Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2009, 1(2): 145-152
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

Synthesis of some new biologically active chalcones and flavones

S. S. Mokle, Y.B. Vibhute*

**Laboratory of Organic Synthesis, P.G. Department of Chemistry,*
Yeshwant Mahavidyalaya, Nanded, M.S, India

Abstract

New chalcones (3a-g) were synthesized from 2-chloro-6-methyl-quinoline-3-carbaldehyde (2) and halohydroxysubstitued acetophenones (1a-g) via Claisen-Schmidt condensation. Further new flavones (4a-g) were synthesized by oxidative cyclisation of chalcones (3a-g) using microwave as well as by conventional method. The structures of synthetic compounds have been characterized by analytical and spectral data. All the synthesized compounds have been evaluated for their antibacterial activity and studied the effect on seed germination of wheat (Triticum aestivum).

Keywords: 2-chloro-6-methyl-quinoline-3-carbaldehyde, halohydroxysubstituted acetophen -ones, chalcones, flavones, antibacterial activity and seed germination.

Introduction

Chalcones, or 1,3-diaryl-2-propen-1-ones, are natural/synthetic compounds belonging to the flavonoid family.Chalcones of plant origin are known[1].Chalcones possess a broad spectrum of biological activities, including potent antimitotic[2], antibacterial[3], antifibrogenic[4], anticancer[5], antitrichomonal[6], anti-inflammatory[7], antileishmanial[8], cytotoxic and anti-trypanosoma cruzi[9] activities. While the flavonoid compounds are a group of natural products found in fruits, vegetables, nuts, seeds and flowers as well as in teas and are important constituent of human diet. They have been demonstrated to possess antioxdidant[10], antihypertensive[11], antiallergic[12], antinocicepative[13], trypsin inhibitors[14], plant growth regulator[15], antibacterial and antifungal[16,17] activities.

In the last few years microwave induced organic reaction enhancement (MORE) chemistry has gained popularity as a non-conventional technique for rapid organic synthesis[18] and many researchers have described accelerated organic reactions, and a large number of papers has appeared. Proving the synthetic utility of MORE chemistry in routine organic synthesis[19,20]. It has been termed as ‘e-chemistry’ because it is easy, effective, economical

and ecofriendly and is belived to be a step toward green chemistry. In view of these observations and in continuation of our work on biologically active chalcones and their heterocycles[21], we have been planned to synthesize the new flavones (4a-g) from chalcones (3a-g) and also studied their antibacterial activity against *Xanthomanas citri* (Xc), *Ervinia carotovara* (Ec), *Escherichia coli* (E. coli) and *Bacillus subtilis* (Bs) using Ampicillin as a standard drug.

Results and Discussion

Chalcones (3a-g) and flavones (4a-g) were synthesized. The structures of newly synthesized compounds have been confirmed on the basis of elemental analysis and spectral data. From antibacterial screening, it was found that compound **3e**, **3f**, **3g**, **4b**, **4e**, **4f** and **4g** exhibited good antibacterial activity against all bacteria at a concentration of 100μg/ml.

Chalcones and flavones have been tested their effect on seed germination of Wheat. All chalcones and flavones showed maximum seed germination than control (distil water) and no any growth of fungi was observed on seeds. The present study reveals that chalcones and flavones which contain iodine, chlorine, bromine, methyl and hydroxy substituents showed good antibacterial than the standard drug Ampicillin. Chalcones and flavones were acting as a growth promoting agents for seed germination of wheat.

