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Contents

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The impact of ozone gas treatment on the amylose/amylopectin ratio in Iraqi jasmine rice grains

Emad Shaker Whaiba,* |Makarim Ali Mousa b

A B S T R A C T

The ratio of amylose to amylopectin has a impact on rice cooking properties. The raw rice grains with moisture levels of 14% and 18% were treated with 30 mg/L ozone for 5 hours and the milled rice was treated for 3 hours, as well. The sample weighed 2 kg and the treatment was carried out in a confined space system with the ozone-mixed air being pushed through it in which amylose was assessed to be 18.93% and amylopectin to be 81.07%. The percentages of amylose and amylopectin in ozone-treated versus non-ozone-treated grains did not change significantly, for both raw and milled rice, at both moisture content and ozone treatment levels. To the storage life, the ozone treatment period for raw and milled rice was determined based on the removal of most microorganisms.

KEYWORDS Treatment; ozone; jasmine rice; amylose; amylopectin.

INTRODUCTION

The rice grain (Oryza sativa L.) is a major food crop. It has been a staple meal in many Asian countries since the ancient times, along with wheat and corn [12]. More over half of the world's population is fed on rice and it plays a critical part in satisfying the growing need for grain as the world's population growth. The amount of rice produced in Iraq was 574,705 tons [4]. One of the most important uses of ozone in agriculture is crop postharvest treatment [20]. The effectiveness of ozone is dependent on a number of parameters, including the used concentration, the qualities of each meal and the ambient conditions like temperature and humidity. Due to the physical structures that come into touch with the gas, each ozone-treated food, such as rice, wheat, or nuts, may behave differently. Consequently, the extensive research are required to better understand its usefulness [5,16]. Ozone is a powerful oxidant that has a wide range of uses in the food industry. Ozone has been used to decontaminate foods such as fruits, vegetables, spices, herbs, drinks, meat, and fish in both gaseous and aqueous forms. In the food processing industry, the ozone processing is one of the most promising nonthermal and bio-friendly procedures. Because of its antibacterial characteristics and potential to change the functional aspects of foods, ozone technology is being more widely used in the food business. The structural alterations offer a variety of applications in the food and industries, including longer shelf life, texture, and moisture retention. The viscosity of starch molecules is altered by the positive reaction of ozonation in carboxyl and carbonyl groups [10]. The advantage of utilizing ozone is that it decomposes converting carbon dioxide into oxygen in the air, leaving fewer residues in the product and obviating the need for removing gas. Ozone is the most promising green technology for improving food safety and quality since it has non-residual qualities and it is an environmentally beneficial solution [10,11]. It's also been given the "Generally Recognized as Safe" designation (GRAS) for food matrix disinfection [8]. The consumer's desire to take rice is mostly determined by its ultimate cooked texture. Following cooking, various rice kinds have varied the textures. The ultimate texture of cooked rice is determined by starch, which is the major component of rice. The amylose concentration and gelatinization temperature are determined by the starch properties [9,3]. Rice texture is an important sensory element in assessing the eating quality of cooked rice. Hardness and stickiness are the two most important factors which influence rice texture and

its eating quality. [13]. A variety of factors influence the texture of cooked rice, including amylose content, post-harvest processing, and cooking method. The most important characteristic is that the amylose level has an impact on the final texture of cooked rice. The structure of amylopectin is considered to determine texture. Regarding its lengthy chain, the ultimate texture of cooked rice is determined by the amylopectin chains [6].

Materials and methods

Sample collection

Random samples was taken from raw rice, Iraqi jasmine variety, harvested in the 2020 season, as stated in (2010) AACC 64-70.02 from the receiving sites of the General Company for Grain Trade of the Ministry of Trade/sites (Babylon, Najaf, and Diwaniyah) drawn by the employees of the receiving sites by 14% of the acceptable moisture content and 18% of the rejected moisture.

A crushing device was used SATAKE RICE MACHINE HUSKER (Type THU, 35A), weighing 250 g of the refined raw rice and is placed in the upper feeding slot where it is closed, then the device is turned on and after that, the feed slot is opened gradually for the passage of the grains through the rolls of the crushing after adjusting them according to the type of grains (i.e. it is essential that the grains passes smoothly). The brown rice is collected in one of the two lower boxes and the quantity is crushed again to obtain the largest amount of brown rice.

A bolishing device was used SATAKE [Testing Mill TM05C]. 200 g of brown rice was weighted and placed it in the upper tank, with the door to the tank was closed. Then, the brown rice grains were passed over the disc stone and the sieve, and it was divided into bleached rice and bran. The device is equipped with a watch timing to determine the appropriate time to reach the required degree of whiteness. Timing was set to 45 seconds in order to reach the degree of whiteness of the milled rice grains to 32 degrees for the control sample T1 according to the Iraqi Standard No. IQS 1343/2019 for rice was issued by the Central Organization for Standardization and Quality Control.

Ozone treatment An ozone treatment system was made by the researcher consisting of the ozone device from Laisen Electronic Devices Company of Chinese origin by the method of the electric charging (Charging) with a pumping capacity of 10 g/hour and a flow speed of 5-7 liters/min. The device worked by pumping air (input) and it passed through a purification processor made of aluminum, from which an air stream was formed in a glass insulator between two parallel electrodes and as a result of the high voltages of the device, the oxygen molecule was broken and the atoms were re-formed in a triple (O3) form and a stream of generated gas was pumped through an output tube (output) and went to a cylindrical container of Acrylonitrile Butadiene Styrene (ABS), 10 cm in diameter and 50 cm in height, with the air flow meter, stainless steel clamp, and plastic connecting tubes made of

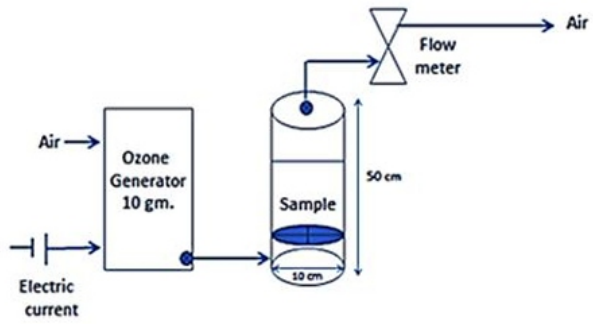

FIGURE 1 Plan–Ozone system for sterilization of rice grains

The raw rice samples (i.e. moisture content 14% and 18%) were for 5 hours, they were exposed to ozone gas at a dosage of 30 mg/L. The treatments after grinding and polishing the raw rice samples: T1: The milled rice from raw rice 14% moisture content of the untreated with ozonation. T2: The milled rice from raw rice 14% moisture content treated ozonized at a concentration of 30 mg/L for 5 hours. T3: The milled rice from raw rice 18% moisture content of untreated with ozonation. T4: The milled rice from raw rice 18% moisture content treated ozonized during 5 hours at a concentration of 30 mg/L. The treatments (T1 and T3) were then subjected to ozone gas at a concentration of 30 mg/L for 3 hours (the milled rice from untreated with ozonation raw rice). T5: The milled rice with a 14% moisture content that was ozonized for 3 hours at a concentration of 30 mg/L. Polyvinylidene Difluoride, sample weight for all treatments 2 kg were placed in the abovementioned cylindrical container and the flow velocity was adjusted by an air flow meter to 5.5 L/min and the used concentration was 30 mg/L, as depicted in Figure 1.T6: The milled rice 18% moisture content treated ozonized at a concentration of 30 mg/L for 3 hours. The ozone treatment time for raw and milled rice was calculated based on the elimination of most microorganisms to prolong the storage time.

