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SYNTHESIS AND ANTICONVULSANT STUDIES OF N-BENZYL-3-[(CHLOROPHENYL) AMINO] PROPANAMIDES

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ABSTRACT

Isomeric N-Benzyl-3-[(chlorophenyl)amino]propanamides were prepared through an uncatalysed amine exchange reaction with benzylamine. The structures of these compounds were established through various spectroscopic techniques. The compounds were screened in mice against maximal electroshock (MES) and subcutaneous pentylene tetrazole (scPTZ) seizure test models as well as the righting reflex test for neurological deficit in mice. The isomers of N-Benzyl-3-[(chlorophenyl)amino] propanamide were found to be active both in the MES and scPTZ tests. The ortho and para isomers were found to be more potent than the standard drug (phenytoin) in the MES test, while all the 3 isomeric benzylated products were found to be far more potent than valproate in both the MES and the scPTZ tests with favourable therapeutic indices signifying their great potential for use against generalized seizures. Acute toxicity studies revealed that N-Benzyl-3-[(chlorophenyl)amino]propanamides are relatively safe.

Keywords: Epilepsy, anticonvulsants, *N-Benzyl-3-[(chlorophenyl)amino]propanamide*

INTRODUCTION

Epilepsy is a common neurological condition, affecting 0.5 to 1 % (45-100 million people) of the population worldwide (Bell and Sander, 2002). Conventional antiepileptic drugs (AEDs) phenobarbital, primidone, phenytoin, carbamazepine, ethosuximide and benzodiazepine, are widely used but exhibit an unfavorable side effect profile and failure to adequately control seizures (Zahn *et al.*, 1998; Battino *et al.*, 2000, Brunton *et al.*, 2009). In the recent years several new drugs (oxcarbazepine, lamotrigine, topiramate, gabapentin, zonisamide, tiagabine, fosphenytoin, vigabatrin and felbamate) have been added to the list of therapeutic agents against epilepsy. However, there is a significant group of patients (up to 30 %) who are resistant to the available antiepileptic drugs (Avanzini and Franceschetti, 2003 and Brunton *et al.*, 2009). The long-established AEDs control seizures in 50% of patients developing partial seizures, and in 60-70 % of those developing generalized seizures (Lopes Lima, 2000; Prucca, 2002; Berk *et al.*, 2001; Duncan, 2002 and Eadie, 2001). Hence, there is an urgent need to develop new AEDs (Szelenyi *et al.*, 2003 and Voskoyl and Clincker, 2009).The search for antiepileptic compounds with a more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry.

Recently, a series of carboxamides possessing the anilide pharmacophore were synthesized and screened for anticonvulsant activity in our laboratory (Idris *et al.,* 2008a, 2008b, and 2008c). Subsequently, we studied the effect of N-benzylation at the amido nitrogen of a section of these carboxamides (the anisidinopropanamides and toluidinopropanamides) and found that, consistent with earlier observations (Clark *et al.*, 1984; Choi *et al.*, 1996; Ho *et al.*, 2001), compounds with improved anticonvulsant profile resulted (Idris *et al.*, 2009 ; Idris *et al.*,2010). In this study we report the effect of N-benzylation at the amido nitrogen on the anticonvulsant activity of isomeric 3-[(chloropheny)amino]propanamides.

MATERIALS AND METHODS

Equipments

All melting points were determined using an Electrothermal melting point apparatus (Model 2038A – England). Elemental carbon, hydrogen and nitrogen were determined with a Parkin Elmer model 240 elemental analyzer (University of leads, England). Chlorine was determined by the Schrodinger combustion (University of Leeds, England). IR spectra were recorded on a Parkin Elmer paragon 1000 as KBr disc (University of Readings, U.K.). Mass spectra were measured on an AP2000 (IS, 70ev) instrument (University of Leads, England). Proton and carbon-13 NMR (^{1}H NMR and ^{13}CNMR) spectra were recorded on a Bùker CWM 250 (250 MHz), or a Joel AL -300 spectrometer (JAPAN) with TMS as an internal standard. The equipment for the MES screening is an Ugo Basile electroconvulsive unit (ECT 800) fitted with ear clip electrodes.

