Indian Journal of Heterocyclic Chemistry
Vol.25 - Number 3&4 (Jan-June 2016) 231-235 ISSN 0971-1627

GREEN SYNTHESIS OF 2,3-DIHYDRO-7-HYDROXY-2-ARYL-6-[(*E*)-3-ARYL ACRYLOYL] CHROMEN-4-ONES AND THEIR ANTIMICROBIAL ACTIVITY

[1]D. Ashok*, [2] M. Sarasija, [2]A. Jeyanthi, [1]D. Shravani and [1] K. Sudershan
[1]Green and Medicinal Chemistry Laboratory, Department of Chemistry,
Osmania University, Hyderabad-500 007, India
[2]Department of Chemistry, Satavahana University, Karimnagar- 505001, India

ABSTRACT A series of new 2,3-Dihydro-7-hydroxy-2-aryl-6-[(*E*)-3-aryl acryloyl]chromen-4-ones **(IIa-f)** have been synthesized by selective mono cyclization of 4,6-Dicinnamoyl resorcinols **(Ia-f)** with silica gel impregnated $NaHSO_4$ under solvent-free conventional heating and microwave irradiation methods. The structures of the synthesized compounds have been confirmed on the basis of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The synthesized compounds were screened for their in vitro antimicrobial activity.

KEYWORDS Monoflavanone, selective cyclization, microwave irradiation, antimicrobial activity.

INTRODUCTION

In recent years green and sustainable chemistry has become a subject of intensive research and the studies in this area have led to the development of cleaner and relatively benign chemical processes. Among them, much effort has been devoted towards microwave assisted organic synthesis (MAOS).[1] Microwave assisted synthesis leads to significant reduced reaction times, enhanced conversions and environment friendly. Flavanones (2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-ones and derivatives), a type of flavonoids widely distributed in nature, continue focusing attention due to their ample range of biological activities such as anti-inflammatory[2], antioxidant[3], antifungal[4], antimycobacterial[4], antimycobacterial[4], antiplasmodial[4], anti-inflammatory[4] and antibacterial[4]. Chalcones are known to exhibit various biological activities such as anti-inflammatory[5], antimalarial[6], antioxidant[7], antileishmanial[8], antibacterial[9], and anticancer[10]. Motivated by the potential bioactivity of flavanones & chalcones and also in contribution to our work on green synthesis of biologically important heterocycles, our aim is to selective synthesis of mono flavanones having chalcone and flavanone moiety i.e., 2,3-Dihydro-7-hydroxy-2-aryl-6-[(*E*)-3-aryl acryloyl] chromen-4-ones **(IIa-f)**. These have been the potential intermediates for the synthesis of mixed heterocyles. Our research group has made considerable efforts to design and put into practice the innovative synthetic protocols adopting more eco-sustainable approaches.[11-13] As a part of our research program on green synthesis, herein we report the benign synthesis of 2,3-Dihydro-7-hydroxy-2-aryl-6-[(**E**)-3-aryl acryloyl] chromen-4-ones with a view to study ease of formation under microwave irradiation method and to evaluate their antimicrobial activity.

RESULTS AND DISCUSSION

Flavanones are generally synthesized by refluxing the 2'-hydroxychalcones in acetic acid[14] or also in ethanol or other suitable solvent, in the presence of an acid catalyst such as sulphuric acid[15], polyphosphoric acid[15], or basic reagents such as pyridine[16] and 1,8-

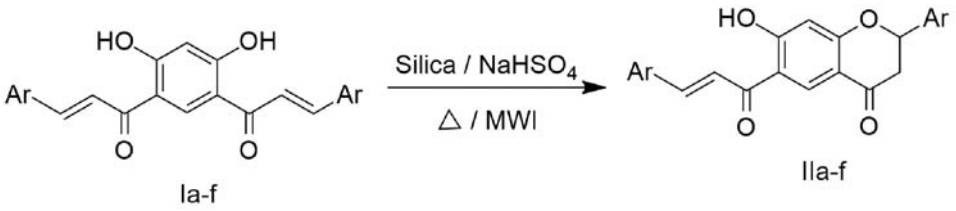
*Corresponding author: E-mail: ashokdou@gmail.com

Journal Homepage :
www.connectjournals.com/ijhc

Published & Hosted by :
www.connectjournals.com

diazabicyclo[5.4.0]undec-7-ene (DBU) in microwave irradiation[17] & triethylamine (TEA) in microwave irradiation[18], the most employed methods require for prolonged reaction time at high temperature.

