Heterocyclic Letters
Vol. 12| No.4|855-869|Aug-Oct|2022
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

REVIEW: CHALCONES AS NATURAL PRODUCTS AND THEIR DERIVATIVES IN BIOLOGICAL ACTIVITIES

F.M.Zahou[a], Ruba A. Alolayan[b] , Nadia A.A.Elkanzi[b] *

[a]Biology Department, college of Science, Jouf University, sakaka, 2014, Saudi Arabia
[b]Chemistry Department, college of Science, Jouf University, sakaka, 2014, Saudi Arabia
Corresponding author (N.A.A.Elkanzi) & E-mail: nahasan@ju.edu.sa&kanzi20@yahoo.com

Abstract
Because of its relatively easy synthesis, chalcone skeleton has been as a point of interest for organic and medicinal chemists from research groups worldwide. Chalcone scaffold constitutes the core of some interesting biologically active natural products. Chalcone derivatives are among feasible potent active agents, such as anticancer, antibacterial, antifungal, antileishmanial, antimalarial, and antiviral. Due to the knowledge of heterocyclic chemistry, recently chalcones bearing heterocyclic moieties have been synthesized and biologically investigated for specific target of diseases.

Keywords: natural products, chalcone derivatives, chalcone synthesis, biological activities, antimalarial agents, antibacterial agents.

Introduction

Chalcones are the aromatic ketones belonging to 1, 3-diaryl-2-propen-1-ones. Chalcones belong to flavinoids. Chemically, they consist of open chain flavinoids in which two aromatic rings are joined by a three carbon unsaturated carbonyl system [I]. chalcones and their derivatives has significant biological activity [II]. Among these wide variety of heterocyclic that have been explored for developing pharmaceutical important molecules pyrrole, pyrimidine[III], pyridine[IV], indole[V], flavones[VI] and pyrimidinethiones [VII] have important role in medicinal chemistry. The presence of reactive unsaturated ketone in chalcone is responsible for antibacterial [VIII-X] and antifungal activities.

1. Synthesis of Chalcone Derivatives and Their Biological Activities

Most of the chalcone moieties have evoked a great deal of interest due to their biological properties and characteristic conjugated molecular architecture. Chalcones have been considered derivatives of the 1, 3-diaryl-2-propene-1-one parent compound composed of two phenolic rings, referred to as the A and B rings. Many of them possess important pharmacological properties, such as analgesic [XI], arthritis [XII], anti-inflammatory [XIII], anti-pyretic [XIV], anti-bacterial [XV], anti-viral [XVI, XVII] and anti-cancer [XVIII, XIX] effects. They were also potentially useful for many industrial products and phytochemical

applications, including food sciences. Nowadays, a number of comparative pharmacological investigations of the chalcones have showed good antioxidant activity with low side effects [XX– XXIII] (Figure 1). Especially, curcumin and its related enones, such as yakuchinones A and B, inhibited the activation of the prosurvival transcription factor nuclear factor-k_ (NF-k_) and up-regulation of cyclooxygenase-2 (COX-2). The chemical synthesis, quantitative structural modification, and a wide variety of biological activities of chalcones were reported in many studies [XXIV–XXVI].

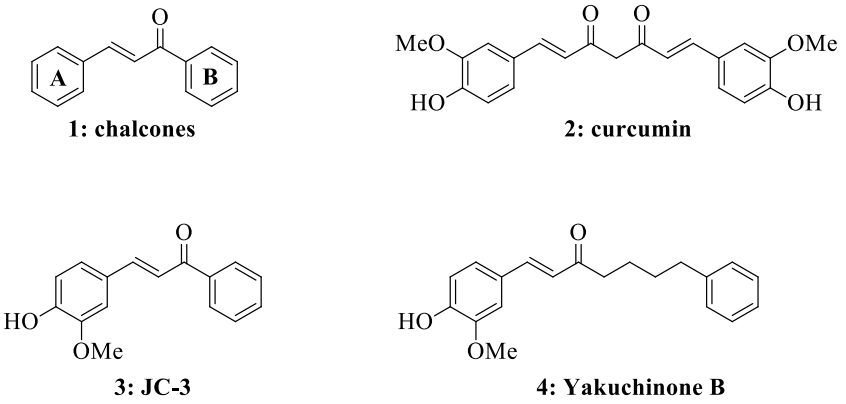
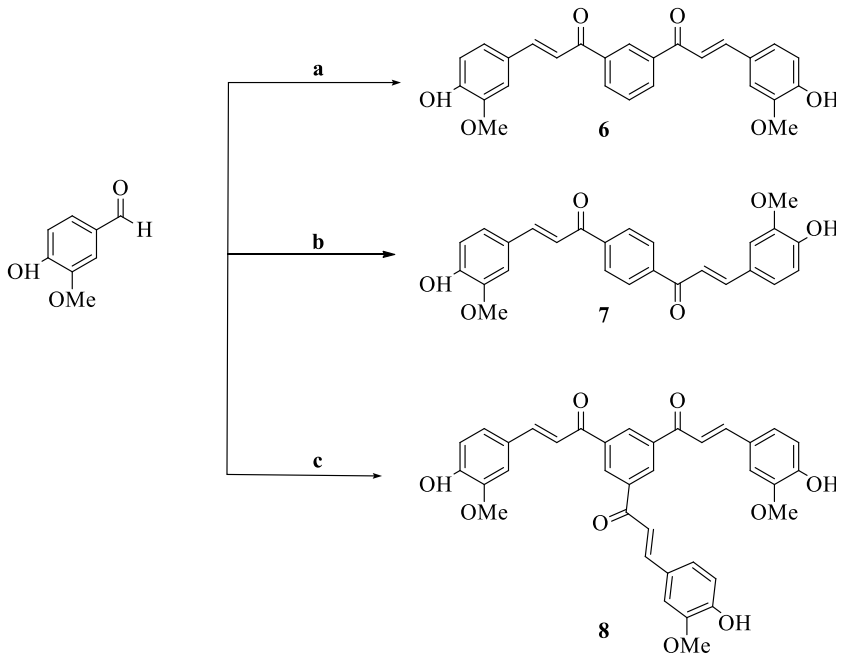


Figure 1. Structures of chalcone 1, curcumin 2, JC-3 3, and yakuchinone B 4.

Naturally occurring chalcones derived from general foods are phloretin and its glucoside phloridzin chalconaringenin, and arbutin. Most of the studies to date, regarding the synthetic approaches of chalcone derivatives [XXVII–XXXI], were reported by the organic and medicinal chemists through the formation of the 1, 4-enones using acid- or base-catalysed condensation reactions of aldehyde and aryl methyl ketones in alcoholic solvents with variable yields.

