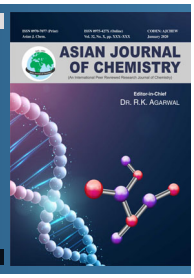
Asian Journal of Chemistry; Vol. 32, No. 2 (2020), 276-280

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22339



Synthesis and Antimicrobial Activity of Some Novel 1,4-Dihydropyridine Trimer Derivatives

D. ASHOKKUMAR, M. GOPALAKRISHNAN and G. RAMALINGAM*

Department of Chemistry, Annamalai University, Annamalai Nagar-608002, India

*Corresponding author: E-mail: drgr_dde@rediffmail.com

Received: 17 July 2019; *Accepted*: 30 August 2019; *Published online*: 30 December 2019; AJC-19712

An efficient multi-component one pot synthesis of some novel bioactive 1,4-dihydropyridine derivatives from melamine using various aldehydes and 1,3-dicarbonyl compounds are reported. This reaction carried out microwave irradiation under solvent free condition using low cost and efficient acetic acid catalyst. The excellent futures of this method are eco-friendly, short reaction time and mild reaction condition. This method is convincing route for highly substituted dihydropyridine trimer synthesis. The synthesized dihydropyridine derivatives are screened for antimicrobial properties.

Keywords: 1,4-Dihydropyridines, Microwave irradiation, Acetic acid catalyst, Antimicrobial properties.

INTRODUCTION

Multi component reaction (MCRs) refers to two are more chemical substance are combined within a one stage process to form products. It's alternative greener way for synthesis of natural products. MCRs are versatile tool in the modern drug synthetic process [1-3]. The 1,4-dihydropyridine is first reported by Arthur Hantzsch in 1882.The heterocyclic ring moieties are very important in organic chemistry. Recent year the six-membered nitrogen containing heterocyclic compounds like 1,4-dihydropyridine it's attract most of chemist due to their medicinal applications [4]. The calcium channel blockers play on versatile role for controlling the large amount of calcium ions entering vascular smooth cells and cardio vascular cell. The hypertension is one of main factors for chronic kidney disease, stock and coronary artery disease [5]. Some dihydropyridines derivatives such as nifedipine, amlodipine and nicardipine are effectively used to cardiovascular agents for hypertension treatment [6]. Many 1,4-dihydropyridine calcium channel blockers are used for the treatment of heart failure [7,8]. The 1,4-dihydropyridine also acts as a Chemo-sensitizer agents [9,10]. The 1,4-dihydropyridine displays verities of biological and medicinal application such as antitumor [11], antimutaganic [12], geroprotectic agents [13], antidiabetic [14], calcium channel blockers [15,16] antimicrobial [17], neurotropic [19], anti-inflammatory [19] antioxidant activities [20] and angina pectoris [21]. The glycosylated dihydropyridine derivatives exhibit best antitubercular activity [22,23]. The 1,4-dihydropyridine derivatives exhibit other beneficial effects *e.g.*, to reduce ventricular pressure, renal production, vascular hypertrophy and antiatherogenic activity [24-26]. Nimodipin, diludine, amlodipine, felodipine these N-substituted 1,4-dihydropyridine are manufactured worldwide [27]. The older synthetic procedure for the 1,4-dihydropyridine is mixing of ethyl acetoacetate, ammonia and aldehydes refluxed at ethanol solvent medium in presence of acetic acid catalyst [28]. This classical approach show the many disadvantages such as, low yield percentage, longer reaction time, using of large amount of organic solvents and hard refluxing condition. Due to this we move to the alternative method for the preparation of 1,4-dihydropyridines. The acid catalyst will be used in most of the 1,4-dihydropyridine synthesis silica sulfuric acid (SSA) [29], (Zn[(L)proline]$_2$) [30], alumina sulfuric acid (ASA) [31], silicagel/sulfonic acid catalyst (SiO_2-SO_3H) [32] phenyl boronic acid [33] sulfated polyborate [34], iodotrimethyl sillane [35]. In this present work we use acetic acid catalyst. In synthetic organic chemistry various types of synthetic routes used for synthesis of organic compounds are reported using different kinds of processes based on solar thermal energy [36] green solvents, ultrasound irradiation [37] solid support [38], Grignard reagent [39] and microwave assisted reaction [40]. Among these methods the microwave assisted reaction method

is best one because of solvent free condition, short reaction time and low cost compared to other method and simple working procedure for this reason microwave assisted reaction for synthesis of organic compounds.