Chemicals

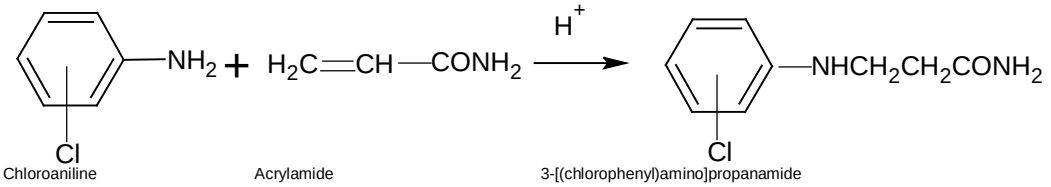
Starting materials were Analar grade and used without further purification. 2-, 3- and 4-[(chloropheny)amino]propanamides used were prepared in the post graduate research laboratory, Department of Pharmaceutical and Medicinal Chemistry, Ahmadu Bello University, Zaria, Nigeria. Benzylamine, propylene glycol, iodine crystals and potassium permanganate were all obtained from BDH chemicals (Pools, England). The solvents (benzene, methanol, chloroform and ethyl acetate were also obtained from BDH chemicals (Pools, England). Phenytoin and pentylenetetrazole (PTZ) were obtained from Sigma-Aldrich (St Louis MO) and valproic acid from Sanofi-synthelabo (USA).

Animals

Swiss albino (male) mice in the weight range 18-30g were used. The animals were inbred in the animal house of the Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria. The animals were kept under standard laboratory conditions (temperature 25±3^{0}C; humidity 45 – 60% and 12 hours light/dark cycle) and were allowed free access to both food (Vital feeds mixed with fish and groundnut cake) and water except when they were removed from their cages for the experiments.

Synthesis

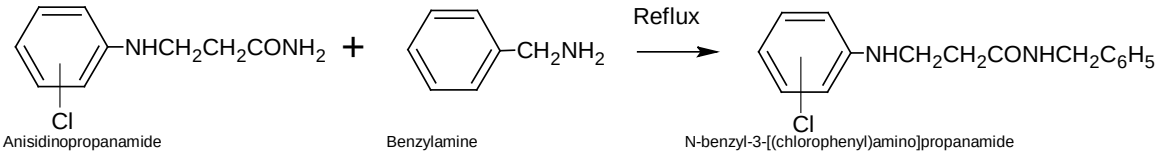
The 3-[(chlorophenyl)amino]propanamides (3-CAP) were previously prepared through Michael reaction between the chloroanilines and acrylamide in the presence of catalytic amounts of p-toluenesulphonic acid (P-TOSA), according to scheme 1 (Idris, 2008)



Chloroaniline Acrylamide 3-[(chlorophenyl)amino]propanamide

Scheme 1 *Synthesis of the 3-[(chlorophenyl)amino]propanamides*

Conversion of 3-[(chlorophenyl)amino]propanamides (3-CAP) to the N-benzyl-3-[(chlorophenyl)amino]propanamides (NB-3-CAP) was achieved by an uncatalysed amine exchange reaction with benzylamine according to scheme 2 below (Idris, 2008)



Anisidinopropanamide Benzylamine N-benzyl-3-[(chlorophenyl)amino]propanamide

Scheme 2. ***Conversion of 3-CAP to NB-3-CAP***

General Procedure for the synthesis

Progress of all the reactions were monitored using thin layer chromatography (TLC) with ethyl acetate as development solvent. Purity of starting materials and of end products were also assessed using TLC. Chromatograms were visualized under U.V fluorescence quenching at 254m or by staining with potassium permanganate solution or iodine vapour. All absorptions are reported in terms of frequency of absorption (cm^{-1}). Data for \$^1$HNMR and ^{13}CNMR are reported as follows; chemical shift (ð ppm), integration and coupling constant in Hz, Multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Data for ^{13}CNMR are reported in terms of chemical shift.

Preparation of the N-benzyl-3-[(chlorophenyl)amino]propanamides

A mixture of about 0.22mole each of the 3-[(clorophenyl)amino]propanamide and benzylamine was refluxed on oil bath (170-180^{0}C) for about 48 hours. The set up was allowed to cool to room temperature and the solid formed was digested in chloroform and collected by filtration. The products were recrystallized in benzene/toluene until a single spot was obtained on TLC. The yields and physical properties of the compounds were recorded (Idris, 2008).

