Arabian Journal of Chemistry (2015) 8, 307–312

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Synthesis, physicochemical and biological evaluation of 2-amino-5-chlorobenzophenone derivatives as potent skeletal muscle relaxants

Rajesh K. Singh *, **Sonia Devi** [1], **D.N. Prasad**

Pharmaceutical Chemistry Division, Shivalik College of Pharmacy, Nangal, Rupnagar, Punjab 140126, India

Received 7 June 2011; accepted 22 November 2011
Available online 3 December 2011

KEYWORDS

2-Aminobenzophenone;
Central Nervous System;
Skeletal muscle relaxant activity;
Physicochemical parameters;
Log *P*;
Rotarod test

Abstract A series of novel 2-amino-5-chlorobenzophenone derivatives (**3a**–**3g**) were prepared by the reaction of 2-(chloroacetamido)-5-chlorobenzophenone and different aniline derivatives by both conventional and microwave methods and structures were confirmed on the basis of their TLC, IR, 1H NMR and CHN elemental studies. Out of the two methods, microwave methods was found to give better yield. All the synthesized compounds were subjected to physicochemical parameters determination for BBB penetration through online software. The log *P* values of most of our test compounds indicate that test compounds have the potential to be CNS active. The experimentally determined and calculated values of log *P* are very much similar to values of log *P* calculated by the online software chemsilico and are in the range required for good CNS activity. The values of other physicochemical parameters like molecular weight, nON value, nOHNH value, *n*-violations and the number of rotatable bonds of all the test compounds also lie between the ranges that are required for good BBB penetration. The compounds were screened for the skeletal muscle relaxant activity and from the investigation, it is quite apparent that all the 2-amino-5-chlorobenzophenone derivatives (**3a**–**3g**) possess significant differences between control group and treated group, $P < 0.001$. Among these 2-amino-5-chlorobenzophenone derivatives, the compound bearing *o*-toluidine as a substituent (**3e**) possesses the highest skeletal muscle relaxant activity.

1. Introduction

2-Aminobenzophenone derivatives are important compounds in organic chemistry because of their application in heterocyclic synthesis and medicines (Walsh, 1980). 2-Aminobenzophenone has been used as starting material for the synthesis of 1, 4-benzodiazepines (Sternbach et al., 1962), proquazone and amfenac as anti-inflammatory agents (Coombs et al., 1973; Welstead et al., 1979; Ottosen et al., 2003). It has also been used for the synthesis of Peptidoaminobenzophenones, a novel class of ring open derivatives of 1, 4-benzodiazepines, evaluated for Central Ner-

* Corresponding author. Tel.: +91 01887 221276, mobile: +91 9417513730; fax: +91 01887 221276.
E-mail address: rksingh244@gmail.com (R.K. Singh).
[1] Present Address: Dept. of Pharmaceutical Chemistry, Laureate Institute of Pharmacy, Kathog, Kangra, Himachal Pradesh, India.
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

1878-5352 © 2011 Production and hosting by Elsevier B.V. on behalf of King Saud University.
http://dx.doi.org/10.1016/j.arabjc.2011.11.013

vous System (CNS) activity. (Felix et al., 1974; Bodor et al., 1977; Hirai et al., 1980). 2-Aminobenzophenone derivatives were also evaluated as antimitotic agents (Liou et al., 2002) and a novel class of bradykinin B_1 receptor antagonists with excellent receptor occupancy in the CNS of hBK B_1 transgenic rats but not a substrate for P-glycoprotein (P-gp) mediated efflux and hence good brain penetration (Su et al., 2008). All these drugs synthesized from 2-aminobenzophenones possess CNS activity. 2-aminobenzophenone derivatives were considered to be of our interest because they fulfill all the structure activity requirements as the benzodiazepine contains. According to SAR study rings A and C and substitutions at these rings and the substitution at the amide nitrogen of ring B are important for the activity of benzodiazepines as shown in Fig. 1. So it was considered to be of interest to synthesize the 2-aminobenzophenones derivatives having all the important pharmacophores required for the CNS activity of benzodiazepines to obtain drugs with high therapeutic index than diazepam. In this 2-amino-5-chlorobenzophenones are subjected to acetylation by treating with chloroacetylchloride to obtain 2-chloroacetamidobenzophenones which are then reacted with different aniline derivatives in the presence of potassium carbonate and DMF by conventional and microwave irradiation methods to obtain different derivatives (Scheme 1).

