Asian Journal of Chemistry; Vol. 27, No. 7 (2015), 2452-2456

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.17914

Microwave-Assisted Synthesis, *in silico* ADME Prediction and Antibacterial Study of 2-(Substituted acetamido)-5-Nitrobenzophenone Derivatives

TIANGANG LI[1], SANDEEP SINGH[2], XING ZHAI[1], XIANGQI MENG[3,*] and RAJESH K. SINGH[2,*]

[1]Beijing University of Chinese Medicine, 11 Bei San Huan Dong Lu, ChaoYang District, Beijing 100029, P.R. China
[2]Department of Pharmaceutical Chemistry, Shivalik College of Pharmacy, Rupnagar-140126, India
[3]Beijing University of Chinese Medicine, Dongzhimen Hospital, Dongcheng District, Beijing 100700, P.R. China

*Corresponding authors: E-mail: rksingh244@gmail.com, xiangqimengbucm@126.com

Received: 29 April 2014; *Accepted*: 23 June 2014; *Published online*: 30 March 2015; AJC-17054

A series of novel 2-amino-5-nitrobenzophenone derivatives (**3-10**) were synthesized and characterized by IR, ^{1}H NMR and CHN elemental studies. All the synthesized compounds were subjected to *in silico* ADME predictions for determination for drug like properties. The values of physico-chemical parameters like molecular weight, nON value, nOHNH value, n-violations and the number of rotatable bonds of all the synthesized compounds also lies between the ranges that are required for good bioavailability. The synthesized compounds were tested for their *in vitro* antibacterial activity against the Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria. Among all the compounds synthesized compounds **4**, **9**, **10** have shown the maximum antibacterial activity in their group whereas compounds **3**, **6**, **8** have shown the minimum antibacterial activity.

Keywords: 2-Aminobenzophenone, Physicochemical parameters, ADME, Lipinski's rule of five, Anti-bacterial activity.

INTRODUCTION

2-Aminobenzophenone derivatives are important compounds in organic chemistry because of their application in heterocyclic synthesis and medicines[1]. 2-Aminobenzophenone has been used as starting material for the synthesis of 1,4-benzodiazepines[2]. Some heterocyclic compounds containing aminobenzophenone moiety possess anti-inflammatory[3-5], anti-tumor[6], antimitotic[7] and skeletal muscle relaxant[8] activities. More recently, their use has been extended to various diseases such as CNS cancer[9], viral infections (non-nucleoside inhibitors of HIV-1 reverse transcriptase)[10] and antivascular effects[11,12]. To the date, much research has been directed towards the synthesis and the novel uses of aminobenzophenones derivatives (Fig. 1).

Recent studies have revealed that aminobenzophenone and its derivatives exhibit potent antimicrobial activities[13,14] and lots of works have been going on synthesis of substituted aminobenzophenone as antibacterial chemotherapeutic regimen (Fig. 2). The objective of present work was to synthesize 2-aminobenzophenone derivatives by conventional and microwave techniques and to evaluate them for their *in vitro* antibacterial activity against different bacterial strains and to evaluate *in silico* ADME (Absorption, Distribution, Metabolism and Excretion) physico-chemical parameters using online software program[15].

EXPERIMENTAL

The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. ^{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. Infrared (IR) spectra were obtained with Perkin Elmer 882 spectrum and RXI, FT-IR model. Elemental analysis was performed on Elementar Vario EL III. Synthesis related to microwave irradiation are 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 0.5 h. All the solvents were dried and freshly distilled prior to use according to standard procedure. The starting compound 2-(chloroacetamido)-5-nitrobenzophenone was earlier synthesized in our lab by microwave irradiation technique[8].