Screening for anticonvulsant activity

Anticonvulsant screening was established by both electrical and chemical procedures as described by Swinyard *et al.,* (1989). Neurotoxicity was assessed according to the procedure described by Swinyard *et al.,* (1952). Each animal was examined for its neurological status before the administration of the test drug. Screenings were conducted at 0.5 and 4hrs after injection of the test compound. All quantitative determinations were carried out at the estimated time of peak anticonvulsant activity of the candidate compounds.

a) *Primary (Qualitative) Evaluation of the 3-[(chlorophenyl)amino]propanamides*

i) The Maximal Electroshock Seizure (MES) Test:

48 male albino mice (18-30g) were randomly divided into six groups of 8 mice per group. Three groups received intraperitoneal (ip) injection of 30, 100 and 300mg/kg respectively of the test compound (dissolved in propylene glycol) while the control group received 25mg/Kg propylene glycol solution (i.p). The other two groups received 20mg/Kg (i.p) of phenytoin and valproic acid respectively. An electrical stimulus (50mA at 60Hz for 0.2sec) was delivered through ear clip electrodes using an Ugo Basile electroconvulsive generator. Abolition of the hind limb tonic extensor component indicates the compounds ability to inhibit MES-induced seizure spread

ii) *The subcutaneous Pentylenetetrazol (scPTZ) Seizure Test*

40 male albino mice (18-30g) were randomly divided into five groups of 8 mice per group. Three groups received intraperitoneal (ip) injection of 30, 100 and 300mg/kg respectively of the test compound (dissolved in propylene glycol) while the other 2 groups received 25mg/kg of the vehicle and 20mg/kg valproic acid IP respectively. 85mg/kg pentyleneterazole (metrazole) was injected subcutaneously. The mice were observed for 30 minutes for the occurrence of seizures. Absence of clonic spasms in the observed time period indicates a compounds ability to abolish the effect of pentylenetetrazole on seizure threshold (Swinyard *et al.*,1989)

iii) *Determination of Minimal Neurotoxicity*
32 male albino mice were randomly divided into 4 groups of eight mice per group. The first, second and third groups were given 30, 100 and 300mg/kg of the compound respectively, while the last group was given 25mg/kg propylene glycol (ip). The mice were placed on their back. Neurological deficit was indicated by inability of the animal to quickly resume their normal posture. The number of mice that showed signs of neurotoxicity at various dose levels was recorded (Swinyard *et al*., 1952)

b) *Secondary (Quantitative) Evaluation of the 3-Benzyl-3[(chlorophenyl)amino]pro-panamides*
i) *Determination of time of peak anticonvulsant effect*
Maximum electroshock (MES) method was employed for the determination. 100mg/kg of the compound was injected intraperitoneally to four groups of mice, each group consisting of six mice. The first group was subjected to MES at 15 minutes, while the second, third and fourth, were given at 30, 45 and 60, minutes respectively. In each case the number of mice protected was recorded. From the data the time of peak anticonvulsant activity was determined (Stables and Kupferberg, 1977)

ii) *Determination of Minimal Neurotoxicity (TD_{50}):*
Groups of eight mice were given graded doses of the candidate compound such that two points were established between limits of 100 percent toxicity and zero percent toxicity. The animals were subjected to righting test as described above. The number of mice that showed sign of neurotoxicity at various dose levels was recorded and the TD_{50} was determined using graphical method of Miller and Tainter (1994).

iii) *Determination of the median effective dose (ED_{50})*
Several groups of at least eight mice per group received various doses of the candidate compound until at least two points were established between the limits of 100 percent protection and zero percent protection using the MES, and ScPTZ tests as described above. The ED_{50} was calculated using the graphical method of Miller and Tainter (1994).