2. Materials and methods

2.1. Experimental

The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. Proton (^{1}H) nuclear magnetic resonance (^{1}H NMR) spectra were obtained using Brucker AC-400 F, 400 MHZ spectrometer and are reported in parts per million (ppm), downfield from tetramethylsilane (TMS) as internal standard. The spin multiplicities are indicated by the symbols: s (singlet), d (doublets), t (triplet), q (quartet), m (multiplet) and br (broad). Infrared (IR) spectra were obtained with Perkin Elmer 882 Spectrum and RXI, FT-IR model using potassium bromide pellets (in cm^{-1}). The ultraviolet spectra were recorded on Shimadzu, UV-1800 spectrophotometer. Elemental analyses were carried out on a Perkin–Elmer 2400 CHN elemental analyzer. Syntheses related to microwave irradiation were carried out in domestic LG little chef microwave oven. Reactions were monitored and the homogeneity of the products was checked by TLC which were prepared with silica gel G and activated at 110 °C for 30 min. The plates were developed by exposure to iodine vapors. Anhydrous sodium sulfate was utilized as drying agents. All solvents were dried and freshly distilled prior to use according to standard procedure.

2.2. Synthesis of 2-(chloroacetamido)-5-chlorobenzophenone

2.2.1. Conventional method

The syntheses of 2-amino-5-chlorobenzophenone and 2-(chloroacetamido)-5-chlorobenzophenone were carried out by literature methods (Sternbach et al., 1961, 1962). In this method, 2-amino-5-chlorobenzophenone **(1)** (1 mole) and chloroacetylchloride (2 mole) in toluene was refluxed for 2.5 h to expel most of the formed hydrogen chloride. The solution was then cooled, washed with ice cold dilute aqueous ammonia solution, dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The recrystallization of the crude residue from alcohol afforded 82% of 2-(chloroacetamido)-5-chlorobenzophenone **(2)**; mp 119–122 °C, lit. (Sternbach et al., 1961) 119–121 °C.

2.2.2. Microwave irradiation method

A solution of 2-amino-5-chlorobenzophenone **(1)** (0.464 g, 2 mmole) and chloroacetylchloride (0.318 ml, 4 mmole) in toluene (20.0 ml) was irradiated for 1 minute in a microwave oven (360 W). The solution was then cooled, washed with ice cold dilute aqueous ammonia solution, dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The recrystallization of the crude residue from alcohol afforded 88% of 2-(chloroacetamido)-5-chlorobenzophenone **(2)**; mp 118–120 °C, lit. (Sternbach et al., 1961) 119–121 °C.