Determination amylose content (Ac)

The amylose content was estimated as stated in AACC 61-03.01 (2022). By dissolving a standard concentration of amylose mg/ml according to the manufacturer's instructions, a standard concentration of amylose mg/mL was prepared. Using a volumetric flask with a capacity of 100 mL, 40 mg of pure potato amylose (Sigma Co.) was weighed. The mixture was then heated in a boiling water bath for 15 minutes with 1 mL of 95 percent ethanol and 9 mL of 1 N sodium hydroxide. The solution was then allowed to cool to the ambient temperature before being filled up with distilled water. Then, a series of standard solutions were prepared by adding (1, 2, 3, 4, and 5) mL of the solution, followed by (0.2, 0.4, 0.6, 0.8, and 1.0) mL of acetic acid 1 N, and 2 mL of 0.2 percent iodine solution to five volumetric flasks of 100 mL, supplied with the distilled water, shaken thoroughly, covered with aluminum foil, and left for 20 minutes before reading with a spectrophotometer at 620 nm. In a 100 mL volumetric flask, the same technique was followed for samples, however, instead of the pure potato amylose, 100 mg of rice flour was used, and 1 mL of 95 percent ethanol was added before adding 9 mL of 1 N sodium hydroxide and thoroughly the mixture was shaken. The solution was then cooked for 15 minutes in a water bath, cooled to the

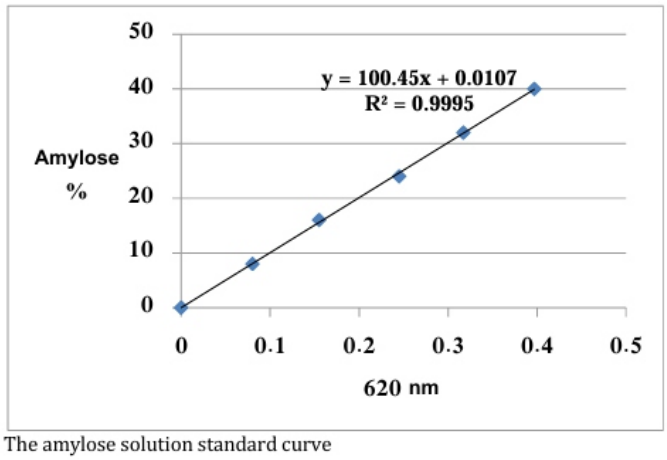

FIGURE 2 The amylose solution standard curve

TABLE 1 The readings from the spectrophotometer for the standard solution of the standard curve

Concentration	Readings
0	0.000
8	0.080
16	0.155
24	0.245
32	0.317
40	0.397

Sample storage

The milled rice and milled rice flour samples was packed in 1.5 liter glass bottles fitted ambient temperature and topped up with distilled water. In a 100 mL volumetric flask, 5 mL of sample solution was combined with 1 mL 1N of acetic acid and 2 mL and 0.2 percent of iodine solution was added to the solution, which was then filled with distilled water. Then after, everything is up to you. The prepared solutions were kept in a dark box for 20 minutes before being used, and then the absorbance was measured [2]

Amylopectin content determination (Ap)

The following equation was used to compute the amount of amylopectin in the sample. Amylopectin = (100 -Amylose %) with a metal screw cap as stated under the storage conditions at the ambient temperature. The storage was lasted for 180 days.

Data analysis

SAS stands for statistical analysis system (2012). The statistical program was used in data analysis to investigate the effect of various treatments on the studied traits using a complete random design (CRD), The Least Significant Difference (LSD) test was used to

TABLE 2 Amylose and amylopectin values for all treatments before and after storage

Treatments	Before Storage		After Storage	
	Amylose %	Amylopectin %	Amylose %	Amylopectin %
T1	18.93	81.07	18.42	81.58
T2	19.03	80.97	18.75	81.25
T5	19.33	80.67	18.90	81.10
T3	18.33	81.67	17.85	82.15
T4	18.73	81.27	18.15	81.85
T6	18.93	81.07	18.35	81.65
LSD values	1.44 NS	3.218 NS	1.06 NS	2.95 NS

Values are the average of three replicates. NS: No significant differences at level (P≤0.05)*.

Percentages of amylose and amylopectin values for white rice and for all treatments before and after storage indicated that the values of amylose before storage was (18.93, 19.03, 19.33, 18.33, 18.73, and 18.93) % for the treatments (T1, T2, T5, T3, T4, and T6), respectively. We noticed a rise in the amylose content between treatments T1 and T2, treatments T1 and T5, between treatments T3 and T4, and treatments T3 and T6 due to ozone treatment. There was no statistical significant difference at the level (P≤0.05)*. The ozone treated rice contained 16.26% amylose, so when cooking it had a high level of stickiness and more viscosity [7]. amylose decreased from 15.27% to 12.64% owing to the oxidation and radical processes that occur with ozonation breakdown of starch molecules as a result of prolonged

exposure to ozone [17]. The amylose content of jasmine rice samples ranged between (10.67-17.54)% (based on dry weight), which classified samples of low amylose rice [18]. Amylopectin values before storage was (81.07, 80.97, 80.67, 81.67, 81.27, and 81.07)% for treatments (T1, T2, T5, T3, T4, and T6), respectively. We noticed a decrease in amylopectin content between treatments compare the significant differences between the means.

Results and discussion

Table 2 shows the levels of amylose and amylopectin in the milled rice samples before and after 180 days of storage.

T1 and T2, treatments T1 and T5, between treatments T3 and T4, and treatments T3 and T6 due to the ozone treatment with no significant differences at the level ($P \leq 0.05$)*. Amylose and amylopectin are the main component of starch which impact on its physical properties such as gelatinization, retraction, viscosity, and elasticity [14,19]. The values of amylose after storage were (18.42, 18.75, 18.90, 17.85, 18.15, and 18.35)% for the treatments (T1, T2, T5, T3, T4, and T6), respectively. We noticed an increase in amylose content between treatments T1 and T2, treatments T1 and T5, between treatments T3 and T4, and treatments T3 and T6 due to the ozone treatment with no significant differences at the level ($P \leq 0.05$)*. Amylolytic enzymes are still active during rice storage; however their activities decline over time and the interior regions of the endosperm has a higher temperature, which is suitable for enzymatic activity (amylase) and the other hydrolytic enzymes, therefore concentration the amylose reduces during storage. Amylose is more susceptible to enzyme attack, whereas amylopectin is more resistant [2].

Amylopectin values after storage were (81.58, 81.25, 81.10, 82.15, 81.85, and 81.65)% for treatments (T1, T2, T5, T3, T4, and T6), respectively. We noticed a decrease in amylopectin content between treatments T1 and T2, treatments T1 and T5, between treatments T3 and T4, and treatments T3 and T6 due to the ozone treatment with no statistical significant differences at the level ($P \leq 0.05$)*. The positive response of the carboxyl and carbonyl groups to ozone causes a change in starch molecules' viscosity and rheological qualities including low viscosity even at large concentrations and favorable binding properties, the ability to form and cohesion. Thus, its application has risen in the food processing sector. The effect of ozone on both physical and chemical properties is primarily rebound and binding. Ozone changes crystallization, expansion rate, and viscosity, the gelatinization temperatures due to the interchange of AC and AC molecules and enzymatic alterations, as well [10].

Conclusion

At both moisture content of ozone treatment of the raw rice and milled rice, there was no significant influence at the level (P0.05)*, on the amount of amylose and amylopectin.