EXPERIMENTAL

All synthetic grade chemicals were collected from Aldrich and Merck chemical companies. The melting points were determined by the open tube capillary method and are uncorrected. The thin layer chromatography (TLC) is used to checking the purity of synthesized compounds. Tacking ^{1}H and ^{13}C NMR spectra of synthesized compounds from Bruker Avance 400 MHz spectrometer using $CDCl_3$ as a solvent TMS is internal standard. The infrared spectra of newly prepared compounds were recorded by using Agilent pro infrared spectrometer.

General synthetic procedure for 1,4-dihydropyridine trimer: A mixture of 1 mmol melamine, 3 mmol aryl aldehyde, 6 mmol ethyl acetoacetate and 2 drops of glacial acetic acid is added (melamine, aryl aldehyde and ethyl acetoacetate are added 1:3:6 ratio respectively). The reaction mixture was well grained lock like as a paste then the reaction mixture is placed in microwave irradiation for 3 min. The thin layer chromatography is used to monitoring reaction process. After completion of the reaction, the reaction mixture was cooled at room temperature. After cooling the reaction mixture poured in to water the solid particles is formed (**Scheme-I**). The products separated by simple filtration method. The product is recrystallized in ethanol to form brown colour solid. The formation of product is confirmed by using spectral techniques.

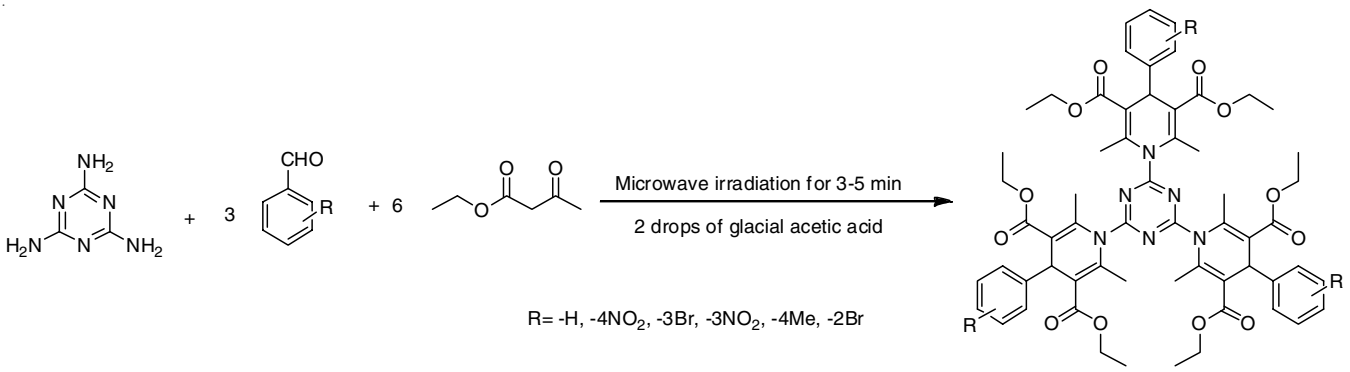
Hexaethyl 1,1',1''-(1,3,5-triazine-2,4,6-triyl)*tris*(2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate) (1a): Brown solid, Yield 72 %, m.p. 120- 122 °C, IR (KBr, ν_{max}, cm^{-1}): 3069 -3156 (aromatic C-H *str.*), 2979-2881 (aliphatic C-H *str.*), 1711 (C=O *str.* for ester group), 1599 (C=N *str.*), 1483 (C=C *str.*); ^{1}H NMR ($CDCl_3$) δ = 6.77-7.87 (m, 15H, Ar-H), 5.03 (s, 3H, CH), 3.98 (m, 12H, CH_2 of ethyl), 2.74 (s, 18H, CH_3 at C-6 and C-7), 1.10 (t, 18H, CH_3 of ethyl); ^{13}C NMR ($CDCl_3$) δ = 164.51 (C=O of the ester), 154.25 (C=N), 150.06 (C-1), 145.50 (C-14), 127.96-139.32 (other aromatic carbon), 102.06 (C-2), 61.11 (methylene carbon), 54.33 (C-3), 17.87 (C-6), 13.99 (C-10). Anal. calcd. for $C_{60}H_{66}N_6O_{12}$: C, 67.78; H,6.26; N,7.90; O,18.06 %.