Acute Toxicity Studies of 3-Benzyl-3-[(chlorophenyl)amino]propanamides in Mice (LD_{50})
LD_{50} determination was conducted using the method of Lorke (1983). In the initial investigation mice were divided into three groups of three mice each, treated with the drugs at 10, 100 and 1000mg/kg body weight intraperitoneally (ip), and observed for 24 hours for signs of toxicity and death. The results of these tests were used as the bases for selecting the subsequent dosages. The LD_{50} was calculated as the square root of the product of the lowest dosage that killed all the animals and the highest dosage survived by the entire animal in the group.

RESULTS
Student's T-test was used to determine level of significance of all results obtained. Results were regarded as significant at $P<0.05$.

Table 1: Physicochemical Properties of N-benzyl- 3-[(chlorophenyl)amino]propanamides

Comp.	Physical appearance	M. pt. (^{0}C)	% Yield	RT (minutes)
2-Cl	Dirty white crystals	159 – 161	73.70	35.125
3-Cl	White granules	142 – 143	81.20	32.194
4-Cl	Pale yellow crystals	153 – 154	76.42	29.332

Table 2: Results of Microanalysis of Isomeric N-benzyl-3-[(chlorophenyl)amino]pro-panamides

Comp.	Elem. Comp	Microanalysis (%) C Found (Cal)	H Found (Cal)	N Found (Cal)	M.wt from MS	Formula
2-Cl	C, H,N	71.91 (71.83)	7.14 (7.04)	9.97 (9.97)	284	$C_{17}H_{20}N_2O_2$
3-Cl	C,H,N	71.87 (71.83)	7.12 (7.04)	9.91 (9.86)	284	$C_{17}H_{20}N_2O_2$
4-Cl	C,H,N	71.93 (71.83)	7.15 (7.04)	9.96 (9.86)	284	$C_{17}H_{20}N_20_2$

Table 3: Infrared Spectra Data for Isomeric N-benzyl-3-[(chlorophenyl)amino]pro-panamides (cm^{-1})

Comp	N-H-str	=C-Har str	C=C	C=O Amide Band I	N-H_{def} Amide Band II	Ar C-N_{str}	C—H_{ipb}	C – H $_{OP}$
2-Cl	3375.00	3059.71	1615.72 1627.16 1579.33	1627.13	1513.62	1279.58	1099.15.	740.62 678.07
3-Cl	3381.43	3260.00	1621.52	1637.29	1524,75	1299.03	1059.75	762.23
4-Cl	3389.50	3169.38	1619.60 1614.82	1646.72	1527.17	1279.69	1079.44	833.32

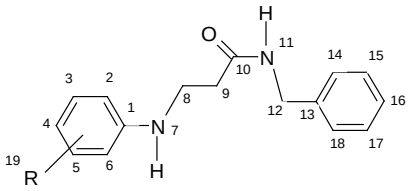


Table 4: ^{1}HNMR Specra Data for Isomeric N-benzyl- 3-[(chlorophenyl)amino]propane-mides

2-Cl δ(ppm) 7.59-7.57 (t, 1H, $^{3}J_{13,14}$ = 5.0,Ar-NH-, H-11), 7.28-7.24 (m, 2H, $^{3}J_{15,14}$ = 7.83, $^{3}J_{15,16}$ = 7.05, $^{3}J_{11,18}$ = 7.83, ^{3}J =7.05, 2Ar-H-15 and H-17), 7.17-7.12 (t, 1H, $^{3}J_{16,15}$ = 7.05, $^{3}J_{16,17}$ = 7.05, Ar-H, H-16), 7.06-7.02 (d; 1H, $^{3}J_{514}$ = 8.11, Ar-H, H-5), 7.04 -7.02 (t, 1H, $^{3}J_{3,2}$ = 7.24, $^{3}J_{3,2}$ = 8.11, Ar-H, H-3), 6.96-6.93 (d, 1H, $^{3}J_{2,3}$ = 8.11, Ar-H, H-2), 6.87-6.85 (dd, 2H, $^{3}J_{14,15}$ = 7.83, $^{3}J_{18,17}$ = 7.83, 2Ar-H, H-14, H-18), 6.77 (s, 1H, Ar-NH-, H-7), 6.75-6.72 (t, 1H, $^{3}J_{4,3}$ = 8.11, $^{3}J_{4,5}$ = 7.84, Ar-H, H-4), 4.54-4.52 (d, 2H $^{3}J_{12,11}$ = 5.0, -NH-CH_2-Ar, H-12), 3.18-3.16 (d, 2H, $^{3}J_{8,9}$ = 7.34, -NH-CH_2-CH_2, H-8), 2.55-2.5 (t, 2H,$^{3}J_{9,8}$ = 7.34, -NH-CH_2-CH_2, H-9)

