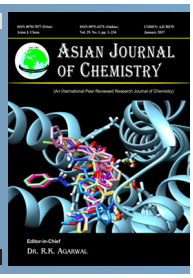
Asian Journal of Chemistry; Vol. 29, No. 2 (2017), 381-384

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2017.20210



Design, Synthesis and Biological Evaluation of 2-[4-(Aryl substituted)piperazin-1-yl]acetamido-5-chlorobenzophenone Derivatives

SHWETA VERMA* and SUSHIL KUMAR

Faculty of Pharmacy, IFTM University, Moradabad-244 001, India

*Corresponding author: E-mail: shweta_iftm@yahoo.in

Received: 23 July 2016; *Accepted*: 28 October 2016; *Published online*: 30 November 2016; AJC-18166

Substituted aryl piperazine and its derivatives have attracted great attention due to its diversity of pharmacological activities and its application in heterocyclic synthesis and medicines. It exerts its action on the CNS as it shows its strong affinity towards serotonin and dopamine receptors. The target compounds were synthesized by first reacting *p*-chloroaniline with chloroacetylchloride to obtain 2-chloro-N-(4-chlorophenyl)acetamide (**1**), the synthesized compound **1** was further treated with benzoyl chloride in the presence of aluminium chloride to get N-(2-benzoyl-4-chlorophenyl)-2-chloracetamide (**2**) and then treated with appropriate phenyl piperazine in DMF in the presence of potassium carbonate. The structures were confirmed on the basis of their TLC, IR, ^{1}H NMR, ^{13}C NMR and mass spectra. The physico-chemical parameters were also determined for blood brain barrier penetration. The log P values of the compounds tested showed that compounds have the potential to be CNS active. The compounds were evaluated for the skeletal muscle relaxant activity and it was found that piperazine derivatives possess significant differences between control group and treated group ($P < 0.001$). Among these derivatives, compound **SA4** possesses the highest skeletal muscle relaxant activity.

Keywords: Aryl piperazine, Serotonin, Dopamine, Blood brain barrier.

INTRODUCTION

Arylpiperazines are an important class of compounds in organic chemistry because of their application in heterocyclic synthesis and different important pharmacological properties. Arylpiperazines and their derivatives constituted an important pharmacophore in various potent marketed drugs. The piperazines compounds have the ability to cross the blood brain barrier as its possess small size and lipophilic nature and so they are used in CNS ailment and in treatment of various disorders including skeletal muscle relaxants, anxiety, psychosis and depression [1-6]. It has been investigated that long chain aryl piperazine (LCAPs) are the major and diverse class of agents which exerts its action on CNS [7,8] and so linked with 2-aminobenzophenone derivatives which was also evaluated as CNS active agents [9]. All the agents synthesized were found to be of our great interest as they exert their action on the CNS and rewarded the structure activity as other CNS active agents avail. In this view 2-amino-5-chlorobenzophenone linked with phenyl piperazines were synthesized (Fig. 1), physico-chemical studies were studied and skeletal muscle relaxant activity was evaluated.

EXPERIMENTAL

The chemicals were procured from E. Merck (Germany) and S.D. Fine Chemicals (India). Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The infrared (IR) spectra of synthesized compounds were recorded in potassium bromide discs on Perkin Elmer Spectrum RX1. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 spectrophotometer (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz) in $CDCl_3$ containing TMS as an internal standard. The UV spectra were recorded on Shimadzu, UV-1800 spectrophotometer. All reagents were of commercial quality and were used without further purification. The reaction's progress was monitored by thin layer chromatography (TLC) which were prepared by using silica gel G and activated at 110 °C for 0.5 h using the solvent system toulene:ethylacetate (4.5:0.5) and spots were visualized in an iodine chamber. All solvents were dried and freshly distilled out prior to use according to standard procedure.

