



GREEN SYNTHESIS OF 4-((UN)SUBSTITUTED BENZYLIDENE)-*N*-ARYLAMINO-2-((UN)SUBSTITUTED STYRYL)-1*H*-IMIDAZOLE-5(4*H*)-ONE DERIVATIVES

V. Anitha Rani^{[a]*} and Y. Bharathi Kumari^[b]

Keywords: Green chemistry, phenylhydrazine, DBU, Schiff bases.

We have achieved an efficient and green synthesis of 4-(benzylidene/substituted benzylidene)-*N*-aryl amino-2-(styryl/substituted styryl)-1*H*-imidazole-5(4*H*)-one derivatives in good yields by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst.

* Corresponding Authors

Fax:

E-Mail: anitha1810@gmail.com

[a] Department of Chemistry, Institute of Aeronautical Engineering, Dundigal, Hyderabad, India

[b] Department of Chemistry, College of Engineering, J. N. T. University, Kukatpally, Hyderabad 500 085, India

INTRODUCTION

Heterocyclic compounds containing imidazole moiety have many pharmacological properties and play an important role in biochemical processes. Highly substituted imidazoles are the key intermediates in the synthesis of various therapeutic agents and act as a subunit in drugs such as Olmesartan, Losartan, Eprosartan (angiotensin II receptor antagonist), Metronidazole (antibiotic), Trifluoperazine (platelet aggregation inhibitor), Dacarbazine (antineoplastic), Cimetidine (H₂-receptor antagonist), methimazole (antithyroid), Pilocarpine (muscarinic receptor agonist), Etomidate (intravenous anesthetic) as well as plant growth regulators,¹ fluorescence labeling agents, biological imaging² and chromophores for non-linear optic systems. These moieties have been reported as antibacterial, anti-inflammatory, antihypertensive, antithrombotic, fungicidal,³ anti-allergic, antiviral⁴ and herbicidal properties. On the other hand, an ionic liquid catalyzed reaction have gained considerable attention because of their interesting properties like high thermal stability, non volatility, eco-friendly benign nature and reusability leading to proceed the reaction effectively with high yields in shorter reaction times.

In view of the diverse pharmacological properties of these potent compounds, many methodologies have been developed using various catalytic systems such as InF₃,⁵ InCl₃·3H₂O,⁶ BF₃·SiO₂,⁷ Zr(acac)₄,⁸ I₂,⁹ n-tetrabutylammonium bromide (TBAB),¹⁰ CAN,¹¹ DABCO,¹² Yb(OTf)₃,¹³ *L*-proline,¹⁴ zirconium(IV)-modified silica gel,¹⁵ *p*-toluenesulfonic acid (*p*-TSA),¹⁶ Recently polyethylene glycol,¹⁷ and molecular iodine¹⁸ were also used efficiently for this reactions. However, many of these reported methods suffer from one or several drawbacks such as low yields, prolonged reaction times, use of toxic, costly, moisture sensitive, excess quantity of reagents, harsh reaction circumstances, special apparatus, difficult workup procedure

and difficulty in recovery and reusability of the catalysts. Therefore, there is still a need to build up an efficient, eco-friendly and easy method for the synthesis of imidazole derivatives

Based on the literature, this prompted us to synthesize 4-(benzylidene/substituted benzylidene)-*N*-arylamino-2-(styryl/substituted styryl)-1*H*-imidazole-5(4*H*)-one derivatives from Schiff bases by making use of DBU as a catalyst.

EXPERIMENTAL

Melting points are uncorrected and taken in open capillary tubes in sulphuric acid bath. TLC was run on silica gel-G and visualization was done using UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr pellets. ¹H NMR spectra were recorded in DMSO-*d*₆ using TMS as internal standard with 400 MHz spectrometer. ¹³C NMR spectra were recorded in DMSO-*d*₆ using TMS as internal standard with 100 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by *Q*+1 value only.