Materials and Methods

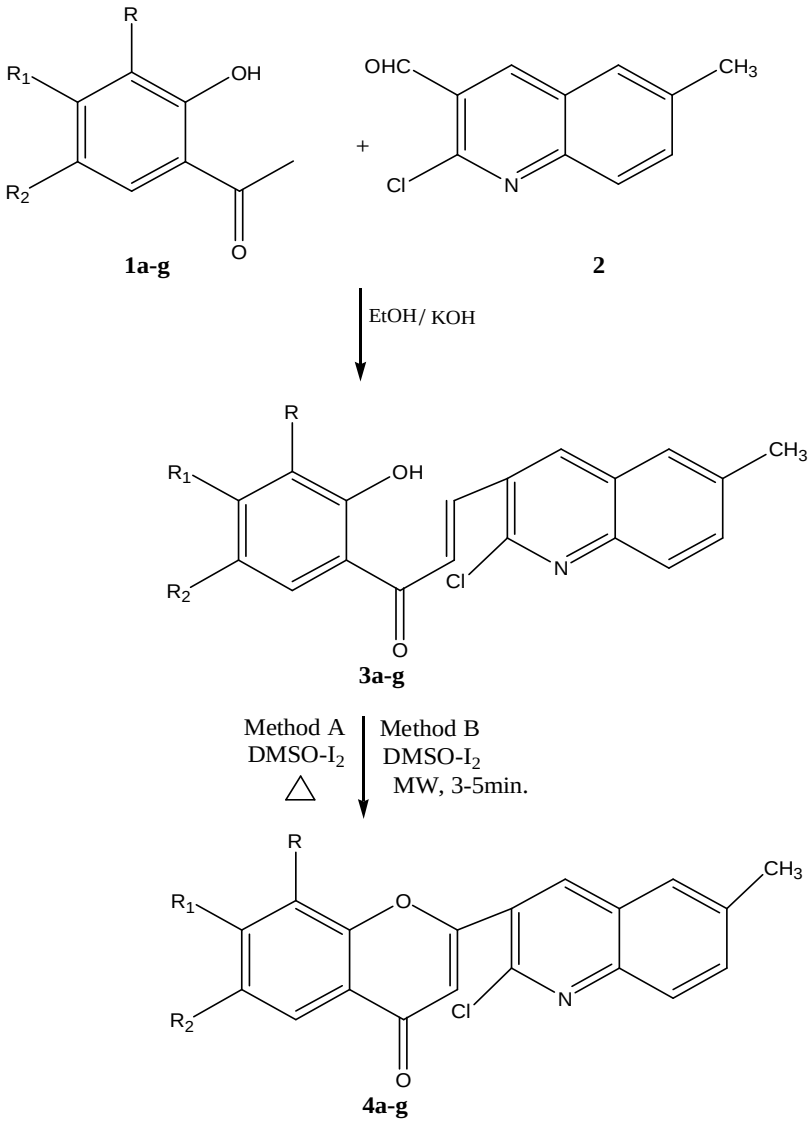
All melting points are taken in open glass capillaries and were found uncorrected. The purity of compounds has been checked by TLC on silica gel G. The IR spectra in KBr were recorded on Shimadzu spectrophotometer and ^{1}HNMR spectra were recorded in DMSO on Varian Inova 300 FT MHz spectrophotometer using TMS as internal standard (δ ppm). Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer.

Experimental: Synthesis of Chalcones (3a-g):
Equimolar quantities of halo substituted 2-hydroxyacetophenone (0.01mol) and 2-chloro-6-methyl- quinoline-3-carbaldehyde (0.01 mol) were dissolved in ethanol (15 ml), under stirring and aqueous KOH (50%, 10 ml) was added dropwise. The reaction mixture was stirred at room temperature and kept for 14-16 hr.The reaction mixture was diluted with water and acidified with 10% HCl.The separated solid was filtered and cryststallised from acetic acid to give compounds (3a-g).

1-(2'-hydroxy-3',5'-diiodophenyl)-3-(2-chloro-6-methyl-quinolin-3-yl)-2- propen-1-one **(3a):** m.p. 179^{0}C. IR (KBr) cm^{-1}: 2999(-OH), 1638(C=O), 1569, 1495(ring C=C), 1050(C-O). ^{1}HNMR (300 MHz, DMSO): δ 2.40 (s, 3H, CH_3), 6.93 (d, 1H, H_α), 7.37 (d, 1H, H_β), 7.38-δ8.49 (m, 6H, Ar-H), 12.94 (s, 1H, Ar-OH). Anal. Calcd. for $C_{19}H_{12}O_2NI_2Cl$ (575.5): C,39.61; H,2.08; N, 2.43. Found: C, 39.70; H, 2.05, N,2.33.

