RJC

RASĀYAN *J. Chem.*
255-260| Special Issue | 2022
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESIS AND EVALUATION OF 4-NITRO CHALCONES: EXPLORING ANTIBACTERIAL ACTIVITY

Ragidi Padma[1], Kumaraswamy Gandla[2,✉], G. Swapna[1], D. Prasanth Kumar[1], G. Pavan Kumar[1] and J. Salomi[1]

[1]Department of Pharmacy, A.M. Reddy Memorial College of Pharmacy, Narasaraopet 522601, Guntur (Dist), Andhra Pradesh, India

[2]Department of Pharmacy, Chaitanya (Deemed to be university), Hanumakonda-506001, Telangana, India

✉Corresponding Author: drkumaraswamygandla@gmail.com

ABSTRACT

Chalcone or (E)-1,3-diphenyl-2-propene-1-one is reported to be a precursor of flavonoids and isoflavonoids and are the open-chain intermediates in aurones synthesis of flavones. With a benzylideneacetophenone scaffold and a three-carbon α, β unsaturated carbonyl bridge connecting the two aromatic nuclei, they can be found in numerous conjugated forms in nature. The aim of this research is to synthesize and characterize some 4-nitro-containing substituted chalcones. The molecules were screened for antibacterial activities against *B. subtilis* and *K. pneumonia*. All the substituted nitro-chalcones (1-4) showed low to moderate antibacterial activity against *B. subtilis* and *K. pneumonia*. The compounds demonstrated ZOI values of 1.5 mm to 3.5 mm for *B. subtilis* and 2.5 mm to 3.5 mm for *K. pneumonia* at 0.1% level whereas ZOI values of 2.5 mm to 3.5 mm for *B. subtilis* and 4.9 mm to 7.2 mm for *K. pneumonia* at 0.2% level. Compound 1 containing dimethylamino demonstrated the best antibacterial activity; however far low activity than the standard drug ciprofloxacin.

Keywords: Chalcone, Nitro, Synthesis, Characterization, Antibacterial, Activity.

RASĀYAN *J. Chem.*, Special Issue, 2022

This manuscript is focusing **SDG-3:** Good Health and Well Being

INTRODUCTION

Natural products have been reported to exhibit promising therapeutic activities. Various naturally derived scaffolds have gained significant importance in modern-day research where more than half of therapeutic agents bear skeletons derived exclusively from nature. Natural products, both in the forms of pharmaceuticals and nutraceuticals (or functional foods) are widely accepted across the globe and are considered relatively safe among the majority of the population. The natural constituents have been the mainstay of various biological activities, of them, the flavonoids class remained the principal candidate. There are more than 4000 polyphenolic compounds known in the plant kingdom for over one billion years. They are ubiquitously found in fruits, vegetables, tea, wine, and are usually subdivided into nine sub-classes including flavones, flavonols, flavanols, flavanones, anthocyanidins, isoflavones, aurones, proanthocyanidins, and chalcones, which have promising cardioprotective activities. Various studies have suggested that dietary intake of natural flavonoids displayed protective, modulatory, and mimetic properties that reduce the risk of atherosclerotic progression, weight control, etc[1]. Chalcone or (E)-1,3-diphenyl-2-propene-1-one is reported to be a precursor of flavonoids and isoflavonoids and are the open-chain intermediates in aurones synthesis of flavones. With a benzylideneacetophenone scaffold and a three-carbon α, β unsaturated carbonyl bridge connecting the two aromatic nuclei, they can be found in numerous conjugated forms in nature. Kostanecki, who first synthesized a number of naturally occurring chromophoric compounds, is credited with coining the word. Chalcone and its derivatives can be synthesized classically by Claisen-Schmidt condensation between benzaldehyde and acetophenone employing sodium hydroxide (40%) solution as a catalyst.[2] Due to its straightforward chemistry, simplicity in synthesis, and plenty of replaceable hydrogen that may produce a wide variety of derivatives, chalcones' chemistry has persisted as a source of intrigue for researchers in the twenty-first century, variety of promising biological activities such as anti-arrhythmic[3], antiplatelet[4], anti-diabetic[5],

http://doi.org/10.31788/RJC.2022.1558131

anti-neoplastic[6], anti-angiogenic[7], anti-retroviral[8], anti-inflammatory[9], anti-gout[10], antihistaminic[11], anti-oxidant[12], anti-obesity[13], hypolipidemic[14], anti-tubercular[15], anti-filarial[16], anti-invasive[17], antimalarial[18], anti-protozoal[19], anti-bacterial[20], anti-fungal[21], anti-ulcer[22], anti-steroidal, immunosuppressant[24], hypnotic[25], anxiolytic, anti-spasmodic, anti-nociceptive, osteogenic, etc.