Preparation of (*Z*)-2-acetamido-*N*-phenyl-3-(phenyl/substituted phenyl)prop-2-enamides (**2a**, **2b**)

A mixture of 4-(benzylidene/substituted benzylidene)-2-methyl oxazolin-5-ones (**1a**, **1b**) (10 mmol) and phenylhydrazine (10 mmol) was dissolved in ethanol and refluxed for 5 h at 80 °C. The completion of the reaction was monitored by TLC (1:3 of EtOAc:hexane). Then this reaction mixture was cooled to room temperature and poured into ice-cold water (50 mL), separated solid product was collected, washed with water (10 mL) and dried. The product was recrystallised from ethanol to obtain (*Z*)-2-acetamido-*N*-phenyl-3-(phenyl/substituted phenyl)prop-2-enamides (**2a**, **2b**). The formation of **2a** and **2b** from oxazolin-5-one derivatives (**1a**, **1b**) has been confirmed from the spectral data.

The IR spectrum of the enamides showed peaks for NH group and C=O and absence of the peak for lactone ring. The ¹H NMR spectra of the enamides showed signals for

NHPH and NHCO groups. The mass spectra of the compounds exhibited molecular ion peaks (M^+) corresponding to their molecular weights.

Preparation of 4-(benzylidene/substituted benzylidene)-*N*-aryl amino-2-(styryl/substituted styryl)-1*H*-Imidazole-5(4*H*)-one derivatives (4 a-1)

Equimolar quantities of (*Z*)-2-acetamido-*N*-phenyl-3-(phenyl/substituted phenyl)prop-2-enamides (**2a-2b**) (10 mmol) and Schiff bases **3a** and **3b** (10 mmol) were mixed together in 20 mL of ethanol in the presence of DBU (1 mmol) as catalyst. The mixture was refluxed for 2 h. The completion of the reaction was checked by TLC (1:3 of EtOAc:hexane), then this reaction mixture was cooled to room temperature and poured into ice-cold water (50 mL). The separated solid product was collected, washed with water (10 mL) and dried. The product was recrystallized from ethanol to obtain 4-(benzylidene/substituted benzylidene)-*N*-aryl amino-2-(styryl/substituted styryl)-1*H*-Imidazole-5(4*H*)-one derivatives (**4a-4l**). The physical (Table 1) and spectral analysis of the compounds is given below.

Table 1. Physical data of the products **4a-4l**.

No.	Starting materials	Mol. formula of product	Yield* , %	M.P., °C
1	2a, 3a	C ₂₄ H ₁₉ N ₃ O	68	165-166
2	2a, 3b	C ₂₅ H ₂₂ N ₃ O ₂	65	168-169
3	2a, 3c	C ₂₄ H ₁₈ N ₃ OF	66	161-162
4	2a, 3d	C ₂₄ H ₁₈ N ₄ O ₃	61	168-171
5	2a, 3e	C ₂₄ H ₁₈ N ₃ OCl	61	154-156
6	2a, 3f	C ₂₄ H ₁₈ N ₃ OCl	65	219-221
7	2b, 3a	C ₂₄ H ₁₈ N ₃ OCl	68	154-156
8	2b, 3b	C ₂₅ H ₂₁ N ₃ O ₂ Cl	68	171-172
9	2b, 3c	C ₂₄ H ₁₈ N ₃ OFCI	68	211-213
10	2b, 3d	C ₂₄ H ₁₈ N ₄ O ₃ C1	63	211-212
11	2b, 3e	C ₂₄ H ₁₈ N ₃ OC1 ₂	64	206-208
12	2b, 3f	C ₂₄ H ₁₈ N ₃ OC1 ₂	69	210-212

* Refers to yields of crude products only.

Spectral analysis of (4*Z*)-4-benzylidene-1-methyl-2-styryl-1*H*-imidazol-5(4*H*)-one derivatives **4a-4l**

4a: IR (KBr): 3444 (-NH), 1668 (-C=O) cm⁻¹. ¹HNMR δ = 7.4-8.0 (m, 17H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 109.5, 109.8, 116.1, 119.3, 123.3, 123.4, 123.4, 127.3, 128.0, 128.8, 130.0, 130.3, 137.1, 137.1, 138.1, 138.6, 141.1, 141.3, 167.1. MS: M+H = 366.