1-(2'-hydroxy-3'-iodo-5'-chlorophenyl)-3-(2-chloro-6-methyl-quinolin-3-yl)-2-propen-1-one **(3b):** m.p. 173^{0}C. IR (KBr) cm^{-1}: 3034(-OH), 1630(C=O), 1568, 1496(ring C=C), 1052(C-O). ^{1}HNMR (300 MHz, DMSO): δ 2.39 (s, 3H, CH_3), 6.98 (d, 1H, H_α), 7.29 (d, 1H, H_β), 7.36- δ8.44 (m, 6H, Ar-H), 13.08 (s, 1H, Ar-OH). Anal. Calcd. for $C_{19}H_{12}O_2NICl_2$ (484): C,47.10; H,2.47; N,2.89. Found: C,47.05; H,2.51; N,2.83.

SCHME :



where,

1a, 3a ,4a: R= I, R_1= H, R_2= I
1b, 3b, 4b: R= I, R_1= H, R_2= Cl
1c, 3c, 4c: R= I, R_1= H, R_2= CH_3
1d, 3d, 4d: R= Br, R_1= H, R_2= Cl
1e, 3e, 4e: R= I, R_1= OH, R_2= I
1f, 3f, 4f: R= Cl, R_1= OH, R_2= Cl
1g, 3g, 4g: R= Br, R_1= OH, R_2= Br

1-(2'-hydroxy-3'-iodo-5'-methylphenyl)-3-(2-chloro-6-methyl-quinolin-3-yl)-2-propen-1-one **(3c):** m.p.149^{0}C. IR (KBr) cm^{-1}: 3067(-OH), 1632(C=O), 1571, 1489(ring C=C), 1045(C-O). ^{1}HNMR (300 MHz, DMSO): δ δ2.41 (s, 6H, CH_3), 6.92 (d, 1H, H_α), 7.33 (d, 1H, H_β), 7.34-δ8.42 (m, 6H, Ar-H), 13.21(s, 1H, Ar-OH). Anal. Calcd. for $C_{20}H_{15}O_2NICl$ (463.5): C,51.77; H,3.23; N,3.02. Found: C,51.84; H,3.19; N,2.94.

1-(2'-hydroxy-3'-bromo-5'-chlorophenyl)-3-(2-chloro-6-methyl-quinolin-3-yl)-2-propen-1-one **(3d):** m.p.150^{0}C. IR (KBr) cm^{-1}: 3080(-OH), 1637(C=O), 1574, 1492(ring C=C), 1055(C-O). ^{1}HNMR (300 MHz, DMSO): δ 2.37 (s, 3H, CH_3), 7.05 (d, 1H, H_α), 7.33 (d, 1H,

H_β), 7.35- δ8.21 (m, 6H, Ar-H), 12.95(s, 1H, Ar-OH). Anal. Calcd. for $C_{19}H_{12}O_2NBrCl_2$ (437): C,52.17; H,2.74; N,3.20. Found: C,52.22; H,2.71; N,3.12.

1-(2'4'-dihydroxy-3',5'-diiodophenyl)-3-(2-chloro-6-methyl-quinolin-3-yl)-2-propen-1-one **(3e):** m.p.156^{0}C. IR (KBr) cm^{-1}: 3386(-OH), 1635(C=O), 1574, 1485 (ring C=C), 1050(C-O). ^{1}HNMR (300 MHz, DMSO): δ 2.39 (s, 3H, CH_3), 6.93 (d, 1H, H_α), 7.30 (d, 1H, H_β), 7.40- δ8.22 (m, 5H, Ar-H), 10.85(s, 1H, 4'Ar-OH), 13.30(s, 1H, 2'Ar-OH). Anal. Calcd. for $C_{19}H_{12}O_3NI_2Cl$ (591.5): C,38.54; H,2.02; N,2.36.Found: C,38.65; H,1.98; N,2.39.