Acknowledgements

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Study of oxidant-antioxidant status cerebrospinal fluid of children with meningitis

Tahar Melki* |Maroua Imène Benamrani |Ahmed Zouaoui

A B S T R A C T

Meningitis, an inflammation of the meninges, is globally distributed as either sporadic or epidemic forms. Acute meningitis of infectious etiology involves viruses or bacteria making the differential diagnosis very difficult. Oxidative and reductive stress are dual dynamic phases experienced by the cells undergoing adaptation towards endogenous or exogenous noxious stimulus. Considering the issue stated, the present study was designed to evaluate the alterations in different biochemical parameters including glucose, protein, oxidative stress in the CSF samples of the meningitis patients (n=36) and compare them with control subjects (n=36). The results revealed significant increase in CSF of total protein, malondialdehyde, albumin, and NO levels in meningitis patients when compared with their respective controls. While Glucose, uric acid, glutathione, Vitamin E and C were significantly decreased in CSF samples, in meningitis patients in comparison to the control group. The findings indicated that oxidative stress due to reactive nitrogen species and altered antioxidant defenses are involved in the pathophysiology of meningitis in humans.

KEYWORDS Cerebrospinal fluid; meningitis; oxidative stress; vitamin E and C.

INTRODUCTION

Cerebrospinal fluid (CSF) is a clear colorless liquid circulating in the intracranial and spinal compartments. At any given time, there is approximately 125 mL to 150 mL of CSF in the body, being in dynamic equilibrium and bathing neurons and glial cells. CSF analysis may support only the suspicion of a nervous system disorder and rarely provides a definitive diagnosis [1-3]. Meningitis is defined as inflammation of the membranes surrounding the brain and spinal cord, including the dura, arachnoid and pia mater [2,4]. It is usually caused by bacteria or viruses, fungal, parasites, but it can be a result of injury, cancer, or certain drugs. It is important to know the specific cause of meningitis because the treatment differs depending on the cause. It is one of the important causes of considerable morbidity and mortality in children' that associated with cerebral compromise which may be responsible for neurological squeal in nearly half of the survivors [5-7]. Oxidative and reductive stress are dual dynamic phases experienced by the cells undergoing adaptation towards endogenous or exogenous noxious stimulus. The former arises due to the imbalance between the production of reactive oxygen species (ROS) or free radicals and antioxidant defense, which may induce tissue injury. It can assessed by measurement of reaction products of oxidative damage, like lipid peroxidation, DNA oxidation and protein oxidation [8,9]. Through pathological redox reactions, ROS can denature biomolecules such as proteins, lipids and nucleic acids. This can initiate tissue damage via apoptosis and necrosis. It plays a significant role in the pathogenesis of meningitis and mechanisms of complications [8-12]. Accordingly, the present study aimed at evaluating the diagnostic and prognostic significance of oxidative stress and antioxidant status in cases of meningitis by serial estimation of these markers in CSF.

Material and methods

A prospective hospital-based study was done during a period of three years from January 2019 to December 2021. All patients from one month to 7 years admitted to the Salahalddin Teaching Hospital in Tikrit province, and Pediatric Hospital in Kirkuk, Iraq with a presumptive diagnosis of meningitis were included in the study.

Inclusion criteria
Inclusion criteria entailed clinical features suggestive of meningitis.

Exclusion Criteria The exclusion criteria were patient suffering from acute or chronic liver disease, neurological disorders like Stroke, ICSOL, patient with history of muscles diseases, and patient suffering from renal diseases. Based on clinical manifestation and laboratory results of CSF which include glucose as well as protein concentration, qualitative and quantitative cytology, Gram stain, ZN stain, 36

TABLE 1 Demographic characteristic of study population

Diagnosis	No. of patients		
	Total	Male	Female
Normal (control)	36	15	21
Tuberculous meningitis	4	1	3
Bacterial meningitis	5	4	1
Viral meningitis	16	10	6
Partial treated meningitis	1	-	1

number of patients were finally selected for the study diagnosed as either Pyogenic or Tubercular Meningitis.

Biochemical assays
The fluid was withdrawn by lumbar puncture, using a spinal needle No.20). The patients lay on a hard bench, taking the lateral reclined position and the needle was gently placed above or beneath the fourth lumber vertebra. The amount of withdrawn C.S.F was not fixed, but usually in the range of (1-3) ml. The CSF was examined grossly for appearance and color. Freshly collected specimens were stored at 4 C°. Turbid specimens were centrifuged at 3000 rpm for 10 minutes before storage. The CSF glucose, protein, GSH, MDA, G-Px, and TAS levels were measured by spectrophotometric kit via Bio labo kit CHOD/PAP-France. Nitric oxide was estimated by the method of Smarason et al., (1997) [13]. Measurement of Vitamin E and C were performed according to the method described by Tietz [14].

Statistical methods
Statistical analysis was performed using standard statistical software (SPSS version 16.0). All data were expressed as mean ± S.D. The data were also tested using student's ttests; P-value of less than 0.05 was taken as significant.
The study included 36 patients with meningitis and 36 healthy subjects as controls. It is evident from Table 2 that there is decrease in levels of MDA (1.29 ± 0.18 vs. 1.01 ± 0.21µmol/L), and NO (23,6 ± 2,8 vs20,3 ± 2,2 µmol). The activities in the patient group were compared with those of control. However, the levels of TAC ,uric acid, Vitamin-C , and GSH, GPx, and Vitamin E were

(

TABLE 2 The (mean ±SD) CSF concentrations of measured biochemical parameters of the patients and the control group

Parameters	Patients group	Control group	P
Glucose (mg/dl)	120 ± 300	33.1 ± 2.8	0.05
Total protein (g/l)	25.80 ±4.30	63.05 ± 8.08	0.00001
MDA (µmol/L)	1.29 ± 0.18	1.01 ± 0.21	<0.001
Uric acid(mg/dl)	1.8 ± 0.09	3.48 ± 1.75	<0.001
NO (µmol)	23.6 ± 2.8	20.3 ± 2.2	<0. 01
Albumin (g/dl)	1.19 ± 0.079	2.13 ± 0.39	p < 0.0001
Total antioxidant capacity (mmol/L)	0.391 ± 0.15	1.67 ± 0.25	<0.001
Glutathione peroxidase (U/g Hb)	40±3.81	57.53±6.53	<0.0084
Vitamin-C (mg/dl)	0.39 ± 0.24	0.88 ± 0.12	<0.001
GSH (mg/dl)	36± 4.15	42.64±4.76	<0. 01
Vitamin E (mg/L)	1.34 ± 0.221	0.740± 0.204	P < 0.05

Discussion

CSF proteins originate from serum and from local intracranial production. A breakdown in the integrity of the blood-brain barrier allows increased levels of serum proteins to access the CSF. Probably the increased membrane permeability may lead to increase CSF enzymes proportionately, helping the differential diagnosis of meningitis [15]. This contributes to the development of increased intracranial pressure, hydrocephalus, brain edema, and cerebral ischemia, all of which can cause neuronal cell death [16, 17]. CSF levels of glucose were significantly increased in the patients compared with the control group. These results were in agreement with a study done by Entedhar et al [17], due to the fact that microorganisms in meningitis significantly lower in the experimental group than those of the controls (0.391 ± 0.15 vs 1.67 ± 0.25 mmol/L), (1.8 ± 0.09 vs 3.48 ± 1.75 mg/dl), (0.39 ± 0.24 vs. 0.88 ± 0.12 mg/dl), and (36± 4.15 vs 42.64±4.76 mg/dl), (40±3.81 vs. 57.53±6.53 U/g Hb) ,and (0.740± 0.204 vs 1.34 ± 0.221 mg/L), respective uses CSF glucose as a source of energy for their metabolism which leads to increase in its level in CSF. The brain is naturally protected from the body's immune system by the barrier that the meninges create between the bloodstream and the brain [18]. The blood-brain barrier is formed by microvascular endothelial cells, astrocytes, and pericytes. This barrier acts by controlling the exchange of substances into and out of the brain and thereby protects the brain from toxins and pathogens [19]. The BBB breakdown occurred at 12 hours after pneumococcal meningitis induction, subsequent to the cytokine production. ROS and RNS have been implicated as mediators of the BBB breakdown, suggesting that the increase of the BBB permeability appears to be related to the presence of NO/O2 − [20].