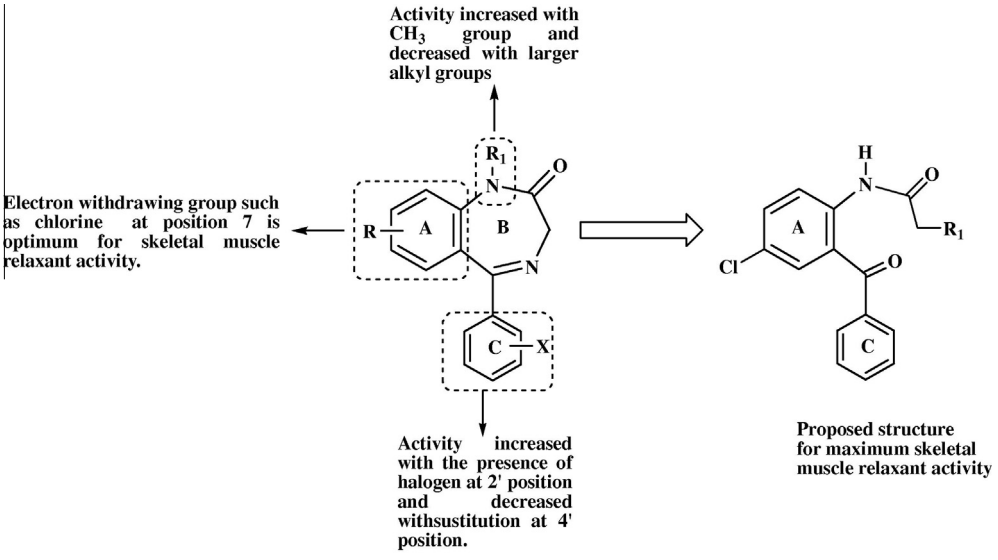
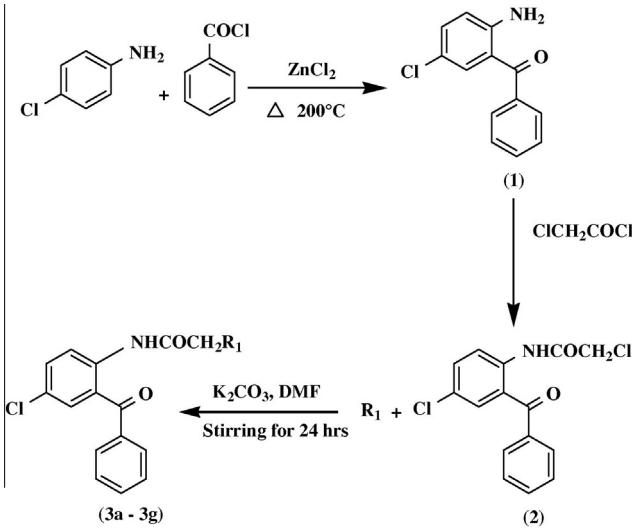
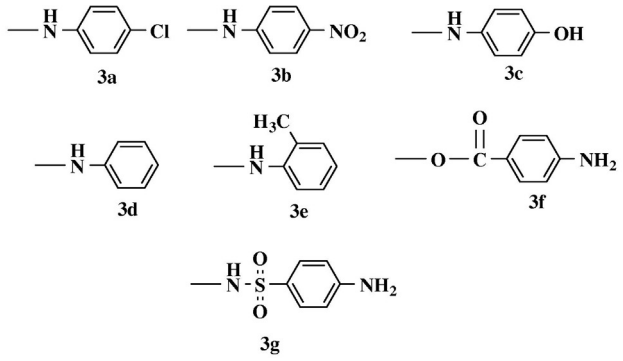


Figure 1 Important pharmacophore of 1,4-benzodiazepine nucleus.



Where R_1 is



Scheme 1 Synthesis of 2-amino-5-chloro-benzophenone derivatives (**3a**–**3g**)

*2.3. General procedure for the synthesis of 2-Amino-5-chlorobenzophenone derivatives (**3a**–**3g**)*

2.3.1. Conventional method

2-Amino-5-chlorobenzophenone derivatives were prepared by stirring the equimolar of 2-(chloroacetamido)-5-chlorobenzophenone and different aniline derivatives in the presence of double mole of potassium carbonate in a minimum quantity of DMF at room temperature for 20–28 h. After that the reaction mixture was poured into ice cold water and the solid product thus separated was collected through filtration.

2.3.2. Microwave irradiation method

A solution of the equimolar of 2-(chloroacetamido)-5-chlorobenzophenone and different aniline derivatives in the presence of double mole of potassium carbonate in a minimum quantity of DMF was irradiated for 2–3 minutes in the microwave oven (360 W). After that the reaction mixture was poured into ice cold water and the solid product thus separated was collected through filtration. The crude solid product was recrystallized from alcohol. The physical characteristics of the synthesized compounds are given in Table 1 and the comparison of % yield and time taken for synthesis by the conventional and microwave method is given in Table 2.