General method for the synthesis of 2-amino-5-nitrobenzophenone derivatives

Conventional method: A mixture of 2-(chloroacetamido)-5-nitrobenzophenone (**2**) (1.60 g, 5 mmol), various amino substituents (5 mmol), anhydrous potassium carbonate (1.38 g, 10 mmol), sodium iodide (0.75 g, 5 mmol) and DMF

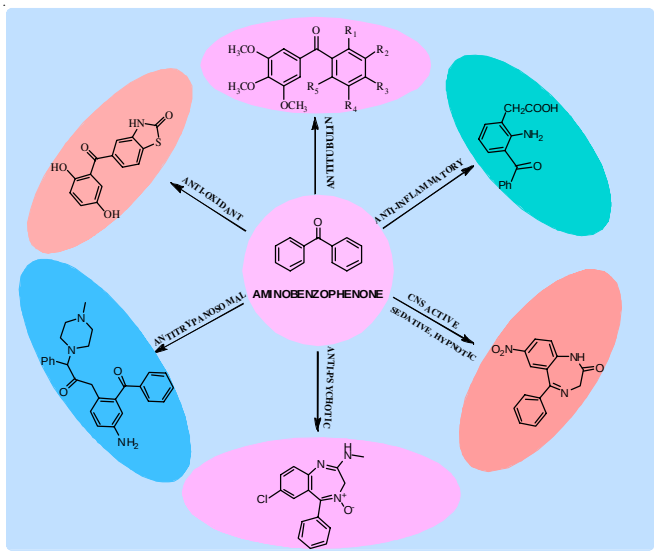


Fig. 1. Pharmacological activities exhibited by aminobenzophenone derivatives

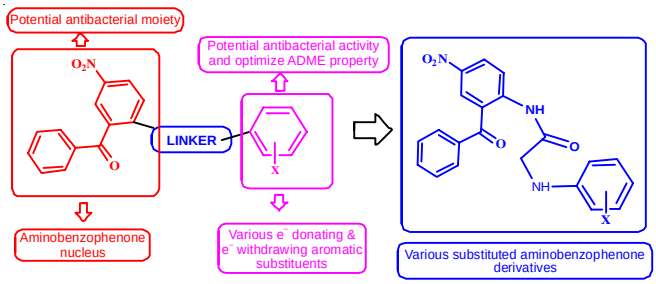


Fig. 2. Design of substituted 2-aminobenzophenone derivatives as potential antibacterial agents

(10 mL) as solvent were stirred for 3 days. The reaction mixture was poured into excess of water and the precipitated material was filtered, washed with water and dried. The product was recrystallized from ethyl acetate to get pure compounds (**3-10**).

Microwave irradiation method: A solution of equimolar of 2-(chloroacetamido)-5-nitrobenzophenone and different aniline derivatives in the presence of double mole of potassium carbonate in a minimum quantity of DMF was irradiated for 3-5 min in microwave oven (360 W) with 30 seconds intermittent time interval. After that reaction mixture was poured into ice cold water and the solid product thus separated was collected through filtration. The crude solid products was recrystallized from alcohol. The comparison of % yield and time taken for the synthesis by conventional and microwave method is given Table-1 and the comparison of % yield and time taken for synthesis by conventional and microwave method is given in Table-2.

2-(2′-Methylanilino)acetamido-5-nitrobenzophenone (3): m.p. 160-163 °C; R_f 0.71 (chloroform); IR (KBr, ν_{max}, cm^{-1}): 3230 (*sec* N-H), 3117 (aromatic C-H), 1717 (ketonic C=O), 1640 (amide C=O), 1579 bend (*sec* N-H), 1348 and 1614 str (N=O), 1442 and 1596 (aromatic C=C) and 1286 (C-N). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.4 (s, 3H, C*H*$_3$), 4.8 (s, 2H, -COC*H*$_2$N), 7.5-8.9 (m, 12H, Ar*H*), 10.5 (brs, 1H, -N*H*CH$_2$-) and 11.8 (brs, 1H, -N*H*COCH$_2$-). Anal. Calcd (%) for $C_{22}H_{19}N_3O_4$: C 67.86, H 4.92, N 10.79; Found (%): C 68.08, H 4.159, N 10.13.