Malondialdehyde is a reactive aldehyde and is one of the many reactive electrophile species that cause toxic stress in cells [21]. CSF malondialdehyde considered one of the final products of lipid peroxidation was found to be significantly increased in present study indicating the destruction in the tight junctions of the endothelial monolayer of BBB and increasing its permeability. This result is in agreement with those of Miric (2010) and Ramakrishnan (2009) [22,23]. Increased levels of MDA in this study are an indication of increased oxidative stress. Antioxidants like superoxide dismutase and glutathione peroxidase are jointly accessed and they are both known to counteract free radicals (reactive

oxygen species) [24].

Glutathione has a role in scavenging ROS and reactive nitrogen species. In accordance with the findings of Hamed et al. (2009.), GSH levels were significantly lower in patients with meningitis compared with those in the control group [25]. Superoxide dismutase as metalloenzymes catalyzes superoxide anion into oxygen and hydrogen peroxide. It is located in mitochondria and plays a critical role as an antioxidant [26].

Uric acid C5H4N4O3 (7,9-dihydro-1Hpurine-2,6,8(3H)-trione) is an end product of purine nitrogen base metabolism and powerful antioxidant [27], as effective as ascorbate, and a potent scavenger scavenger of radicals formed by the reactive oxygen and nitrogen species. Uric acid can act as a neuroprotective agent not only by eliminating Pn's oxidative toxicity but also by effectively scavenging downstream radicals of peroxynitrite (PN) – that is, CO3 • − and NO2 •, produced following the rapid reaction of PN with CO2 [28]. UA might suppress increased BBB permeability by protecting against PNinduced damage and directly scavenging. SUA protects the BBB's integrity and reduces its permeability. It also reduces inflammatory cell infiltration and thereby relieves brain inflammation [29]. Our results showed that patients with meningitis have lower CSF UA due to overconsumption of UA in scavenging excessive oxidative stress [30], being in line with previous reports [31]. Albumin, accounting for about 70% of the plasma colloid osmotic pressure, plays a vital role in maintaining the normal fluid distribution and constitutes the main circulating antioxidant system in the body. As potent scavengers of ROS derived from oxidative stress, albumin is the major source of extracellular reduced sulfhydryl groups (SH) [32]. Recent studies have shown that evaluation of albumin in CSF and serum specimen obtained at the same time can predict disruption of BBB and meningitis [33]. Increased amount of specific plasma protein in CSF is neither synthesized, nor metabolized intra thecally so in CSF which is free of contaminating blood so albumin in CSF must come from plasma through BBB [34]. Munoz-Sanchez [35] stated that the serum albumin, specifically block echovirus by inhibiting the un coating step in the virus replication cycle. That is to say that in man, echovirus infection may be modulated by serum albumin. Nitric oxide (NO) is produced by the action of endothelial nitric oxide synthase [36]. The mechanism by which NO may contribute to the pathophysiology of meningitis is not understood. NO produced by phagocytes has been shown to be either cytocidal or cytostatic for a variety of cells. Within the target cells, NO disrupts various enzyme systems associated with mitochondrial respiration, DNA replication, and the citric acid cycle. The enzyme inactivation is accomplished by NO chelation of iron cofactors necessary for the function of these enzymes. A plausible scenario in which NO inactivates these iron-containing enzyme systems in the microvascular endothelial cells that constitute a major site of the BBB, thereby causing cellular destruction or alteration and loss of integrity of the BBB may be postulated [37]. The NO activity in CSF in M significantly is higher in patients than in that of the control group. This was similar to the previous studies [38, 39]. Increased nitric oxide production in cerebrospinal fluid during the acute phase of bacterial meningitis may result from the inflammatory process and tissue injury

Vitamin C is a water-soluble antioxidant compound. It reduces compounds such as free radicals through its electron donating capacity, being oxidized to dehydroascorbate, and acts as a co-antioxidant by regenerating alpha tocopherol from alpha-tocopheroxyl radical produced during scavenging of oxygen free radicals [40,41]. A significant decrease in CSF vitamin C is seen in patients with meningitis compared with the control group in this study. A similar observation was made by Miricet al [23], showed low vitamin C levels in CSF of tuberculous meningitis patients. Low CSF vitamin C level as observed here was probably due to increased utilization of the vitamin to mitigate the toxicity of free radicals.

In this study we found that the CSF vitamin E level in the patients was significantly lowered than that of

the healthy group due to their free radical scavenging action and to preserve the body antioxidant reserve and in normalization of vascular superoxide formation [42].

Total Antioxidant Capacity (TAC), defined as the moles of oxidants neutralized by one liter of solution, is a biomarker measuring the antioxidant potential of body fluids [43]. In the present study, serum TAC was significantly lower in patients with meningitis when compared with the control group, which was in accordance with that of Aycicek et al. [44]., and Imad A.J. Thanoon et al [45], showing that there is significant decrease in TCA in meningitis, indicating that a considerable amount of serum TAS the undergoes oxidation under these conditions. In conditions of excessive ROS production, the decrease can also induce the damage of BBB endothelial cells, contributing to further CNS infiltration by macrophages and T-lymphocytes [46]. In sum, changes in oxidants and antioxidants were observed and their possible role in pathogenesis of meningitis. This study may play an important role in the diagnosis and more accurate treatment for the patients suffering from viral meningitis.

Conclusion

Changes in oxidants and antioxidants observed suggest production of reactive oxygen species and their possible role in pathogenesis of meningitis.

Acknowledgements

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Spectrophotometric determination of Mesalazine by formation of ion pair complex

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A B S T R A C T

A simple, developed, fast, and accurate spectrophotometric method was examined to determine Mesalazine (MES) in its pure form and pharmaceutical preparation (Pentasa). It was based on the formation of an ion pair complex between MES and the Amaranth (AMA) reagent to give a purple color product which gives its highest absorption at the wavelength of 556 nm. The best conditions for complex formation were found (time, temperature, optimal reagent concentration, and pH). The linearity of the method for the complex consisting ranged from 5-45 µg/mL, the Sandell's index was 0.01934 µg/cm2, the molar absorption coefficient was 7917.338 L/mol.cm and the detection limit was 0.03772 µg/mL, the quantitative limit was 0.11432 µg/mL, the percent recovery range was Rec% between (100.9671-95.5512) %, and the relative standard deviation rate RSD% between (0.3752-0.2926)%. It was found that the method is accurate and precision and has been successfully applied to estimate the MES in its pharmaceutical preparation, in direct methods, and in multi standard additions.

KEYWORDS Ion pair; mesalazine; amaranth.

