

LETTER ARTICLE

Green and Efficient Synthesis of Flavones and Chromones Using Heteropolyacids as Catalyst in Glycerol

María Belén Colombo Migliorero¹, Valeria Palermo^{1*}, Edwin Alexis Alarcón Durango², Aída Luz Villa Holguín², Patricia Graciela Vázquez¹, Ángel Gabriel Sathicq¹ and Gustavo Pablo Romanelli^{1*}

¹Centro de Investigación y Desarrollo en Ciencias Aplicadas 'Dr. J.J. Ronco' (CINDECA-CONICET), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata (UNLP), La Plata, Argentina;

²Environmental Catalysis Research Group, Chemical Engineering Department, Universidad de Antioquia (UdeA), Medellín, Colombia

ARTICLE HISTORY

Received: July 21, 2017
Revised: April 17, 2018
Accepted: April 22, 2018

DOI:
10.2174/1570178615666180509150014

Abstract: Organic solvents are required to carry out most organic transformations, which cause environmental pollution because of their low volatility. Glycerol, a side product obtained from biodiesel production, has emerged as a friendly solvent due to its advantageous properties. In this paper, an efficient procedure for the synthesis of flavones and chromones, using heteropolyacids as recyclable catalyst and glycerol as the solvent, is presented. The use of heteropolyacids as catalysts allows for excellent yields, easy separation and recovery, low environmental impact, and low cost. Glycerol can also be readily recovered and used over again. In addition, the presented method provides other advantages such as the low formation of waste and the replacement of corrosive mineral acids.

Keywords: Flavones, Chromones, Glycerol, Heteropolyacids, Catalytic procedure, Green solvent.

1. INTRODUCTION

The design of suitable procedures for the synthesis of typical and new compounds is an area of huge interest since the early nineties when Green Chemistry emerged. These 'green' procedures seek to reduce contamination by the use of strategies that include processes with high atom economy, the utilization of recyclable catalysts, and alternative energy sources in order to reduce energy consumption, such as sonochemistry, microwave or light, avoiding the use of solvents and auxiliary substances [1].

The replacement of conventional solvents with more environmentally friendly alternatives is one of the main targets in Green Chemistry, especially in organic synthesis, where the use of solvents accounts for 80%-90% of mass utilization in a typical process, which makes it the main source of waste both in industries and laboratories [2-5].

Glycerol is usually produced as a by-product of triglyceride transesterification in the production of natural fatty acid derivatives, such as biodiesel. These acid derivatives are

employed in many areas from pharmaceuticals and food products to alternative fuels [6]. Therefore, as the production of glycerol rises, its price decreases. In addition, glycerol is a biodegradable, innocuous, recyclable and reusable liquid manufactured from renewable sources, and shows similar properties to an ionic liquid [2, 7]. Recently, Diaz-Álvarez *et al.* published a review article on the different applications of glycerol as a suitable solvent in organic reactions [8].

Several synthetic transformations have been conducted in glycerol in recent years, most of them with similar and even higher efficiency and selectivity than those performed in conventional organic solvents [9].

In addition to the use of new solvents in organic synthesis, catalysis represents an excellent alternative to increase the reaction selectivity and minimize secondary product formation. Heterogeneous solid acids have many advantages over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture. Among the heterogeneous catalysts, heteropolyacids (HPAs) and related compounds are a field of increasing importance worldwide. We reported the use of an HPA catalyst with a Keggin structure for different organic transformation reactions, for example, azlactones [10], quinoxalines [11], xanthenes [12], dihydropyrimidinones [13], hexahydropyrimidines [14], quinolines [15], and imidazoles [16].

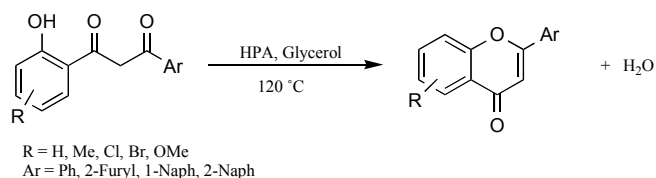
*Address correspondence to these authors at the Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J. Ronco" (CINDECA-CCT-CONICET), Universidad Nacional de La Plata, Calle 47 N° 257, B1900AJK La Plata, Argentina; Tel/Fax: +54-221-421-1353; E-mail: gpr@quimica.unlp.edu.ar; vpalermo@quimica.unlp.edu.ar

On the other hand, flavones (2-phenylchromones) and other arylchromones, such as 2-naphthylchromones and 2-furylchromones, are a group of organic compounds having the benzo- γ -pyrone skeleton, mostly containing OH as a substituent, which are members of the natural product family called flavonoids [17, 18]. Flavones are widely distributed in nature, especially in the plant kingdom, in many cases as glycosides. They are secondary metabolites found in stems, leaves, buds, bark, thorns, roots, rhizomes, flowers, pollen, fruits, seeds, and roots [19, 20].