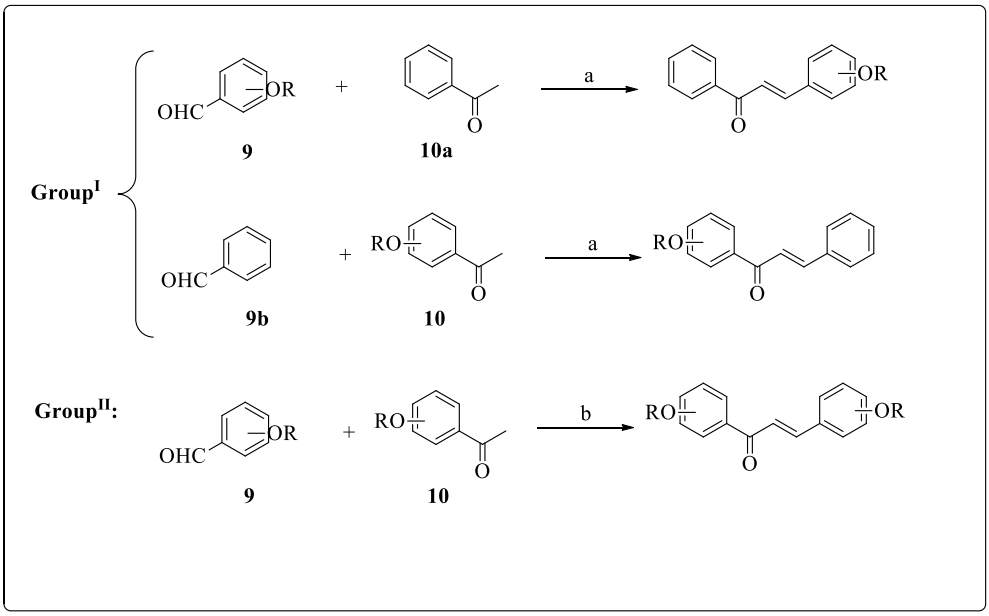
An interesting biological report of chalcone derivatives described the potential antioxidant activities of conjugated phenolic enones by the Vander Jagt group [XXXII]. The OH group described the neuroprotective effects of benzylideneacetophenone derivatives on excitotoxicity and inflammation via the phosphorylated janus tyrosine kinase 2/phosphorylated signal transducer and activator of transcription 3 and mitogen-activated protein K pathways, and compound (**6)**was more potent than compound (**3)** in the aspect of proteasome inhibition, which induced apoptosis significantly in the prostate cancer cells [XXXIII, XXXIV]. The Ryu group demonstrated that the optimal length of linker between aryl groups played an important role for the biological activity, and the Di Pietro group showed that potent bis-chalcone inhibitors were identified, the efficiency depending on both position of the central ketone groups and the number and positions of lateral methoxy substituents in breast cancer resistance protein inhibition [XXXV, XXXVI].



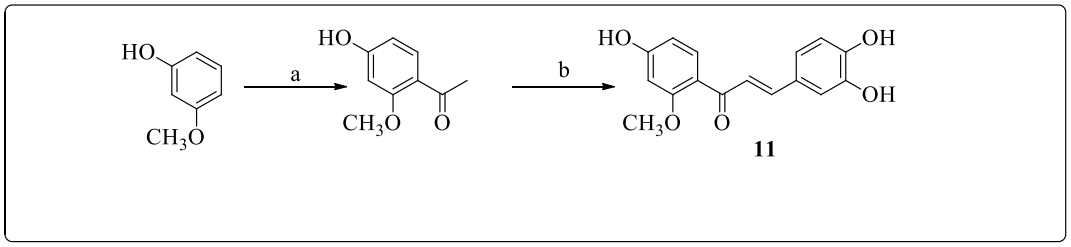
Scheme 1: Reagents and conditions: (a) 1,3-diacetylbenzene, c-H_2SO_4, EtOH, reflux 3 h; (b) 1,4-diacetylbenzene, c-H_2SO_4, EtOH, reflux 3 h; and (c) 1,3,5-triacetylbenzene, c-H_2SO_4, EtOH, reflux 3 h.

Chalcone derivatives as potential non-purine xanthine oxidase inhibitors

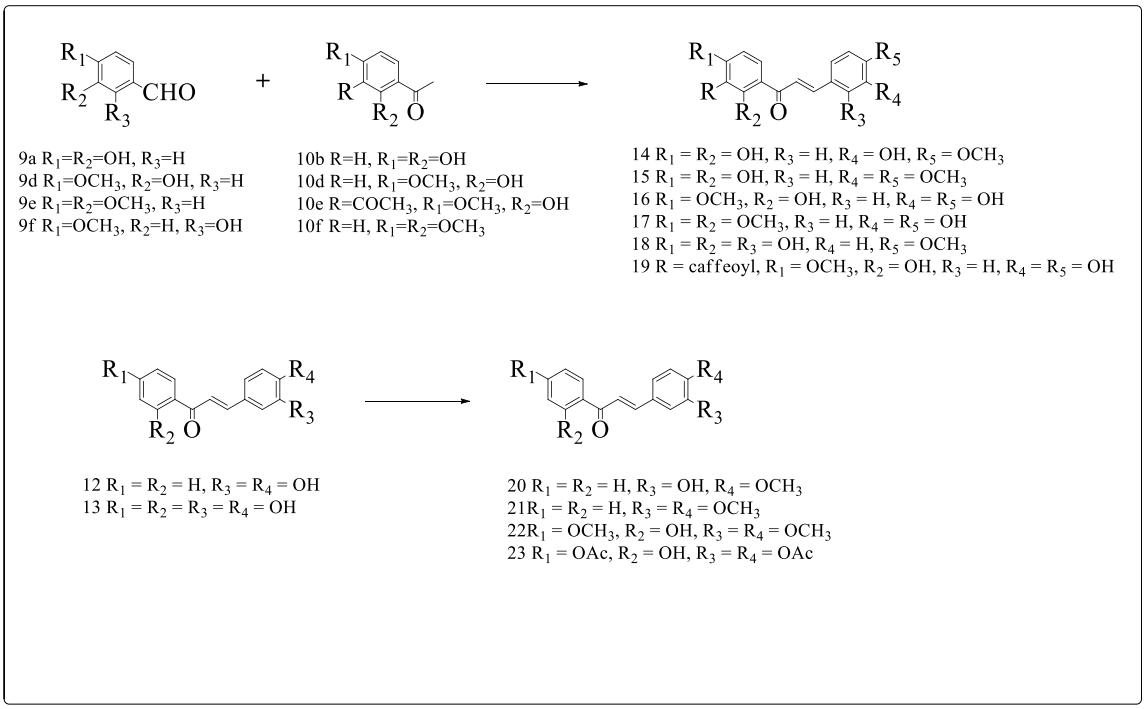
Chalcones are within a class of chemical compounds that widely exist in a variety of medicinal plants. Claisen– Schmidt condensation, a base catalyzed condensation, was found to be most convenient to synthesize chalcones. Their flexible structure allows them to possess a large number of biological activities including antitumor, antifungal, antiprotozoal, antimitotic, and antiviral [XXXVII]. Some chalcone derivatives exhibited potent XO inhibitory activity [XXXVIII]. Our preliminary screening to search for XO inhibitory activity of Vietnamese medicinal plants revealed that the methanolic extract of *Caesalpinia sappan's* heartwood exhibited significant XO inhibitory activity with an IC50 value of 14.2 μg/mL [XXXIX]. The bioactivity- guided fractionation of MeOH extract of *C. sappan*'s heartwood was carried out. Sappanchalcone (**11**) was isolated from EtOAc-soluble fraction (IC50, 12.8 μg/mL); this compound displayed the most potent activity with an IC50 value of 3.9 μM, comparable to that of allopurinol (IC50, 2.5 μM) [XXXIX]. To study the possibility of using (**11)** as gout treatment required a large amount of this compound but the amount of (**11)** in *C. sappan* is very low. The synthesis of (**11)** was carried out by Heck coupling reaction followed by demethylation [XL]. Therefore, objectives of this research are design and synthesis of (**11)** and other chalcone derivatives by Claisen– Schmidt condensation and then evaluate their XO inhibitory activity.