INTRODUCTION

Mesalazine is known as mesalamine according to the American nomenclature as well as 5-amino-2-hydroxybenzoic acid according to the regular label [1]. Mesalazine is an anti-inflammatory drug. It is used in the treatment of inflammatory bowel disease, such as ulcers of the colon, anus or rectum, and protects against Crohn's disease through the development of cancer in people who suffer from inflammatory bowel disease [2]. Figure 1 displays the chemical structure of mesalazine [3].

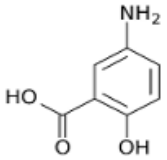


FIGURE 1 Mesalazine chemical structure [3]

MES can reduce the production of proinflammatory prostaglandins and leukotrienes [4], whereas ulcerative colitis is a condition that causes long-lasting inflammation along with sores (ulcers) in the large intestine (colon) and rectum [5]. Commonly effects result in colon cancer, skin, eye, and joint inflammation, which usually occurs due to IBD flare-ups [6,7]. MES also exhibits various significance in controlling mucosa by inhibiting bacterial peptides and cell injury through trapping most reactive oxygen species resulting in reducing its toxicity thereby blocking the production of prostaglandins [8,9]. With its significance in the pharmaceuticals industry, quality control in pharmacopeia through various analytical methods has been used to analyze MES in actual samples, such as chromatographic [10,11.12,15], fluorescence spectroscopyic
[13], electrochemical [14,16], and spectrophotometric [15] methods. Among these, electrochemical methods were found to be useful for rapid response, sensitive and selective determination of

pharmaceutical applications [17]. various The aim of the present study is to develop a simple and economy method for determination of MES in pure and in pharmaceutical form. This method is based on the ion pair formation.

Practical part
Apparatuses used

Many devices were used in this method such as: Sensitive balance (with four digits) Sartorius-Germany, Uv-Vis Spectrophotometer Double Beam, Shimadzu 1650- Japan, Uv-Vis Spectrophotometer Single Beam, Spectrophotometer-200705044, China. pH-meter, Jenway-3310, Ultrasonic water bath, LabTech-Korea.

The chemical materials
High-purity materials were used as: Mesalazine (Sigma-Aldrich), (Trisodium Amaranth (4E)-3-oxo-4-[(4-sulfonato-1naphthyl) disulfonate hydrazono] has a chemical formula ($C_{20}H_{11}N_2Na_3O_{10}S_3$) from (Sigma-Aldrich), Ethanol (GCC-England), Hydrochloric acid (BDH-U.K), and Sodium hydroxide (FlukaSwitzerland).

Standard solutions
Standard Mesalazine solution (1000 µg/mL) Solution was prepared by dissolving 0.1 g of Mesalazine in a specific volume of hot distilled water in a 100 mL volumetric flask, and then the volume was completed to the limit of the mark with the same solvent so that the concentration becomes 1000 µg/mL as a stock solution. Next, 10 mL of the solution was withdrawn and transferred to a 100 mL volumetric flask, and the solution was diluted with distilled water to the limit of the mark, so that the concentration was 100 µg/mL as a working solution.

Amaranth (AMA) reagent solution (100 µg/mL)
It was prepared by dissolving 0.1 g of the dye in a specific volume of ethanol in a 100 mL volumetric flask, and then the volume was completed to the limit of the mark with the same solvent, to be the concentration to 1000 µg/mL as a stock solution. Then 10 mL of the solution was transferred to a 100 mL volumetric flask, and the solution was diluted with ethanol to the limit of the mark, so that the concentration was 100 µg/mL as a working solution.

Hydrochloric acid solution (0.01M)
The solution was prepared by diluting 0.08 mL of concentrated acid (11.86 M) in volumetric flask with a capacity of 100 mL, and then the volume was completed to the mark with distilled water.

Sodium hydroxide solution with an approximate concentration (0.01 M)
Solution was prepared by dissolving 0.04 g of solid sodium hydroxide in a specific volume of distilled water in a 100 mL volumetric flask, then the volume was filled up to the mark of the same solvent.

Pharmaceutical solution (Pentasa) (1000 µg/mL)
10 Tablets of Pentasa, manufacturing site ferring international center–Germany, and the average weight of one tablet containing 500 mg of Mesalazine was taken, the powder was placed in a volumetric flask of 500 mL, then a certain amount of hot water was added and the volumetric flask was shaken and put it in an ultrasound water bath for 10 min. The volume was filled up by the same solvent and filtered it by

Whatman No.42 filter paper. From the filtrated solution (1000 µg/mL Mesalazine) transferred 10mL to a 100 mL volumetric flask and diluted with distilled water up to the mark so that the concentration was 100 µg/mL.

Preparation of the ion pair complex

Prepare the ion pair complex for Mesalazine by mixing 1 mL of Mesalazine (100 µg/mL) with 1 mL of AMA dye (100 µg/mL) in a 10 mL volumetric flask, then complete the volume to the mark by distilled water. A range of wavelengths was between 190 to 800 nm and it was scanned, and then the resulting complex gave a new peak at 556 nm

Table 1 illustrates that (10 µg/mL) was the optimum dye concentration through which the resulting complex gives the highest absorption, so it was chosen as the best dye concentration.

TABLE 1 The optimum dye concentration for the ion association complex of MES

Conc.of AMA µg/mL	Absorbance
2	0.211
4	0.449
6	0.722
8	0.899
10	**0.920**
12	0.465
14	0.258
16	0.221

which was adopted in subsequent experiments.

Experimental conditions

Optimum concentration of dye In order to choose the best dye concentration with the resulting complex giving the highest absorption, the increased concentration (2-16 µg/mL) of standard AMA dye solution (100 µg/mL) were added in 10 mL volumetric flask containing a fixed volume of 1 mL of standard Mesalazine solution (100 µg/mL), the volume was filled up by water to the mark level. Then, the absorption values for the complex formed versus the blank solution were recorded, as indicated in Table 1.

A study was conducted to choose the optimum pH at which the complex formed giving the highest absorption. This study was conducted at different pH values ranging (6.7-9.2) and the absorption values for the complex formed at each of these values were recorded and depicted in Table 2.

TABLE 2 The effect of the acid function on the ionic association complex of MES

Addition	Volume(mL)	Absorbance	pH
HCl (0.01)M	0.1	0.984	6.7
	0.2	0.972	6.2
	0.3	0.940	5.9
Without addition	-----	0.999	7.3
NaOH (0.01)M	0.1	0.998	7.6
	0.3	0.999	8.1
	0.5	0.997	8.5
	0.7	0.998	9.2

The results in Table 2 demonstrate that adding the acid led to a decrease in the absorption of the colored product so its use was avoided, and that adding the base did not have a noticeable effect on the value of the complex absorption which was formed, so the acid and base addition was dispensed and the natural pH of the complex was adopted (7.3) without any addition.

The optimum temperature

In order to choose the optimum temperature at which the resulting complex gives the highest absorption, the measurement process was performed for the complex with a temperature range of 5-60 oC which was depicted in Table 3.

TABLE 3 The effect of temperature on the ion pair complex of MES

Temperature	Absorbance
5	1.087
10	1.097
15	1.104
20	1.105
25	**1.107**
30	1.106
35	1.100
40	1.102
45	1.104
50	1.105
55	1.106
60	1.102

It is clear from the results of this study and as indicated in Table 3 that the maximum absorption was at the laboratory temperature, while the decrease in the absorption of the colored product formed when the temperature is increased. The laboratory temperature was therefore adopted in subsequent experiments, as high heat causes decrease absorbance gradually

Time effect

A study was conducted to find the constancy and stability of the complex formed between MES and the AMA dye by choosing the optimal time at which the complex formed gives the highest absorption, and Table 4 demonstrates the values of complex absorption at different times, ranging from the beginning of preparing the complex to a limit of 60 min.