Many flavones exhibit different biological properties, for example, anti-HIV [21], anti-allergenic [22], anxiolytic [23], gastroprotective [24], anticarcinogenic [25], antioxidant [26, 27], antibacterial [28, 29], antifungal [28], and antiviral [29] activity. Besides, the monoamine oxidase enzyme inhibition, which catalyzes the deamination of a range of monoamines producing H_2O_2 and the corresponding amines, has been reported [30]. Furthermore, flavones have a repelling property against some phytophagous insects (*Spodoptera litura*, *Spodoptera frugiperda* and *Coptotermes sp.* subterranean termite) [31-33].

Given the great importance of flavones and related compounds, several methods for their synthesis have been developed, including acylation of 4-hydroxycoumarins and cyclodehydration [17] cyclization of chalcones [34], Wittig reaction [35], and Kostanecki-Robinson strategy [36]. One of the most widely used procedures consists of the acylation of an *o*-hydroxyacetophenone with an aromatic acid halide obtaining an aryl ester, which, in the presence of one basic catalyst (the Baker-Venkataraman rearrangement), is transformed into a 1,3-diaryl-1,3-diketone, and finally gives a 2-arylchromone by cyclodehydration [35, 37]. Several catalytic processes have been described to perform this transformation, e.g., sulfuric acid [38], copper (II) chloride in ethanol and microwave radiation [39], P_2O_5 under grinding conditions [40], cationic exchange resins in isopropanol [41], Preysslner and Wells-Dawson heteropolyacids bulk and supported on silica [42,43], and $KHSO_4$ under solvent-free conditions [44].

In this letter, we report a simple, clean and environmentally friendly procedure for the preparation of flavones and chromones from 1-(2-hydroxyphenyl)-3-aryl-1,3-propanodione using $H_3PMo_{12}O_{40}$ as a recyclable catalyst in glycerol (Scheme 1).



Scheme (1). Synthesis of flavone and chromone derivatives in HPA/glycerol system.

2. RESULTS AND DISCUSSION

This work describes the preparation of substituted flavones and chromones in a reaction medium composed of a

green solvent (glycerol, which could be obtained from biomass) and a reusable catalyst (commercial PMo). The flavone and chromone synthesis involves the cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanodiones (Scheme 1).

Initially, a noncatalytic system using 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanodione (1 mmol) and glycerol (30 mmol) was tested. It was observed that under the experimental conditions (120°C, 30 min) only a 10% yield of flavone was detected. This indicates that, from a practical point of view, the reaction practically does not take place in the absence of a catalyst (Table 1, entry 1).

Then, two Keggin heteropolyacids (PMo and SiMo) were tested in the previous reaction, obtaining excellent results at 120°C in 30 min. The highest yield was attained using PMo catalyst (99%, Table 1, entry 2) and a lower yield was obtained with SiMo (90%, Table 1, entry 3), according to the decrease of their acidic strength [45], associated to the major susceptibility to reduction of SiMo to form the ‘heteropoly blue’, which result in a decrement of the acidity [46].

Table 1. Effect of catalyst on flavone yield.

Entry	Catalyst	Yield (%) ^a
1	None	10
2	PMo	99
3	SiMo	90

Reaction conditions: 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione, 1 mmol; catalyst, 5% mmol; glycerol, 30 mmol; reaction time, 30 min; temperature, 120°C; stirring.
^aDetermined by GC.