Scheme 2: Synthesis of chalcones in group I and group II. Reagents and conditions: a KOHaq, MeOH, ultrasound-assisted; b KOHaq, ultrasound assisted



Scheme 3: Synthesis of sappanchalcone (**11**). Reagent and conditions: a CH_3COOH, polyphosphoric acid, 60 °C, 30 min; b) 2',4'- dihydroxy acetophenone, KOH 12 M, ultrasound-assisted, 80 °C, 8
min.



Scheme 4: Synthesis of chalcone derivatives (14–23).

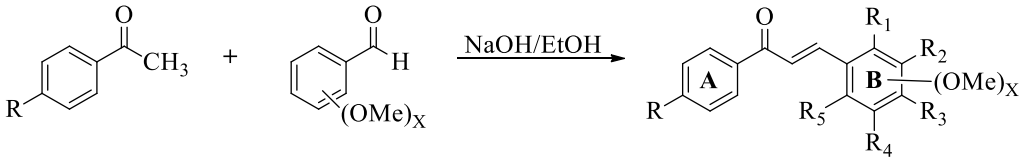
Chalcone Derivatives as Antimalarial Agents

Chalcones are natural products that can be obtained synthetically using a relatively simple synthesis procedure. The general method applied to synthesize chalcones is the Claisen-Schmidt reaction, while a modern alternative to synthesize chalcones uses the palladium-catalyst cross coupling reactions of styryltrifluoroborates with benzoyl chlorides [XLI]. Chalcone derivatives are well known for their broad spectrum of pharmacological activities, inclusing radical scavenger [XLII], antihepatotoxic [XLIII], anticancer [XLIV], and antimalarial properties [XLV]. Alkoxylated chalcone derivatives exhibited higherantimalarial activity compared to hydroxylated chalcones [XLVI].

The synthesis and bioactivity of the prepared compounds were already reported. The interaction of compounds (**24**–**26)** with bovine serum albumin (BSA)—a protein mainly responsible for the transportation of a number compounds in a living system—has been studied, and it was found that compound (**24)** was the most reactive [XLVII]. Furthermore, compound (**26)** was used as intermediate in the synthesis of phthalimide derivatives as analgesic and anti-inflammatory agents [XLVIII]. Continuous-flow hydration-condensation reactions between phenylacetylene and benzaldehyde derivatives using Amberlyst (**38)** as heterogeneous catalyst was applied for the synthesis of compounds (**31)**, (**33)**, and (**35)** in excellent yield [XLIX]. Compound (**33)** exhibited good anticancer activity toward the A549, PC3, MCF-77, HT-29, and WRL68 cancer cell lines [l], while compound (**35)** showed potential anticancer, anti-inflammatory, and antioxidant activity [LI]. Based on the background, herein we report the synthesis of methoxychalcone derivatives designed to inhibit the *Pf*Fd-*Pf*FNR interaction and analyze the interaction through docking experiments.

the chalcones were prepared by the reaction of equimolar amounts of acetophenone and benzaldehyde derivatives in ethanol using a 40% NaOH solution as catalyst. By applying these reaction conditions, good to excellent yields were obtained (**Table 1**) [LII].

Preparation of chalcones derivatives.



24-40

Scheme 5

Compound	R	R_1	R_2	R_3	R_4	R_5
24	NH_2	OCH_3	H	H	H	H
25	NH_2	H	OCH_3	H	H	H
26	NH_2	H	H	OCH_3	H	H
27	NH_2	OCH_3	OCH_3	H	H	H
28	NH_2	OCH_3	H	OCH_3	H	H
29	NH_2	OCH_3	H	H	OCH_3	H
30	NH_2	H	H	H	H	H
31	H	OCH_3	H	H	H	H
32	H	H	H	OCH_3	H	H
33	H	H	H	OCH_3	H	H
34	H	OCH_3	OCH_3	H	H	H
35	H	OCH_3	H	OCH_3	H	H
36	H	OCH_3	H	H	OCH_3	H
37	Br	H	H	OCH_3	H	H
38	Br	OCH_3	H	OCH_3	H	H
39	Br	OCH_3	H	H	OCH_3	H
40	H	H	H	H	H	H

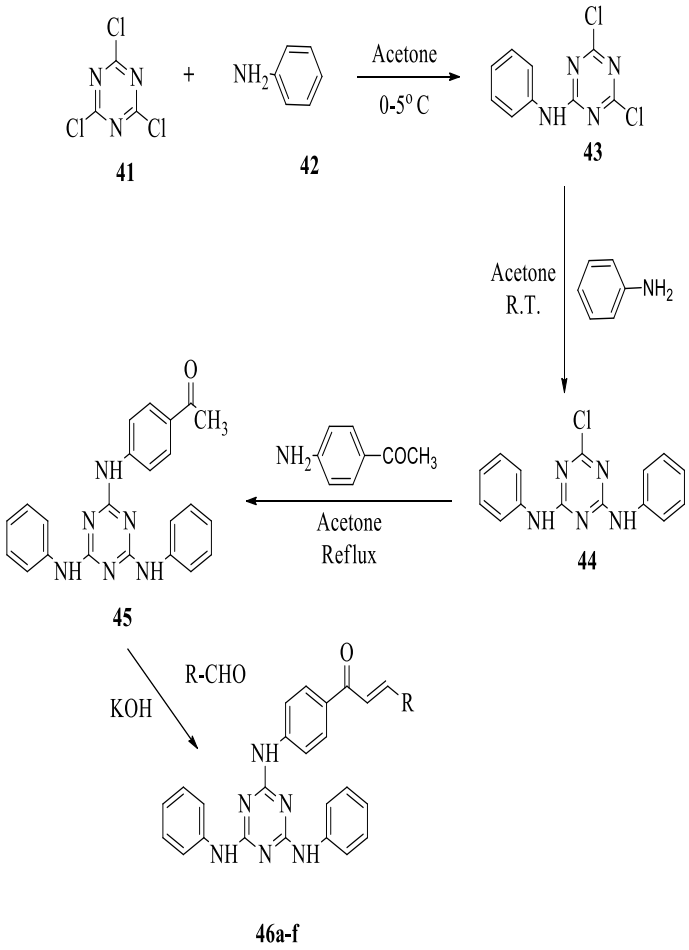
Chalcone Derivatives as Antibacterial Agents