Hexaethyl 1,1',1''-(1,3,5-triazine-2,4,6-triyl)*tris*(2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate) (1b): Brown solid, Yield 77 %, m.p. 127- 129 °C, IR (KBr, ν_{max}, cm^{-1}): 3017-3114 (aromatic C-H *str.*), 2967 (aliphatic C-H *str.*), 1716 (C=O *str.* for ester group), 1624 (C=N *str.*), 1517 (C=C *str.*); ^{1}H NMR ($CDCl_3$) δ = 7.31-8.40 (m, 12H, Ar-H), 5.93 (d, 3H, CH), 4.34 (q, 12H, CH_2 of ethyl), 2.25 (t, 18H, CH_3 at C-6 and C-7), 1.26 (s, 18H, CH_3 of ethyl); ^{13}C NMR ($CDCl_3$) δ = 166.49 (C=O of the ester), 151.06 (C=N), 148.40 (C-1), 146.99 (C-14), 127.96-139.32 (other aromatic carbon), 103.27(C-2), 62.17 (methylene carbon), 50.08 (C-3), 14.03 (C-6), 14.09 (C-10). Anal. calcd. for $C_{60}H_{63}N_9O_{18}$: C, 60.14; H,5.30; N,10.52; O,24.04 %.

Hexaethyl 1,1',1''-(1,3,5-triazine-2,4,6-triyl)*tris*(4-(3-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (1c): Brown solid, Yield 73 %, m.p. 123-125 °C, IR (KBr, ν_{max}, cm^{-1}): 3059-3124 (aromatic C-H *str.*), 2849-2918 (aliphatic C-H *str.*), 1713 (C=O *str.* for ester group), 1550 (C=N *str.*), 1485 (C=C *str.*); ^{1}H NMR ($CDCl_3$) δ = 7.18-8.19 (m, 12H, Ar-H), 4.88 (s, 3H, CH), 4.16 (m, 12H, CH_2 of ethyl), 2.17 (m, 18H, CH_3 at C-6 and C-7), 1.15(m, 18H, CH_3 of ethyl); ^{13}C NMR ($CDCl_3$) δ = 165.60 (C=O of the ester), 153.82 (C=N), 146.05 (C-1), 143.61 (C-14), 122.27-132.84 (other aromatic carbon), 101.57 (C-2), 60.09 (methylene carbon), 55.62 (C-3), 18.66 (C-6), 14.15 (C-10). Anal. calcd. for $C_{60}H_{63}Br_3N_6O_{12}$: C, 55.44; H, 4.89; Br, 18.44; N, 6.47; O, 14.77 %.