1-(2'4'-dihydroxy-3',5'-dichlorophenyl)-3-(2-chloro-6-methyl-quinolin-3-yl)-2-propen-1-one **(3f):** m.p.175^{0}C. IR (KBr) cm^{-1}: 3400(-OH), 1635(C=O), 1577, 1485 (ring C=C), 1056(C-O). ^{1}HNMR (300 MHz, DMSO): δ 2.35 (s, 3H, CH_3), 6.96 (d, 1H, H_α), 7.31 (d, 1H, H_β), 7.42- δ8.29 (m, 5H, Ar-H), 10.95(s, 1H, 2'Ar-OH), 13.27(s, 1H, 4'Ar-OH). Anal. Calcd. for $C_{19}H_{12}O_3NCl_3$ (408.5): C,55.81; H,2.93; N,3.42. Found: C,55.88; H,3.01; N,3.38.

1-(2'4'-dihydroxy-3',5'-dibromophenyl)-3-(2-chloro-6-methyl-quinolin-3-yl)-2-propen-1-one **(3g):** m.p.181^{0}C. IR (KBr) cm^{-1}: 3392(-OH), 1637(C=O), 1569, 1483 (ring C=C), 1050(C-O). ^{1}HNMR (300 MHz, DMSO): δ 2.39 (s, 3H, CH_3), 6.97 (d, 1H, H_α), 7.32 (d, 1H, H_β), 7.40- δ8.26 (m, 5H, Ar-H), 10.89(s, 1H, 2'Ar-OH), 13.28(s, 1H, 4'Ar-OH). Anal. Calcd. for $C_{19}H_{12}O_3NBr_2Cl$ (497.5): C,45.82; H,2.41; N,2.81. Found: C,45.90; H,2.47; N,2.76.

Synthesis of Flavones (4a-g):

Method A:
Chalcone (0.01 mol) was suspended in DMSO (10 ml) and a crystal of iodine was added to it. The mixture was refluxed for 30-45 min. and diluted with water. The solid obtained was filtered off, washed with 20% sodium thiosulfate and crystallized from ethyl alcohol to give compounds (4a-g). It gave positive Mg/HCl test (yellow colouration).

Method B:
Chalcone (0.01 mol) was suspended in DMSO (10 ml) and a crystal of iodine was added to it. The mixture was irradiated in microwave oven for the appropriate time (Table1) at 650 W. After completion of reaction as followed by TLC examination, the solid product was washed with 20% sodium thiosulfate and crystallized from ethyl alcohol to give compounds (4a-g). It gave positive Mg/HCl test (yellow colouration).

2-(2-Chloro-6-methyl-quinolin-3-yl)-6,8-diiodo-chromen-4-one **(4a):**
m.p.198^{0}C. IR (KBr) cm^{-1}: 1645(C=O), 1570, 1495 (ring C=C). ^{1}HNMR (300 MHz, DMSO): δ 2.41 (s, 3H, OCH_3), 7.09 (s, 1H, COCH), 7.40- δ8.22 (m, 6H, Ar-H). Anal. Calcd. for $C_{19}H_{10}O_2NI_2Cl$ (573.5): C,39.75; H,1.74; N, 2.44. Found: C, 39.70; H, 1.70, N,2.39.

6-Chloro-2--(2-Chloro-6-methyl-quinolin-3-yl)-8-iodo-chromen-4-one **(4b):**
m.p.189^{0}C. IR (KBr) cm^{-1}: 1645(C=O), 1571, 1493(ring C=C). ^{1}HNMR (300 MHz, DMSO): δ 2.39 (s, 3H, OCH_3), 6.97 (s, 1H, COCH), 7.30- δ8.15 (m, 6H, Ar-H). Anal. Calcd. for $C_{19}H_{10}O_2NICl_2$ (482): C,47.30; H,2.07; N,2.90. Found: C,47.23; H,2.01; N,2.86.