Due to the rapid development of resistance towards antibiotics, there is a constant need for the development of new antibacterial agents. There are many molecules containing ring such as imidazole, triazole, pyrazole, benzimidazole, benzotriazole, oxypurine, pyrimidinyl, naphtyl, 1, 3-dioxolane, thiosemicarbazone, pyridine, furan, thiophene which have shown antibacterial activity [LIII-LVI]. Use of various pharmacophore that are not common to microorganisms or against which resistance has not been observed should be focused to develop novel antibacterial agents.

Chalcones are the aromatic ketones which belong to 1, 3-diaryl-2- propen-1-ones, which forms the central core for the synthesis of variety of important biologically active compounds. The compounds with the backbone of chalcone have been reported to exhibit a wide variety of pharmacological activity including antimalarial [LVII], antibacterial [LVIII], antituberculosis [LIX], anticancer [LX], anti-inflammatory [LXI], antifungal [LXII], antioxidant [LXIII], antileishmanial [LXIV].

During the last few years the potential of s-triazine derivatives in agrochemical and medicinal properties have been subjected to investigation. It is found that substituted s-triazine derivatives are an important class of compounds having antibacterial, anticancer, antitumor, antiviral, antifungal and antimalarial activities [LXV, LXVI]. Many acetamido derivatives have been synthesized and have showed antibacterial activity and other activities too [LXVII]. Chalcones are a class of compounds that provides an option of developing inexpensive, easily synthetic and therapeutic antibacterial agents. The s-triazine [LXVIII-LXXIV] and acetamido [LXXV - LXXVIII].

Series 1: S-Triazine containing Chalcone
Series 2: Acetamido containing Chalcone

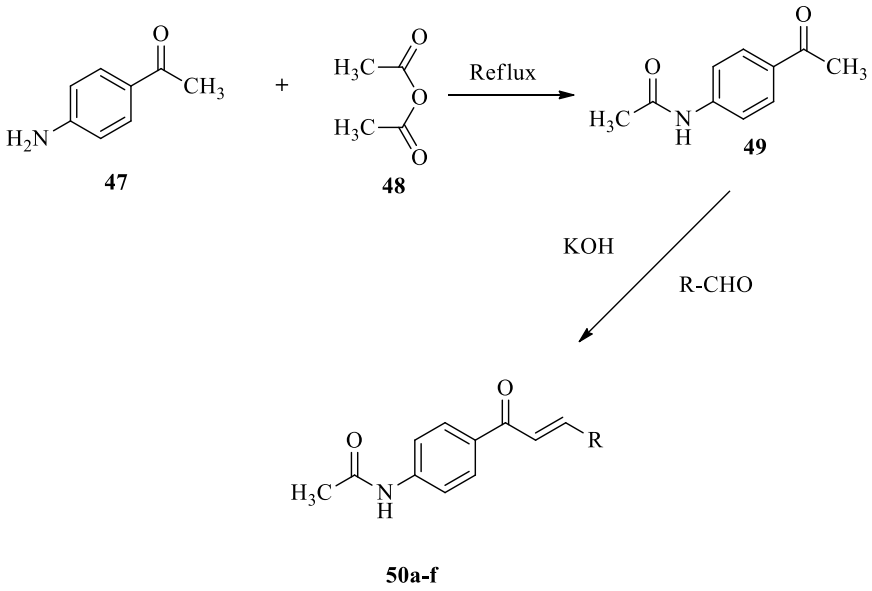


46a-f

Schematic procedure for synthesis of series-46a-f compounds

Compound No.	R
46a	5-methylfurfural
46b	3-nitrobenzaldehyde
46c	2-chlorobenzaldehyde
46d	2-bromobenzaldehyde
46e	3-bromobenzaldehyde
46f	4-bromobenzaldehyde

Scheme 6



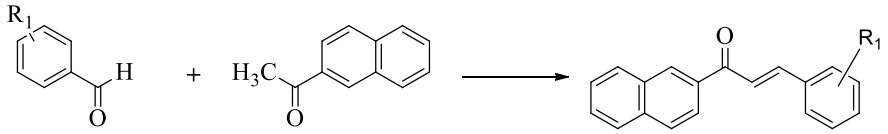
47 **48** **49** **50a-f**

Schematic procedure for synthesis of series-50a-f compounds

Compound No.	R
50a	5-methylfurfural
50b	3-nitrobenzaldehyde
50c	2-chlorobenzaldehyde
50d	2-bromobenzaldehyde
50e	3-bromobenzaldehyde
50f	2-methoxybenzaldehyde

Scheme 7

Chalcones (**51a-g**) was prepared by reaction of aryl aldehydes and 2-acetyl naphthalene, the synthesized compounds exhibit antibacterial and antifungal [LXXIX].



51a-g
51a.R=H
b,R=4-Cl
c,R=4-Br
d,R=4-f
e,R=CH_3
f,R=4-OCH_3
g,R=4-NO_2

Scheme 8

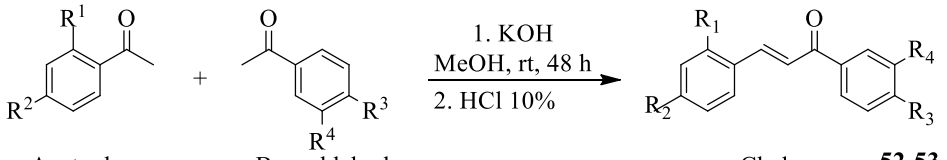
Biological evaluation of chalcone analogues with dual antioxidant mechanisms as potential anti-ischemic stroke agents.