Synthesis of 2-chloro-N-(4-chlorophenyl)acetamide: *p*-Chloroaniline (2.5 g, 0.02 mol) was dissolved in 25 mL toluene and chloroacetylchloride (9.04 g, 0.08 mol) was gradu-

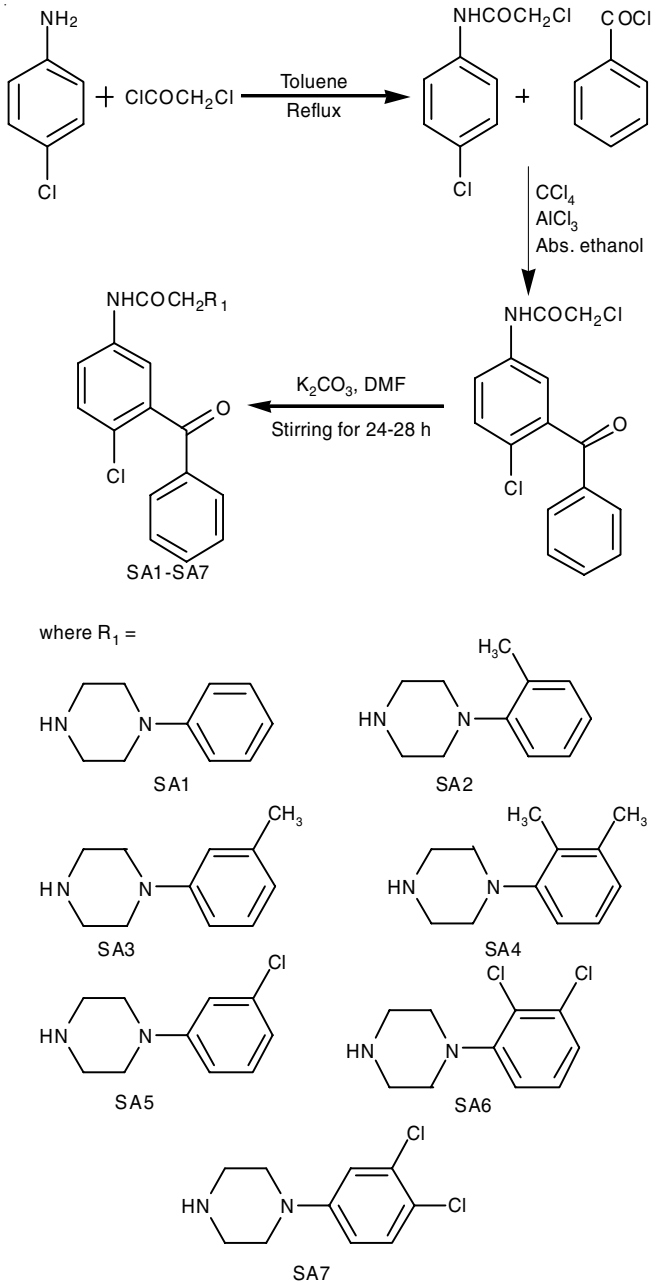


Fig. 1. Synthesis of 2-[4-(aryl substituted)piperazin-1-yl]acetamido-5-chlorobenzophenone derivatives

ally added with stirring. The mixture was allowed to reflux for 6-7 h to expel most of the formed HCl. The completion of reaction was indicated by TLC using silica gel G as stationary phase and toulene:ethyl acetate (4.5:0.5). It was then cooled to room temperature and washed with ice cold aqueous ammonia solution, dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The recrystallization of the product was carried out with alcohol which gives 82 % of product.

N-(2-Benzoyl-4-chlorophenyl)-2-chloracetamide: 2-Chloro-N-(4-chlorophenyl)acetamide was dissolved in CCl_4 and then mixed with benzoyl chloride in equimolar quantity. Finely powdered anhydrous aluminum chloride was added with frequent shaking during 10 min to the contents of the flask. The mixture was allowed to reflux for 8-9 h. The reaction's progress was monitored by thin layer chromatography (TLC) using silica gel G using the solvent system toulene:ethyl acetate (4.5:0.5) and spots were visualized in an iodine chamber. The mixture was then poured into crushed ice. The solid product so obtained was washed with aq. NaOH followed by water.