2-(2-Chloro-6-methyl-quinolin-3-yl)-8-iodo-6-methyl-chromen-4-one **(4c):**
m.p.178^{0}C. IR (KBr) cm^{-1}: 1632(C=O), 1565, 1490(ring C=C). ^{1}HNMR (300 MHz, DMSO): δ δ2.45 (s, 6H, CH_3), 7.01(s, 1H, COCH), 7.39- δ8.20 (m, 6H, Ar-H). Anal. Calcd. for $C_{20}H_{12}O_2NICl$ (461.5): C,52.00; H,2.60; N,3.33. Found: C,51.94; H,2.69; N,3.39.

8-Bromo-6-chloro-2-(2-Chloro-6-methyl-quinolin-3-yl)-chromen-4-one **(4d):**
m.p.173^{0}C. IR (KBr) cm^{-1}: 1647(C=O), 1567, 1496(ring C=C). ^{1}HNMR (300 MHz, DMSO): δ 2.41 (s, 3H, CH_3), 7.08 (s, 1H, CHOH), 7.40- δ8.10 (m, 6H, Ar-H). Anal. Calcd. for $C_{19}H_{10}O_2NBrCl_2$ (435): C,52.41; H,2.29; N,3.21. Found: C,52.50; H,2.23; N,3.27.

2-(2-Chloro-6-methyl-quinolin-3-yl)-7-hydroxy-6,8-diiodo-chromen-4-one **(4e):**
m.p.180^{0}C.IR (KBr) cm^{-1}: 3409(-OH), 1639(C=O), 1570, 1489 (ring C=C). ^{1}HNMR (300 MHz, DMSO): δ 2.43 (s, 3H, CH_3), 7.05 (s, 1H, CHOH), 7.38- δ8.19 (m, 5H, Ar-H), 10.96(s, 1H, Ar-OH). Anal. Calcd. for $C_{19}H_{10}O_3NI_2Cl$ (589.5): C,38.67; H,2.37; N,2.36.Found: C,38.74; H,1.75; N,2.39.

*6,8-Dichloro-2--(2-Chloro-6-methyl-quinolin-3-yl)-7-hydroxy-chromen-4-one***(4f):**
m.p. 201^{0}C. IR (KBr) cm^{-1}: 3401(-OH), 1644(C=O), 1581, 1489 (ring C=C). ^{1}HNMR (300 MHz, DMSO): δ 2.41 (s, 3H, CH_3), 7.06 (s, 1H, CHOH), 7.48- δ8.25 (m, 5H, Ar-H), 10.94(s, 1H, Ar-OH). Anal. Calcd. for $C_{19}H_{10}O_3NCl_3$ (406.5): C,56.06; H,2.46; N,3.44. Found: C,55.97; H,2.51; N,3.37.

*6,8-Dibromo-2-(2-Chloro-6-methyl-quinolin-3-yl)-7-hydroxy-chromen-4-one***(4g):**
m.p.192^{0}C. IR (KBr) cm^{-1}: 3400(-OH), 1648(C=O), 1567, 1488 (ring C=C). ^{1}HNMR (300 MHz, DMSO): δ 2.45 (s, 3H, CH_3), 7.02 (s, 1H, CHOH), 7.42- δ8.36 (m, 5H, Ar-H), 10.95(s, 1H, Ar-OH). Anal. Calcd. for $C_{19}H_{10}O_3NBr_2Cl$ (495.5): C,46.01; H,2.01; N,2.82. Found: C,45.94; H,2.06; N,2.74.

Table 1: Physical data of synthesized Flavones (4a-g)

Compound code	Reaction Period (min.)		Yield (%)	
	Method A (min.)	Method B (min.)	Method A	Method B
4a	40	4.5	71	85
4b	35	5	63	87
4c	30	3.5	58	92
4d	40	3	69	96
4e	30	3.5	70	90
4f	40	4.5	68	88
4g	35	3.5	75	90

Antibacterial screening
The antibacterial activity of newly synthesized compounds (**3a-g** and **4a-g**) was determined by agar diffusion method[22]. The compounds were evaluated for antibacterial activity was against *Xanthomanas citri* (Xc), *Ervinia carotovara* (Ec), *Escherichia coli* (E. coli) and *Bacillus subtilis* (Bs).The antibiotic *Ampicillin* (100μg/mL) was used as standard antibiotic

and 1% DMSO was used as solvent control. The culture strains of bacteria were maintained on nutrient agar slant at 37±0.5°C for 24 h. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterial saline (0.85%) of 10^5 CUF/ mL dilution. The wells of 6mm diameter were filled with 0.1 mL of solution at fixed concentration 100µg/mL separately for each bacterial strain. All the plates were incubated at 37±0.5°C for 24 h. The zone of inhibition of compounds was measured using mm scale.