EXPERIMENTAL

Material and Methods

After being cleaned during the distillation process, commercially available solvents were employed. Glass plates with silica gel coating and pre-coated Aluminum TLC plates that were purchased from Merck were both used to monitor the completion of reactions (Germany). By using elemental analysis, purified chemicals were identified. IR, ^{1}H EI-mass spectrometry, ^{13}C NMR, and NMR. On a Perkin-Elmer model, IR spectra were captured in KBr**.** 1620 FTIR spectrophotometer, ^{1}H NMR, and ^{13}C NMR spectra were captured using a CDCl3/DMSO-based solvent in a Brucker AvanceII 300 MHz spectrophotometer, and mass spectra were captured using a JEOL mass spectrometer. CrysAlisPro (CrysAlisPro 1.171.39.46 (Rigaku Oxford Diffraction, 2018)) was used to measure XRD.

Chemicals

All analytical grade reagents, starting materials, reactants, solvents, chemicals, etc. were procured exclusively from Sigma Aldrich, Germany.

Instrumentation and Software

The UV spectra of solutions were captured using the Shimadzu UV-1800, UV-Visible double beam spectrophotometer with a matching 1 cm quartz cuvette (Shimadzu Corporation, Kyoto, Japan). The spectral band has a 0.5 nm width. For the construction and analysis of PCR and PLS models, Unscrambler ® and Microsoft Excel were utilized, whereas Matlab ® and Microsoft Excel were used for the development and analysis of CLS models.

General Procedure

Synthesis of Target Compounds

With the help of an ethanolic NaOH solution, the -CHO (aldehyde) portion of the starting material (1) interacts with the -COCH3 (acetyl) portion of the reactant (2) to create the benzylideneacetophenone (chalcone) scaffold (3) that contains the -hydroxy ketone function (Scheme-1).figure-1.

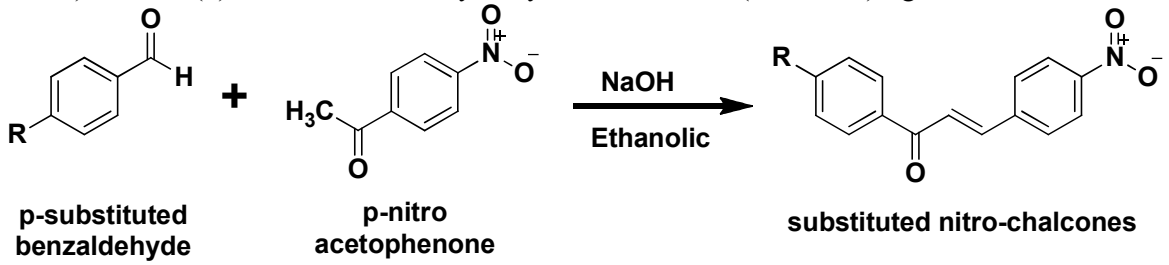

Fig.-1: Fabrication of Substituted Nitro-Chalcones

Synthetic Protocol

An equimolar concentration (0.01 M) of the starting material substituted benzaldehyde and the reactant p-nitro acetophenone were made to reflux in the presence of 20 mL aqueous solution of sodium hydroxide containing 25 mL of 90% ethanol. The mixture for the reaction was left to stand all night. The content was transferred over crushed ice containing dilute HCl (a few drops) and stirred vigorously using a glass rod. The obtained product was separated by filtration, thoroughly washed, and suitably recrystallized (Fig.-2).