The influence of temperature on 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanodione conversion was analyzed using 5% mmol of PMo, and the results are listed in Table 2. In order to obtain the optimal temperature, the reaction was studied at six temperatures (20, 60, 80, 100, 120, and 140°C, Table 2). The experimental reaction conditions were: 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanodione (1 mmol), PMo 5% mmol, stirred for 30 min. No reaction was observed at 20 and 60°C (Table 2, entries 1 and 2), and a low flavone yield (5%) at 80°C (Table 2, entry 3). A temperature increase led to a higher flavone yield. For example, for a reaction time of 30 min at 100°C, the flavone yield was 75% (Table 2, entry 4) and at 120°C, at the same time, it was 99% (Table 2, entry 5). Finally, at a higher temperature (140°C) the reaction yield was considerably lower (90%, Table 2, entry 6), due to the several unidentified side products that were detected by TLC. For this reason, 120°C was used as the ideal temperature to continue the analysis of other reaction variables.

Besides, flavone synthesis was studied as a function of reaction time at 120°C, and the results are shown in Table 3. It can be seen that the flavone yield increased with the reaction time up to 30 min, and then it remained at a constant level (99% at 30 min and 99% at 45 min, Table 3, entries 3 and 4).

Table 2. Effect of temperature on flavone yield.

Entry	Temperature (°C)	Yield (%) ^a
1	20	-
2	60	-
3	80	5
4	100	75
5	120	99
6	140	90

Reaction conditions: 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione, 1 mmol; PMo, 5% mmol; glycerol, 30 mmol; reaction time, 30 min; stirring. ^a Determined by GC.

Table 4 displays the effect of the amount of PMo catalyst on the flavone yield. The experimental reaction conditions were: 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione, 1 mmol; glycerol, 30 mmol; 120°C; 30 min, and different amounts of PMo (1, 3, 5, 7 and 10% mmol). It can be observed that the yields improved from 79% to 99% when the amount of PMo increased from 3% to 5% mmol (Table 4, entries 2 and 3). No relevant changes in reaction yields were observed with further increase of the amount of PMo (7% mmol, 98%, Table 4, entry 4). Thus, 5% mmol of PMo is a suitable amount for this reaction.

Table 3. Effect of reaction time on flavone yield.

Entry	Reaction time	Yield (%) ^a
1	10	43
2	20	82
3	30	99
4	45	99
5	60	97

Reaction conditions: 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione, 1 mmol; PMo, 5% mmol; glycerol, 30 mmol; reaction temperature, 120°C; stirring. ^a Determined by GC.

Table 4. Effect of catalyst amount (PMo) on flavone yield.

Entry	Catalyst amount (% mmol)	Yield (%) ^a
1	1	23
2	3	79
3	5	99
4	7	98
5	10	99

Reaction conditions: 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione, 1 mmol; glycerol 30 mmol; reaction temperature, 120°C; reaction time, 30 min; stirring. ^a Determined by GC.

The reuse of the catalyst was investigated in consecutive cyclodehydration reactions of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione. At the end of each run, the reaction product was extracted with ethyl acetate, and the glycerol/PMo system was used in the next run. The results, which are presented in Table 5, showed that the glycerol/catalyst system was reused in four sequential runs, and no appreciable loss of its catalytic activity was observed (99%, 97%, 97%, and 96% of flavone yield, respectively).

Table 5. Flavone yield in glycerol/PMo system reuse.

Entry	Catalytic Cycle	Yield (%) ^a
1	1	99
2	2	97
3	3	97
4	4	96

Reaction conditions: 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione, 1 mmol; PMo, 5% mmol; glycerol, 30 mmol; reaction temperature, 120°C; reaction time, 30 min; stirring. ^a Determined by GC.

Taking into account the optimized conditions: substituted 1-(2-hydroxyphenyl)-3-aryl-1,3-propanedione (1 mmol), glycerol (30 mmol), PMo (5% mmol) at 120°C, and 20-30 min, twelve flavones and chromones were prepared with excellent yields (82%-98%, Tables 6 and 7). The desired products were obtained in all the cases with high selectivity, almost free of secondary products. No relevant stereoelectronic effects on the yields due to the substituent were observed.

Finally, in order to quantify how much 'greener' the methodology is, the atom economy (AE), environmental factor (E factor), and process mass intensity (PMI) were calculated for each reaction product (see Supplementary Material) [47]. These parameters, listed in Tables 6 and 7, show that the reactions are theoretically green, because of the high AE value (> 92%), which is experimentally confirmed by the low E factor and PMI values (< 19, the typical values in fine chemistry being between 5 and 50).