*2.3.3. 2-(4′-Chloroanilino)acetamido-5-chlorobenzophenone (**3a**)*

IR (KBr cm^{-1}): 3346 (Sec N–H str), 3100 (Aromatic C–H str), 2984 (Aliphatic C–H str), 1661 (C=O str), 1487 (Aromatic C=C str), 1229 (C–N str) and 761 (C–Cl str) ^{1}H NMR (DMSO-$d_{6\ 1\delta}$ ppm): 4.19 (s, 2H, –COCH_2N), 7.26–8.60 (m, 12H, Ar–*H*) and 11.46 (br s, 1H, –N*H*COCH$_2$–) Anal. Calcd. for $C_{21}H_{16}N_2O_2Cl_2$: C, 63.17; H, 4.04; N, 7.02; Found: C, 63.07; H, 4.02; N, 7.09.

*2.3.4. 2-(4′-Nitroanilino)acetamido-5-chlorobenzophenone (**3b**)*

^{1}H NMR ($CDCl_3$ 1δ ppm): 4.19 (s, 2H, –COCH_2N), 7.26–8.60(m, 12H, Ar–*H*) and 11.46 (br s, 1H, –N*H*COCH$_2$–) Anal. Calcd. for $C_{21}H_{16}N_3O_4Cl$: C, 61.54; H, 3.94; N, 10.25; Found: C, 61.49; H, 3.98; N, 10.18.

*2.3.5. 2-(4′-Hydroxyanilino)acetamido-5-chlorobenzophenone (**3c**)*

IR (KBr cm^{-}1): 3277 (O–H str), 2921 (Aliphatic C–H str), 1654 (Amide C=O str), 1510 (Aromatic C=C str) and 1249 (C–N str) ^{1}H NMR ($CDCl_3$ 1δ ppm): 4.28 (s, 2H, –COCH_2N), 6.3 (s, 1H, Ar–O*H*), 7.26–8.67 (m, 12H, Ar–*H*) and 11.25 (br s, 1H, –N*H*COCH$_2$–) Anal. Calcd. for $C_{21}H_{17}N_2O_3Cl$: C, 66.23; H, 4.50; N, 7.36; Found: C, 63.07; H, 4.02; N, 7.09.

*2.3.6. 2-Anilinoacetamido-5-chlorobenzophenone (**3d**)*

IR (KBr cm^{-1}): 3346 (Sec N–H str), 2984 (Aliphatic C–H str), 1661 (Amide C=O str), 1487 (Aromatic C=C str) and 1229 (C–N str) ^{1}H NMR ($CDCl_3$ 1δ ppm): 4.28 (s, 2H, –COCH_2N), 7.26–8.67 (m, 13H, Ar–*H*) and 11.25 (br s, 1H, –N*H*COCH$_2$–) Anal. Calcd. for $C_{21}H_{17}N_2O_2Cl$: C, 69.14; H, 4.70; N, 7.68; Found: C, 69.08; H, 4.74; N, 7.62.

*2.3.7. 2-(2′-Methylanilino)acetamido-5-chlorobenzophenone (**3e**)*

IR (KBr cm^{-1}): 3240 (Sec N–H str), 2929 (Aliphatic C–H str), 1700 (Ketonic C=O str), 1634 (Amide C=O str), 1515 (Aromatic C=C str) and 1242 (C–N str) ^{1}H NMR ($CDCl_3$ 1δ ppm): 2.35 (s, 3H, Ar–CH_3), 4.73 (s, 2H, –COCH_2N), 7.26–8.69 (m, 12H, Ar–*H*) and 11.38 (br s, 1H, –N*H*COCH$_2$–) Anal. Calcd. for $C_{22}H_{19}N_2O_2Cl$: N, 7.39; Found: N, 7.45.