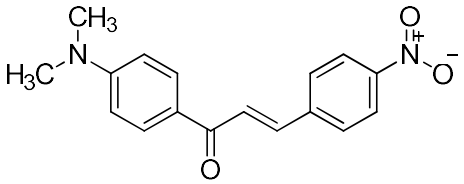

Fig.-2a: (*E*)-1-(4-(dimethylamino)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one (1)

Yellowish color; Yield: 94%; Rf: 0.71 (benzene: ethylacetate – 3:1 v/v); m.p.: 121-123°C; λmax: 305 nm; FTIR (KBr) υ (cm-1): 2824.22 (C-H), 2603.27 (C-O), 1639.2 (C=O), 1578.45 (Ar•C-C); 1H-NMR (δ, ppm, CDCl3): 2.82 (6H, s), 6.79-7.05 (3H, 6.85 (ddd, J = 8.4, 1.1, 0.5 Hz), 6.98 (d, J = 16.6 Hz)), 7.71-7.93 (5H, 7.77 (ddd, J = 8.4, 1.8, 0.5 Hz), 7.83 (ddd, J = 8.7, 2.2, 0.5 Hz), 7.86 (d, J = 16.6 Hz)), 8.08 (2H, ddd, J = 8.7, 1.9, 0.5 Hz); 13C-NMR (δ, ppm, CDCl3): 40.3 (2C, s), 112.0 (2C, s), 121.2 (1C, s), 123.8 (2C, s), 128.6 (2C, s), 130.3 (1C, s), 130.6 (2C, s), 135.5 (1C, s), 144.1 (1C, s), 147.3 (1C, s), 150.9 (1C, s), 188.9 (1C, s); MS: M+ 296.12, m/z: 296.12 (100.0%), 297.12 (18.7%), 298.12(Fig.-2b).

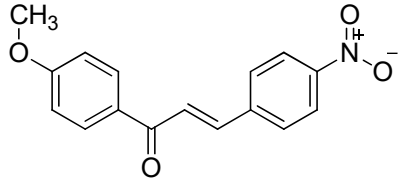

Fig.-2b: *E*)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (2)

FTIR (KBr) (cm-1): 2935.13 (C-H), 2719.14 (C=O), 1680.66 (Ar•C-C), 1134.92 (C-O); 1H-NMR (, ppm, CDCl3): 3.85 (3H, s), 6.90-7.13 (3H, 6.97 (d, J = 16.5 Hz), 7.07 (ddd, J = 8.3, 1.2, (1C, s), 144.1 (1C, s), 147.3 (1C, s), 159.8 (1C, s), 188.9 (1C, s); MS: M^+ 283.08, m/z: 283.08 (100.0%), 284.09 (17.6%), 285.09 (2.3%); Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94; O, 22.59, Found: 66.73; H, 4.54; N, 4.83; O, 21.69(Fig.-3).

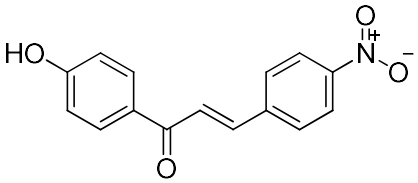

Fig.-3: (*E*)-1-(4-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (3)

Buff color; Yield: 55%; Rf: 0.33 (benzene: ethylacetate – 3:1 v/v); m.p.: 94-96°C; λmax: 342 nm; FTIR (KBr) υ (cm-1): 3026.87 (C-H), 2904.33 (C=O), 1592.48 (Ar•C-C), 1211.46 (C-O); 1H-NMR (δ, ppm, CDCl3): 6.80-7.03 (3H, 6.87 (ddd, J = 8.3, 1.1, 0.4 Hz), 6.96 (d, J = 16.5 Hz)), 7.59 (2H, ddd, J = 8.3, 1.8, 0.4 Hz), 7.77-7.99 (3H, 7.84 (ddd, J = 8.7, 2.3, 0.5 Hz), 7.92 (d, J = 16.5 Hz)), 8.08 (2H, ddd, J = 8.7, 1.9, 0.5 Hz); 13C-NMR (δ, ppm, CDCl3): 115.7 (2C, s), 121.2 (1C, s), 123.8 (2C, s), 128.6 (2C, s), 130.3 (1C, s), 130.7 (2C, s), 135.5 (1C, s), 144.1 (1C, s), 147.3 (1C, s), 157.4 (1C, s), 188.9 (1C, s); MS: M+ 269.07, m/z: 269.07 (100.0%), 270.07 (16.7%), 271.08 (1.3%); Anal. Calcd. for $C_{15}H_{11}NO_4$(Fig.-4).