In addition, the green parameters, namely, reaction yield (RY), the reciprocal of stoichiometric factor (1/SF), atom economy (AE), reaction mass efficiency (RME), and material recovery parameter (MRP), are represented in a pentagon, in order to detect the most sensitive points for a suitable reaction [48]. Each axis varies between zero and one, representing the greenest process when all parameters are equal to one, which results in a regular pentagon (see Supplementary Material). Figs. (1 and 2) show the radial pentagon for the synthesis of flavone and 2-(2-furyl)chromone, respectively. It is observed that the metrics values are close to the vertices of the radial pentagon in both syntheses, indicating that they are greener processes. MRP is equal to 1 because the catalyst, reaction and purification solvents were quantitatively recovered and water is the only by-product.

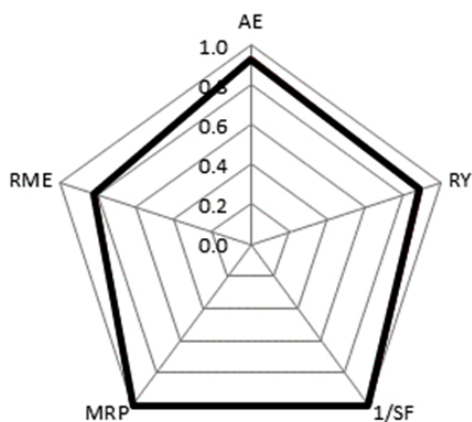


Fig. (1). Radial pentagon for the synthesis of flavone.

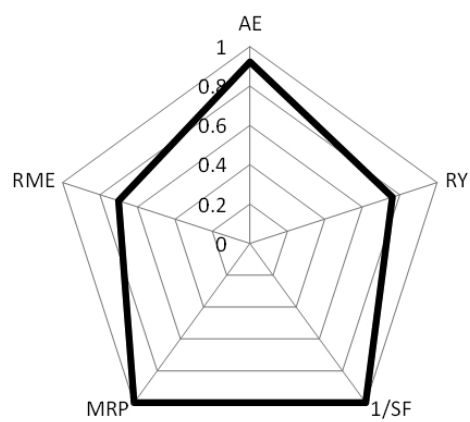
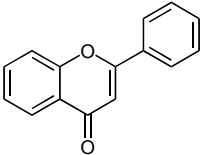
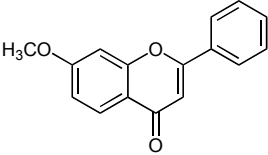
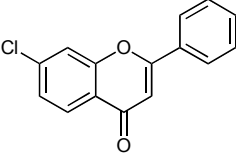
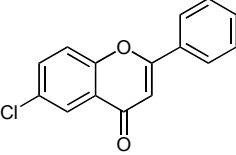
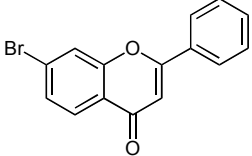
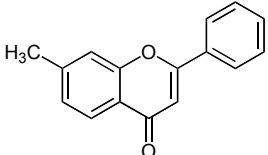


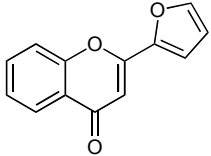
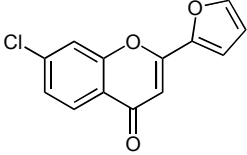
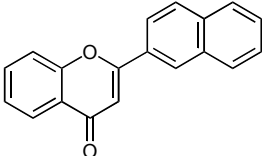
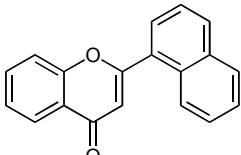
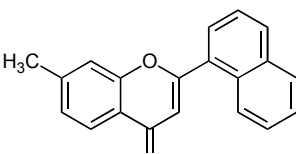
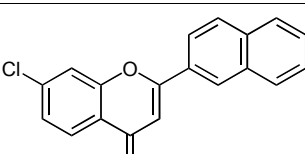
Fig. (2). Radial pentagon for the synthesis of 2-(2-furyl)chromone.

Table 6. Synthesis of substituted flavones.

Entry	Product	Time (min)	Yield (%) ^a	AE (%)	E Factor	PMI
1		20	89	92.5	14.28	15.28
2		20	85	93.3	13.24	14.24
3		30	82	93.5	13.50	14.50
4		30	83	93.5	13.32	14.32
5		30	81	94.4	11.71	12.71
6		20	93	92.9	12.82	13.82

Reaction conditions: 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones, 1 mmol; PMo, 5% mmol; solvent: glycerol, 30 mmol; temperature 120°C; stirring. ^aIsolated pure product.