4b: IR (KBr): 3436 (-NH), 1674 (-C=O) cm⁻¹. ¹HNMR δ = 4.2 (s, 3H, -CH₃), 7.4-8.0 (m, 16H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 109.4, 109.5, 115.3, 114.2, 123.3, 123.4, 123.5, 126.2, 127.0, 128.4, 130.2, 130.4, 137.2, 137.4, 138.2, 138.5, 141.0, 141.3, 165.2. MS: M+H = 396.

4c: IR (KBr): 3432 (-NH), 1664 (-C=O) cm⁻¹. ¹HNMR δ = 7.4-8.0 (m, 16H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 110.3, 110.8, 114.3, 118.2, 122.2, 123.2, 123.5, 125.2, 127.2, 127.2, 130.4, 130.9, 137.2, 137.6, 138.4, 138.6, 141.8, 141.9, 165.8. MS: M+H = 385.

4d: IR (KBr): 3443 (-NH), 1674 (-C=O) cm⁻¹. ¹HNMR δ = 7.4-8.0 (m, 16H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³C- NMR δ = 108.6, 109.6, 115.4, 116.8, 122.1, 123.2, 123.7, 124.6, 125.3, 128.3, 130.4, 130.7, 137.7, 137.8, 138.3, 138.5, 141.4, 141.5, 166.7. MS: M+H = 412.

4e: IR (KBr): 3433 (-NH), 1662 (-C=O) cm⁻¹. ¹HNMR δ = 7.4-8.0 (m, 16H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 109.7, 109.8, 116.3, 119.4, 123.2, 123.4, 123.5, 127.6, 128.2, 128.4, 130.2, 130.5, 137.6, 137.8, 138.1, 138.2, 141.4, 141.8, 166.3. MS: M+H = 401.

4f: IR (KBr): 3434 (-NH), 1653 (-C=O) cm⁻¹. ¹HNMR δ = 7.4-8.0 (m, 16H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 109.5, 109.8, 116.1, 119.3, 123.3, 123.4, 123.4, 127.3, 128.0, 128.8, 130.0, 130.3, 137.1, 137.1, 138.1, 138.6, 141.1, 141.3, 167.1. MS: M+H = 400.

4g: IR (KBr): 3442 (-NH), 1663 (-C=O) cm⁻¹. ¹HNMR δ = 7.4-8.0 (m, 16H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 109.4, 109.6, 114.5, 119.6, 120.4, 123.3, 123.3, 127.5, 128.3, 128.8, 130.4, 130.6, 137.4, 137.5, 138.1, 138.6, 141.2, 141.3, 167.5. MS: M+H = 401.

4h: IR (KBr): 3425 (-NH), 1664 (-C=O) cm⁻¹. ¹HNMR δ = 4.3 (s, 3H, -CH₃), 7.4-8.0 (m, 16H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 109.7, 109.9, 116.1, 118.3, 121.9, 122.4, 123.4, 127.2, 128.2, 128.7, 130.2, 130.3, 137.1, 137.2, 138.1, 138.8, 141.1, 141.3, 167.2. MS: M+H = 432.

4i: IR (KBr): 3434 (-NH), 1664 (-C=O) cm⁻¹. ¹HNMR δ = 7.4-8.0 (m, 16H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 108.6, 109.7, 116.4, 118.5, 123.5, 123.6, 123.3, 126.3, 128.3, 128.8, 130.2, 130.3, 137.1, 137.8, 138.1, 138.2, 141.1, 141.4, 167.4. MS: M+H = 420.