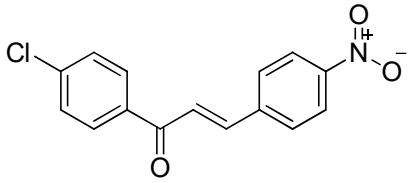

Fig.-4: (*E*)-1-(4-chlorophenyl)-3-(4-nitrophenyl)prop-2-en-1-one (4)

White color; Yield: 27%; Rf: 0.86 (benzene: ethylacetate – 3:1 v/v); m.p.: 109-110°C; λmax: 283 nm; FTIR (KBr) υ (cm-1): 2944.95 (C-H), 2828.27 (C-O), 1706.63 (C=O), 1572.37 (Ar•C-C), 808.028 (C-Cl); 1H-NMR (δ, ppm, CDCl3): 6.97 (1H, d, J = 16.5 Hz), 7.52 (2H, ddd, J = 8.7, 1.3, 0.5 Hz), 7.68-8.14 (7H, 7.74 (ddd, J = 8.7, 1.8, 0.5 Hz), 7.84 (ddd, J = 8.7, 2.2, 0.5 Hz), 7.96 (d, J = 16.5 Hz), 8.08 (ddd, J = 8.7, 1.9, 0.5 Hz)); 13C-NMR (δ, ppm, CDCl3): 121.2 (1C, s), 123.8 (2C, s), 128.6 (2C, s), 128.7 (2C, s), 130.3-130.5 (3C, 130.3 (s), 130.4 (s)), 133.7 (1C, s), 135.5 (1C, s), 144.1 (1C, s), 147.3 (1C, s), 188.9 (1C, s); MS: M+ 287.03, m/z: 287.03 (100.0%), 289.03 (32.0%), 288.04 (16.5%), 290.04 (5.4%), 289.04 (1.9%);

Antibacterial Activity

The antibacterial activity was tested on Pseudomonas aeruginosa and Bacillus subtilis. The comparison of several chemicals with ciprofloxacin helped to obtain the minimum inhibitory concentration (MIC) values. The in vitro antibacterial activity of TEBC was tested by the disc diffusion method under standard

conditions using the Muller Hinton Agar medium. The test organisms were first cultured in nutrient broth, incubated for 24 hr at 37°C±1°C, and then freshly prepared bacterial cells were spread onto the Muller Hinton agar plates in a laminar flow cabinet. The extract was dissolved in dimethylsulfoxide (DMSO) and soaked onto sterile discs of Whatman filter paper No. 1 (6 mm diameter). The discs were then placed onto the surface of the previously prepared bacterial plates and incubated. After 24 hr of incubation at 37°C±1°C.

RESULTS AND DISCUSSION

The structure of the chalcone compound was clarified by spectroscopic research. The FT-IR spectra confirmed the emergence of a novel ketonic carbonyl group as well as the lack of the previously observed aldehydic carbonyl group.[26-27] Additionally, the proton-NMR concentrated on a few crucial features of the structure. The aromatic protons were clearly found in the 6.8 to 8.2 ppm range. The signal at 3.99 ppm allowed for the identification of the hydroxyl protons. The mass spectra showed the appearance of the base peak matching the molecule's molecular mass along with some fragmented products with m/z of around 100, indicating the production of the chalcone derivative.[28] The ratios from the CHN analysis showed that they closely matched the theoretical values.

Antibacterial Activity

All the substituted nitro-chalcones (1-4) showed low to moderate antibacterial activity against *B. subtilis* and *K. pneumonia*. The compounds demonstrated ZOI values of 1.5 mm to 3.5 mm for *B. subtilis* and 2.5 mm to 3.5 mm for *K. pneumonia* at 0.1% level whereas ZOI values of 2.5 mm to 3.5 mm for *B. subtilis* and 4.9 mm to 7.2 mm for *K. pneumonia* at 0.2% level. Compound 1 containing dimethylamino demonstrated the best antibacterial activity[29-30] values were shown in Table-1; however far low activity than the standard drug ciprofloxacin.