TABLE 4 The effect of time on the ionic association complex of MES

Time(min)	Absorbance
0	**1.235**
5	1.232
10	1.230
15	1.227
20	1.226
25	1.226
30	1.227
35	1.227
40	1.227
45	1.226
50	1.228
55	1.227
60	1.227

It was found from the Table 4 that there is no significant effect of the time factor on the formation process of the complex, that is, the compound was almost stable from the moment of the reaction until 60 min, and the time of the reaction moment was adopted in subsequent experiments.

Job method

A study was conducted to determine the ratio of the drug to the ratio of the (AMA) dye in the ionic complex, according to the Job method for continuous changes. absorption values for the complex formed were measured against the blank's solution as displayed in Figure 2.

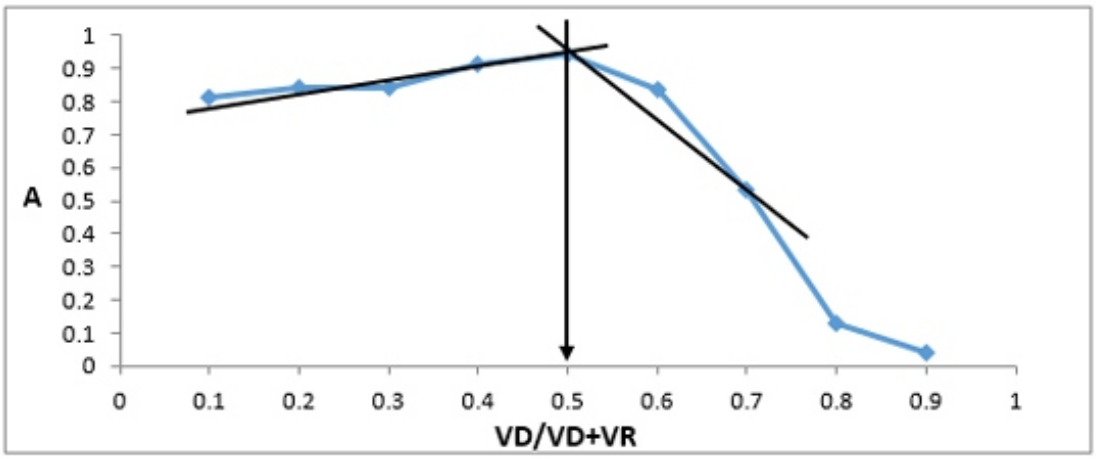


FIGURE 2 The correlation ratio of the MES complex

Through the results obtained from the Job method, it was found that the complex formed under the best conditions is composed of equal molar ratios of the drug and the dye at a ratio of (1:1), respectively.

Calibration curves

The calibration curve for the MES ion pair complex with AMA was constructed under

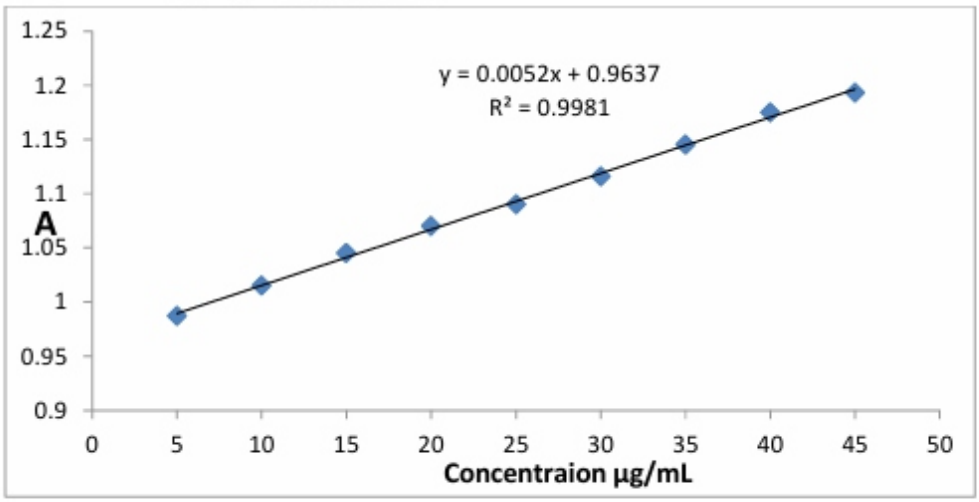


FIGURE 3 The calibration curve for MES complex

Accuracy and precision for method

A study was conducted to calculate the accuracy and precision of the proposed method, by calculating the Rec% value to express the accuracy of the results, and the RSD% for expressing the precision of the the pre-established best conditions. The linearity of the method was between 5-45 µg/mL, the Sandell's index was 0.01934 µg/cm2, and molar absorption coefficient was 7917.338 L/mol.cm. The detection limit was 0.03772 µg/mL and the quantitative limit was 0.11432 µg/mL. Figure 3 displays the calibration curve for the MES complex.15,25,45 µg/mL) of the calibration curve, and by performing six readings for each measurement process conducted in which the values of Rec% ranged were found between (95-100.3846)% and the values of RSD% between (0.2926-0.3752)%, as indicated in Table 5.

TABLE 5 The accuracy and precision of MES ion pair complex

Conc.of MES taken µg/mL	A	Conc.of MES found µg/mL	Rec %	RSD %
15	1.045	15.0576	100.3846	0.3752
25	1.090	23.75	95	0.2926
45	1.193	44.6730	99.2735	0.3412

Applications

Direct

Method

The proposed method was applied at pharmaceutical preparation (Pentasa), with different concentrations (20, 30, and 40)

TABLE 6 Applying the direct method of the ionic complex of the drug

Conc.of MES taken µg/mL	A	Conc.of MES found µg/mL	Rec %	RSD %
20	1.063	19.0961	95.4807	0.2040
30	1.113	28.7115	95.7051	0.2253
40	1.170	39.6730	99.1825	0.2370

Standard additions method

Mesalazine was determinate in the Pentasa pharmaceutical preparation using the multiple standard additions method. (0.5) mL of the prepared solution of pharmaceutical preparation with a concentration of (100 µg/mL) was added to a series of volumetric flasks (seven flasks) of 10 mL capacity. Increasing volumes of MES standard solution (100 µg/mL) were added ranged from (0.5-3) mL, and the seventh

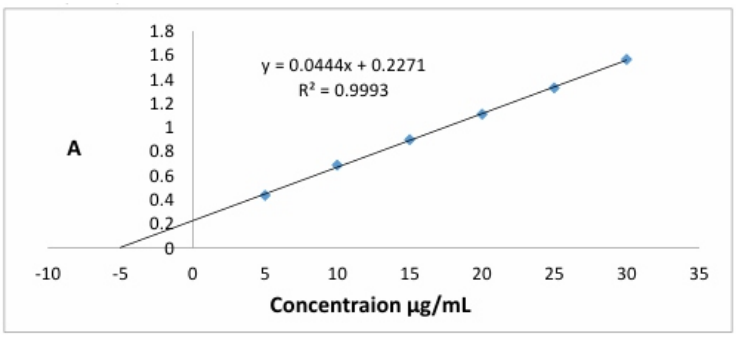


FIGURE 4 Standard additions curve

Final absorption spectrum for MES complex

According to the obtained optimum conditions, the final absorption spectrum of the MES complex versus the blank solution