Table 7. Synthesis of substituted chromones.

Entry	Product	Time (min)	Yield (%) ^a	AE (%)	E Factor	PMI
1		20	76	92.2	17.68	18.68
2		20	78	93.2	14.81	15.81
3		25	88	93.8	11.83	12.83
4		25	89	93.8	11.68	12.68
5		25	82	94.1	12.15	13.15
6		25	84	94.5	11.04	12.04

Reaction conditions: 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones, 1 mmol; PMo, 5% mmol; solvent: glycerol, 30 mmol; reaction time, 20-30 min; temperature, 120°C; stirring.
^aIsolated and pure product.

3. EXPERIMENTAL SECTION

3.1. General Remarks

Chemicals were purchased from Aldrich, Fluka and Merck companies and were used after purification by standard procedures (distillation and recrystallization), to prepare the starting 1,3-diketones. H₃PMo₁₂O₄₀ (PMo) and H₄SiMo₁₂O₄₀ (SiMo) catalysts (Fluka) were dried overnight prior to their use. Glycerol (>99%, Sigma-Aldrich) was used without further purification.

The progress of reactions was monitored by TLC, using Merck silica gel GF₂₅₄, 0.25 mm thickness. Ultraviolet light, iodine vapor, or acidic vanillin were used for TLC visualization. Column chromatography was performed using Merck silica gel (230-400 mesh) following the standard methods.

All the yields were obtained by gas chromatography using Shimadzu 2014 equipment. The concentrations were calculated with an internal standard method. The products were identified by comparison of physical data (mp, TLC and NMR) with those reported or with authentic samples prepared by conventional methods using sulfuric acid as a catalyst [37]. The melting points of the compounds were determined in sealed capillary tubes and are uncorrected. ¹H NMR and ¹³C NMR spectra were obtained on a Bruker DPX 400 spectrometer, in CDCl₃ or DMSO-d₆ solutions (data are reported in Supplementary Material).

Starting 1,3-diketones were prepared following a method described elsewhere: commercial *o*-hydroxyacetophenones were transformed into *o*-benzoyloxyacetophenone, with the subsequent application of Baker-Venkataraman rearrange-

ment to 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanediones, using conventional basic catalysis in pyridine [37].

3.2. Representative Procedure for the Synthesis of Flavone Using PMo as a Catalyst in Glycerol

In a 10 mL glass vial equipped with a small magnetic stirring bar, a mixture of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione (1 mmol), glycerol (30 mmol) and PMo (5% mmol) was stirred at 120°C for 30 min. When the reaction time was over, 3 mL ethyl acetate was added in portions (3 x 1 mL) to extract the reaction product. The extracts were combined, and the organic solution was dried (anhydrous Na₂SO₄) and concentrated in vacuum. The solid products were recrystallized from methanol, ethanol or hexane.

3.3. Catalyst Reuse

After extraction of the product with ethyl acetate, the catalyst remains dissolved in glycerol. Thus, consecutive assays can be performed by adding the substrate. Catalyst stability tests were carried out running four consecutive experiments, under the same reaction conditions.

CONCLUSION

A green, versatile and simple method for the synthesis of flavone and chromone derivatives was developed by cyclodehydration of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanodiones, using PMo as a catalyst, in glycerol as green media, at 120°C.

The use of this system afforded excellent yields, thanks to the catalytic capacity of PMo. The innovation of this methodology is the use of glycerol as a solvent that, besides being available from biomass, allows the use of relatively high temperature (120°C, with the consequent shorter reaction times). The high solubility of PMo in glycerol enables the easy separation of the products from the reaction medium by simple extraction with an organic solvent, such as ethyl acetate. This permits the recovery of the catalyst/solvent system for further use in a new catalytic cycle.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Colombian authors are thankful to Colciencias (project 404-2009) and UdeA (CENIVAM RC 432). Argentinian authors acknowledge ANPCyT (PICT 0409), CONICET (PIP 003), ERANET-1, and UNLP for financial support. VP, AGS, PGV, and GPR are members of CONICET.

SUPPLEMENTARY MATERIAL

Supplementary Material contains melting points, ¹H NMR and ¹³C NMR spectra of synthesized flavone and chromone, and the definitions of green parameters.