Stroke, becoming one of the leading causes of morbidity and mortality across the world, brings increasingly great pressure to human lives. The large majority (85%) of strokes is ischemic stroke, that is, stroke resulting from an occlusion of a major cerebral artery, and commonly it occurs in the middle cerebral artery [LXXX, LXXXI]. Although remarkable advances have been made in understanding the pathophysiology of cerebral ischemia, effective therapies are still a troubling aspect of human. To date, intravenous thrombolysis has been regarded as an effective strategy for the treatment of acute ischemic stroke [LXXXII]. However, rapid reperfusion accompanied by a large number of reactive oxygen species (ROS) by thrombolytic therapies, could exacerbate brain injury, namely cerebral ischemia-reperfusion injury(CIRI).Among a series of mechanisms related to the pathogenesis of CIRI, oxidative stress has been considered as the main reason [LXXXIII, LXXXIV]. Oxidative stress, arising from the uncontrolled production of ROS beyond the neutralizing capacity of the various endogenous defense systems, including enzymatic and non-enzymatic matters, leads to cerebral cell apoptosis and neuronal damage [LXXXV – LXXXVII]. Therefore, exogenous supplementation of antioxidants with ROS scavenging activity would be a potential therapy to cerebral ischemia- reperfusion injury prevention. Currently, there are two main classes of antioxidants based on the mechanism of inhibiting ROS:(1) compounds that can directly react with ROS are the so-called direct antioxidants, which have the ability to break down the procession of radical chain reactions, like edaravone, resveratrol, quercitin and so on [LXXXVIII–XC]. (2)Indirect antioxidants are compounds that do not directly react with ROS but are involved in activating cellular endogenous antioxidant signaling pathways and promoting the transcription of a broad range of cytoprotective genes to remove ROS, where KEAP1/ NRF2/ARE is one of the important antioxidative signaling pathways. Many indirect antioxidants, such as TBHQ, curcumin and sulforaphane, that modify cysteine residues in the protein KEAP1, cause the dissociation of NRF2 from the inhibitory partner KEAP1 and facilitate NRF2 to translocate into the nucleus,whereNRF2 binds to the antioxidant-responsive element(ARE)consensus sequence to activate the transcription of a panel of cytoprotective genes (phase II genes) [XC- XCII]. Despite extensive research on these two types of antioxidants, most antioxidants have been unsuccessful for clinically treating stroke except edaravone and other very few antioxidants. Moreover, direct and indirect antioxidants are not particularly effective in treating cerebral ischemia-reperfusion injury, which may be related to its own “birth defects”. Direct antioxidants are short-lived, which may need to be continually provided to halt the process of cerebral ischemia-reperfusion injury. While stimulation of cellular endogenous antioxidant defense pathways by indirect antioxidants require a certain time, and during the period of time before activating the pathway, there is a risk that the brain would be irreversibly damaged by ROS insult, since indirect antioxidants itself could not remove ROS immediately. Besides, up till now, there have been no reports about "dual-antioxidant mechanism action "for antioxidant therapy via both directly and indirectly scavenging ROS. Moreover, it is not clear whether antioxidants with dual-antioxidant mechanism may have a better prospect than the ones with mono-antioxidant mechanism for cerebral ischemia-reperfusion injury therapy. Herein, we hypothesized that antioxidant agents with ROS scavenging activity directly and indirectly may be more effective therapeutic strategies for stroke treatment. Natural products and their synthetic analogues have been shown to be invaluable resources in drug discovery [XCIII–XCV]. Chalcones or (E)-1, 2-diphenyl-2-propene-1-ones, make up a group of natural products that attach to the flavonoid family [XCVI]. They consist in various of flowers, fruits, vegetables, and have been reported to possess many biological properties including antioxidant [XCVII–XCIX], antibacterial [C], anticancer [CI, CII], antiangiogenic [CIII], and anti-inflammatory activities [CIV, CV]. Among all the biological activities, the antioxidant activity has been extensively studied. Given that a number of small molecules bearing polyhydroxyl groups exhibit a great efficacy in antioxidant activity due to their potent abilities to scavenge ROS directly [CVI–CIX], and it is well- known that the electrophilic α, β-unsaturated ketone moiety (Michael acceptor) on a chalcone can result inactivation of theNRF2 pathway [CX], polyhydroxy chalcones thus may be considered as monomers to study the potential of double antioxidative properties. In the study, we reported a number of novel (E)-3, 4-dihydroxychalcone

analogues as anti-ischemic stroke agents that attenuate oxidative stress by directly scavenging ROS and indirectly through KEAP1/ NRF2/ARE pathway activation, leading to massive ROS elimination and subsequent inhibition of the ischemia-reperfusion-related brain injury in animals

Chalcone Derivatives and Their *in vitro* Anticancer Test against Breast (T47D) and Colon (WiDr) Cancer Cell Line

It is necessary to develop a safer chemopreventive agent so that the side effects are relatively small compared with surgery and radiation [CXI]. One of the compounds that have potential as a chemoprevention agent is chalcone. In the view of [CXII], they succeed to isolate the chalcone from 8.5 kg of *Desmodium renifolium* and obtained 25.9 mg (0.0003%) isolates of prenylchalcone. This chalcone has excellent pharmacological activity as anticancer against leukemia (NB4), lung (A549) and breast (MCF-7) cancer cell with IC50 3.40; 3.196; and 3.40 µg/mL respectively. However, the isolation methods are less due to the little amount of the isolate. According to [CXIII] and [CXIV], chalcone can be synthesized by Claisen- Schmidt condensation using acetophenone and benzaldehyde derivatives using acid or base catalysts. An important factor influencing the anticancer activity of chalcones contained in Cα and Cβ unsaturated bond. Besides that, the presence of hydroxy, methoxy, and prenyl in the ring A is known to inhibit the growth of cancer cells by attacking the cell nucleus area, while the presence of the hydroxy group and methoxy in ring B can affect an active part of the cell, so that the cell cannot have cleavage. However, the addition of the hydroxyl group at position C6' ring A does not indicate specific activity and can reduce cytotoxicity of chalcones [CXV]. According to [CXVI], the chloro and methoxy groups in ring B can contribute to the anti-proliferation activity of chalcones. While, [CXVII] compared the effect of the position of the methoxy on C2, C3, and C4 to the anticancer activity of chalcones, this study showed that the methoxy group is most active as anticancer on the C4 position of ring B chalcones. Also [CXVIII] compared the effect of halogen groups and its position on the C2, C3, and C4 to cell inhibitory activity. The results showed that the chloro group on C4 position have the best cytotoxic activity. A lot of chalcone have been synthesized by the previous researcher especially for the methoxylated chalcone in ring B [CXIX, CXX].



Chalcone 52: R_1= H; R_2= OH; R_3= OCH_3 ; R_4= H, 96%
Chalcone 53: R_1= H; R_2= OH; R_3= R_4= OCH_3, 97%
Chalcone 54: R_1= H; R_2= OH; R_3= Cl; R_4= H, 96%
Chalcone 55: R_1= R_2= OH ; R_3= Cl; R_4= H, 93%

Scheme 9

Conclusion

Our reviews describe the biological properties of chalcone and their derivatives and descript some method for synthesis and naturally occurring of chalcone, these chalcons have various biological activities such as inhibitors, antimicrobial, anticancer, anti-ischemic stroke agents and antioxidant properties activity.