General procedure for the synthesis of N-(2-benzoyl-4-chlorophenyl)-2-chloracetamide derivatives (SA1-SA7): N-(2-Benzoyl-4-chlorophenyl)-2-chloracetamide derivatives were prepared by stirring the equimolar of N-(2-benzoyl-4-chlorophenyl)-2-chloracetamide and different substituted arylpiperazine 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-[4-(Phenyl)piperazin-1-yl]acetamido-5-chlorobenzophenone (SA1): IR (KBr, ν_{max}, cm^{-1}): 3240 (NH amide), 3047 (CH, arom.), 2921 (CH aliph.), 1703 (C=O ketone), 1645 (C=O amide), 1284 (C-N arom.), 1236 (C-N aliph.), 748 (C-Cl). ^{1}H NMR (300 MHz; $CDCl_3$, δ): 2.77-3.39 (m, 8H, pip. ring), 3.25 (s, 2H,CH_2CO), 6.89-8.68 (m, 13H, Ar-H), 11.55 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ): 196.47, 169.89, 151.14, 137.50, 133.17, 133.02, 131.77, 130.09, 129.10, 128.50, 127.52, 126.31, 123.06, 119.66, 116.11, 62.28, 77.21, 76.79, 53.51, 48.92.

2-[4-(2-Methylphenyl)piperazin-1-yl]acetamido-5-chlorobenzophenone (SA2): IR (KBr, ν_{max}, cm^{-1}): 3234 (NH amide), 3058 (CH, arom.), 2929 (CH aliph.), 1693 (C=O ketone), 1650 (C=O amide), 1282 (C-N arom.), 1240 (C-N aliph.), 746 (C-Cl). ^{1}H NMR (300 MHz; $CDCl_3$, δ): 2.77-3.91 (m, 8H, pip. ring), 3.25 (s, 2H, CH_2CO), 3.88 (s, 3H, CH_3), 6.89-8.67 (m, 12H, Ar-H), 11.52 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ): 195.36, 170.12, 151.22, 141.19, 137.59, 137.45, 133.09, 133.02, 131.64, 130.09, 130.07, 128.51, 127.49, 126.47, 123.11, 122.91, 120.91, 118.34, 111,17, 62.34, 77.35, 76.67, 52.34, 53.77.

2-[4-(3-Methylphenyl)piperazin-1-yl]acetamido-5-chlorobenzophenone (SA3): IR (KBr, ν_{max}, cm^{-1}): 3236 (NH amide), 3050 (CH, arom.), 2929 (CH aliph.), 1697 (C=O ketone), 1650 (C=O amide), 1282 (C-N arom.), 1240 (C-N aliph.), 746 (C-Cl). ^{1}H NMR (300 MHz; $CDCl_3$, δ): 2.77-3.91 (m, 8H, pip. ring), 3.25 (s, 2H, CH_2CO), 3.88 (s, 3H, CH_3), 6.80-8.61 (m, 12H, Ar-H), 11.52 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ): 196.36, 170.12, 152.22, 141.19, 137.59, 137.45, 133.09, 133.02, 131.64, 130.09, 130.07, 128.51, 127.49, 126.47, 123.11, 122.91, 120.91, 118.34, 111,17, 62.34, 77.35, 76.67, 52.34, 53.77.