Hexaethyl 1,1',1''-(1,3,5-triazine-2,4,6-triyl)*tris*(2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate) (1d): Brown solid, Yield 78 %, m.p. 132- 134 °C, IR (KBr, ν_{max}, cm^{-1}): 3097 (aromatic C-H *str.*), 2928-2975 (aliphatic C-H *str.*), 1700 (C=O *str.* for ester group), 1647 (C=N *str.*), 1559 (C=C *str.*); ^{1}H NMR ($CDCl_3$) δ = 7.27-8.27(m, 12H, Ar-H), 5.82 (t, 3H, CH), 4.08 (s, 12H, CH_2 of ethyl), 2.23 (m, 18H, CH_3 at C-6 and C-7), 1.13(m, 18H, CH_3 of ethyl); ^{13}C NMR ($CDCl_3$) δ = 165.42 (C=O of the ester), 153.75 (C=N), 146.29 (C-1), 142.10 (C-14), 126.44-139.38 (other aromatic carbon), 101.28 (C-2), 60.23 (methylene carbon), 55.01 (C-3), 18.66 (C-6), 14.15 (C-10). Anal. calcd. for $C_{60}H_{63}N_9O_{18}$: C, 60.14; H, 5.30; N, 10.52; O, 24.04 %.

Hexaethyl 1,1',1''-(1,3,5-triazine-2,4,6-triyl)*tris*(2,6-dimethyl-4-p-tolyl-1,4-dihydropyridine-3,5-dicarboxylate) (1e): Brown solid, Yield 71 %, m.p. 126- 128 °C, IR (KBr, ν_{max}, cm^{-1}): 3117 (aromatic C-H *str.*), 2920 (aliphatic C-H *str.*), 1690 (C=O *str.* for ester group), 1644(C=N *str.*), 1542 (C=C *str.*); ^{1}H NMR ($CDCl_3$) δ = 7.08-7.94(m, 12H, Ar-H), 5.59 (d, 3H, CH), 4.04 (d, 12H, CH_2 of ethyl), 2.36 (m, 25H, CH_3 at C-6, C-7 and c-17), 1.29 (t, 18H, CH_3 of ethyl); ^{13}C NMR ($CDCl_3$)



Scheme-I: Synthesis of 1,4-dihydropyridine trimer derivatives (**1a-f**)

δ = 165.69 (C=O of the ester), 153.69 (C=N), 146.41 (C-1), 143.83 (C-14), 126.64-129.88 (other aromatic carbon), 101.34 (C-2), 59.99 (methylene carbon), 55.61 (C-3), 21.54(C-17) 14.14 (C-6), 13.93 (C-10). Anal. calcd. for $C_{63}H_{72}N_6O_{12}$: C, 68.46; H, 6.57; N, 7.60; O, 17.37 %.

Hexaethyl 1,1',1''-(1,3,5-triazine-2,4,6-triyl)*tris*(4-(2-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (1f): Brown solid, Yield 76 %, m.p. 127- 129 °C, IR (KBr, ν_{max}, cm^{-1}): 3058 (aromatic C-H *str.*), 2897-2977 (aliphatic C-H *str.*), 1696 (C=O *str.* for ester group), 1647 (C=N *str.*), 1541 (C=C *str.*); ^{1}H NMR ($CDCl_3$) δ = 6.90-7.67(m, 12H, Ar-H), 5.95 (t, 3H, CH), 4.52 (s, 12H, CH_2 of ethyl), 2.95 (d, 18H, CH_3 at C-6 and C-7), 1.18 (s, 18H, CH_3 of ethyl); ^{13}C NMR ($CDCl_3$) δ = 165.38 (C=O of the ester), 158.30 (C=N), 146.73 (C-1), 145.89 (C-14), 122.67-131.09 (other aromatic carbon), 100.82 (C-2), 60.20 (methylene carbon), 55.34 (C-3), 18.76 (C-6), 14.16 (C-10). Anal. calcd. for $C_{60}H_{63}Br_3N_6O_{12}$: C, 55.44; H, 4.89; Br, 18.44; N, 6.47; O, 14.77 %.

Antimicrobial activity: The newly synthesized 1,4-dihydropyridine trimers (**1a-f**) compounds were well tested against eight set of microorganisms like as two Gram-positive bacteria, two Gram-negative bacteria and four fungal species were used in this present study. Disk diffusion method was used in this present work. All the materials were purchased from Aldrich and Merck chemical companies and Muller Hinton agar was used to culture bacterial strains.