REFERENCES

- Gawande, M.B.; Bonifácio, V.D.B.; Luque, R.; Branco, P.S.; Varma, R.S. *ChemSusChem*, **2014**, 7(1), 24-44.
- Díaz-Álvarez, A.E.; Cadierno, V. *Appl. Sci.*, **2013**, 3(1), 55-69.
- Anastas, P.T.; Warner, J.C. *Green Chemistry: Theory and Practice*, Oxford University Press: New York, **2000**.
- Nelson, W.M. *Green Solvents for Chemistry: Perspectives and Practice*, Oxford University Press: New York, **2003**.
- Constable, D.J.C.; Jimenez-Gonzalez, C.; Henderson, R.K. *Org. Process Res. Dev.*, **2007**, 11(1), 133-137.
- Othman, M.F.; Adam, A.; Najafi, G.; Mamat, R. *Renew. Sust. Energ. Rev.* **2017**, 80, 694-709.
- Mohd Zaid, H. F.; Chong, F. K.; Abdul Mutalib, M. I. *Fuel*, **2017**, 192, 10-17.
- Díaz-Álvarez, A.E.; Francos, J.; Lastra-Barreira, B.; Crochet, P.; Cadierno, V. *Chem. Commun.*, **2011**, 47(22), 6208-6227.
- Díaz-Álvarez, A.E.; Francos, J.; Croche, P.; Cadierno, V. *Curr. Green Chem.*, **2014**, 1(1), 51-65.
- Romanelli, G.; Autino, J.C.; Vázquez, P.; Pizzio, L.; Blanco, M.; Cáceres, C. *Appl. Catal. A Gen.*, **2009**, 352(1-2), 208-213.
- Ruiz, D.M.; Autino, J.C.; Quaranta, N.; Vázquez, P.G.; Romanelli, G.P. *Sci. World J.*, **2012**, 2012, 1-8.
- Rivera, T.S.; Blanco, M.N.; Pizzio, L.R.; Romanelli, G.P. *Green Chem. Lett. Rev.*, **2012**, 5(3), 433-437.
- D'Alessandro, O.; Sathicq, A.G.; Palermo, V.; Sanchez, L.M.; Thomas, H.; Vázquez, P.; Constantieux, T.; Romanelli, G. *Curr. Org. Chem.*, **2012**, 16(23), 2763-2769.
- Palermo, V.; Sathicq, Á.; Constantieux, T.; Rodríguez, J.; Vázquez, P.; Romanelli, G. *Catal. Lett.*, **2015**, 145(4), 1022-1032.
- Bennardi, D.O.; Blanco, M.N.; Pizzio, L.R.; Autino, J.C.; Romanelli, G.P. *Curr. Catal.*, **2015**, 4(1), 65-72.
- Gorsd, M.; Sathicq, G.; Romanelli, G.; Pizzio, L.; Blanco, M. *J. Mol. Catal. A Chem.*, **2016**, 420, 294-302.
- Barton, D.; Ollis, W.D.; Sammes, P.G. In: *Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds*; Barton, D.; Ollis, W.D.; Sammes P.G. Ed.; Pergamon Press: Oxford, England, **1979**; Vol. 4, pp. 659-692.
- Thakar, K.; Gill, C. *J. Indian Chem. Soc.*, **1983**, 60, 668-670.
- Di Carlo, G.; Mascolo, N.; Izzo, A.A.; Capasso, F. *Life Sci.*, **1999**, 65(4), 337-353.
- Martens, S.; Mithöfer, A. *Phytochemistry*, **2005**, 66(20), 2399-2407.
- Wu, J.H.; Wang, X.H.; Yi, Y.H.; Lee, K.H. *Bioorg. Med. Chem. Lett.*, **2003**, 13(10), 1813-1815.
- Yano, S.; Tachibana, H.; Yamada, K. *J. Agric. Food Chem.*, **2005**, 53(5), 1812-1817.
- Marder, M.; Zinczuk, J.; Colombo, M.I.; Wasowski, C.; Viola, H.; Wolfman, C.; Medina, J.H.; Rúveda, E.A.; Paladini, A.C. *Bioorg. Med. Chem. Lett.*, **1997**, 7(15), 2003-2008.
- Ares, J.J.; Outt, P.E.; Randall, J.L.; Murray, P.D.; Weisshaar, P.S.; O'Brien, L.M.; Ems, B.L.; Kakodkar, S.V.; Kelm, G.R.; Kershaw, W.C.; Werchowski, K.M.; Parkinson, A. *J. Med. Chem.*, **1995**, 38(25), 4937-4943.
- Kosmider, B.; Osiecka, R. *Drug Dev. Res.*, **2004**, 63(4), 200-211.
- Costantino, L.; Rastelli, G.; Gamberini, M.C.; Vinson, J.A.; Bose, P.; Iannone, A.; Staffieri, M.; Antolini, L.; Del Corso, A.; Mura U.; Albasini, A. *J. Med. Chem.*, **1999**, 42(11), 1881-1893.
- Han, R.M.; Zhang, J.P.; Skibsted, L.H. *Molecules*, **2012**, 17(2), 2140-2160.
- Harborne, J.B.; Williams, C.A. *Phytochemistry*, **2000**, 55(6), 481-504.
- Sánchez, I.; Gómez-Garibay, F.; Taboada, J.; Ruiz, B.H. *Phytother. Res.*, **2000**, 14(2), 89-92.
- Jia, W. Z.; Cheng, F.; Zhang, Y.J.; Ge, J.Y.; Yao, S.Q.; Zhu, Q. *Chem. Biol. Drug. Des.*, **2017**, 89(1), 141-151.
- Ohmura, W.; Doi, S.; Aoyama, M.; Ohara, S. *J. Wood Sci.*, **2000**, 46, 149-153.
- Havsteen, B.H. *Pharmacol. Ther.*, **2002**, 96(2-3), 67-202.
- Romanelli, G.P.; Virla, E.G.; Duchowicz, P.R.; Gaddi, A.L.; Ruiz, D.M.; Bennardi, D.O.; Ortiz, E.D.V.; Autino, J.C. *J. Agric. Food Chem.*, **2010**, 58(10), 6290-6295.
- Staunton, J. In: *Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds*; Barton, D.; Ollis, W.D.; Sammes P.G. Ed.; Pergamon Press: Oxford, England, **1979**; Vol. 4, pp. 687-688.