Notes

The authors declare no competing financial interest.

Acknowledgments

The authors gratefully acknowledge financial support from Jouf University (Kingdom of Saudi Arabia).

References

i D.N. Dhar, In chemistry of chalcones and related compounds, 1st ed., John Wiley, New York, **1981**, pp. 56

Ii Z. Nowakowska, *Eur. J. Med. Chem*. **2007**, 42, 125-137.

Iii C.J. Shishoo, U.S. Pathak, K.S. Jain, *Ind. J. Chem*. **1999**, 33B, 684-689.

Iv P. Venturalla, A. Bellino, I. Piozzi, *Farmco. Ed. Sci*. **1971**, 591-596

V J.A. Mickey, H.H. Saraf, *Ind. J. Chem*. **1998**, 37B, 68-72

VI S. Alam, *J. App. Sci*. **2005**, 5(2), 327-333

VII D.N. Dhar, In chemistry of chalcones and related compounds, 1st ed., John Wiley, New York, **1981**, pp.1-15

VIII S.S. Tiwari, A. Singh, *J. Ind. Chem. Soc*. **1961**, 38, 931-932

IX A.O. Fatima, *J. Heterocycl Chem*. **2004**, 41, 327-333

X M.S.Y. Khan, *Ind. J. Chem*. **2003**, 42B, 1970-1975

XI G.S.B.Viana, M.A.M.Bandeira, F.J.A Matos, Phytomedicine **2003**, 10, 189–195. [CrossRef] [PubMed]

XII J. Rojas, M. Payá, J.N. Domínguez, M.L. Ferrándiz, Eur. J. Pharmcol. **2003**, 465, 183–189. [CrossRef]

XIII Z.Nowakowska, Eur. J. Med. Chem. **2007**, 42, 125–137. [CrossRef] [PubMed]

XIV M. Al Rahim, A. Nakajima, N. Misawa, K.Shindo, K. Adachi, Y.Shizuri, Y. Ohizumi, T. Yamakuni, Eur. J. Pharmacol. **2008**, 600, 10–17. [CrossRef] [PubMed]

XV S.F. Nielsen, M.L. arsen, T. Boesen, K. Schonning, H. Kromann, J. Med. Chem. **2005**, 48, 2667–2677. [CrossRef] [PubMed]

XVI M.A. Ali, M. Shaharyar, E.De Clercq, J. Enzyme Inhib. Med. Chem. **2007**, 22, 702–708. [CrossRef] [PubMed]

XVII J.C. Onyilagha, B. Malhotra, M. Elder, C.J. French, G.H.N. Towers, Can. J. Plant Pathol. **1997**, 19, 133–137. [CrossRef].

XVIII M.T. Konieczny, W. Konieczny, M. Sabisz, A.Skladanowski, R.Wakiec, E.Augustynowicz-Kopec, Z. Zwolska, Chem. Pharm. Bull. **2007**, 55, 817–820. [CrossRef] [PubMed]

XIX M. Gschwendt, W. Kittstein, G. Furstenberger, F. Marks, Cancer Lett. **1984**, 25, 177–185. [CrossRef]

XX P.S. Bhale, H.V. Chavan, S.B. Dongare, S.N. Shringare, Y.B. Mule, S.S. Nagane, B.P. Bandgar, Bioorg. Med. Chem. Lett. **2017**, 27, 1502–1507. [CrossRef] [PubMed]

XXI M. Sokmen, M.A. Khan, Inflammopharmacology **2016**, 24, 81–86.

XXII E. Hofmann, J. Webster, T. Do, R. Kline, L. Snider, R. Hauser, G. Higginbottom, A. Campbell, L. Ma, S. Paula, Bioorg. Med. Chem. **2016**, 24, 578–587. [CrossRef] [PubMed]

XXIII C.L. Miranda, J.F. Stevens, V. Ivanov, M. McCall, B. Frei, M.L. Deinzer, D.R. Buhler, J. Agric. Food. Chem. **2000**, 48, 3876–3884. [CrossRef] [PubMed]

XXIV C. Nakamura, N. Kawasaki, H. Miyataka, E. Jayachandran, I.H. Kim, K.L. Kirk, T. Taguchi, Y. Takeuchi, H. Hori, T. Satoh, Bioorg. Med. Chem. **2002**, 10, 699–706. [CrossRef]

XXV P.H. Park, H.S. Kim, J. Hur, X.Y.Jin, Y.L.Jin, D.H. Sohn, Arch. Pharm. Res. **2009**, 32, 79–89. [CrossRef] [PubMed]

XXVI F.L. Ansari, S. Umbreen, L. Hussain, T. Makhmoor, S.A. Nawaz, M.A. Lodhi, S.N. Khan, F. Shaheen, M.I. Choudhary, Atta-ur-Rahman, Chem. Biodivers. **2005**, 2, 487–496. [CrossRef] [PubMed]

XXVII W.S. Burnham, R.W. Sidwell, R.L. Tolman, M.G. Stout, J. Med. Chem. **1972**, 15, 1075–1076. [CrossRef] [PubMed]

XXVIII P. Boeck, C.A.B. Falcao, P.C. Leal, R.A. Yunes, V. Cechinel, E.C. Torres-Santos, B. Rossi-Bergmann, Bioorg. Med. Chem. **2006**, 14, 1538–1545. [CrossRef] [PubMed]

XXIX J.N. Dominguez, C. Leon, J. Rodrigues, N.G. de Dominguez, J. Gut, P.J. Rosenthal, J. Med. Chem. **2005**, 48, 3654–3658. [CrossRef] [PubMed]

XXX J. Quintin, J. Desrivot, S. Thoret, P. Le Menez, T. Cresteil, G. Lewin, Bioorg. Med. Chem. Lett. **2009**, 19, 167–169. [CrossRef] [PubMed]

XXXI O. Prakash, A. Kumar, A. Sadana, R. Prakash, S.P. Singh, R.M. Claramunt, D. Sanz, I. Alkorta, J. Elguero, Tetrahedron **2005**, 61, 6642–6651. [CrossRef]

XXXII W.M. Weber, L.A. Hunsaker, S.F. Abcouwer, L.M. Deck, D.L. Vander Jagt, Bioorg. Med. Chem. **2005**, 13, 3811–3820. [CrossRef] [PubMed]

XXXIII S. Jang, Jung, J.C.; Kim, D.H.; Ryu, J.H.; Lee, Y.; Jung, M.; Oh, S. J. Pharmacol. Exp. Ther. **2009**, 328, 435–447. [CrossRef] [PubMed]

XXXIV Y.H. Lee, J. Yun, J.C. Jung, S. Oh, Y.S. Jung, Pharmazie **2016**, 71, 274–279. [PubMed]