2-[4-(2,3-Dimethylphenyl)piperazin-1-yl]acetamido-5-chlorobenzophenone (SA4): IR (KBr, ν_{max}, cm^{-1}): 3234 (NH amide), 3058 (CH, arom.), 2929 (CH aliph.), 1693 (C=O ketone), 1650 (C=O amide), 1282 (C-N arom.), 1240 (C-N aliph.), 746 (C-Cl). ^{1}H NMR (300 MHz; $CDCl_3$, δ): 2.77-3.91 (m, 8H, pip. ring), 3.25 (s, 2H, CH_2CO), 3.86 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 6.77-8.57 (m, 11H, Ar-H), 11.52 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ): 196.36, 170.12, 152.22, 141.19, 137.59, 137.45, 133.09, 133.02, 131.64, 130.09, 130.07, 128.51, 127.49, 126.47, 123.11, 122.91, 120.91, 118.34, 111,17, 62.34, 77.35, 76.67, 52.34, 53.77.

2-[4-(2-Chlorophenyl)piperazin-1-yl]acetamido-5-chlorobenzophenone (SA5): IR (KBr, ν_{max}, cm^{-1}): 3239 (NH amide), 3045 (CH arom.), 2921 (CH aliph.), 1703 (C=O ketone), 1645 (C=O amide), 1284 (C-N arom.), 1236 (C-N ali), 748

(C-Cl). ^{1}H NMR (300 MHz; $CDCl_3$, δ): 2.77-3.34 (m, 8H, pip. ring), 3.24 (s, 2H,CH_2CO), 6.77-8.57 (m, 12H, Ar-H), 11.54 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ): 198.55, 169.79, 149.76, 137.48, 132.21, 133.05, 131.81, 130.06, 127.91, 128.52, 128.46, 127.55, 126.24, 123.04, 117.31, 62.20, 77.23, 76.75, 53.33, 48.97.

2-[4-(2,3-Dichlorophenyl)piperazin-1-yl]acetamido-5-chlorobenzophenone (SA6): IR (KBr, ν_{max}, cm^{-1}): 3240 (NH amide), 3047 (CH arom.), 2921 (CH aliph.), 1703 (C=O ketone), 1645 (C=O amide), 1284 (C-N arom.), 1236 (C-N ali), 748 (C-Cl). ^{1}H NMR (300 MHz; $CDCl_3$, δ): 2.77-3.34 (m, 8H, pip. ring), 3.24 (s, 2H,CH_2CO), 6.54-8.32 (m, 11H, Ar-H), 11.54 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ): 196.55, 169.79, 149.76, 137.48, 133.21, 133.05, 131.81, 130.06, 128.91, 128.52, 128.46, 127.55, 126.24, 123.04, 117.31, 62.20, 77.23, 76.75, 53.33, 48.97.

2-[4-(3,4-Dichlorophenyl)piperazin-1-yl]acetamido-5-chlorobenzophenone (SA7): IR (KBr, ν_{max}, cm^{-1}): 3238 (NH amide), 3045 (CH arom.), 2911 (CH aliph.), 1701 (C=O ketone), 1646 (C=O amide), 1279 (C-N arom.), 1236 (C-N ali), 750 (C-Cl). ^{1}H NMR (300 MHz; $CDCl_3$, δ): 2.77-3.34 (m, 8H, pip. ring), 3.24 (s, 2H,CH_2CO), 6.49-8.38 (m, 11H, Ar-H), 11.54 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ): 196.55, 169.79, 149.76, 137.48, 133.21, 135.05, 133.81, 130.06, 128.91, 128.54, 128.46, 127.55, 126.24, 123.04, 117.31, 62.20, 77.23, 76.75, 53.33, 48.97.

Evaluation of physico-chemical parameters: The drugs were synthesized in such a way that they have the potency to cross the blood brain barrier (BBB) and found to be CNS active. To attain such behaviour, lipophilicity is an important parameter for distribution and active transport of drug in biological system. The partition coefficient is the first most and important parameter which defines the lipophilicity. Partition coefficient can be determined by shake-flask method and by different computational methods. The log P value of all the compounds were determined experimentally and through online softwares [11] and was calculated by Moriguchi method [10]. Other parameters like molecular weight, n ON value, n OHNH value, *n*-violations and number of rotatable bonds are determined through online softwares [12] (Tables 1 and 2).