*2.3.8. 2-(4′-Aminobenzoyloxy)acetamido-5-chlorobenzophenone (**3f**)*

IR (KBr cm^{-1}): 3473 and 3367 (Primary N–H str), 3240 (Sec N–H str), 3056 (Aromatic C–H str), 2948 (Aliphatic C–H str), 1701 (Ketonic C=O str), 1643 (Amide C=O str), 1515 (Aromatic C=C str), 1242 (C–N str) and 1100 (C–O str) ^{1}H NMR ($CDCl_3$ 1δ ppm): 4.32 (s, 2H, Ar–NH_2), 5.20 (s, 2H, –COCH_2N), 7.17–7.56 (m, 12H, Ar–*H*) and 9.68 (br s, 1H, –N*H*COCH$_2$–) Anal. Calcd. for $C_{21}H_{17}N_2O_4Cl$: N, 6.85; Found: N, 6.79.

*2.3.9. 2-Sulfanilamidoacetamido-5-chlorobenzophenone (**3g**)*

IR (KBr cm^{-1}): 3481 and 3370 (Primary N–H str), 3265 (Sec N–H str), 3056 (Aromatic C–H str), 2948 (Aliphatic C–H str), 1710 (Ketonic C=O str), 1665 (Amide C=O str), 1520(Aromatic C=C str), 1250 (C–N str) and 1100,1160 (C–O str) ^{1}H NMR ($CDCl_3$ 1δ ppm): 4.12 (s, 2H, Ar–NH_2), 4.57 (s, 2H, –COCH_2N), 7.27–8.64 (m, 12H, Ar–*H*) and 11.26 (br s, 1H, –N*H*COCH$_2$–) Anal. Calcd. for $C_{22}H_{19}$

Table 1 Characterization data of synthesized compounds (**3a**–**3g**).

S. No.	Compound	Mp (°C)	R_f value	Solvent system
1	**3a**	92–94	0.735	Toluene: ethyl acetate (9:1)
2	**3b**	131–134	0.729	Toluene: ethyl acetate (9:1)
3	**3c**	101–104	0.816	Chloroform
4	**3d**	114–117	0.724	Ethyl acetate
5	**3e**	118–120	0.821	Chloroform
6	**3f**	130–132	0.634	Ethyl acetate
7	**3g**	230–234	0.623	Ethyl acetate

Table 2 Comparison of % yield and time taken by compounds from both methods.

S. No.	Compound	Conventional		Microwave	
		Yield (%)	Time (h)	Yield (%)	Time (min)
1	**3a**	42	20	75	2
2	**3b**	27	24	58	2
3	**3c**	24	28	55	3
4	**3d**	34	24	65	2.5
5	**3e**	59	26	80	2.5
6	**3f**	63	28	83	3
7	**3g**	28	24	56	2

Table 3 Experimental log *P* values

S. No.	Compound	Abs.	Conc. (μg/ml)	Drug (mg) in distilled H_2O	Drug (mg) in *n*-octanol	Log *P* = C(org)/C(aq)
1	**3a**	0.106	8.150	1.85	8.15	4.40
2	**3b**	0.160	8.242	1.76	8.24	4.68
3	**3c**	0.066	7.784	2.21	7.78	3.50
4	**3d**	0.585	8.091	1.91	8.09	4.24
5	**3e**	0.241	7.843	2.16	7.84	3.63
6	**3f**	0.255	8.270	1.73	8.27	4.78
7	**3g**	0.062	7.640	2.36	7.64	3.24

Table 4 Partition coefficient values experimental values vs calculated value.

S. No.	Compound	miLog *P*[a]	CSlog *P*[b]	*C*log *P*[c]	Observed log *P* (experimental)
1	**3a**	5.705	4.24	4.24	4.40
2	**3b**	4.986	3.678	1.78	4.68
3	**3c**	4.548	3.24	2.27	3.50
4	**3d**	5.027	3.91	3.064	4.24
5	**3e**	5.428	3.94	3.277	3.63
6	**3f**	4.938	4.664	3.306	4.78
7	**3g**	3.314	3.04	1.03	3.24

[a] www.molinspiration.com/cgi-bin/properties.
[b] www.chemsilico.com/cs_products/products.html.
[c] Moriguchi et al. (1992)

N_2O_2Cl: C, 69.75; H, 5.05; N, 7.39; Found: C, 69.69; H, 5.09; N, 7.44.