XXXV H.J. Lee, J.S. Kim, J.W. Yoon, H.-D. Kim, J.-H. Ryu, Chem. Pharm. Bull. **2006**, 54, 377–379. [CrossRef] [PubMed]

XXXVI E. Winter, N.P. Devantier, L.D.Chiaradia-Delatorre, C. Gauthier, R.A. Yunes, R.J.Nunes, T.B. Creczynski-Pasa, A. Di Pietro, J. Med. Chem. **2014**, 57, 2930–2941. [CrossRef] [PubMed]

XXXVII J. Zhang, X. Fu, N. Yang, Q. Wang, Sci. World J. **2013**, 649485

[XXXVIII] Y. Niu, H. Zhu, J. Liu, H. Fan, L. Sun, W. Lu, X. Liu, L. Li, Chem Biol Interact. **2011**, 189,161–166

XXXIX M. Nguyen, S. Awale, Y. Tezuka, Q. Tran, S. Kadota, Chem Pharm Bull. **2005**, 53,984–988

XL A. Bianco, C. Cavarischia, M. Guiso, Eur. J. Org. Chem. **2004**, 2894–2898.

XLI M. Al-Masum, Ng. Eunice, M.C.Wai, *Tetrahedron Lett*. **2011**, *52*, 1008–1010.

XLII B.T. Kim, J.C. Chun, K.J. Hwang, *Bull. Korean Chem. Soc*. **2008**, *29*, 1125–1130.

XLIII S.A. Khan, B. Ahmed, T. Alam, *Pak. J. Pharm. Sci*. **2006**, *19*, 290–294.

XLIV G. Yoon, B.Y. Kang, S.H. Cheon, *Arch. Pharm. Res*. **2007**, *30*, 313–316.

XLV S.K. Awasthi, N. Mishra, B. Kumar, M. Sharma, A. battacharya, L.C. Mishra, V.K. Bhasin, *Med. Chem. Res*. **2009**, *18*, 407–420.

XLVI M. Liu, P. Wilariat, M.L. *J. Med. Chem*. **2001**, *44*, 4443–4452.

XLVII S. Garg, M. Singh, N. Raghav, *I.J.P.S.R.* **2014**, *5*, 2657–2661.

XLVIII R. A. Pophale, M.N. Deodhar, *Der. Pharma. Chemic*, **2010**, *2*, 185–193.

XLIV M. Rueping, T. Bootwicha, H. Baars, E. Sugiono, *Beilstein J. Org. Chem.* **2011**, *7*, 1680–1687.

l S. Syam, S.I. Abdelwahab, M.A. Al-Mamary, S. Mohan, *Molecules* **2012**, *17*, 6179–6195.

LI B.D. Bandgar, S.S. Gawande, R.G. Bodade, J.V. Totre, C.N. Khobragade, *Bioorg. Med. Chem.* **2010**, *18*, 1364–1370.

LII H. Suwito, J. Jumina, M. Mustofa, P. Pudjiastuti, M. Z. Fanani, Y. Kimata-Ariga, R. Katahira, T. Kawakami, T. Fujiwara, T. Hase, H. Mohd Sirat, N. N.

T. Puspaningsih, Molecules **2014**, 19, 19(12), 21473-88. doi: 10.3390/molecules191221473.

LIII M. M. Gonzalez-Chavez, F. Mendez, *Molecules* **2011**, 16, 175-189.

LIV H. B. Kucuk, A. Yusufoglu, *Molecules*, **2011**, 16, 6806- 6815.

LV A. M. Asiri, S. A. Khan, *Molecules*, **2010**, 15, 4784-4791.

LVI T. D. Tran, T. T. N. Nguyen, *Molecules*, **2012**, 17, 6684-6696.

LVII R. Kumar, D. Mohanakrishnan, *European Journal of Medicinal Chemistry* **2010**, 45, 5292-5301.

LVIII C. Zhen-Hua, Z. Chang-Ji, *European Journal of Medicinal Chemistry* **2010**, 45, 5739-5743.

LIX R. H. Hans, E. M. Guantai, Bioorganic *& Medicinal Chemistry Letters* **2010**, 20, 942-944.

LX P. Singh, R. Raj, *European Journal of Medicinal Chemistry* **2011**, 30, 1-7.

LXI B. P. Bandgar, S. S. Gawande, *Bioorganic & Medicinal Chemistry* **2009**, 17, 8168-8173.

LXII L. C. Tavares, S. Johann, *European Journal of Medicinal Chemistry* **2011**, 46, 4448-4456.

LXIII B. P. Bandgar, S. S. Gawande, *Bioorganic & Medicinal Chemistry* **2010**, 18, 1364-1370.

LXIV C. R. Andrighetti-Frohner, K. N. Oliveira, *European Journal of Medicinal Chemistry* **2009**, 44, 755-763.

LXV K. Srinivas, U. Srinivas, Bioorganic *& Medicinal Chemistry Letters* **2005**, 15, 1121-1123.

LXVI J. Modha, N.Datta, *Il Farmaco* **2001**, 56: 641-646.

LXVII G. K. Sharma, S. Kumar, Der *Pharmacia Lettre* **2010**, 2 (2), 223-230.

LXVIII R. Mohammad, P. Mehdi, *World J Microbiol. Biotechnol*. **2010**, 26, 317-321.

LXIX O. Guiping, C. Xue-Jian, *Journal of Agriculture and Food Chemistry* **2008**, 56, 10160-10167.

LXX S. C.S. hetty, V. C.Bhagat, Asian *Journal of Chemistry* **2008**, 20 (7), 5037-5045.

LXXI S. M. El-Moghazy, F. F.Barsoum, *Medicinal Chemistry Research* **2012**, 21, 1722 -1733.

LXXII H. S. Abdel-Sattar, N. Ekhlass, Organic *Chemistry Current Research* **2012**, 1 (5), 1-8.

LXXIII H. A.Saadeh, I. M. Mosleh, Molecules **2009**, 14, 2758-2767.

LXXIV Z. Rezaei, S. Khabnadideh, Arch. *Pharm. Chem. Life Sci*. **2011**, 344, 658- 665.

LXXV K. Ilango, P. Valentina, *Research Journal of Pharmaceutical, Biological and Chemical Sciences* **2010**, 1 (2), 354-359.

LXXVI B. Sutariya, S. K. Raziya, *Indian Journal of Chemistry* **2007**, 46B, 884-887.

LXXVII R. S.Koti, G. D. Kolavi, *Indian Journal of Chemistry* **2006**, 45B, 1900-1904.

LXXVIII S. M. Hipparagi, V. Ranjeeta, *International Research Journal of Pharmacy* **2011**, 2 (2), 157-162.

LXXIX V. Arora, P. Arora, H. S. Lamba, Der Pharmacia Lettre **2012**, 4(2), 554-557.