2-(4′-Nitroanilino)acetamido-5-nitrobenzophenone (4): m.p. 157-158 °C; R_f 0.73 (chloroform:methanol (9:1); IR (KBr, ν_{max}, cm^{-1}): 3344 (*sec* N-H), 3063 (aliphatic C-H), 1664 (amide C=O), 1610 (ArC=O), 1492 (aromatic C=C) and 1279 (C-N). ^{1}H NMR ($CDCl_3$) δ (ppm): 4.2 (s, 2H, -COC*H*$_2$N), 7.3-8.6 (m, 12H, Ar*H*), 10.3 (brs, 1H, -N*H*CH$_2$-) and 11.5 (brs, ^{1}H NHCOCH$_2$-). Anal. Calcd (%) for $C_{21}H_{16}N_4O_6$: C 60.00, H 3.84, N 13.33; Found: C 63.99, H 4.010, N 12.96.

2-(4′-Aminobenzoyloxy)acetamido-5-nitrobenzophenone (5): m.p. 134-136 °C; R_f 0.71 (ethyl acetate); IR (KBr,

TABLE-1
COMPARISON OF % YIELD AND TIME TAKEN BY COMPOUNDS FROM BOTH METHODS

S.No.	Compounds	Conventional		Microwave	
		Yield (%)	Time (h)	Yield (%)	Time (min)
1.	**3**	58	20	75	3.0
2.	**4**	27	24	58	3.5
3.	**5**	62	28	55	4.0
4.	**6**	51	24	65	3.0
5.	**7**	35	26	80	4.5
6.	**8**	33	28	83	4.0
7.	**9**	28	24	56	5.0
8.	**10**	41	24	62	3.5

TABLE-2
ADME PHYSICO-CHEMICAL PARAMETERS VALUES OF
2-AMINOBENZOPHENONE DERIVATIVES WITH THEIR OPTIMUM RANGES

Parameters	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
miLOGP (< 5)	4.709	4.267	3.33	4.757	4.219	4.308	2.595	4.986
TPSA (< 160)	104.02	149.84	144.32	104.02	149.84	104.02	164.18	104.02
nAtoms	29.0	31.0	31.0	29.0	31.0	28.0	32.0	29.0
MWt. (< 500)	389.41	420.38	419.39	389.41	420.38	375.38	454.46	409.82
nON (≤ 10)	7	10	9	7	10	7	10	7
nOHNH (≤ 5)	2	2	3	2	2	2	4	2
nViolations (1 or < 0)	0	0	0	0	0	0	0	0
nRotb (<10)	7	8	8	7	8	7	8	7
Volume < 400	346.32	353.10	356.62	346.32	353.10	329.76	372.48	343.30

ν_{max}, cm^{-1}): 3346 (*sec* N-H), 3062 (aromatic C-H), 2923 (aliphatic C-H), 1719 (ester C=O), 1644 (amide C=O), 1611 (ArC=O), 1493 (aromatic C=C), 1095 (C-N) and 1157 (C-O), 1529, 1279 str (N=O), 1746 str ester (C=O). ^{1}H NMR (DMSO-d_6) δ (ppm): 4.6 (s, 2H, -$COCH_2$-), 5.9 (s, 2H, ArNH_2), 7.4-8.0 (m, 12H, Ar*H*) and 10.6 (brs, 1H, -N*H*$COCH_2$-). Anal. Calcd (%) for $C_{22}H_{17}N_3O_6$: C 63.01, H 4.09, N 10.02; Found: C 64.41, H 4.130, N 10.85.

2-(4′-Methylanilino)acetamido-5-nitrobenzophenone (6): m.p. 120-124 °C; R_f 0.81 (chloroform); IR (KBr, ν_{max}, cm^{-1}): 3320 (*sec* N-H), 3086 (aliphatic C-H), 1652 (amide C=O), 1620 (ArC=O), 1494 (aromatic C=C) and 1242 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.4 (s, 3H, Ar-CH_3), 4.5 (s, 2H, -$COCH_2$N), 7.5-8.9 (m, 12H, Ar*H*), 10.5 (brs, 1H, -N*H*CH_2-) and 11.8 (brs, 1H, -N*H*$COCH_2$-). Anal. Calcd (%) for $C_{22}H_{19}N_3O_4$: C 67.86, H 4.92, N 10.79; Found: C 68.10, H 4.378, N 11.13.