Table 2: Antibacterial activity data of synthesized compounds

Compound code	Zone of inhibition (mm)			
	B. subtilis	**E. coli**	**X. citri**	**E. carotovara**
3a	16	18	16	20
3b	15	10	12	19
3c	11	13	17	09
3d	14	17	10	13
3e	26	25	23	24
3f	28	28	27	29
3g	25	28	26	27
4a	11	16	10	12
4b	23	22	18	21
4c	14	19	12	15
4d	13	14	13	12
4e	25	27	26	24
4f	27	25	21	29
4g	24	27	25	27
Control	----	----	----	----
Std(100µg/mL)	25	26	25	27

Germination Assay

The newly synthesized compounds were tested for effect on seed germination of wheat (Triticum aestivum) by using moist blotter plate method[23]. In this method ten seeds of wheat were arranged on the blotter paper (8.5cm) in pre sterilized Petri plates (10cm). The control was treated with only distilled water, then, 2ml (0.01%) of each solution and distilled water were added to the seeds on the blotter paper. The experiments were carried out under natural light and at room temperature for ten days. The seed germination in the form of root length and shoot length were measured (in cm) at the end of experiment.

Table 3: Effect of synthesized compounds on seed germination of Wheat (*Triticum aestivum*)

Compound code	Seed germination of wheat (cm)	
	Mean of shoot length	**Mean of root length**
3a	5.4	6.0
3b	6.5	10.5
3c	6.1	9.8

3d	11.3	10.1
3e	5.0	12.4
3f	5.9	4.9
3g	5.5	10.3
4a	8.6	8.8
4b	5.0	6.1
4c	6.4	10.0
4d	5.1	6.6
4e	8.8	5.3
4f	5.0	6.0
4g	7.7	6.9
Control	4.9	6.0

Conclusion

In summary, we have synthesized some bioactive chalcones having 2-chloro-6-methyl quinolinyl moiety and convert them into flavones by using conventional method as well as microwave irradiation. Short reaction time, clean reaction with high yield (85-96%) than conventional method is the advantages of microwave irradiation method. The antibacterial study show that compound **3e, 3f, 3g,4b, 4e, 4f** and **4g** were found to be more active as compared with standard drug and all new synthesized compounds were acting as a growth promoting agents in seed germination of wheat.

Acknowledgement

Authors are also grateful to UGC New Delhi for sanctioning Major Research Grant and the Director, IICT, Hyderabad for providing spectral analysis of newly synthesized compounds. The authors are thankful to Principal, Yeshwant Mahavidyalaya, Nanded for providing laboratory facilities.

References

[1] E.Hijova, *Bratisl Lek Listy*, **2006**, 107(3), 80.
[2] S. Ducki, R. Forrest, J.A. Hadfield, A. Kendall, N.J. Lawrence, A.T. McGown and D. Rennnison, *Bioorg.Med.Chem.Lett.*, **1998**, 8, 1051.
[3] V.Opletalova, *Cesk.Slov.Farm.*, **2000**, 49, 278.
[4] S.H.Lee, J.X.Nan, Y.Z.Zhao, S.W.Woo, E.J.Park, T.H.Kang, G.S.Seo, Y.C.Kim and D.H.Sohn, *Planta. Med.*, **2003**, 69, 990.
[5] M.T.Konieczny, W. Konieczny, M.Sabisz, A.Skladanowski, R.Wakiec, E. Augustynowicz-Kopec and Z.Zwolska, *Chem. Pharm. Bull.*, **2007**, 55, 817.
[6] A.O.Oyedapo, V.O.Mankanju, C.O.Adewunmi, E.O.Iwalewa and T.K.Adenowo, *Afr.J.Trad. CAM* **2004**,1,55.
[7] F.Jin, X.Y.Jin, Y.L.Jin, D.W.Sohn, S.-A.Kim, D.H.Sohn, Y.C.Kim and H.S.Kim, *Arch.Pharm.Res.*, **2007**, 30(11), 1359.
[8] T.Narender, T.Khaliq, Shweta, Nishi, N.Goyal and S.Gupta, *Bioorg.Med.Chem.*, **2005**, 13, 6543.