2.4. Physicochemical evaluation

Target compounds were designed to be CNS active, hence the parameters were selected which effect blood-brain barrier (BBB). Lipophilicity is an important aspect of transport and distribution of drugs in biological systems. The level of drug lipophilicity is estimated by the partition coefficient. Lipophilicity was the first of the descriptors to be identified as important for CNS penetration. Partition coefficient (log *P*) determination is done by shake-flask method and by computational methods. To access whether test compounds have potential are likely to be permeate BBB, several computational methods are available. The log *P* value of all the test

Table 5 Physicochemical parameters values.[a]

S. No.	Compound	M.W	*n*ON value	*n*OHNH value	*n*-Violations	Rotatable bonds
1	**3a**	399.277	4	2	1	6
2	**3b**	409.829	7	2	0	7
3	**3c**	380.831	5	3	0	6
4	**3d**	364.832	4	2	1	6
5	**3e**	378.859	4	2	1	6
6	**3f**	408.841	6	3	1	6
7	**3g**	443.912	7	4	0	7

[a] www.molinspiration.com/cgi-bin/properties.

compounds was calculated (Moriguchi et al., 1992), determined experimentally and computed through online softwares (www.molinspiration.com/cgi-bin/properties, xxxx). Other physicochemical parameters like molecular weight, nON value, nOHNH value, *n*-violations and number of rotatable bonds are determined through online software. (www.chemsilico.com/cs_products/products.html., xxxx) Results are shown in Table 4 and 5.

*2.4.1. Experimental determination of partition coefficient of 2-amino-benzophenone derivatives (**3a–3g**)*

Partition coefficient was determined in between *n*-octanol and distilled water using a modified procedure based on the method of Fugita et al. (1964). Standard plot of compounds **(3a–3g)** were prepared in *n*-octanol. Various standard solutions of concentrations 0, 4, 8, 12 and 16 μg/ml were prepared from a stock solution (100 μg/ml) of compounds **(3a–3g)** in λ_{max} 341, 345, 235, 339, 333, 328, 341 nm respectively. Accurately weighed quantity of compounds (10 mg) was taken in glass stopper tubes containing equal volumes (50 ml) of distilled water and *n*-octanol. The tubes were shaken for 6 h using water bath shaker. After 24 h, the organic phase was separated with the help of a separating funnel. The absorbance was measured on UV spectrophotometer at appropriate wavelength after making dilution to10 μg/ml. Results are shown in Table 3.

2.5. Skeletal muscle relaxant activity

(Kulkarni, 1993) The biological evaluation of eight synthesized compounds for skeletal muscle relaxant activity was carried out by Rotarod test. Diazepam was used as a standard drug. Albino mice weighing (20–25 g) were used for the study. Animals were housed under standard conditions and allowed free access to both food and water *ad libitum*.

The experimental protocols were approved by Institutional Animal Ethics Committee and a written permission from in house ethics committee has been taken to carry out (Reference no. 1080/C/07/CPCSEA on dated 03-April-2010) and complete this study.

2.6. Rotarod test

Mice were placed on a horizontal wooden rod rotating at a speed of 25 rpm. The mice capable of remaining on the top for 1 min or more, in three successive trials were selected for the study. The selected animals were divided into ten groups ($n = 5$). The stock solutions of all the test samples and standard were prepared by suspending in 1% *w*/*v* carboxy methyl cellulose. Carboxy methyl cellulose (4 ml/kg) and diazepam (4 mg/kg) were given to group 1 and 2. Test sample 10 mg/kg was injected into group 3. Each group of animals was then placed on the rod at an interval of 30 min. The animals that failed more than once on the Rotarod for 1 min were considered as passed the test.

Table 6 Skeletal muscle relaxant activity by Rotarod test.