LXXX R.W. Flynn, R.S. MacWalter, A.S. Doney, Neuropharmacology **2008**, 55,250–6.

LXXXI J. Durai Pandian, V. Padma, P. Vijaya, P.N. Sylaja, J. M. Murthy, Int. J. Stroke **2007**, 2,17–26.

LXXXII K.Uchino, JAMA Neurol. **2017**, 74, 1269.

LXXXIII J. Wu, J. Ling, X. Wang, T. Li, J. Liu, Y. Lai, J. Med. Chem. **2012**, 55, 7173–81.

LXXXIV E. Candelario- Jalil, Curr. Opin. Investig. Drugs **2009**, 10, 644–54.

LXXXV T.L. Yen, C.K. Hsu, W.J. Lu, C.Y. Hsieh, G. Hsiao, D.S.Chou, J. Agric. Food Chem.**2012**, 60, 1937–44.

LXXXVI H.K. Eltzschig, T.Eckle, Nat. Med. **2011**, 17, 1391–401.

LXXXVII E. Pantazi, M. Bejaoui, E. Folch-Puy, R. Adam, J.Roselló-Catafau, Expert. Opin. Pharmacother.**2016**, 17, 169–79.

LXXXVIII P.C. Trippier, K. JansenLabby, D.D. Hawker, J.J. Mataka, R.B.Silverman, J. Med. Chem. **2013**, 56,3121–47.

LXXXIX A. Pérez-González, A. Galano, J. Phys. Chem. B **2011**, 115, 1306–14.

XC A.T. Dinkova-Kostova, P. Talalay, Mol. Nutr. Food Res. **2008**, 52, S128–38.

XCI K.A. Jung, M.K.Kwak, Molecules **2010**, 15, 7266–91.

XCII S. Magesh, Y. Chen, L.Hu, Med. Res. Rev. **2012**, 32, 687–726.

XCIII Z. Guo, Acta. Pharm. Sin. B **2017**, 7, 119–36.

XCIV D. Rigano, C. Sirignano, O.Taglialatela- Scafati, Acta. Pharm. Sin. B **2017**, 7, 427–38.

XCVI J.Z. Wu, Y.Y. Xi, L.L. Huang, G. Li, Q.Q. Mao, C.Y. Fang, J. Nat. Prod. **2018**, 81, 2567–75.

XCVII J.R. Dimmock, D.W. Elias, M.A. Beazely, N.M.Kandepu, Curr. Med. Chem. **1999**, 6, 1125–49.

XCVIII H. Niu, W. Wang, J. Li, Y. Lei, Y. Zhao, W.Yang, Eur. J. Med. Chem. **2017**, 138,212–20.

XCIX J.H. Cheng, C.F. Hung, S.C. Yang, J.P. Wang, S.J. Won, C.N.Lin, Bioorg. Med. Chem.**2008**, 16, 7270–6.

C M.R. El Sayed Aly, H.H. Abd El Razek Fodah, S.Y.Saleh, Eur. J. Med. Chem. **2014**, 76, 517–30.

CI J.Z. Wu, C. Wang, Y. P.Cai, J. Peng, D.L. Liang, Y.J. Zhao, Med. Chem. Res. **2012**,21,444–52.

CII P. Lorenzo, R. Alvarez, M.A. Ortiz, S. Alvarez, F.J. Piedrafita, Á.R.DeLera, J. Med.Chem.**2008**,51,5431–40.

CIII M. Zhu, J.B. Wang, J.W. Xie, L.P. Chen, X.Y. Wei, X. Jiang, Eur. J. Med. Chem. **2018**,157,1395–405.

CIV S. Tuncel, J. Fournier-dit-Chabert, F. Albrieux, V. Ahsen, S. Ducki, F. Dumoulin, Org.Biomol.Chem.**2012**, 10, 1154–7.

CV Y.L. Zhang, J. Z. Wu, S.L. Ying, G.Z. Chen, B.B. Wu, T.T. Xu, Sci. Rep. **2016**, 6, 25130–42.

CVI J. Wu, J. Li, Y. Cai, Y Pan, F. Ye, Y. Zhang, J. Med. Chem. **2011**, 54, 8110–23.

CVII J.C. Menezes, S.P. Kamat, J.A. Cavaleiro, A. Gaspar, J. Garrido, F. Borges, Eur. J. Med. Chem. **2011**, 46,773–7.

CVIII A. Gaspar, M. Martins, P. Silva, E.M. Garrido, J. Garrido, O. Firuzi, J. Agric. Food Chem. **2010**, 58,11273–80.

CIX P. Cos, P. Rajan, I. Vedernikova, M. Calomme, L. Pieters, A.J. Vlietinck, Free Radic. Res. **2002**, 36,711–6.

CX J. Teixeira, F. Cagide, S. Benfeito, P. Soares, J. Garrido, I. Baldeiras, J. Med. Chem. **2017**, 60, 7084–98.

CXI V. Kumar, S. Kumar, M. Hassan, H. Wu, R.K. Thimmulappa, A. Kumar, J. Med. Chem. **2011**, 54, 4147–59.

CXII A. Kamuhabwa, C. Nashimo, P. de Witte, *J. Ethnopharmacol.* **2000**, 70 (2), 143–149.

CXIII Y.P. Li, Y.C. Yang, Y.K. Li, Z.Y. Jiang, X.Z.Huang, W.G.Wang, X.M. Gao, Q.F. Hu, *Phytochem. Lett.* **2014**, 9, 41–45.

CXIV C.B. Patil, S.K. Mahajan, S.A. Katti, *J. Pharm. Sci. Res.* **2009**, 1 (13), 11–12.

CXV M. Loudon, 2010, *Organic Chemistry*, University of Colorado, Colorado.

CXVI K. Zenger, S. Dutta, M.G. Genton, *Toxicology* **2015**, 336, 26– 33.

CXVII C.W. Mai, M. Yaeghoobi, N. Abd-Rahman, Y.B. Kang, M.R. Pichika, *Eur. J. Med. Chem.* **2014**, 77, 378–387.

CXVIII H. Suwito, J. Jumina, M. Mustofa, N. Ni'matuzahroh, N.N.T. Puspaningsih, *Pharma. Chem.* **2015**, 7 (3), 89–94.

CXIX J. Zhang, F.J. Ji, Y. Gu, X.Y. Zhang and S.X. Qiao, *Molecules* **2014**, 18 (8), 10081– 10094.

CXX A. Sultan, A.R. Raza, K.M.Khan, M.N. Tahir, N. Saari, *Molecules* **2013**,18 (8), 10081– 10094.

CXXX E. Susanti, S. Matsjeh, Mustofa, T.D. Wahyuningsih, *Indones. J. Chem.* **2014**, 14 (2), 174– 178.

Received on November 17, 2021