Antibacterial activity: The 1,4-dihydropyridine compounds (**1a-f**) are subjected to *in vitro* activity test against different class as of bacteria. The main aim of this work was to identify how much amount of (MIC) minimum inhibitory concentration is required to fully inhibit the growth of culture on this disc. The synthesized compound dissolved in DMSO the 100 µg/mL concentration is used for test. The chlorophinical act as a control. After coating of the synthesized compounds, the disc was placed on ampidantate temperature 37 °C and after 24 h the inhibition zone was measured.

Antifungal screening: The newly prepared 1,4-dihydropyridine trimer derivatives (**1a-f**) are tested against some kinds of fungal species such as *Trichoderma* sp., *A. parasitica*, *Aspergillus niger* and *Chrysosporium* sp. The disc diffusion methodology is used to determine the antifungal activity ability newly prepared 1,4-dihydropyridine derivatives. The Sabouraud's dextrose used as a medium. In this present work, we used the clotrimazole as standard drug. The tested compounds concentration 100 µg/mL is prepared by using on DMSO solvent. After growth of culture the 1,4-dihydropyridine compounds (100 µg/mL) concentration is spot on this disc. The disc is placed at 37 °C temperature for 24 h. After 1 day the zone of inhibition (mm) was measured.

RESULTS AND DISCUSSION

We have followed the Hantzsch 1,4-dihydropyridine synthetic method for preparation of some novel 1,4-dihydropyridine derivatives. Melamine, ethylacetoacetate and various aryl aldehydes are used in this synthetic process. Initially the condensation reaction is carried out in normal condensation setup like as 250 mL round bottom flask with condenser. The melamine, ethylacetoacetate and aryl aldehyde are added appropriative ratio in ethanol solvent at 70 °C in presence of acetic acid catalyst for 15 h. The formation of products is very low because solubility factor of melamine. The melamine is not soluble in most of the solvents but fully soluble in DMSO. The DMSO is more hazarders compared to other solvents so avoid the DMSO solvent in this present work. In this present work we used microwave irradiation method to overcome these kinds of problem. The condensation reaction is carried out in microwave irradiation with optimized reaction condition. The hope of this method is to avoid polluted solvents, very short reaction time for 3-5 min and good yield. From IR spectra the aromatic region is observed at 3156-3059 cm^{-1}. The characteristic absorption peaks observed at 2979-2881 cm^{-1} corresponding to aliphatic region. The ester carbonyl group (-COOR-) appears at 1711 cm^{-1}. The melamine ring C=N appears at 1599 cm^{-1}. The ^{1}H NMR spectrum shows some important signals at δ 1.15 ppm (t, 18H, CH_3 of ethyl) this signal indicate presence of three methyl group in compound. The aromatic proton appears at δ 6.77 to 7.87 ppm (m, 15H). The δ 5.03 ppm (s, 3H) signal is confirms presence of three -CH- proton. The quadrate signal appears at δ 3.92 ppm due to three $-CH_2-$ protons (q, 12H, CH_2 of ethyl). The methyl group $-CH_3$ appears at δ 2.74 ppm (S, 18H, CH_3). The ^{13}C NMR spectrum shows ester carbonyl group (-COOR-) at δ 166 ppm. The aromatic carbon appears at δ 127-139 ppm. The methylene carbon appears at δ 61.11 ppm. The strong signal appears at δ 54 ppm is due to (C-3) carbon. The C-1 carbon appears at δ 150 ppm. The δ 102 ppm is corresponding to C-2 carbon. The melamine C=N (C 20, carbon) appears at 154 ppm.

Antibacterial activity: The newly synthesized 1,4-dihydropyridine derivatives were subjected to antibacterial activity against two Gram-positive bacteria and two Gram-negative bacteria. In this present work we are prepared four different concentrations 25, 50, 75, 100 µg/mL among these concentrations the 100 µg/mL show the best activity against both Gram-positive and Gram-negative bacteria. In this present work the chlorophinical as a control. The inhibition zone is measured (mm). Table-1 shows the antibacterial activities of both Gram-negative and Gram-positive bacteria. From the experimental data the compound **1d** show the best activity against *Shigella*. The compound **1e** and **1f** show the better activity against *Streptococcus* and *Staphylococcus aureus*, respectively.