S. No.	Treatment	Dose	Rotarod Test
1	CMC (Control)	4 ml/kg	2.45 ± 1.2
2	Diazepm (Standard)	4 mg/kg	69.70 ± 3.3*
3	**3a**	10 mg/kg	18.95 ± 13.2*
4	**3b**	10 mg/kg	18.83 ± 3.7*
5	**3c**	10 mg/kg	53.57 ± 3.5*
6	**3d**	10 mg/kg	29.66 ± 7.0*
7	**3e**	10 mg/kg	28.53 ± 10.2*
8	**3f**	10 mg/kg	55.16 ± 2.5*
9	**3g**	10 mg/kg	39.19 ± 8.2*

Data are mean ± SEM; ($n = 5$); $P < 0.001$ followed by ANOVA.
* Significant difference between control group and treated group.

2.7. Statistical analysis

The mean value ± SEM was calculated for each parameter. The results were analyzed statistically by ANOVA and significant difference was found between control group and treated group, $P < 0.001$. The results of experiments by proper statistical analysis are tabulated in Table 6.

3. Results and discussion

We describe herein the synthesis of 2-Amino-5-chlorobenzophenone derivatives, **(3a–3g)** by conventional and microwave methods. For the synthesis of target compounds, first, the 2-(chloroacetamido)-5-chlorobenzophenone **(2)** was prepared by the conventional and microwave irradiation technique in which 2-amino-5-chlorobenzophenone **(1)** and chloroacetylchloride are treated in the presence of toluene. After that the derivatives **(3a–3g)** were prepared by the reaction of 2-(chloroacetamido)-5-chlorobenzophenone **(2)** and different aniline derivatives in the presence of potassium carbonate in a minimum quantity of DMF with conventional and microwave methods. It was observed that from both conventional and microwave methods, the microwave method was found to give the better yield. All the synthesized compounds **(3a–3g)** were

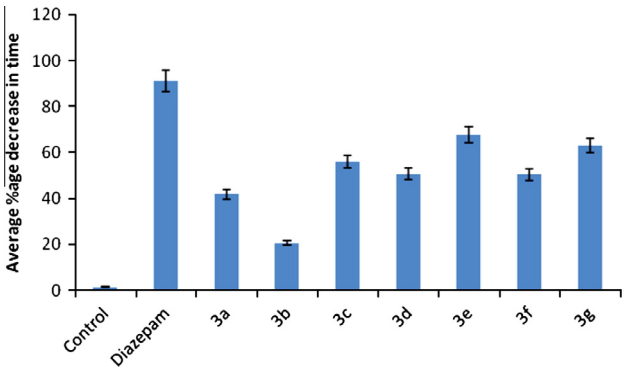


Figure 2 Graph of average %age decrease in time by Rotarod test.

purified by successive recrystallization using ethanol. The purity of the synthesized compounds was checked by performing TLC. The structures of the synthesized compounds were determined by their FTIR and ^{1}H NMR. In accordance with the data obtained from physicochemical evaluation studies the log *P* values of most of our test compounds indicate that the test compounds have the potential to be CNS active. Experimentally determined values of log *P* of the test compounds were less than 5. Calculated values of log *P* of the test compounds were also less than 5. According to molinspiration, the log *P* value of most of the test compounds was less than 5 except **3a, 3d** and **3e** and by chemsilico all the test compounds have log *P* value less than 5. From all the above data it is concluded that experimentally determined and calculated values of log *P* are very much similar to values of log *P* calculated by the online software Chemsilico. According to the rule of five, compounds with the number of violations not more than 1 shows good bioavailability and bioactivity and all the test compounds have the number of violations in the range of 0–1. Compounds with *n*OHNH value (H-bond donors) less than 5 show increased solubility in cellular membranes and all the test compounds have *n*OHNH value in the range of 2–4 which is less than 5. Compounds with *n*ON value (H-bond acceptors) less than 10 and molecular weight less than 500 show good CNS activity and all the test compounds have *n*ON value in the range of 4–7 and molecular weight in the range of 364.832–443.912. The number of rotatable bonds for CNS activity should not be more than 10 and all the test compounds have the number of rotatable bonds in the range of 6–7.