2-(2′-Nitroanilino)acetamido-5-nitrobenzophenone (7): m.p. 137-139 °C; R_f 0.68 (chloroform:methanol (9:1); IR (KBr, ν_{max}, cm^{-1}): 3332 (*sec* N-H), 3061 (aromatic C-H), 1677 (amide C=O), 1640 (ArC=O), 1505 (aromatic C=C), 1212 (C-N), 701 bend (C-H), 1577 and 1253 str (N=O). ^{1}H NMR (DMSO-d_6) δ (ppm): 4.2 (s, 2H, -$COCH_2$N), 7.2-8.1 (m, 12H, Ar*H*), 9.8 (brs, 1H, -N*H*CH_2-) and 12.6 (brs, 1H, -N*H*$COCH_2$-). Anal. Calcd (%) for $C_{21}H_{16}N_4O_6$: C 60.00, H 3.84, N 13.33; Found: C 61.49, H 3.669, N 13.96.

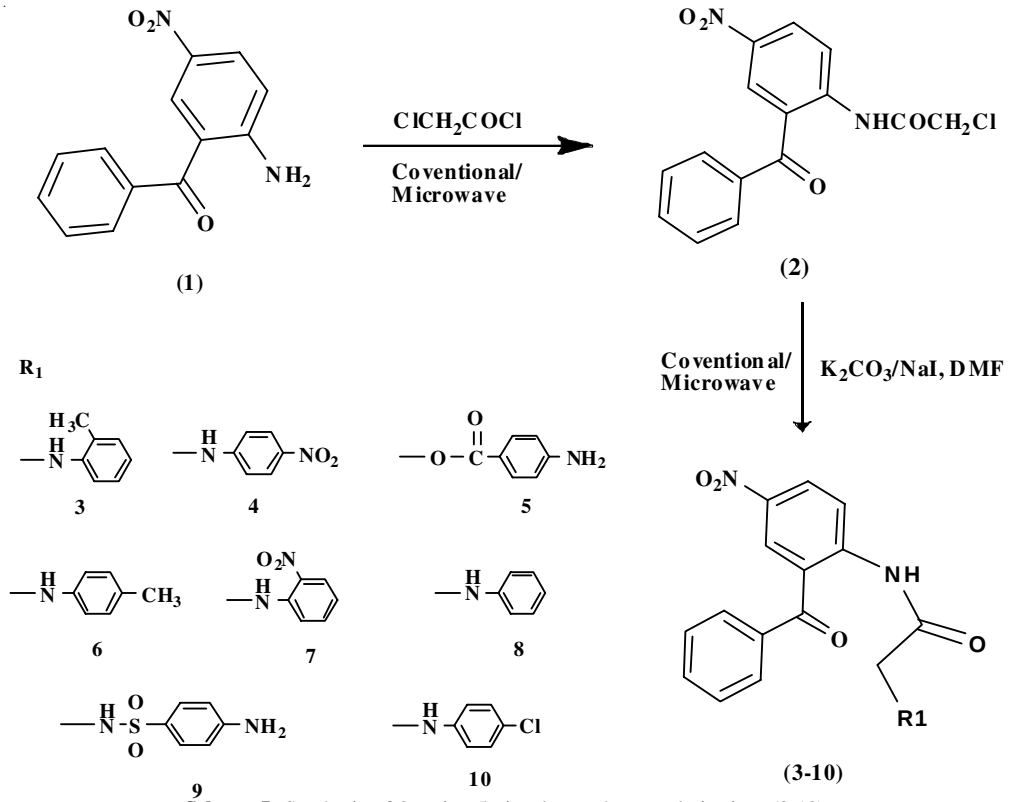
2-Anilinoacetamido-5-nitrobenzophenone (8): m.p. 116-118 °C; R_f 0.70 (ethyl acetate); IR (KBr, ν_{max}, cm^{-1}): 3346 (*sec* N-H), 3062 (aromatic C-H), 2923 (aliphatic C-H), 1644 (amide C=O), 1611 (ArC=O), 1493 (aromatic C=C), 1279 (C-N), 1529 and 1337 str (N=O). ^{1}H NMR (DMSO-d_6) δ (ppm): 4.5 (s, 2H, -$COCH_2$N), 7.5-8.8 (m, 13H, Ar*H*), 10.3 (brs, 1H, -N*H*CH_2-) and 11.9 (brs, 1H, -N*H*$COCH_2$-). Anal. Calcd (%) for $C_{21}H_{17}N_3O_4$: C 67.19, H 4.56, N 11.19; Found: C 68.81, H 4.04, N 11.26.