Table-1: Antibacterial Activity of Substituted Nitro-Chalcones

Compounds	*B. subtilis*		*K. pneumonia*	
	0.1%	0.2%	0.1%	0.2%
1	3.4	6.8	3.5	7.2
2	3.5	5.4	2.6	7.1
3	1.5	3.5	2.6	5.2
4	2.2	3.1	2.5	4.9
Ciprofloxacin	4.3	8.1	4.8	9.7

CONCLUSION

The generated chalcone molecules, which contained nitro-containing acetophenone in ring-B and substituted benzaldehyde in ring-A, exhibited average anti-bacterial action against B. subtilis and K. pneumonia. It was discovered to be less potent and active than the typical compounds (ciprofloxacin). The latest finding will open up new chalcone research directions and inspire scientists to continue creating potent chemicals based on the benzylideneacetophenone scaffold.

ACKNOWLEDGEMENTS

These authors were very thankful to Principal, A.M Reddy College of Pharmacy, Narsaraopet, Andhra Pradesh and also thankful to Management, Chaitanya (Deemed to be University), Hanumakonda, Telangana for providing all necessary facilities to our entire research work.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

Dr. Kumaraswamy Gandla http://orchid.org/0000-0003-3138-5647
Ragidi Padma http://orchid.org/0000-0002-9818-819X
G.Swapna http://orchid.org/0000-0001-4540-8566

D. Prasanth Kumar http://orchid.org/0000-0001-2785-5936
G. Pavan Kumar http://orchid.org/0000-0001-76982-2343
J. Salomi http://orchid.org/0000-0001-2336-0725

REFERENCES

1. Z. H. Lu, X. J. Gu, K. Z. Shi, X. Li, D. D. Chen, L. Chen, *Arabian Journal of Chemistry*, **10(5)**, 624 (2017), https://doi.org/10.1016/j.arabjc.2014.11.002
2. O. P. Pravin, B. B. Sanjay, *Arabian Journal of Chemistry*, **9**, 588(2016), https://doi.org/10.1016/j.arabjc.2013.08.0271878-5352
3. G. Vincent, F. Christophe, R. Millet, R. Mansouri, P. Chavatte, V. Levacher, J. F. Brière, *European Journal of Medicinal Chemistry*, **58**, 396(2012), https://doi.org/10.1016/j.ejmech.2012.10.031
4. R. Fioravanti, A. Bolasco, F. Manna, F. Rossi, F. Orallo, F. Ortuso, S. Alcaro, R. Cirilli, *European Journal of Medicinal Chemistry*, **45(12)**, 6135(2010), https://doi.org/10.1016/j.ejmech.2010.10.005
5. H. Khalilullah, S. Khan, M. J. Ahsan, B. Ahmed, *Bioorganic and Medicinal Chemistry Letters*, **21(24)**, 7251(2011), https://doi.org/10.1016/j.bmcl.2011.10.056
6. M. R. Bhosle, A. R. Deshmukh, S. Pal, A. K. Srivastava, R. A. Mane, Bioorganic and Medicinal Chemistry Letters, 25,2442 (2015), DOI:10.1016/j.bmcl.2015.03.068
7. S. Viveka, Dinesha, P. Shama, G. K. Nagaraja, S. Ballav, S. Kerkar, *European Journal of Medicinal Chemistry*, **101**, 442(2015), https://doi.org/10.1016/j.ejmech.2015.07.002
8. A. Adhikari, B. Kalluraya, K. V. Sujith, K. Gouthamchandra, R. Jairam, R. Mahmood, R. Sankolli, *European Journal of Medicinal Chemistry*, **55**, 467(2012), https://doi.org/10.1016/j.ejmech.2012.07.002
9. R. Aggarwal, S. Kumar, P. Kaushik, D. Kaushik, G. K. Gupta, *European Journal of Medicinal Chemistry*, **62**, 508(2013), https://doi.org/10.1016/j.ejmech.2012.11.046
10. B. N. Acharya, D. Saraswat, M. Tiwari, A. K. Shrivastava, R. Ghorpade, S. Bapna, M. P. Kaushik, *European Journal of Medicinal Chemistry*, **45(2)**, 430(2010), https://doi.org/10.1016/j.ejmech.2009.10.023
11. A. Adhikari, B. Kalluraya, K. V. Sujith, K. Gouthamchandra, R. Jairam, R. Mahmood, R. Sankolli, *European Journal of Medicinal Chemistry*, **55**, 467 (2012), https://doi.org/10.1016/j.ejmech.2012.07.002
12. E. A. Begum, Y. C. Samiye, U. Gulberg, Y. Kemal , E. Rahmiye, *Bioorganic and Medicinal Chemistry Letters*, **24**, 3278(2014), https://doi.org/10.1016/j.bmcl.2014.06.015
13. R. M. Kumbhare, T. L. Dadmal, M. JanakiRamaiah, K. S. V. Kishore, L. Pushpavalli, S. Tiwari.,K. Appalanaidu, Y. KhageswarRao, M. Bhadra, *Bioorganic and Medicinal Chemistry Letters*, **25(3)**, 654(2015), https://doi.org/10.1016/j.bmcl.2014.11.083
14. C. K. Sharad, B. P. Vishal, K. R. Dipak, *European Journal of Medicinal Chemistry*, **84**, 51(2014), https://doi.org/10.1016/j.ejmech.2014.07.008
15. J. A. Mohamed, G. S. Jeyabalan, S. Savita, J. Naresh, K. Lalit, K. S. Lalit, Y. Hemant, S. Lokesh, G. K. Rajput, S. D. Narendra, P. Ravindra, B. J. Chandra, *Bioorganic &. Medicinal Chemistry Letters*, **21**, 5259(2011), https://doi.org/10.1016/j.bmcl.2011.07.035
16. F. A. Bakr, A. Ehab, A. M. Hanan, E. A. A. Ghada, *European Journal of Medicinal Chemistry*, **52**, 263(2012), https://doi.org/10.1016/j.ejmech.2012.03.023
17. Y. W. Mohmmad, R. B. Abdul, A. Amir, H. L. Dae, C. Inho, A. Fareeda, *European Journal of Medicinal Chemistry*, **54**, 845(2012), https://doi.org/10.1016/j.ejmech.2012.03.049
18. V. R. Kamalraj, S. Senthil, P. Kannan, *Journal of Molecular Structure*, **892**, 210(2008), https://doi.org/10.1016/j.molstruc.2008.05.028