***in vitro* antifungal screening:** The antifungal inhibition zone values (mm) are shown in Table-2. Compounds (**1a-f**) were tested against *Aspergillus niger*, compounds **1b** and **1d** show nil activity, compound **1e** show best activity compared to the standard drug molecule clotrimazole. Compound **1d** show less activity and compound **1e** show highest activity against *Trichoderma* Sp. The compounds **1a-f** were screened for *A. parasitica* compounds **1b** and **1d** had no activity compound **1e** delivered to best activity. Compounds **1a-f** was tested against *Chrysosporium* Sp. The compounds **1b** and **1d** show no activity, compound **1e** show less activity and compound **1f** show the best activity compared to the standard clotrimazole drug molecule. All newly prepared compounds (**1a-1f**) are tested against four different fungal species. From this activity result the compound **1e** exhibit best activity compared to the standard clotrimazole drug molecule.

TABLE-1
ANTIBACTERIAL ACTIVITY OF NEWLY SYNTHESIZED 1,4-DIHYDROPYRIDINE DERIVATIVES (**1a-f**)

Compounds	*E. coli*				*Shigella*				*Streptococcus*				*Staphylococcus aureus*			
Conc. (µg/mL)	25	50	75	100	25	50	75	100	25	50	75	100	25	50	75	100
1a	–	–	8	11	–	–	–	10	–	–	–	8	–	–	–	11
1b	–	–	–	10	–	–	–	10	–	–	8	11	–	–	–	8
1c	–	–	8	11	–	–	–	10	–	–	–	9	–	–	–	9
1d	–	–		10	–	–	8	11	–	–	9	11	–	–	8	10
1e	–	–	–	11	–	–	8	10	–	–	–	14	–	–	8	11
1f	–	–	8	11	–	–	–	9	–	–	–	11	–	–	–	13
Control	15				18				19				19			

TABLE-2
ANTIFUNGAL ACTIVITY OF THE NEWLY SYNTHESIZED 1,4-DIHYDROPYRIDINE DERIVATIVES (**1a-f**)

Compounds	*Trichoderma* Sp.				*A. niger*				*A. parasitica*				*Chrysosporium* Sp			
Conc. (µg/mL)	25	50	75	100	25	50	75	100	25	50	75	100	25	50	75	100
1a	–	–	7	11	–	–	8	9	–	–	–	7	–	–	8	10
1b	–	–	–	9	–	–	–	–	–	–	–	–	–	–	–	–
1c	–	–	7	9	–	–	–	8	–	–	–	9	–	–	8	10
1d	–	–		8	–	–	–	–	–	–	–	–	–	–	–	–
1e	–	–	10	12	–	–	11	14	–	–	8	12	–	–	7	10
1f	–	–	8	10	–	–	–	9	–	–	–	9	–	–	9	11
Control	26				23				26				24			

Conclusion

The new series of some novel 1,4-dihydropyridine trimer derivatives are synthesized by using microwave owen in acetic condition. All the synthesized 1,4-dihydropyridines trimers have given good yield with satisfactory elemental analysis. The newly synthesized 1,4-dihydropyridine derivatives were screened for antibacterial and antifungal activity. It is inferred from Tables 1 and 2 out of six synthesized compounds compounds **1a**-**1f**, compound **1d** show effective activity against both Gram-negative and Gram-positive bacteria that is, against *Shigella* bacteria and *Streptococcus* bacteria respectively. Compound **1e** show the best activity against Gram-negative *Streptococcus* bacteria and compound **1f** effective against Gram-negative *Staphylococcus aureus*. From this experimental antibacterial screening activity it is concluded that the newly prepared 1,4-dihydropyridine derivatives show on unique and better activity against both Gram-negative and Gram-positive bacteria. The antifungal screening data give clear information about the newly synthesized (**1a-f**) compounds, among these six compounds the compound **1e** show the best activity compared with standard drug molecule. This finding information is useful for further studies in this field.