4j: IR (KBr): 3428 (-NH), 1650 (-C=O) cm⁻¹. ¹HNMR δ = 7.4-8.0 (m, 17H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 109.3, 109.5, 115.1, 118.3, 121.3, 122.4, 123.5, 126.3, 127.0, 128.3, 130.2, 130.3, 135.1, 136.2, 138.2, 138.5, 141.1, 141.2, 166.8. MS: M+H = 447.

4k: IR (KBr): 3440 (-NH), 1662 (-C=O) cm⁻¹. ¹HNMR δ = 7.4-8.0 (m, 17H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 109.3, 109.6, 115.3, 116.3, 121.2, 122.2, 123.2, 124.5, 126.4, 127.6, 130.1, 130.3, 137.2, 138.2, 138.7, 138.9, 141.7, 141.8, 167.6. MS: M+H = 437.

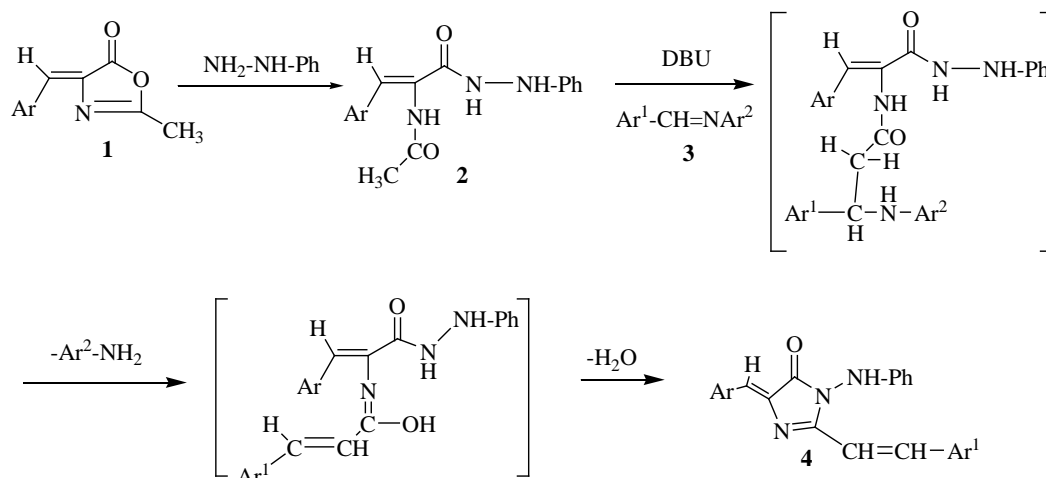
4l: IR (KBr): 3430 (-NH), 1665 (-C=O) cm⁻¹. ¹HNMR δ = 7.4-8.0 (m, 17H, Ar-H, =CH-Ar and NH), 8.0-8.4 (d, 2H, -CH=CH). ¹³CNMR δ = 109.2, 109.6, 116.5, 119.3, 123.2, 123.6, 123.8, 127.3, 128.3, 128.5, 130.3, 130.3, 137.5, 137.7, 138.1, 138.8, 141.2, 141.3, 167.3. MS: M+H = 437.

RESULTS AND DISCUSSION

As illustrated in scheme 1, the azalactone (*Z*)-4-benzylidene-2-methyloxazol-5(4*H*)-one **1(a-b)** were treated with phenylhydrazine and refluxed for 4-4.5 h in ethanol to produce (*Z*)-2-acetamido-*N*-phenyl-3-(phenyl/substituted phenyl)prop-2-enamides (**2a,2b**). Then, **2a** and **2b** were reacted with the Schiff bases (benzylidene/substituted benzylidene)anilines (**3a-3f**) in the presence of DBU as a

catalyst in ethanol medium under reflux condition for 1-1.5 h to produce 4-(benzylidene/substituted benzylidene)-*N*-aryl amino-2-(styryl/substituted styryl)-1*H*-Imidazole-5(4*H*)-one derivatives (**4a-4l**). A reasonable mechanism has been formulated for the formation of these imidazole-5-ones (**4a-4l**). The IR spectrum of the compound showed absorption bands for NH, C=O, Ar, C=C, C-N and the ¹H

NMR showed the signals for aromatic, two distinct signals for olefinic protons and signals for amide protons. ¹³C NMR showed signals for -C=C, (-C=C) Ar, (C-N), (-C=N) and (C=O). The mass spectrum of the compound **4a-4l** showed the molecular ion peaks corresponding to molecular weight of the compounds. The spectral data confirms the structure of **4a-4l**.