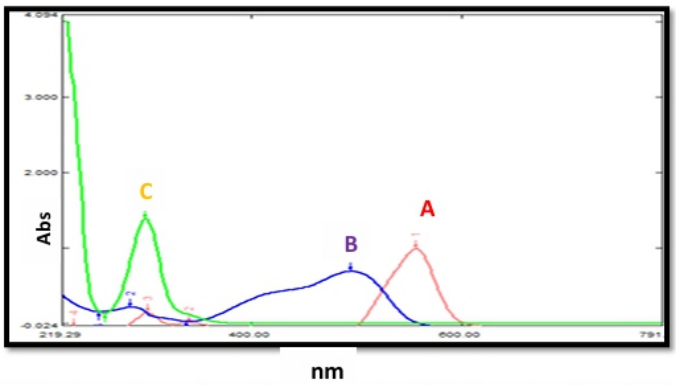


FIGURE 5 The absorption spectrum of ion pair complex (A), AMA spectrum (B) and MES spectrum (C)

Comparing the analytical properties of the proposed method

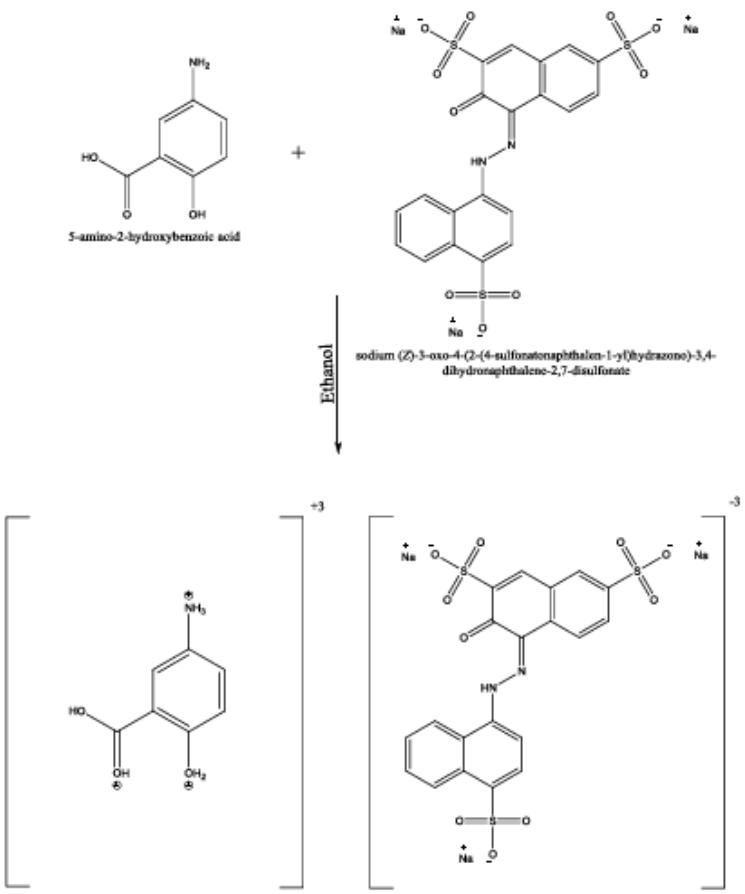
TABLE 7 Comparing the proposed method with another spectral method

Parameters	Present Method	Other Method[1]
λ_{max} (nm)	556	346
Beer's law range (µg/mL)	5-45	0.48-12
T (^{0}C)	25	40
L.O.D (µg/mL)	0.03772	0.053
L.O.Q (µg/mL)	0.11432	0.176
Correlation coefficient (R^2)	0.9981	0.9987
Sandell's index (µg/cm^2)	0.01934	0.02356
ε (L/mol.cm)	7917.338	6500
Rec% Average	100.3905	98.04
RSD%	0.3752- 0.2926	1.70

Suggested reaction equation

From the results obtained from the study of the ratio of the complex binding formed and according to Job's method for continuous was recorded to confirm the result, as a new peak of the complex appeared at the wavelength 556 nm while the value of (λmax) of the pigment was AMA 494 nm and MES 298 nm, as depicted in Figure 5.

changes, an equation for the interaction of mesalazine with AMA was proposed, as demonstrated in the following diagram.



Ion pair complex

Conclusion

The ion pair method was used to determine MES in its pure drug and Pentasa pharmaceutical form. This method was based on the reaction of MES with AMA reagent to formation of a purple complex. The highest absorption was given at 556 nm wavelength, and the obtained results showed the percentile recoveries values, the relative standard deviation, the detection limit, and the quantitative limit that the method is accurate and precise, which indicates the success of the proposed method for MES determination. Acknowledgements This research was supported department of Chemistry, College of Education, University of Samarra.

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Comparing the effect of drugs atorvastatin and rosuvastatin on the level of laboratory markers acute coronary syndrome patients

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A B S T R A C T

Pharmacotherapy is one of the most important measures for improving the health status of patients, which can play a key role in this regard. The present study was performed to compare the effect of atorvastatin plus rosuvastatin on the value of laboratory markers in CVD patients. This research is a clinical trial study, whose research population consisted of the patients with ACS in Ilam city in 2021. The patients were randomly assigned into three groups: control, intervention A (receiving atorvastatin), and intervention B (receiving rosuvastatin). The patients who met the inclusion criteria were enrolled in the study through available sampling, for all of whom the required tests were performed. The laboratory variables including tests of triglyceride, cholesterol, ALT, AST, ALP, LDH, and LDL, using a single device which was in the laboratory in Ilam city were completed and the documents related to them were considered as assessment criteria. The data analysis was done using SPSS 16 software. The table indicated the comparison of laboratory index scores before and after taking rosuvastatin. According to the findings, in all laboratory indices after taking rosuvastatin, the status of the index has changed significantly to improve the patient's health status ($p < 0.05$). Considering the greater effect of rosuvastatin compared to atorvastatin on improving the laboratory variables, prescription of this drug is suggested for improving the status of CVD patients.

KEYWORDS Atorvastatin; rosuvastatin; laboratory markers.

INTRODUCTION

The cardiovascular system, as a muscle pump responsible for blood circulation throughout the entire body, is perfused by the coronary artery system, with this system being composed of a set of arteries and veins. Any defect in the cardiovascular system can lead to devilment of cardiovascular disease (CVD), causing various complications in patients [1]. CVD is known as the most common cause of mortality in industrial countries, and in Iran, as well. It has further shown an ascending trend in the recent years, the age of developing CVD has decreased considerably which is really concerning [2]. Heart coronary diseases include a wide range of diseases including the unstable angina, chronic stable angina, silent ischemia, cardiomyopathy, myocardial infarction, and sudden cardiac death. Coronary artery disease is a type of heart disease with a high prevalence, and can lead to complications as well as morality in 26% of premature deaths in men and 16% of premature deaths in women [3,4]. CVD has different risk factors including family history, sedentary lifestyle, poor diet, tobacco consumption, and history, or development of chronic diseases such as diabetes [5,6]. The major symptoms of heart disease include dyspnea at rest, or during activity, as well as fatigue causing activity intolerance. Patients with heart disease may experience various consequences including low quality of life, poor treatment adherence, and weak self-management, all of which could affect the improvement of the disease. As such, the proper therapeutic interventions are required [7].Pharmacotherapy is one of the most important measures for improving the health status of patients, which can play a key role in this regard. Various drugs are used for improving CVD patients, including atorvastatin and rosuvastatin [8-10]. In patients with mild to severe hyperlipidemia, the use of lipid-lowering drugs can lead to decrease lipid levels and

improve the patient status [11]. In CVD patients, triglyceride, cholesterol, AST, ALT, ALP, LDH, and LDL tests are effective to measure the health status of patients, and identifying the suitable drug for adjusting these tests can be effective in improving patients [12,13].