In accordance with the data obtained from skeletal muscle relaxant activity, all the synthesized compounds have shown significant differences between control group and treated group, $P < 0.001$, ANOVA. These results showed that compounds have good muscle relaxant activity. As evidenced by average %age decrease in time Fig. 2. Compound bearing substituents o-toluidine (**3e**) has shown the highest skeletal muscle relaxant activity and compounds bearing substituents sulfanilamide (3 g), p-aminophenol (**3c**), *p*-aminobenzoic acid (**3f**) and aniline (**3d**) also possess good skeletal muscle relaxant activity at dose (10 mg/kg).

4. Conclusion

In conclusion, a series of novel 2-Amino-5-chlorobenzophenone derivatives were prepared by both conventional and microwave irradiation method. Microwave irradiation method was found to give better yield. All the synthesized compounds were subjected to physicochemical parameters determination for BBB penetration through experimental and online software. The compounds were screened for skeletal muscle relaxant activity and from the investigation, it is quite apparent that all the 2-amino-5-chlorobenzophenone derivatives (**3a**–**3g**) possess skeletal muscle relaxant activity.

Acknowledgements

Authors are thankful to All India Council for Technical Education (AICTE), New Delhi, India and Punjab State Council for Science and Technology (PSCST), Punjab, for providing financial support for this research work. Authors are also thankful to Panjab University, Chandigarh, India, for cooperation in getting the spectral data.

References

Bodor, N., Sloan, K.B., Higuchi, T., 1977. J. Med. Chem. 20, 1435.
Coombs, R.V., Danna, R.P., Denzer, M., Hardtmann, G.E., Huegi, B., Koletar, G., Koletar, J., Ott, H., Jukniewicz, E., 1973. J. Med. Chem. 16, 1237.
Felix, A.M., Winter, D.P., Wang, S.S., Kulesha, I.D., Pool, W.R., Hane, D.L., Sheppard, H., 1974. J. Med. Chem. 17, 422.
Fujita, T., Iwasa, J., Hansch, C., 1964. J. Am. Chem. Soc. 86, 5175.
Hirai, K., Ishiba, T., Sugimoto, H., Sasakura, K., Fujishita, T., Toyoda, T., Tsukinoki, Y., Joyama, H., Hatakeyama, H., Hirose, K., 1980. J. Med. Chem. 23, 764.
Kulkarni, S.K., 1993. Hand Book of Experimental Pharmacology, second ed. Vallabh Prakashan, New Delhi, p. 122.
Liou, J.P., Chang, C.W., Song, J.S., Yang, Y.N., Yeh, C.F., Tseng, H.Y., Lo, Y.K., Chang, Y.L., Chang, C.M., Hsieh, H.P., 2002. J. Med. Chem. 45 (12), 2556.
Moriguchi, I., Hirono, S., Liu, Q., Nakagome, I., Matsushita, Y., 1992. Chem. Pharm. Bull. 40 (1), 127–130.
Ottosen, E.R., Sorenson, M.D., Bjorkiing, F., Nielsen, T.S., Fjording, M.S., Aaes, H., Binderup, L., 2003. J. Med. Chem. 46 (26), 5651.
Sternbach, L.H., Fryer, R.I., Metlesics, W., Reeder, E., Sach, G., Saucy, G., Stempel, A., 1962. J. Org. Chem. 27, 3788.
Sternbach, L.H., Reeder, E., Keller, O., Metlesics, W., 1961. J. Org. Chem. 26, 4488.
Su, D-S., Lim, J.L., Tinney, E., Wan, B-L., Murphy, K.L., Reiss, D.R., Harrell, M., O'Malley, S.S., Ransom, R.W., Chang, R.S.L., Pettibone, D.J., Yu, J., Tang, C., Freidionger, R.M., Bock, M.G., Anthony, N.J., 2008. J. Med. Chem. 51 (13), 3946.
Walsh, D.A., 1980. Synthesis, 677.
Welstead, W.J., Moran, J.H.W., Stauffer, H.F., Turnbull, L.B., Sancilio, L.F., 1979. Amer. Chem. Soc. 22, 1074.
www.molinspiration.com/cgi-bin/properties
< http://www.chemsilico.com/cs_products/products.html >