[9] J.C.Aponte, M. Verastegui, E.Malaga, M.Zimic, M.Quiliano, A.J.Vaisberg, R.H.Gilman and G.B.Hammond, *J.Med.Chem.,* **2008**, 51, 6230.
[10] H.Yoo, S.H.Kim, J.Lee, H.J.Kim, S.H.Seo, B.Y.Chung, C.Jin and Y.S.Lee, *Bull.Korean Chem.Soc.,* **2005**, 26(12), 2057.
[11] J.X.Li, B.Xub, Q.Chai, Z.X.Liu, A.P.Zhao and L.B.Chan, *Chin.J.Physiol.,* **2005**, 48, 101.
[12] T.Inoue, Y.Sugimoto, H.Masuda and C.Kamei, *Biol.Pharm.Bull.,* **2002**,25, 256.
[13] S.Umamaheswari, S.Viswanathan, B.W.C.Sathiyasekaran, S.Parvathavarthini and S.Ramaswamy, *Indian J.Pharm.Sci.,* **2006**, 68(6), 749.
[14] T.Maliar, A.Jedinak, J.Kadrabova and E.Sturdik, *Eur.J.Med.Chem.,* **2004**, 39, 241.
[15] J.M.Keriko, S.Nakajima, N.Baba, Y.Isozaki and J.Iwasa, *Sci.Rep.Agr.OKAYAMA,* **1995**, 84, 7.
[16] S.Mostahar, P.Katun and A.Islam, *J.Biol.Sci.,* **2007**, 7(3), 514.
[17] S.Katade, U.Phalgune, S.Biswas, R.Wakharkar, and N.Deshpande, *Indian J.Chem.*, **2008**, 47B, 927.
[18] R.S.Verma, *Green Chemistry*, **1999**,1, 43.
[19] M.Kidwai, B.Dave and R.Venkataramanan, *Indian J.Chem.,* **2002**, 41B , 2414.
[20] R.Borah, D.J.Kalita and J.C.Sarma, *Indian J.Chem.*, **2002**, 41B, 1032.
[21] a) Y.B.Vibhute and M.A.Basser, *J.Indian Chem.Soc.*, **2001**, 78, 319. b) Y.B.Vibhute and M.A.Basser, *Indian J.Chem.,* **2003**, 42B, 202. c) S.S. Mokle, M.A. Sayyed, Kothawar and Chopde, *Int. J. Chem. Sci.,* **2004**, 2(1), 96. d) S.S. Mokle, M.A. Sayyed, S.R. Bhusare, R.P. Pawar and Y.B. Vibhute, *Chemistry: An Indian Journal* **2005**, 2(9), 302. e) V.A.Navale, S.S.Mokle, Archana Y.Vibhute, K.G.Karamunge, S.B.Junne and Y.B. Vibhute, *Asian J.Research Chem.,* **2009**, 2(4), 1. f) S.S.Mokle, S.V.Khansole, R.B.Patil and Y.B.Vibhute, *Int.J.Pharma and BioSci.,* (In press) g) S.S.Mokle, A.Y.Vibhute, M.A.Sayyed, S.V.Khansole, Y.S.Nalwar, *Research J.Pharm. and Tech.*(In press)
[22] C.H. Collins, Microbiological Methods. London: Buterworths, **1967**.
[23] Neergaard and Paul, Seed Pathology. Vol.I-III. London: The Mac Millan Press Ltd., **1977**.