The selective synthesis of compounds **(IIa-f)** has been carried out by reacting 4,6-Dicinnamoyl resorcinols **(Ia-f)** with silica gel impregnated $NaHSO_4$ under solvent-free microwave irradiation. Silica/$NaHSO_4$ catalyst offers



Ia-f IIa-f

	a	b	c	d	e	f
Ar	C_6H_5	4-CH_3-C_6H_4	4-OCH_3-C_6H_4	2-Cl-C_6H_4	3-Cl-C_6H_4	2-Furyl

advantages over harsh catalysts and organic solvents. In this reaction in addition to desired products **(IIa-f)** small quantity of bisflavanones are also formed, and are characterized with authentic samples.

The synthetic route to compounds **IIa-f** is shown in Scheme 1. Our aim is to synthesize title compounds to utilize them for the synthesis of bis-heterocyclic compounds of biological interest. The reaction time has been reduced from hours to minutes using microwave assisted synthesis, with improved yields. The advantage obtained by the use of microwave irradiation in relation to a conventional heating method is demonstrated in the present study **(Table-3)**. All the compounds synthesized were well characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

The structures of products were elucidated by spectral methods. In the IR spectrum of **IIc** contained three characteristic peaks at 1689 cm^{-1} (flavanone corbonyl), 1633 cm^{-1} (cinnamoyl carbonyl) and 3246 cm^{-1} (-OH) which indicates the formation of monocyclised product. In ^{1}H-NMR spectrum of **IIc** registered three double doublets observed at d 2.9, J =17.2, 3.2 Hz, 3.1, *J*=17.2, 13.2 Hz, and 5.45, *J*=13.2, 3.2 Hz, assigned to C_3-Hax, C_3-Heq and C_2-Hax respectively. In aliphatic region two singlets at d 3.82 and 3.86 integrating for three protons each were assigned to two methoxy protons. Two doublets at 7.55, *J*=16.1 Hz, and 7.93, *J*=16.1 Hz, integrating for one porton each assigned to Ca-H and Cß-H respectively. In the `aromatic region two singlets at d 8.62 and 6.55 integrating for one proton each registered were assigned to C_4-H and C_7-H respectively. A doublet at 7.68 integrating for two protons was assigned to ortho protons of cinnamoyl group. A doublet at 7.40 integrating for two protons was assigned to ortho protons of flavanone phenyl group. A doublet at 6.97 integrating for four protons was assigned to ortho protons of cinnamoyl group and flavanone phenyl group. A singlet registered at d 13.8 integrating for hydroxyl proton. ^{1}H-NMR spectral data clearly supports the formation of monocyclised product. ^{13}C-NMR spectrum of **IIc** showed characteristic peaks at 192.70, 189.79, 169.98, 166.54, 162.39, 160.30, 145.84, 130.98, 130.67, 130.34, 127.60, 127.43, 117.40, 166.22, 114.67, 114.42, 114.08, 105.18, 105.13, 79.69, 79.63, 55.32 and 43.93. The mass spectra of **IIc** contained the peak *m/z* = 431 (100%) $[M + H]^+$.

Antimicrobial Activity

All the synthesized compounds were screened for their antimicrobial activity against two strains of gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), two strains of gram-negative bacteria (*Echerichia coli, Pseudomonas aeruginosa*), as well as three strains of fungi (*Aspergillus niger, Penicillium italicum and Fusarium oxysporum*). Standard antibiotic drugs Amoxicillin for bacteria and *Mycostatin* for fungi were used at a concentration of 100 mg/ml for comparisons. The antimicrobial activity of these compounds has been evaluated by filter paper disc method[19] after dissolved in DMF to attain a 100 mg/ml solution. The inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimetres at the end of an incubation period of 3 days at 37 °C for *Echerichia coli* and at 28 ºC for other bacteria and fungi, DMF alone showed no inhibition zone. Among the compounds screened **IIb, IId** and **IIf** shown good antibacterial activity. Compounds **IIc, IId** and **IIf** shown good antifungal activity (Table-1 & Table-2).