2-Sulphanilamidoacetamido-5-nitrobenzophenone (9): m.p. 232-235 °C; R_f 0.75 (chloroform:methanol (9.5:0.5); IR (KBr, ν_{max}, cm^{-1}): 3134 (*sec* N-H), 3046 (aromatic C-H), 2998 (aliphatic C-H), 1667 (amide C=O), 1667 (ArC=O), 1508 (aromatic C=C), 1226 (C-N) and 1620 and 1340 str (N=O), 910 str. (S-N). ^{1}H NMR (DMSO-d_6) δ (ppm): 4.2 (s, 2H, -$COCH_2$NH-), 7.2-8.6 (m, 12H, Ar*H*), 9.2 (s, 2H, Ar-NH_2), 10.5 (brs, 1H, -N*H*CH_2-) and 10.9 (brs, 1H, -N*H*$COCH_2$-). Anal. Calcd (%) for $C_{21}H_{18}N_4O_6S$: C 55.80, H 3.99, N 12.33; Found: C 56.04, H 3.678, N 12.95.

2-(4′-Chloroanilino)acetamido-5-nitrobenzophenone (10): m.p. 112-114 °C; R_f 0.80 (chloroform:methanol (9:1); IR (KBr, ν_{max}, cm^{-1}): 3239 (*sec* N-H), 1641 (amide C=O), 1618 (ArC=O), 1513 (aromatic C=C), 1090 (C-N), 1547 and 1328 str (N=O), 697 str (C-Cl). ^{1}H NMR (DMSO-d_6) δ (ppm): 4.2 (s, 2H, -$COCH_2$NH-), 6.9-8.2 (m, 12H, Ar*H*), 9.9 (brs, 1H, -N*H*CH_2-) and 11.9 (brs, 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 63.10, H 3.69, N 10.50.

RESULTS AND DISCUSSION

For the synthesis of target compounds, first, the 2-(chloroacetamido)-5-nitrobenzophenone (**2**) was prepared by treating 2-amino-5-nitrobenzophenone (**1**) with chloroacetylchloride in the presence of toluene. After that the derivatives (**3-10**) were prepared by the reaction of 2-(chloroacetamido)-5-nitrobenzophenone (**2**) and different aniline derivatives in the presence of potassium carbonate in a minimum quantity of DMF by conventional and microwave method (**Scheme-I**). Microwave irradiation method was found to give the better yield (Table-1).



Scheme-I: Synthesis of 2-amino-5-nitro-benzophenone derivatives (3-10)

TABLE-3
ZONE OF INHIBITION (IN mm) OF *Staphylococcus aureus* AND *Escherichia coli* OF TEST COMPOUNDS AT A CONCENTRATION OF 50, 100, 150 and 200 µg/mL

Compounds	Zone of inhibition (mm)							
	Staphylococcus aureus				*Escherichia coli*			
	50 (µg/mL)	100 (µg/mL)	150 (µg/mL)	200 (µg/mL)	50 (µg/mL)	100 (µg/mL)	150 (µg/mL)	200 (µg/mL)
Amoxycillin	12	13	16	17	10	12	15	18
Comp-3	2	4	5	6	2	2	5	6
Comp-4	3	5	6	8	3	4	6	8
Comp-5	2	3	6	7	2	2	4	6
Comp-6	2	4	5	6	2	3	4	5
Comp-7	2	3	5	7	2	3	5	7
Comp-8	2	3	4	6	2	4	6	7
Comp-9	3	3	5	8	2	4	5	8
Comp-10	3	4	5	8	2	3	5	8

The structures of the synthesized compounds were determined by IR, NMR and CHN elemental studies.