3-Cl δ(ppm) 9.26 (S, 1h, Ar-NH-, H-7), 7.60-757 (t, 2H, $^{3}J_{11,12}$ = 5.0, -CO-NH-, H-11), 28-7.23 (m, $^{3}J_{15,14}$ = 7.83,$^{3}J_{15,16}$ = 7.05, $^{3}J_{17,18}$ 7.83, $^{3}J_{17,16}$= 7.05 2Ar-H, H-15 and H-17), 7.17-7.13 (t, 1H, $^{3}J_{16,15}$ = 7.05, $_{3}J_{16,17}$ = 7.05, Ar-H, H-16), 6.99-6.98 (t, 1H, $^{3}J_{3,2}$ =8.2, $^{3}J_{3,4}$ = 8.04, Ar-H, H-3), 6.94-6.94 (s, 1H, Ar-H, C-6).6.89- (d, 1H, $^{3}J_{2,3}$ 8.2, Ar-H, H-2), 6.88-6.85 (dd, 2H, $^{3}J_{14,15}$ ==7.83, $^{3}J_{18,17}$ = 7.83, H-14, H-18), 4.54-4.52 (t, 2H, $^{3}J_{12,11}$ = 5.0, -CO-NH_2-CH_2-, H-12), 3.23-3.19 (t, 2H, $^{3}J_{8,9}$ = 7.34, Ar-NH-CH_2-CH_2-, H-8), 2.55-2.51 (t, 2H, $^{3}J_{9,8}$ = 7.34,-NH-CH_2-CH_2-, H-9).

4-Cl δ(ppm) 8.67 (s, 1H, Ar-NH,H-7), 7.6-7.59 (t, 1H, $^{3}J_{11,12}$ = 5.0, -CO-NH, H-11), 7.58-7.55 (dd, 2H, $^{3}J_{2,3}$ = 8.71, $^{3}J_{6,5}$ = 8.71, 2Ar-H, H-2 and H-6), 7.30-7.28 (dd, 2H, $^{3}J_{3,2}$ = 8.71, $^{3}J_{5,6}$ = 8.71, 2Ar-H, H-3 and H-5), 7.27-7.23 (m,2H, $^{3}J_{15,14}$ = 7.83, $^{3}J_{15,16}$ =7.05, $^{3}J_{17,16}$ = 7.05, $^{3}J_{17,18}$ =7.83, 2Ar-H H-15, H-17), 7.17-7.12 (t, 1H, $^{3}J_{16,15}$ = 7.05, $^{3}J_{17,16}$ = 7.05, Ar-H, H-16), 687-6.85 (dd, 2H, $^{3}J_{14,15}$ = 7.83, $^{3}J_{18,17}$ = 7.83, 2Ar-H, H-14 and H-18), 4.54-4.521 (d, 2H, $^{3}J_{12,11}$ = 5.0, -NH-CH_2-Ar, H-12), 324-3.19 (t, 2H, $^{3}J_{8,9}$ = 7.34, -NH-CH_2-CH2- H-8), 2.55-2.51 (t, 2H 3$J_{9,8}$ = 7.34, -NH-CH_2-CH_2, H-9).

Table 5. 13C-NMR Spectra for the N-benzyl-3-[(chlorophenyl)amino]propanamide.
2-Cl 171.70 (1C,-CO- C-10), 167.00 (1C, ArC, C-1), 137.60 (1C, Arc, C-13), 128.82 (1C, ArC, C-5), 128.71 (2C, ArC, C-14 &C-18), 128.60 (2C, ArC, C-15 and C-17), 127.40 (1C, ArC, C-16), 125.80 (1C, ArC, C-4), 119.08 (1C, ArC, C-6), 111.03 (1C, ArC, C-2), 42.53 (1C, -NH-CH_2-Ar, C-12), 39.90 (1C,-NH-CH_2-CH_2, C-8), 32.33 (1C,-NH-CH_2- CH_2-, C-9).