Table-1: Antibacterial activity of Compounds IIa-f

Compound No.	Gram Positive Bacteria		Gram Negative Bacteria	
	Staphylococcus aureus	Bacillus subtilis	Pseudomonas aeruginosa	Escherichia coli
IIa	11	07	06	16
IIb	24	09	08	26
IIc	14	07	06	14
IId	22	09	08	24
IIe	14	07	06	16
IIf	26	10	09	24
Amoxicillin	30	12	10	30

Table-2: Antifungal activity of Compounds IIa-f

Compound No	Aspergillus niger	Penicillium italicum	Fusarium oxysporum
IIa	06	09	10
IIb	07	06	14
IIc	11	18	21
IId	10	16	23
IIe	07	09	12
IIf	09	17	21
Mycostatin	12	20	25

Table-3: Physical data of the compounds (IIa-f).

Compound	m.p. (oC)	Conventional method		Microwave irradiation method	
		Time (hr.)	Yield (%)	Time (min.)	Yield (%)
IIa	180	1.5	38	1	60
IIb	196	2	40	1	65
IIc	180	2	42	1.5	58
IId	182	1.5	39	1	57
IIe	180	2	41	1.5	55
IIf	196	2	44	1.5	59

EXPERIMENTAL

Chemistry

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked routinely by the silica gel F_{254} (Merck). All the reagents and solvents were reagent grade and used without further purification. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60-120 mesh) packed in glass columns. Microwave irradiation reactions were carried out in Milestone multi SYNTH microwave system. IR Spectra were recorded on Shimadzu FTIR 8400s spectrophotometer. NMR spectra were recorded on Avance 300 spectrometer (300 MHz, instrument in DMSO-d_6, with TMS as internal standard). Mass Spectra were recorded on Shimadzu mass spectrometer. Elemental analysis was determined by using Thermofinnigan CHNS analyzer.

General procedure for synthesis of 2,3-Dihydro-7-hydroxy-2-aryl-6-[(*E*)-3-aryl acryloyl] chromen-4-ones (IIa-f).

a) Conventional heating method:

The 4,6-Dicinnamoyl resorcinols **(Ia-f)** (0.001mol) was added to 4 gm of Silica gel impregnated with 2 gm sodium hydrogen sulphate. It was mixed thoroughly and then transferred in to round bottom flask and kept in oil bath at 110^{0}C for 1.5-2 h. The progress of reaction was monitored by TLC. After completion of the reaction, it was directly transferred into silica gel column and eluted with EtOAc:hexane (1:4), the solvent was evaporated under vacuum and recrystallized from ethanol to afford pure 2,3-Dihydro-7-hydroxy-2-aryl-6-[(*E*)-3-aryl acryloyl] chromen-4-ones **(IIa-f)** as white powder.

b) Microwave irradiation method:

The 4,6-Dicinnamoyl resorcinols **(Ia-f)** (0.001mol), was added to 4 gm of silica gel impregnated with 2 gm sodium hydrogen sulphate. It was mixed thoroughly and then transferred into quartz tube and inserted into teflon vial with screw capped and then subjected to microwave irradiation at the constant temperature 110^0 C for 1-1.5 min. The progress of reaction was monitored by TLC. After completion of the reaction, it was directly transferred into silica gel column and eluted with EtOAc:hexane (1:4v/v) the solvent was evaporated under vacuum and recrystallized from ethanol to afford pure 2,3-Dihydro-7-hydroxy-2-aryl-6-[(*E*)-3-aryl acryloyl] chromen-4-ones **(IIa-f)** as white powder.