Molinspiration, web based software was used to obtain parameter such as MiLogP, TPSA, drug likeness. MiLog P parameter is used to check good permeability across the cell membrane. TPSA is related to hydrogen bonding potential of compound. Calculation of volume developed at molinspiration is based on group contributors. Number of rotatable bonds measures molecular flexibility. It is a very good description of absorption and bioavailbility of drugs. Through drug likeness data of molecule, it can be checked molecular properties and structure feature irrespect to known drugs.

According to the rule of five, compounds with number of violations not more than 1 shows good bioavailability and all the test compounds have zero number of violations of rule's of five. Compounds with nOHNH value (H-bond donors) less than 5 shows increase solubility in cellular membranes and all the test compounds have nOHNH value in the range of 2 to 4 which is less than 5. All values of other physicochemical parameters of all the synthesized compounds lie between the ranges that are required for good oral absorption[16] (Table-2).

Antibacterial activity of synthesized compounds was tested by Agar plate diffusion method[17] against two bacterial strains: *Staphylococcus aureus* (gram+ve) (ATCC-29737) and *Escherichia coli* (gram-ve) (ATCC-8739) procured from IMTECH, Chandigarh. After the setting of media, 2 mL of bacterial culture was poured in Petri dishes and sprayed over agar media. Different concentrations of test compound (50, 100, 150 and 200 µg/mL) were placed in each hole of the Petri dish. The plates were incubated at 37 °C for 24 h for bacteria strains. The diameter of zones of inhibition formed around the disc was measured after 24 h for the bacteria plates (Table-3). Amoxycillin was used as standard or positive control while DMSO was used as a solvent and as negative controls. Although none of the synthesized compounds have shown to have good antibacterial activity. However (compounds **4**, **9**, **10**) have shown the maximum antibacterial activity in their group whereas (compounds **3**, **6**, **8**) have shown the minimum antibacterial activity (Figs. 3 and 4).

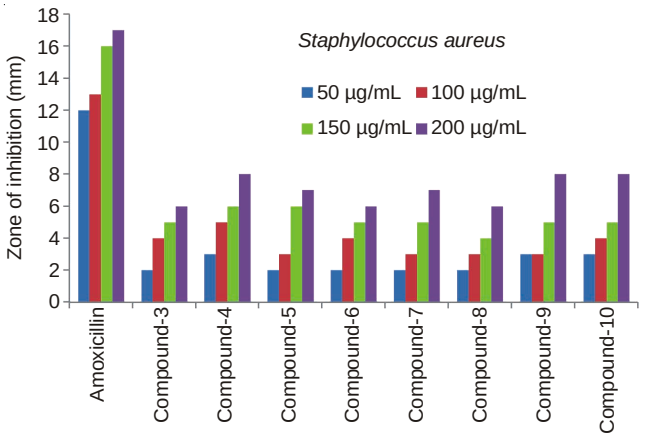


Fig. 3. Graphical representation of zone of inhibition at 50, 100, 150 and 200 µg/mL of test compounds against *Staphylococcus aureus*

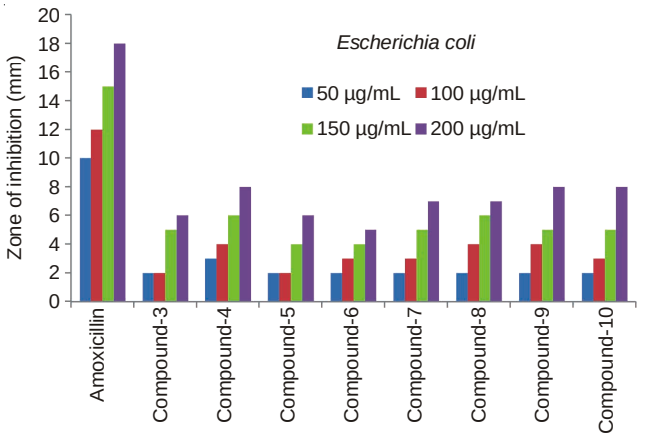


Fig. 4. Graphical representation of zone of inhibition at 50, 100, 150 and 200 µg/mL of test compounds against *Escherichia coli*

Conclusion

In conclusion, a series of novel 2-amino-5-nitrobenzophenone derivatives were prepared by both conventional and microwave irradiation method. Microwave irradiation method was found to give the better yield. All the synthesized compounds were subjected to *in silico* ADME prediction for drug like properties through experimental and online software. The antibacterial activity of the synthesized compound was evaluate. None of the compounds have exhibited significant antibacterial activity. The study revealed that 2-aminobenzophenone is a rich source of exploitation. Hence further modification of 2-aminobenzo-phenone moiety by substitution of different groups at different positions may provide more potent antibacterial agents in future.