ACKNOWLEDGEMENTS

The authors are thankful to the department of chemistry at Annamalai University for providing all research facilities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. D. Prajapati, N. Rajesh, S. Borthakur and Y. Dommaraju, *RSC Adv.*, **5**, 24327 (2015); https://doi.org/10.1039/C5RA00796H.
2. A. Domling and I. Ugi, *Angew. Chem. Int. Ed.*, **39**, 3168 (2000); https://doi.org/10.1002/1521-3773(20000915)39:18<3168::AID-ANIE3168>3.0.CO;2-U.
3. L. Weber, *J. Curr. Med. Chem.*, **9**, 2085 (2002); https://doi.org/10.2174/0929867023368719.
4. M. Hayashi, Y. Kawashita and N. Nakamichi, *Org. Lett.*, **4**, 3955 (2002); https://doi.org/10.1021/ol0268135.
5. A.K. Oyebamiji and B. Semire, *Bull. Pharm. Res.*, **6**, 105 (2016).
6. J.L. Reid, P.A. Meredith and F. Pasanisi, *J. Cardiovasc. Pharmacol.*, **7**, S18 (1985).
7. C.E. Sunkel, M. Fau de Casa-Juana, L. Santos, A.G. Garcia, C.R. Artalejo, M. Villarroya, M.A. Gonzalez-Morales, M.G. Lopez and J. Cillero, *J. Med. Chem.*, **35**, 2407 (1992); https://doi.org/10.1021/jm00091a008.
8. D. Vo, W.C. Matowe, M. Ramesh, M. Iqbal, M.W. Wolowyk, S.E. Howlett and E.E. Knaus, *J. Med. Chem.*, **38**, 2851 (1995); https://doi.org/10.1021/jm00015a007.
9. V. Klusa, *Drugs Future*, **20**, 135 (1995); https://doi.org/10.1358/dof.1995.020.02.284117.
10. R. Boer and V. Gekeler, *Drugs Future*, **20**, 499 (1995).
11. M.B. El-Ashmawy, M.A. El-Sherbeny and N.S. El-Gohary, *J. Med. Chem. Res.*, **22**, 2724 (2013); https://doi.org/10.1007/s00044-012-0272-y.
12. P.P. Mager, R.A. Coburn, A.J. Solo, D.J. Triggle and H. Rothe, *Drug Des. Discov.*, **8**, 273 (1992).
13. R. Mannhold, B. Jablonka, W. Voigt, K. Schönafinger and E. Schraven, *J. Med. Chem.*, **27**, 229 (1992); https://doi.org/10.1016/0223-5234(92)90006-M.
14. F. Mikhail Gordeev, D.V. Patel and E.M. Gordon, *J. Org. Chem.*, **61**, 924 (1996); https://doi.org/10.1021/jo951706s.
15. R. Mahinpour, L. Moradi, Z. Zahraei and N. Pahlevanzadeh, *J. Saudi Chem. Soc.*, **22**, 876 (2018); https://doi.org/10.1016/j.jscs.2017.11.001.
16. G.W. Zamponi, *Drug Dev. Res.*, **42**, 131 (1997); https://doi.org/10.1002/(SICI)1098-2299(199711/12)42:3/4<131::AID-DDR4>3.0.CO;2-R.
17. H.-A.S. Abbas, H.N. Hafez and A.-R.B.A. El-Gazzar, *Eur. Med. Chem.*, **46**, 21 (2011); https://doi.org/10.1016/j.ejmech.2010.09.071.
18. A. Krauze, S. Germane, O. Eberlin lnE š, I. Šturms, V. Klusa and G. Duburs, *Eur. Med. Chem.*, **34**, 301 (1999); https://doi.org/10.1016/S0223-5234(99)80081-6.