Experimental determination of partition coefficient of 2-[4-(aryl substituted) piperazin-1-yl] acetamido-5-chlorobenzophenone derivatives (SA1-SA7): For the determination of log P values (partition coefficient) experimentally the two phases of lipophilic and hydrophilic were carried out in between *n*-octane and distilled water using a modified procedure based on Fujita and Hansch method [13]. The standard plot of compounds (SA1-SA7) were prepared in *n*-octane and various standard solutions of concentrations 0, 4, 8, 12 and 16 g/mL were prepared from a stock solution (100 g/mL) of compounds (**SA1-SA7**) in maximum wavelength 333, 324, 246, 342, 335, 322, 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 g/mL (Table-3).

TABLE-1
PHYSICO-CHEMICAL PARAMETERS VALUES

Compd.	m.w.	nON value	nOHNH value	n-Violation	Rotatable bonds
SA1	434.95	5	2	0	6
SA2	448.97	5	2	0	6
SA3	448.97	5	2	0	6
SA4	464.97	6	2	0	7
SA5	464.97	6	2	0	7
SA6	464.97	6	2	0	7
SA7	469.39	5	2	0	6

TABLE-2
PARTITION COEFFICIENT VALUES
EXPERIMENTAL *vs.* CALCULATED VALUE

Compd.	mi log P	C log P	Observed log P (experimental)
SA1	5.34	4.11	4.64
SA2	5.76	4.14	4.31
SA3	5.79	4.452	4.34
SA4	5.35	4.32	4.26
SA5	5.57	4.83	4.31
SA6	5.40	4.32	4.61
SA7	5.97	4.99	2.92

TABLE-3
EXPERIMENTAL log P VALUES

Compd.	Abs.	Conc. (μg/mL)	Drug (mg) in distilled water	Drug (mg) in octanol	log P = C(org)/C(aq)
SA1	0.108	8.232	1.77	8.23	4.64
SA2	0.167	8.123	1.88	8.12	4.31
SA3	0.170	8.132	1.87	8.13	4.34
SA4	0.239	8.109	1.9	8.10	4.26
SA5	0.245	8.122	1.88	8.12	4.31
SA6	0.251	8.221	1.78	8.22	4.61
SA7	0.224	7.454	2.55	7.45	2.92

Skeletal muscle relaxant activity: Swiss albino mice weighing (20-25 g) were used for the study. All the animals were housed under standard conditions and maintained on the suitable nutritional conditions for an acclimatization period of 7 days prior to experiment. Water was allowed *ad libitum* under hygienic conditions. Diazepam was used as standard drug.

Rotarod test-for muscle relaxation: The rota rod consist of a metal rod coated with rubber and the speed was adjusted to 25 rpm and the mice were placed on a horizontal wooden rod rotating at a speed of 25 rpm. The mice which have the ability to remain on the revolving rod for 5 min in three successive trials were used as the test. Swiss albino mice were divided into nine groups (n = 5). The stock solutions of all the test samples and standard were prepared by suspending in 1 % w/v carboxy methylcellulose. Group I was served as control which received carboxy methyl cellulose (10 mL/kg) animals of group II received standard drug diazepam at a dose of (5 mg/kg). Test sample 10 mg/kg was injected into test groups. Each group of animals was then placed on the rod at an interval of 0.5 h. The animals that failed more than once on the rotarod for 1 min were considered as passed the test.

Statistical analysis: The mean value ± SEM was calculated for each parameter and the results were calculated statistically

by ANOVA and significant difference was found between control group and treated group, $P < 0.001$ (Table-4).