3-Cl (ppm) 171.70 (1C,-CO-C-10), 146.11 (1C, ArC, C-1), 137.60 (1C, ArC, C-13), 133.58 (1C, ArC, C-5), 128.97 (1C, ArC, C-3), 128.71 (2C, ArC, C-14 & E18), 128.60 (2C, ArC, C-15 and C-17), 127.40 (1C, ArC, C-16), 122.22 (1C, ArC, C-4), 117.60 (1C, ArC, C-6), 115.11 (1C, ArC, C-2), 42.53 (1C, -NH-CH_2-Ar, C-12), 39.90 (1C, -NH-CH_2-CH_2, C-18), 32.33 (1C, -NH-CH_2-CH_2-, C.9)

4-Cl δ(ppm) 171.70 (1C,-CO-, C-10) 148.72 (1C, Ar-C, C-1), 137.60 (1C, Ar-C, C-13), 130.02 (2C, Ar-C, C-2andC-6), 128.60 (2C, ArC, C-15 and C-17), 127.04 (1C, ArC,C-16), 121.70 (1C, ArC, C-4), 113.53 (2C, ArC, C-3, & C-5), 42.53 (1C,-NH-CH_2-Ar, C-12), 39.90 (1C, -NH-CH_2-CH_2, C-8), 32.33 (1C, -NH-CH_2-CH_2- C-9).

Table 6: Results for Phase I Anticonvulsant Screening of Isomeric N-Benzyl-3-[(chlorophenyl)amino]propnamides in MES and scPTZ Tests and the Righting Reflex Test in Mice.

COMP	Protection against MES Induced Seizures		Protection against scPTZ Induced Seizures		Protection against RightingReflex Text	
	0.5hr	4hrs	0.5hr	4hrs	0.5hr	4hrs
2-Cl	+++	+++	+++	+++	++	+
3-Cl	++	++	++	++	++	++
4-Cl	+++	++	+++	+++	+++	
CONT*	-	-	-	-	-	-

Statistical analysis was conducted by the student T-test p< 0.05 compare to vehicle treated control groups; Key. +++: activity at 30mg/kg; ++; activity at 100 mg/kg; +; activitiy at 300 mg/kg; - no activity even at 300 mg/kg or not determined; *Control group was given propylene glycol (vehicle) 25mg/kg.

Table 7 Quantitative Anticonvulsant Activities (Phase II) of N-Benzyl-3-[(chlorophenyl)amino]propanamides

Comp	$ED_{50}^{\#,+}$MES	$ED_{50}^{\#,+}$ scPTZ	$TD_{50}^{\#,+}$	PIb MES	PIb scPTZ
2-Cl	9.20 (8.35 – 11.01)	15.70 (8.98 - 27.30)	56.60 (39.30 – 81.60)	4.8	3.6
3-Cl	23.40 (15.50 - 35.40)	25.30 (16.00 – 40.00)	72.40 (59.50 – 88.20)	3.1	2.9
4-Cl	5.15 (26.37 – 34.31)	11.18 (6.39 – 17.15)	69.87 (42.67 – 91.22)	13.6	6.2
PHT	9.51 (8.14 – 10.45)	>300	65.45 (52.48 – 72.09)	6.9	2.9
VAP	271.54(246.93-337.85)	148.49(122.95-176.95)	424.57(368.88-450.38)	1.6	2.9
CTR*		-	-	-	-

Key: #: All doses are measured in mg/kg, b: 95% confidence limits are given parentheses, (-): Means no activity at 100mg/kg, *: Control group was given propylene glycol (vehicle) 25mg/kg

Table 8: Results of acute toxicity test (LD_{50}) for the N-Benzyl- 3-[(chlorophenyl) amino]propanamides