Spectral Data:

6-Cinnamoyl-7-hydroxy-2-phenylchroman-4-one (IIa): IR (KBr, cm^{-1}): 3285 (OH), 1680(C=O), 1634(C=O) and 1620 (CH=CH). ^{1}H-NMR (300 MHz, DMSO-d_6) d 13.84 (s, 1H, OH), 8.37 (s, 1H, H-5), 7.70 (d, 1H, *J*=16.2 Hz, Cß-H), 7.48 (d, 1H, *J*=16.2 Hz, C_a-H), 6.75-6.80 (m, 10H, Ar-H), 6.43 (s, 1H, H-8), 5.32 (dd, 1H, *J*=13.1, 3.4 Hz, C_2-H), 2.89 (dd, 1H, *J*=17.2, 13.1 Hz, C_3-H_{ax}), 2.83 (dd, 1H, *J*=17.2, 3.4 Hz, C_3-H_{eq}). ^{13}C NMR (75 MHz, DMSO-d_6): d 199.9, 191.7, 171.8, 169.1, 149.2, 142.7, 138.2, 130.8, 129.0, 128.7, 128.0, 127.7, 126.4, 119.4, 114.2, 113.5, 106.5, 82.4 and 48. Found, %: C, 77.83; H, 4.94. $C_{24}H_{18}O_4$, Calculated, %: C, 77.82; H, 4.90. *M* 371 $[M+H]^+$.

(*E*)-7-Hydroxy-2-(p-tolyl)-6-(3-(p-tolyl)acryloyl) chroman-4-one (IIb): IR (KBr, cm^{-1}): 3210 (OH), 1682(C=O), 1638(C=O) and1625 (CH=CH). ^{1}H-NMR (300 MHz, DMSO-d_6) d 14.12 (s, 1H, OH), 8.64 (s, 1H, H-5), 7.80 (d, 1H, *J*=16.4 Hz, $C_ß$-H), 7.66 (d, 1H, *J*=16.4 Hz, C_a-H), 7.01-7.41 (m, 8H, Ar-H), 6.60 (s, 1H, H-8), 5.61(dd, 1H, *J*=13.4, 3.2 Hz, C_2-H), 3.17 (dd, 1H, *J*=17.2, 13.4 Hz, C_3-H_{ax}), 2.93 (dd, 1H, *J*=17.2, 3.2 Hz, C_3-H_{eq}), 2.45 (m, 6H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): d 200.1, 192.9, 170.7, 162.7, 149.2, 137.7 137.3, 136.5, 135.6, 129.7, 129.3, 129.0, 127.7, 127.1, 113.4, 112.9, 104.9, 82.2, 47.8 and 27.3. Found, %: C, 78.39; H, 5.59. $C_{26}H_{22}O_4$, Calculated, %: C, 78.37; H, 5.57. M 399 $[M+H]^+$.

(*E*)-7-Hydroxy-2-(4-methoxyphenyl)-6-(3-(4-methoxyphenyl)acryloyl)chroman-4-one (IIc). IR (KBr, cm^{-1}): 3246 (OH), 1689(C=O), 1633(C=O and1627 (CH=CH). ^{1}H-NMR (300 MHz, DMSO-d_6) d 13.81 (s, 1H, OH), 8.62 (s, 1H, H-5), 7.93 (d, 1H, *J*=16.1 Hz, $C_ß$-H), 7.68 (d, 2H, Ar-H), 7.55 (d, 1H, *J*=16.1 Hz, C_a-H), 7.40 (d, 2H, Ar-H), 6.97 (d, 4H, Ar-H, ortho to OCH3), 6.55 (s, 1H, H-8), 5.45(dd, 1H, *J*=13.2, 3.2 Hz, C_2-H), 3.10 (dd, 1H, *J*=17.2, 13.2 Hz, C_3-H_{ax}), 2.92 (dd, 1H, *J*=17.2, 3.2 Hz, C_3-H_{eq}), 3.86 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): d 192.70, 189.79, 169.98, 166.54, 162.39, 160.30, 145.84, 130.98, 130.67, 130.34, 127.60, 127.43, 117.40, 166.22, 114.67, 114.42, 114.08, 105.18, 105.13, 79.69, 79.63, 55.32 and 43.93. Found, %: C, 72.58; H, 5.16. $C_{26}H_{22}O_6$, Calculated, %: C, 72.55; H, 5.15. *M* 431 $[M+H]^+$.