TABLE-4
SKELETAL MUSCLE RELAXANT ACTIVITY BY ROTAROD TEST

Treatment	Dose	Rotarod test
CMC (Control)	10 mL/kg	2.34 ± 1.5
Diazepam (Standard)	2 mg/kg	65.56 ± 3.5
SA1	5 mg/kg	16.25 ± 12.9
SA2	5 mg/kg	17.83 ± 4.1
SA3	5 mg/kg	52.37 ± 3.7
SA4	5mg/kg	58.16 ± 6.9
SA5	5 mg/kg	27.51 ± 10.24
SA6	5 mg/kg	54.16 ± 2.5
SA7	5 mg/kg	38.19 ± 7.7

RESULTS AND DISCUSSION

The synthesis of 2-[4-(aryl substituted)piperazin-1-yl]-acetamido-5-chlorobenzophenone derivatives was carried out by first reacting *p*-chloroaniline with chloroacetyl chloride to obtain 2-chloro-N-(4-chlrophenyl)acetamide (**1**). The synthesized compound (**1**) was further treated with benzoyl chloride in the presence of aluminium chloride to get N-(2-benzoyl-4-chlorophenyl)-2-chloracetamide (**2**) and then treated with appropriate phenyl piperazine in DMF in the presence of potassium carbonate. All the synthesized compounds (**SA1-SA7**) were purified by successive recrystallization using ethanol and the purity was checked by performing TLC. The structures were determined by their FTIR and ^{1}H NMR. In accordance with the data obtained from physico-chemical evaluation studies the log P values of most of our test compounds indicate that the test compounds have the potential to be CNS active.

From 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.

Conclusion

A series of novel piperazine derivatives were synthesized and evaluated for skeletal muscle relaxant activity. The compound bearing *m*-methoxy as a substituent (SA4) possesses the highest skeletal muscle relaxant activity.

ACKNOWLEDGEMENTS

The authors are thankful to Faculty of Pharmacy IFTM University, Moradabad for providing support for this research work. Authors are also thankful to Jamia Hamdard University, New Delhi, for cooperation in getting the spectral data.

REFERENCES

1. H.R. Bürki, E. Eichenberger, A.C. Sayers and T.G. White, *Pharmacopsychiatry*, **8**, 115 (1975).
2. A.C. Sayers, H.R. Burki, W. Ruch and H. Asper, *Psychopharmacology*, **41**, 97 (1975).
3. R. Menegatti, A.C. Cunha, V.F. Ferreira, E.F.R. Perreira, A. El-Nabawi, A.T. Eldefrawi, E.X. Albuquerque, G. Neves, S.M.K. Rates, C.A.M. Fraga and E.J. Barreiro, *Bioorg. Med. Chem.*, **11**, 4807 (2003).
4. C.T. Sadashiva, J.N.N. Sharath Chandra, K.C. Ponnappa, T.V. Gowda and K.S. Rangappa, *Bioorg. Med. Chem. Lett.*, **16**, 3932 (2006).
5. G.I. Papakostas and M. Fava, *Eur. Psychiatry*, **22**, 444 (2007).
6. M.A. Katzman, *J. Affect. Disord.*, **128**, S11 (2011).
7. J. Obniska, M. Pawlowski, M. Kolaczkowski and A. Czopek, *Pol. J. Pharmacol.*, **55**, 553 (2003).
8. S. Kumar, A.K. Wahi and R. Singh, *Eur. J. Med. Chem.*, **46**, 4753 (2011).
9. D.-S. Su, J.L. Lim, E. Tinney, B.-L. Wan, K.L. Murphy, D.R. Reiss, C.M. Harrell, S.S. O'Malley, R.W. Ransom, R.S.L. Chang, D.J. Pettibone, J. Yu, C. Tang, T. Prueksaritanont, R.M. Freidinger, M.G. Bock and N.J. Anthony, *J. Med. Chem.*, **51**, 3946 (2008).
10. S. Moriguchi, S. Hirono, Q. Liu, I. Nakagome and Y. Matsushita, *Chem. Pharm. Bull. (Tokyo)*, **40**, 127 (1992).
11. www.molinspiration.com/cgi-bin/properties.
12. www.chemsilico.com/cs_product/products.html.,xxxx.
13. T. Fujita, J. Iwasa and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).