- [35] Verma, A.K.; Pratap, R. *Tetrahedron*, **2012**, 68(41), 8523-8538.
- [36] Staunton, J. In: *Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds*; Barton, D.; Ollis, W.D.; Sammes P.G. Ed.; Pergamon Press: Oxford, England, **1979**; Vol. 4, pp. 678-679.
- [37] Furniss, B.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. *Vogel's Textbook of Practical Organic Chemistry*; Longman: New York, **1989**; 5th Ed., pp. 1193-1194.
- [38] Banerji, A.; Goomer, N.C. *Synthesis*, **1980**, 1980 874-875.
- [39] Kabalka, G.W.; Mereddy, A.R. *Tetrahedron Lett.*, **2005**, 46(37), 6315-6317.
- [40] Sharma, D.; Makrandi, J.K. *Green Chem. Lett. Rev.*, **2009**, 2(3), 157-159.
- [41] Hoshino, Y.; Takeno, N. *Bull. Chem. Soc. Jpn.*, **1987**, 60(5), 1919-1920.
- [42] Bennardi, D.O.; Romanelli, G.P.; Sathicq, A.G.; Autino, J.C.; Baronetti, G.T.; Thomas, H.J. *Appl. Catal. A Gen.*, **2011**, 404(1-2), 68-73.
- [43] Bennardi, D.O.; Romanelli, G.P.; Jios, J.J.; Autino, J.C.; Baronetti, G.T.; Thomas, H.J. *Arkivoc*, **2008**, 2008(11), 123-130.
- [44] Pérez, M.; Ruiz, D.; Autino, J.; Sathicq, A.; Romanelli, G. *C. R. Chimie*, **2016**, 19(5), 551-555.
- [45] Bennardi, D.; Romanelli, G.; Autino, J.; Pizzio, L.; Vázquez, P.; Cáceres, C.; Blanco, M. *Reac. Kinet. Mech. Cat.* **2010**, 100(1), 165-174.
- [46] Török, B.; Bucsi, I.; Beregszászi, T.; Kapocsi, I.; Molnár, Á. *J. Mol. Catal. A Chem.*, **1996**, 107, 305-311.
- [47] Sheldon, R.A. *Chem. Soc. Rev.*, **2012**, 41, 1437-1451.
- [48] Andraos J The algebra of organic synthesis: green metrics, design strategy, route selection, and optimization. CRC Press, Taylor & Francis Group: Boca Raton, **2012**.