(*E*)-2-(2-Chlorophenyl)-6-(3-(2-chlorophenyl) acryloyl)-7-hydroxychroman-4-one (IId). IR (KBr, cm^{-1}): 3250 (OH), 1678(C=O), 1640 (C=O) and 1635 (CH=CH). ^{1}H-NMR (300 MHz, DMSO-d_6) d 13.94 (s, 1H, OH), 8.69 (s, 1H, H-5), 7.79 (d, 1H, *J*=16.6 Hz, $C_ß$-H), 7.65 (d, 1H, *J*=16.6 Hz, Ca-H), 7.10-7.61 (m, 8H, Ar-H), 6.75 (s, 1H, H-8), 5.86 (dd, 1H, *J*=13.4, 3.1 Hz, C_2-H), 3.13 (dd, 1H, *J*=17.2, 13.4 Hz, C_3-H_{ax}), 2.92 (dd, 1H, *J*=17.2, 3.1 Hz, C_3-H_{eq}). ^{13}C NMR (75 MHz, DMSO-d_6): d 200.9, 172.7, 170.1, 166.8, 149.2, 140.4, 133.1,

132.5, 131.2, 130.8, 129.4, 129.1, 128.8, 128.6, 127.8, 127.1, 126.8, 123.4, 114.2, 113.5, 106.5, 71.9 and 44.2. Found, %: 65.65; H, 3.68. $C_{24}H_{16}C_{l2}O_4$, Calculated, %: C, 65.62; H, 3.67. *M* 439 $[M+H]^+$.

(*E*)-2-(3-Chlorophenyl)-6-(3-(3-chlorophenyl) acryloyl)-7-hydroxychroman-4-one (IIe). IR (KBr, cm^{-1}): 3230 (OH), 1680(C=O), 1645(C=O) and 1625 (CH=CH). ^{1}H-NMR (300 MHz, DMSO-d_6): d 14.01 (s, 1H, OH), 8.16 (s, 1H, H-5), 7.90 (d, 1H, *J*=16.4 Hz, $C_ß$-H), 7.56 (d, 1H, *J*=16.4 Hz, C_a-H), 7.02-7.15 (m, 8H, Ar-H), 6.51 (s, 1H, H-8), 5.52 (dd, 1H, *J*=13.1, 3.2 Hz, C_2-H), 3.16 (dd, 1H, *J*=17.2, 13.1 Hz, C_3-H_{ax}), 2.94 (dd, 1H, *J*=17.2, 3.2 Hz, C_3-H_{eq}). ^{13}C NMR (75 MHz, DMSO-d_6): d 196.9, 189.7, 166.8, 164.1, 145.2 142.1, 136.5, 134.5, 134.2, 130.8, 130.4, 130.1, 128.1, 127.8, 127.0, 126.5, 125.3, 124.5, 121.4, 114.2, 113.5, 102.5, 78.5, and 43.0. Found, %: C, 65.66; H, 3.67. $C_{24}H_{16}C_{l2}O_4$. Calculated, %: C, 65.62; H, 3.67. *M* 439 $[M+H]^+$.

(*E*)-2-(Furan-2-yl)-6-(3-(furan-2-yl)acryloyl)-7-hydroxychroman-4-one (IIf). IR (KBr, cm^{-1}): 3250 (OH), 1682 (C=O), 1640 (C=O) and 1620 (CH=CH). ^{1}H-NMR (300 MHz, DMSO-d_6): d 13.82 (s, 1H, OH), 8.76 (s, 1H, H-5), 8.01 (d, 1H, *J*=16.1 Hz, $C_ß$-H), 7.66 (d, 1H, *J*=16.1 Hz, C_a-H), 7.01-7.30 (m, 2H, Ar-H), 6.79 (s, 1H, H-8), 6.76 (d, 1H, ß'-H, furyl), 6.71 (d, 1H, ß'-H, furyl), 6.63 (d, 1H, ß-H, furyl), 6.36 (d, 1H, ß-H, furyl), 5.52 (dd, 1H, *J*=13.2, 3.4 Hz, C_2-H), 3.14 (dd, 1H, *J*=17.4, 13.2 Hz, C_3-H_{ax}), 2.93 (dd, 1H, *J*=17.4, 3.4 Hz, C_3-H_{eq}). ^{13}C NMR (75 MHz, DMSO-d_6): d 194.2, 181.2, 170.8, 168.1, 151.5, 147.2, 145.4, 141.8, 139.8, 139.2, 130.6, 127.4, 124.7, 124.5, 114.2, 113.5, 110.8, 102.5, 76.7 and 43.5. Found, %: C, 68.60; H, 4.05. $C_{20}H_{14}O_6$. Calculated, %: C, 68.57; H, 4.03. M 351 $[M+H]^+$.

