14,18**); 121.60 (**C-16**); 128.24 (**C-21,25**); 129.00 (**C-15,17,22,24**); 132.12 (**C-20**); 138.80 (**C-13**); 168.84 (**C-19**); 171.66 (**C-7**).
5g	^{1}HNMR ($CDCl_3$)	1.42-2.10 (m, 10H, cyclohexane, **H-*9,10***); 3.46 (t, *J* = 5.66, 4H, **H-*8,11***); 3.74 (s, 3H, **H-*25***); 6.94-7.84 (m, 9H, aromatic).
	^{13}CNMR ($CDCl_3$)	20.00 (**C-*3,5***); 25.42 (**C-*9,10***); 27.64 (**C-*4***); 31.10 (**C-*2,6***); 49.22 (**C-*8,11***); 55.90 (**C-*25***); 85.14 (**C-*1***); 114.62 (**C-*21,23***); 121.60 (**C-*13,17***); 124.42 (**C-*15***); 126.66 (**C-*19***); 128.52 (**C-*20,24***); 129.00 (**C-*14,16***); 139.12 (**C-*12***); 164.14 (**C-*22***); 169.26 (**C-*18***); 171.90 (**C-*7***).
6a	^{1}HNMR (DMSO-D6)	1.38-1.61 (m, 10H, cyclohexane, **H-*9,10***); 2.44 (m, 4H, **H-*8,11***); 2.50 (s, 2H, **H-*7***); 4.44 (s, 2H, **H-*18***); 6.91-7.26 (m, 10H, aromatic).
	^{13}CNMR ($DMSO-D_6$)	21.77 (**C-*3,5***); 25.91 (**C-*9,10***); 31.76 (**C-4**); 38.77 (**C-*2,6***); 52.03 (**C-*18***); 56.48 (**C-*1***); 60.02 (**C-*8,11***); 64.86 (**C-*7***); 124.18 (**C-*13,17***); 125.90 (**C-*15***); 127.70 (**C-*22***); 127.75 (**C-*20,24***); 129.07 (**C-*21,23***); 130.14 (**C-*14,16***); 141.66 (**C-*19***); 147.79 (**C-*12***).
6e	^{1}HNMR (DMSO-D6)	1.39-1.72 (m, 10H, cyclohexane, **H-*9,10,11***); 2.24 (t, *J* = 6.24, 4H, **H-*8,12***); 2.50 (s, 2H, **H-*7***); 4.62 (s, 2H,**H-*19***); 6.58-7.20 (m, 9H, aromatic).