Compound	LD_{50} (mg/kg)
2-Cl	811.50
3-Cl	7I4.80
4-Cl	987.47

DISCUSSION

Melting points are uncorrected. The *ortho* isomer of the N-benzyl-3-[(clorophenyl)amino]propanamides has a higher melting point than the other two isomers (table 1), very much unlike what obtains in the methyl and methoxy analogues of the anilinopropanamides where the para isomers have the higher melting points (Idris *et al*, 2009; Idris et al., 2010). Moreover, the product yields (81-73%) are better than were for the other two isomers. The results for micro analytical studies are given in Table 2 and are within ± 0.4 percent of theoretical values. Thus, we had no problem establishing the empirical formula and, by extension, the molecular formula (having obtained the molecular weight from the mass spectra). The IR spectra show prominent peaks at 3390-3375 cm^{-1} (-N-H stretching vibrations), 3169-3060cm^{-1} (aromatic =C-H stretching frequencies), 1632-1606 cm^{-1} (aromatic carbon-carbon stretching vibrations), 1647-1627cm^{-1} (carbonyl frequency vibrations usually referred to as amide band I), 1527-1514cm^{-1} (N-H deformation usually referred to as amide band II), 1299-1280cm^{-1} (-C-N stretching frequencies of secondary amines), 1099-10560cm^{-1} (in plane bending vibrations of methylene groups) and 833-678cm^{-1} (out of plane bending vibrations) (table 3) (Kalsi, 2007). The fragmentation pattern in the mass spectra is typical of secondary amines, the most prominent peaks occurring at m/z (%intensity) 288 (40, M^+) and 140 (100).The proton positions are as indicated in Table 4. Coupling protons were detected using correlated spectroscopy (COSY) and the J values were estimated using a computer ACD software. The result of DEPT analysis revealed X-CH, Y-CH_2, Z-CH_3 and quaternary carbons (table 5). 2-D NMR spectra were used to establish connectivity between fragments.

Anticonvulsant activity was defined by obtaining percentage response of at least 37.5 (or a quantal response of 3/8). In the preliminary investigation, all the three isomers of the N-benzyl-3-[(chlorophenyl)amino]propanamides showed good activity in both the MES and scPTZ tests at a dose of 30mg/kg, 0.5hr and 4.0hrs after intraperitoneal injection of the drugs (Table 6). The results for the quantitative analysis are given in Table 7. On a general note, and, as observed in the methyl- and methoxy- analogues (Idris *et al*., 2009; Idris *et al*., 2010), N-benzylation at the amido nitrogen brought about increase in anticonvulsant potency and a broadening of the spectrum of activity of the 3-anilinopropanamides. The margin of safety of these compounds also improved following N-benzylation. Even in the case of the ortho-substituted isomer where there was a small decease in potency(MES ED_{50} 9.20mg/kg : 5.07mg/kg; Sc-PTZ ED_{50} 15.70mg/kg : 12.70mg/kg), the therapeutic index increased [PI (TD_{50}/ED_{50}) 3.60: 2.00] showing the extent to which N-benzylation favourably affects the quality of these compounds as candidate anticonvulsant agents. Furthermore, prior to the benzylation the *para* chloro isomer was the least potent of the three 3-chloroanilinopropanamides against electrically induced seizure. N-benzylation reverses this order. N-Benzyl-3-[(4-chlorophenyl)anino]-propanamide (the *para* chloro isomer) is now the most potent isomer (MES ED_{50} = 5.15mg/kg) with an incredibly high therapeutic index [PI (TD_{50}/ED_{50}) =13.6]. For the meta isomer, N-Benzylation caused increase in potency in both MES and sc-PTZ tests (MES ED_{50} 23.40mg/kg : 30.70mg/kg; sc-PTZ ED_{50} 25.30mg/kg : over 100mg/kg). It could therefore be said that the N-benzyl-3-[(clorophenyl)amino]propanamides are similar to valproate in their ability to inhibit MES and scPTZ-induced seizures in mice although they are by far more potent. The compounds therefore have the potential for being useful in the treatment of generalized seizures.

CONCLUSION

N-benzylation of the 3-[(clorophenyl) amino]propanamides at the *amido* nitrogen modifies their anticonvulsant property. While these compounds protect the animals against MES-induced seizures their N-benzyl counterparts inhibit both MES- and scPTZ-induced seizures. Consequently, the N-benzyl-3-[(clorophenyl)amino]propanamides have the potential for being useful in the treatment of generalized seizures.

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