Scheme 1. Synthesis of 4-(benzylidene/substituted benzylidene)-*N*-aryl amino-2-(styryl/substituted styryl)-1*H*-Imidazole-5(4*H*)-one derivatives.

The IR spectra of **1a** and **1b** showed the presence of NH-stretching absorptions for NH and absence of stretching absorptions of lactone ring. The ¹H NMR data showed signals for NH, which are D₂O exchangeable and mass spectra which confirms the molecular weight of the compounds.

The cyclocondensation of **1a** and **1b** with Schiff bases to produce (4*Z*)-4-(benzylidene/ substituted benzylidene)-*N*-aryl amino-2-(styryl/substituted styryl)-1*H*-imidazol-5(4*H*)-one derivatives (**4a-4l**) is supported by IR spectra showing the absence of N-H stretching absorptions of the amide group. The ¹H NMR spectra showed the disappearance of peaks for NH and appearance of peaks for 2-styryl protons. ¹³C NMR spectra of the compound **3a-3l** shows signals for the presence of C=C (C=C)Ar, C-N, C=N and C=O. Finally the mass spectrum of the compounds **4a-4l** confirmed the molecular weight of the compounds there by supporting the structure of the title compound (4*Z*)-4-(benzylidene/ substituted benzylidene)-*N*-aryl amino-2-(styryl/substituted styryl)-1*H*-imidazol-5(4*H*)-one derivatives (**4a-4l**).

CONCLUSION

One pot green synthesis for the preparation of imidazolone derivatives (**4a-4l**) in high purity and excellent yields has been developed by making use of DBU as a catalyst.

REFERENCES

¹Freedman, J., Loscalzo, J., *New Therapeutic Agent in Thrombosis and Thrombolysis*, 3rd edition, Taylor and Francis, **2009**.

- ²Sun, Y. F., Huang, W., Lu, C. G., Cui, Y. P., The synthesis, two-photon absorption and blue upconversion fluorescence of novel, nitrogen-containing heterocyclic chromophores, *Dyes Pigments*, **2009**, *81*, 10–17. <https://doi.org/10.1016/j.dyepig.2008.08.003>
- ³Pozhershkii, A. F., Soldalnikov, A. T., Katritzky A. R., In *Heterocycles in Life and Society*, Wiley, New York, **1997**.
- ⁴Horton, D. A., Bourne, G. T., Sinythe M. L., The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures, *Chem. Rev.*, **2003**, *103*, 893–930. <https://doi.org/10.1021/cr020033s>
- ⁵Reddy, M. V., Jeong Y. T., *J. Fluorine Chem.*, A concise and versatile synthesis of 2-amino-3-cyanopyridine derivatives in 2,2,2-trifluoroethanol, **2012**, *142*, 45–51. <https://doi.org/10.1016/j.jfluchem.2012.06.009>
- ⁶Saikat, D. S., Parasa, H., Dilip, K., An efficient and one-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles catalyzed by InCl₃·3H₂O, *Tetrahedron Lett.*, **2008**, *49*, 2216–2220. <https://doi.org/10.1016/j.tetlet.2008.02.053>
- ⁷Sadeghi, B., Mirjalili, B. B. F., Hashemi, M. M., BF₃·SiO₂: an efficient reagent system for the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles, *Tetrahedron Lett.*, **2008**, *49*, 2575–2577. <https://doi.org/10.1016/j.tetlet.2008.02.100>
- ⁸Khosropour, A. R., Ultrasound-promoted greener synthesis of 2,4,5-trisubstituted imidazoles catalyzed by Zr(acac)₄ under ambient conditions, *Ultrason. Sonochem.*, **2008**, *15*, 659–664. DOI: [10.1016/j.ultsonch.2007.12.005](https://doi.org/10.1016/j.ultsonch.2007.12.005)
- ⁹Mazaahir, K., Poonam, M., Vikas, B., Rishi, K. S., Abdul, S. E., One-pot synthesis of highly substituted imidazoles using molecular iodine: A versatile catalyst, *J. Mol. Catal. A: Chem.*, **2007**, *265*, 177–182. <https://doi.org/10.1016/j.molcata.2006.10.009>
- ¹⁰Chary, M. V., Keerthysri, N. C., Srinivasu, V. N. V., Lingaiah, N., Srinivas, K., Tetrabutylammonium bromide (TBAB) in isopropanol: An efficient, novel, neutral and recyclable catalytic system for the synthesis of 2,4,5-trisubstituted imidazoles, *Catal. Commun.*, **2008**, *9*, 2013–2017. <https://doi.org/10.1016/j.catcom.2008.03.037>