ACKNOWLEDGEMENTS

The authors are thankful Principal Dr. D.N. Prasad, Shivalik College of Pharmacy, Nangal for providing the necessary facilities to carry out the research work. The authors are also thankful to Panjab University, Chandigarh, India and IIIM, Jammu for cooperation in getting the spectral data and CHN elemental studies respectively. This research was supported by project YETP0821.

REFERENCES

1. D.A. Walsh, *Synthesis*, 677 (1980).
2. L.H. Sternbach, R.I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stempel. *J. Org. Chem*., **27**, 3788 (1962).
3. R.V. Coombs, R.P. Danna, M. Denzer, G.E. Hardtmann, B. Huegi, G. Koletar, J. Koletar, H. Ott and E. Jukniewicz, *J. Med. Chem*., **16**, 1237 (1973).
4. W.J. Welstead Jr., J.H.W. Moran, H.F. Stauffer, L.B. Turnbull and L.F. Sancilio, *J. Am. Chem. Soc.*, **22**, 1074 (1979).
5. E.R. Ottosen, M.D. Sørensen, F. Björkling, T. Skak-Nielsen, M.S. Fjording, H. Aaes and L. Binderup, *J. Med. Chem*., **46**, 5651 (2003).
6. S. Cortez-Maya, E. Cortes, S. Hernández-Ortega, T.R. Apan and M. Martínez-García, *Synth. Commun*., **42**, 46 (2012).
7. J.P. Liou, C.W. Chang, J.S. Song, Y.N. Yang, C.F. Yeh, H.Y. Tseng, Y.K. Lo, Y.L. Chang, C.M. Chang and H.P. Hsieh, *J. Med. Chem*., **45**, 2556 (2002).
8. R.K. Singh, S. Devi and D.N. Prasad, *Arab. J. Chem*.; doi:10.1016/j.arabjc.2011.11.013.
9. R.K. Singh, D.N. Prasad and T.R. Bhardwaj, *Med. Chem. Res*., **22**, 5901 (2013).
10. P. Cheng, Q. Zhang, Y.-B. Ma, Z-Y. Jiang, X.M. Zhang, F.X. Zhang and J.J. Chen, *Bioorg. Med. Chem. Lett*., **18**, 3787 (2008).
11. J.-P. Liou, J.-Y. Chang, C.-W. Chang, C.-Y. Chang, N. Mahindroo, F.-M. Kuo and H.-P. Hsieh, *J. Med. Chem*., **47**, 2897 (2004).
12. J.P. Liou, Y.L. Chang, F.M. Kuo, C.W. Chang, H.Y. Tseng, C.C. Wang, Y.N. Yang, J.Y. Chang, S.-J. Lee and H.-P. Hsieh, *J. Med. Chem*., **47**, 4247 (2004).
13. L. Sun, J. Wu, M. Luo, X. Wang, M. Pan, Z. Gou and D. Sun, *Molecules*, **16**, 9739 (2011).
14. A. Sakunpak and P. Panichayupakaranant, *Food Chem*., **130**, 826 (2012).
15. Molinspiration Cheminformatics, Bratislava, Slovak Republic, Available from: http://www.molinspiration.com/cgi-bin/properties.
16. C.A. Lipinski, F. Lombardo, B.W. Dominy and P.J. Feeney, *Adv. Drug Deliv. Rev*., **23**, 3 (1997).
17. Indian Pharmacopoeia. Government of India, Ministry of Health and Welfare, Published by Controller of Publication, New Delhi, vol. II, A105 (1996).