ACKNOWLEDGEMENTS

Authors are thankful to the Head, Department of Chemistry, Osmania University, Hyderabad for providing laboratory facilities and to the Director, CFRD Osmania University for providing spectral data. One of the authors D.S. is grateful to UGC New Delhi for the award of Fellowship.

REFERENCES

[1] C. Oliver Kappe, Controlled microwave heating in Modern organic Synthesis, *Angew Chem. Int. Ed.* 43, (**2004**), 6250.

[2] D. Niamen, J. T. Mbafor, Z. T. Fomum, A. Kamanvi, J. C. Mbanya, M. C. Recio, R. M. Giner, S. Manez, and J. L. Rios, *Planta Med.* 70, (**2004**), 104.

[3] M. Cavia-Saiz, M. D. Busto, M. C. Pilar-Izquierdo, N. Ortega, M. Perez-Mateos, and P. Muniz, *J. Food and Agric. Sci.* 90, (**2010**), 1238.

[4] Noppamas, Soonthornchareonnon, Lersak Ubonopas, Songsri Kaewsuwan, and Mansong Wuttiudomlert, *Thai Journal of Phytopharmacy*, 11(2), (**2004**), 19.

[5] S. Mukherjee, V. Kumar, Prasad, A. K., Raj, H. G., Bracke, M. E., Olsen, C. E., Jain, S. C., Parmar., and V. S., Bioorg. *Med. Chem.*, 9, (**2001**), 337.

[6] H. K. Hsieh, L. T. Tsao, J. P. Wang, and C.N. Lin, *J. Pharm. Pharmacol.*, 52(2), (**2000**), 163.

[7] M. Satyanarayana, P. Tiwari, B. K. Tripathi, A. K. Srivastava, and R. Pratap, *Bioorg Med Chem*, 12, (**2004**), 883.

[8] V. J. Ram, A. S. Saxena, S. Srivastava, S. Chandra, Bioorg. *Med. Chem. Lett.*, 10, (**2000**), 2159.

[9] C. J. Zheng, S.M. Jiang, Z.H. Chen, B. J. Ye, and H. R. Piao, *Arch. Pharm. Chem. Life Sci*. 344, (**2011**), 689.

[10] L. Zhai, M. Chen, J. Blam, T. G. Theander, S. B. Chiristensen, A. Kharazmi, *J. Antimicrob. Chemother*., 43, (**1999**), 793.

[11] D. Ashok, K. Sudershan, and M. Khalilullah, *Green Chem. Lett. Rev.* 5, (**2012**), 121.

[12] D. Ashok, D. Mohan Gandhi, G. Srinivas, and A. Vikas kumar, *Med. Chem. Res*. 23(6), (**2014**), 3005.

[13] D. Ashok, V. Hanumantha, Rao, and Srinivas, Peddola., *Heterocyclic. Commun*, 19(5), (**2013**), 363.

[14] R. Chaturvedi, P. N. Patil, and N. B. Mulchandani, *Indian J. Chem.* 31B, (**1992**), 340.

[15] S. Babber, S. Chandra, and A. K. Aggarwal, *Indian J. Chem.* 26B, (**1987**), 797.

[16] G. Sagrera, V. López, E. Pandolfi, G. Seoane, T. Eicher, *Información Tecnológica*, 9, (**1998**), 11.

[17] T. Patonay, R. S. Varma, A. Vass, A. Levai, and J. Dudas, *Tetrahedron Lett.* 42, (**2001**), 1403.

[18] C. Ramesh Kamboj, Geeta Sharma, Dinesh Kumar, Rita Arora, Chetan Sharma, and K. R. Aneja, *Int. J. Chem.Tech. Research*, 3 (2), (**2011**), 901.

[19] H. J. Benson, Microbiological Applications, W. C. Brown Publications, Boston, MA, USA., 5th edn, (**1990**).

Received 21 Jan. 2016; Accepted 2016