- ¹¹Rajanarendar, E., Murthy, K. R., Nagi Reddy, M., A mild and efficient four component one-pot synthesis of 2,4,5-triphenyl-(1H-1-imidazolyl)isoxazoles catalyzed by ceric ammonium nitrate, *Indian J. Chem.*, **2011**, *50B*, 926–930. <http://hdl.handle.net/123456789/12099>
- ¹²Murthy, S. N., Madhav, B., Nageswar, Y. V. D., DABCO as a mild and efficient catalytic system for the synthesis of highly substituted imidazoles via multi-component condensation strategy, *Tetrahedron Lett.*, **2010**, *51*, 5252–5257. <https://doi.org/10.1016/j.tetlet.2010.07.128>
- ¹³Wang, L. M., Wang, Y. H., Tian, H., Yao, Y. F., Shao, J. H., Liu, B., Ytterbium triflate as an efficient catalyst for one-pot synthesis of substituted imidazoles through three-component condensation of benzil, aldehydes and ammonium acetate, *J. Fluorine Chem.*, **2006**, *127*, 1570–1573. <https://doi.org/10.1016/j.jfluchem.2006.08.005>
- ¹⁴Subhasis, S., Ganesh, C. N., Pallavi, S., Singh, M. S., L-Proline: an efficient catalyst for the one-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles, *Tetrahedron*, **2009**, *65*, 10155–10161. <https://doi.org/10.1016/j.tet.2009.10.019>
- ¹⁵Sharma, R. K., Sharma, C., Zirconium(IV)-modified silica gel: Preparation, characterization and catalytic activity in the synthesis of some biologically important molecules, *Catal. Commun.*, **2011**, *12*, 327–331. <https://doi.org/10.1016/j.catcom.2010.10.011>
- ¹⁶Mohammad, M. K., Kiumars, B., Iman, K., p - TSA Catalyzed Synthesis of 2,4,5-Triarylimidazoles from Ammonium Heptamolybdate Tetrahydrate in TBAI, *J. Chin. Chem. Soc.*, **2007**, *54*, 829-833. <https://doi.org/10.1002/jccs.200700121>
- ¹⁷Nalage, S. V., Kalyankar, M. B., Patil, V. S., Bhosale, S. V., Deshmukh, S. U. and Pawar, R. P., An Efficient Nuncatalytic Protocol for the Synthesis of Trisubstituted Imidazole in Polyethylene Glycol Using Microwaves, *The Open Catal. J.*, **2010**, *3*, 58-61. DOI: [10.2174/1876214X01003010058](https://doi.org/10.2174/1876214X01003010058)
- ¹⁸Parveen, A., Ahmed, M. R., Shaikh, K. A., Deshmukh, S. P. and Pawar, R. P., Efficient synthesis of 2,4,5-triaryl substituted imidazoles under solvent free conditions at room temperature, *Arkivoc*, **2007**, *16*, 12-18.

Received: 24.08.2019.

Accepted: 11.10.2019.