	^{13}CNMR (DMSO-D_6)	21.00 (**C-*3,5***); 25.82 (**C-*9,10,11***); 28.22 (**C-*4***); 34.74 (**C-*2,6***); 49.12 (**C-*19***); 53.46 (**C-*1***); 54.92 (**C-*8,12***); 58.86 (**C-*7***); 114.44 (**C-*21,25***); 118.48 (**C-*16***); 128.64 (**C-*22,24***); 129.42 (**C-*21,25***); 130.62 (**C-*15,17***); 132.62 (**C-*23***); 134.60 (**C-20**); 149.62 (**C-*13***).
6i	^{1}HNMR (DMSO-D6)	1.38-1.76 (m, 10H, cyclohexane); 2.38 (t, 4H, *J* = 5.20 **H-*8,11***); 2.52 (s, 2H, **H-*7***); 3.68 (t, 4H, *J = 5.*56, **H-*9,11***); 3.72 (s, 3H, **H-**25); 4.62 (s, 2H, **H-*18***); 6.68-7.20 (m, 9H, aromatic).
	^{13}CNMR (DMSO-D_6)	21.20 (**C-3,5**); 28.42 (**C-*4***); 34.82 (**C-*2,6***); 49.22 (**C-*18***); 53.62 (**C-*1***); 54.24 (**C-*8,11***); 55.88 (**C-*25***); 60.00 (**C-*7***); 66.84 (**C-*9,10***); 114.10 (**C-*21,23***); 114,90 (**C-*13,17***); 118.62 (**C-*15***); 128.60 (**C-*19***); 129.24 (**C-*20,24***); 130.36 (**C-*14,16***), 149.60 (**C-*12***); 159.20 (**C-*22***).
9a	^{1}HNMR ($CDCl_3$)	1.22-1.80 (m, 10H, cyclohexane); 3,64 (s, 2H, **H-*7***); 4.61 (s, 2H, **H-*9***); 4.71 (s, 2H, **H-*8***); 7.01-7.56 (m, 15H, aromatic).
9f	^{1}HNMR ($CDCl_3$)	1.38-1.74 (m, 10H, cyclohexane); 2.72 (t, *J* = 5.42, 2H, **H-*9***), 3.52 (s, 2H, **H-*7***); 3.74 (t, *J* = 5.40, 2H, **H-*8***); 4.62 (s, 2H, **H-*22***); 6.85-7.20 (m, 14H, aromatic).
	^{3}CNMR ($CDCl_3$)	21.40 (**C-*3,5***); 28.20 (**C-*4***); 33.42 (**C-*2,6***); 36.22 (**C-*9***); 49.36 (**C-*22***); 54.50 **C-**1); 76.20 (**C-*7***); 76.86 (**C-*8***); 114.32 (**C-*17,21***); 118.46 (**C-*19***); 126.00 (**C-*13***); 127.82 (**C-*11,15***); 128.84 (**C-*12,14***); 129.60 (**C-*25,27***); 129.42 (**C-*24,28***); 130.20 (**C-*18,20***); 132.62 (**C-*26***); 134.66 (**C-*23***); 139.50 (**C-*10***); 149.62 (**C-*16***).
9h	^{1}HNMR ($CDCl_3$)	1.26-1.82 (m, 10H, cyclohexane); 3.39 (s, 2H, **H-*7***); 4.19 (s, 2H, **H-*27***); 5.50 (s, 1H, **H-*8***); 7.09-7.47 (m, 19H, aromatic).
	^{13}CNMR ($CDCl_3$)	21.77 (**C-*3,5***); 25.90 (**C-*4***); 31.73 (**C-*2,6***); 47.26 (**C-*27***); 56.48 **(C-*1***); 77.51 (**C-*7***); 80.10 (**C-*8***); 125.82 (**C-*22,26***); 126.83 (**C-*24***); 127.24 (**C-*12,18***); 127.40 (**C-*10,14,16,20***); 127.61 (**C-*30,32***); 128.12 (**C-*11,13,17,19***); 128.34 (**C-*29,33***); 128.51 (**C-*23,25***); 138.65 (**C-*31***); 142.17 (**C-*9,15***); 143.43 (**C-*28***); 153.09 (**C-*21***).
9k	^{1}HNMR ($CDCl_3$)	0.99-1.07 (m, 6H, **H-*11,12***); 1.34-1.85 (m, 10H, cyclohexane); 2.52-2.56 (m, 4H, **H-*10,13***); 2.60 (t, *J= 5.80, Hz,* 2H, **H-*9***); 3.36 (s, 2H, **H-*7***); 3.46 (t, *J= 5.80 Hz,* 2H, **H-*8***); 3.60 (s, 3H, **H-*15***); 4.16 (s, 2H, **H-*14***); 6.78-7.25 (m, 9H, aromatic).
10b	^{1}HNMR ($CDCl_3$)	1.37-1.74 (m, 10H, cyclohexane); 2.38, 2.63 (d, 2H, **H-*10***); 2.86 (t, 1H, **H-*9***); 3.52 (s, 2H, **H-*7***); 3.38,3.63 (d, 2H, **H-*8***); 4.61 (s, 2H, **H-*17***); 6.85-7.24 (m, 9H, aromatic).
	^{13}CNMR ($CDCl_3$)	21.20 (**C-*3,5***); 28.40 (**C-*4***); 33.32 (**C-*2,6***); 44.20 (**C-*10***); 49.30 (**C-*17***); 50.42 (**C-*9***); 54.56 (**C-*1***); 74.22 (**C-*8***); 75.84 (**C-*7***); 114.28 (**C-*12,16***); 118.62 (**C-*14***); 128.70 (**C-*20,22***); 129.42 (**C-*19,23***); 130.00 (**C-*13,15***); 132.60 (**C-*21***); 134.60 (**C-*18***); 149.64 (**C-*11***).
11a	^{1}HNMR ($CDCl_3$)	1.32-1.74 (m, 10H, cyclohexane); 1.06 (d, 6H, *J* = 6 Hz, **H-*14,15***); 2.09 (s, 1H, exchangeable **H); 2**.10 (s, 1H, exchangeable **H);** 2.58, 2.83 (d, *J= 6.1 Hz,* 2H, **H-*10***); 2.96 (m,1H, **H-*11***); 3.58 (s, 2H, **H-*7***); 3.40, 3.64 (d, *J* = 5.82 Hz, 2H, **H-*8***); 3.88 (m, 1H, **H-*9***); 4.62 (s, 2H, **H-*14***); 7.11-7.55 (m, 10H, aromatic).

* Arbitrary numbering is given to the compounds for ^{1}H & ^{13}C NMR data to facilitate the location of the specified atoms.

2. Pharmacology

All the tested compounds are used as bases suspended in 7% tween 80 and administered intraperitoneal

2.1. Determination of the anticonvulsant activity using maximal pentylenetetrazol seizures test [6]

Experiments were carried out with two groups. The first group was divided into 5 subgroups (8 mice each) and received individually diphenylhydantoin sodium (0.06, 0.10 and 0.20 mmol/kg) as well as valproic acid (0.17 and 0.24 mmol/kg) as reference standards. The second group was divided into 24 subgroups (8 mice each), each of which was injected with one of the tested compounds at the dose of 0.11 mmol/kg (c.f. **Table 1)**. Two hours later [7] pentylenetetrazol (90mg/kg) was administered intraperitoneal (i.p.). The survival rate was chosen as index for protective effects.

2.2. Determination of lethal dose 50 (LD_{50}) [8]

The LD_{50} of the most potent compounds among the series was determined using Behrens and Schlosser method. Groups of 5 animals each were used. The first group served as control and was injected i.p. with the corresponding volume of the vehicle (7% tween 80). Other groups were injected i.p. with the tested compounds in doses ranging from 0.0525-0.650 mmol/kg. Animals were observed and the mortality rates were recorded within the first 24 hours after compounds administration. The LD_{50} were determined according to the following formula:

$LD_{50} = Dm - \sum (z \times d)/n$, where:

Dm = highest dose which kill all animals in the group.

z = the mean of dead animals in two successive groups.

d = the constant factor between two successive groups.

n = the number of animals in each of the dose levels.

2.3 Determination of effective dose 50 (ED_{50}) [9]

The ED_{50} of the most potent compounds was statistically evaluated according to the method of Litchfield and Wilcoxo.

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