19. N. T. Pokhodylo, R. D. Savka, V. S. Matiichuk, N. D. Obushak, *Russian Journal of General Chemistry*, **79**, 309(2009), https://doi.org/10.1134/S1070363209020248
20. H. S. Dong, H. C. Wang, Z. L. Gao, R. S. Li, F. H. Cui, *Journal of Heterocyclclic Chemistry*, **47**, 389(2010), https://doi.org/10.1002/jhet.336
21. S. Sathiya, S. Nandhabala, N. Hari, R. Paranthaman, A. Sankar, R. Ravikumar, *Rasayan Journal of Chemistry*, **12(4)**, 2260(2019), https://doi.org/10.31788/RJC.2019.1245383
22. M. Malathi, D. Prabhakara Chary, *Rasayan Journal of Chemistry*, **12(3)**, 1347(2019), https://doi.org/10.31788/RJC.2019.1235290
23. S. Sathiya, S. Nandhabala, N. Hari, R. Paranthaman, A. Sankar, R. Ravikumar, *Rasayan Journal of Chemistry*, **12(4)**, 2260(2019), https://doi.org/10.31788/RJC.2019.1245383
24. V. Larasati, W. Pangkahila and A.A.G. Budhiarta, *Jurnal of Kedokteran dan Kesehatan*, **3**, 2(2016)
25. M. Malathi, D. Prabhakara Chary, *Rasayan Journal of Chemistry*, **12(3)**, 1347(2019), https://doi.org/10.31788/RJC.2019.1235290
26. S. Karunakar, S. Swarnlata, *Indian Journal of Pharmaceutical Education and Research*, **42(2)**, 127(2008)
27. V. Iwari, V.Sharma, *International Journal of Research in Pharmaceutical Sciences*, **8(2)**, 214(2017)
28. P. Ravisankar, V. Swathi, S. Babu, S. Sultana, *IOSR Journal of Pharmacy and Biological Sciences*, **12(6)**, 17(2017).
29. F. Duarte Patrícia, A.C. Marcia, D.B. Caroline and R. B. M. Carla, *Ciência Rural. Santa Maria*, **46(7)**, 747(2016), https://doi.org/10.1590/0103-8478cr20141516
30. M. A. U. Huq, A. M. Rahman and T. Hossain, *Journal of Paediatric Surgeons of Bangladesh*, **1(2)**, 148(2007)

[RJC-8131/2022]