19. S. Bahekar and D. Shinde, *Acta Pharm.*, **52**, 281 (2002).
20. A.M. Vijesh, A.M. Isloor, S.K. Peethambar, K.N. Shivananda, T. Arulmoli and N.A. Isloor, *Eur. Med. Chem.*, **46**, 5591 (2011); https://doi.org/10.1016/j.ejmech.2011.09.026.
21. S.F. Flaim and R. Zelis, *J. Fed. Proc.*, **40**, 2877 (1981).
22. A. Shah, H. Gaveriya, N. Kawase, S.M. Saito, H. Sakagami, Y. Satoh, A. Solymosi and K. Walfard *J. Anticanc. Res.*, **20**, 373 (2000).
23. G. Gunics, S. Farkas, N. Motohashi, A. Shah, G. Harsukh, M. Kawase and J. Molnár, *Int. J. Antimicrob. Agents*, **20**, 227 (2002); https://doi.org/10.1016/S0924-8579(02)00159-0.
24. T. Godfraind and S.J. Salomone, *J. Cardiovasc. Pharmacol.*, **S1**, 30 (1997).
25. P.A. Van Zwieten, *Blood Press.*, **7**, 5 (1998); https://doi.org/10.1080/080370598438999.
26. W.G. Nayler, *J. Clin. Basic Cardiol.*, **2**, 155 (1999).
27. B. Loev and K.M. Snader, *J. Org. Chem.*, **30**, 1914 (1965); https://doi.org/10.1021/jo01017a048.
28. C. Pramanik, P. Patil, S. Kotharkar, N.K. Tripathy and M.K. Gurjar, *Tetrahedron Lett.*, **54**, 3043 (2013); https://doi.org/10.1016/j.tetlet.2013.03.090.
29. N. Koukabi, E. Kolvari, M.A. Zolfigol, A. Khazaei, B.S. Shaghasemi and B. Fasahati, *Adv. Synth. Catal*., **354**, 2001 (2012); https://doi.org/10.1002/adsc.201100352.
30. V. Sivamurugan, R.S. Kumar, M. Palanichamy and V. Murugesan, *Heterocycl. Chem.*, **42**, 969 (2005); https://doi.org/10.1002/jhet.5570420534.
31. M. Arslan, C. Faydali, M. Zengin, M. Kucukislamoglu and H. Demirhan, *Turk. J. Chem.*, **33**, 769 (2009); https://doi.org/10.3906/kim-0812-5.
32. R. Gupta, R. Gupta, S. Paul and A. Loupy, *Synthesis*, 2835 (2007); https://doi.org/10.1055/s-2007-983839.
33. A. Debache, A. Belfaitah, B. Carboni, R. Boulcina and S. Rhouati, *Synth. Lett.*, 509 (2008); https://doi.org/10.1055/s-2008-1032093.
34. D.S. Rekunge, C.K. Khatri and G.U. Chaturbhuj, *Tetrahedron Lett.*, **58**, 1240 (2017); https://doi.org/10.1016/j.tetlet.2017.02.038.
35. G.A. Olah and S.C. Narang, *Tetrahedron*, **38**, 2225 (1982); https://doi.org/10.1016/0040-4020(82)87002-6.
36. R.A. Mekheimer, A.A. Hameed and K.U. Sadek, *J. Green. Chem.*, **10**, 592 (2008); https://doi.org/10.1039/b715126h.
37. A. Shaabani, A.H. Rezayan, A. Rahmati and M. Sharifi, *Monatsh. Chem.*, **137**, 77 (2006); https://doi.org/10.1007/s00706-005-0405-9.
38. S.T. Patel, J.M. Percy and R.D. Wilkes, *J. Org. Chem.*, **61**, 166 (1996); https://doi.org/10.1021/jo951516h.
39. B. Loev, M.M. Goodman, K.M. Snader, R. Tedeschi and E. Macko, *J. Med. Chem.*, **17**, 956 (1974); https://doi.org/10.1021/jm00255a010.
40. M. Kidwai, S. Saxena, R. Mohan and R. Venkataramanan, *J. Chem. Soc., Perkin Trans. I*, 1845 (2002); https://doi.org/10.1039/B205539M.