Objectives

Considering the significance of CVD and the role of healthcare team in treating these patients, the present study was performed to compare the effect of atorvastatin plus rosuvastatin on the value of laboratory markers in CVD patients.

Methods

Study design

This research is a clinical trial study, in which the research population consisted of patients with ACS in Ilam city in 2021.

Study population

The sample size, based on the previous studies, included 85 patients

Inclusion and exclusion criteria

Inclusion criteria

The inclusion criteria included developing MI based on the opinion of physician as well as the clinical documents of the patient's file, residence in Ilam city, the age range between 18 and 75 years, the patient's written informed consent for participation, and receiving Ethics Approval IR.MEDILAM.REC.1400.084

Exclusion criteria

Code No. Lack of cooperation or patient's refusal to continue their participation in the study at any time of the research, the presence of any complication for the patient in the course of study (such as hospitalization, patient's death, etc.), changing the patient's drugs according to the physician's order, the clinical status of the patient, the lack of treatment adherence, and failure to take drugs properly, as well as the lack of cooperation to undergo tests were considered as the exclusion criteria.

Data gathering

Demographic characteristic

The demographic information, which was completed for patients using patient's clinical file and interview with them, included age, gender, place of residence, education, and body mass index (BMI). The laboratory variables including tests of triglyceride, cholesterol, ALT, AST, ALP, LDH, and LDL, using a single device which was in the laboratory of Shahid Mostafa Khomeini Hospital in Ilam city were completed and the documents related to them were considered as assessment criteria.

Method of research

The patients were randomly assigned into three groups: control, intervention A (receiving atorvastatin), and intervention B (receiving rosuvastatin). The patients who met the inclusion criteria were enrolled in the study through available sampling, for all of whom the required tests were performed. Patient allocation to the groups was performed as blocks of size 4 random allocation. Briefly, first the size of each block was maintained in the block of size 4, and then the blocks were specified using www.randomizer.org site, the numbers were assigned to them, whereby the individuals selected

numbers across the envelopes randomly. Group 1 received atorvastatin tablet 40 mg once a day for 3 months, and group 2 took rosuvastatin tablet 40 mg once per day for 3 months. Next, the triglyceride, cholesterol, ALT, AST, ALP, LDH, and LDL tests were performed again on the patients, and their results were compared with the preintervention stage.

Ethical approval

The informed consent for participation in the study, allocation of patients to the control group, as well as intervention A and

TABLE 1 Demographic characteristics of patients under study

Variable		Atorvastatin N (%)	Rosuvastatin N (%)	p-value
Gender	Man	20 (50.0%)	20 (50.0%)	1.00
	Female	20(50.0%)	20 (50.0%)	
Marital status (%)	Single	4 (10%)	6 (15%)	0.46
	Married	36 (90%)	34 (85%)	
Location (%)	City	22 (55%)	22 (55%)	1.00
	Village	18 (45%)	18 (45%)	
Education (%)	Literate	20 (50%)	20 (50%)	1.00
	Illiterate	20 (50%)	20 (50%)	
Age, (years) (Mean ± SD)		59.1 (1.7)	57.9 (1.8)	0.66
BMI (kg/m2) (Mean ± SD)		26.8 (0.3)	26.2 (0.2)	0.09

intervention B through random allocation, freeness of all drugs and tests used for the patients, and the confidentiality of patients' information were among the ethical principles observed in this research. The data analysis was done using SPSS 16 software and via statistical tests of mean, standard deviation, as well as frequency distribution table for reporting demographic variables. To compare the significance of the demographic variables, the independent t-test and Chi-square were employed. Likewise, to compare the laboratory markers, the inferential statistics were used.

Results

Table 1 indicates the demographic characteristics of the patients under study. According to the findings of Table 1, there was no significant difference among the demographic characteristics of the 3 groups, including control group, test A, and test B ($P > 0.05$). Table 2 presents the comparison of laboratory index scores before and after taking rosuvastatin. According to the findings, in all laboratory indices after taking rosuvastatin, the status of the index has changed significantly to improve the patient's health status ($p < 0.05$).

TABLE 2 The difference between the mean of laboratory variables before and after taking rosuvastatin

Variable	Mean Before	Mean After	Difference in Averages	P-value
ALT	46.30 (0.5)	31.05 (0.7)	15.25 (0.4)	<0.001*
ALKp	211.55 (6.22)	172.03 (6.6)	39.53 (2.9)	<0.001*
AST	46.23 (0.4)	30.50 (0.7)	15.13 (0.4)	<0.001*
LDL	199.63 (8.7)	136.03 (6.9)	63.60 (5.5)	<0.001*
HDL	21.88 (0.7)	42.15 (1.1)	-20.28 (1.2)	<0.001*
TG	272.43 (11.9)	192.10 (11.8)	80.33 (3.1)	<0.001*
CHLE	277.05 (6.8)	204.00 (7.5)	73.08 (2.1)	<0.001*
CRP	21.90 (1.3)	12.83 (1.2)	9.08 (0.5)	<0.001*

Table 3 reveals the comparison of laboratory index scores before and after taking atorvastatin. According to the findings, in all laboratory indices after taking atorvastatin, the status of the index has changed significantly to improve the patient's health status ($p < 0.05$). TABLE 3 The difference between the mean of laboratory variables before and after taking

TABLE 3 The difference between the mean of laboratory variables before and after taking atorvastatin

Variable	Mean Before	Mean After	Difference in Averages	P-value
ALT	47.80 (0.8)	37.70 (1.0)	10.10 (0.4)	<0.001*
ALKp	200.13 (3.9)	171.73 (5.1)	28.40 (2.7)	<0.001*
AST	47.88 (1.2)	38.38 (1.2)	9.50 (0.5)	<0.001*
LDL	217.75 (4.7)	188.80 (4.4)	28.95 (1.5)	<0.001*
HDL	20.20 (0.8)	35.95 (1.1)	-15.75 (0.7)	<0.001*
TG	298.38 (9.1)	222.65 (8.4)	75.73 (3.8)	<0.001*
CHLE	293.15 (5.7)	220.28 (5.8)	72.88 (3.9)	<0.001*
CRP	20.83 (1.0)	14.60 (1.0)	6.23 (0.2)	<0.001*

Discussion

Heart disease has a significant prevalence and is influenced by the other chronic diseases such as diabetes which are of high significance for this group of patients as one of the ways to reduce the complications of the disease should be a priority (14-17). The proposed study was performed to compare the effect of atorvastatin and rosuvastatin on the laboratory markers of CVD patients. According to the findings, atorvastatin showed a significant effect on improving the status of laboratory markers in CVD patients. After taking this drug, the status of AST and ALT of the patients diminished significantly. In the study by YongLi et al., in which 47 patients had been assigned into placebo and atorvastatin groups, the patients received atorvastatin 40 mg for one year. It was found that consumption of this drug could lead to reduced cholesterol and LDL of the examined patients [18]. In the study by Fassett et al., in which atorvastatin had been used to examine the status of blood biomarkers of kidney disease patients, 120 patients had been assigned to placebo (n=61) and intervention (n=56) groups. It was found that atorvastatin led to significant reduction of eGFR of patients [19], which is in line with the results of this study regarding improvement of laboratory markers after taking atorvastatin. Based on the findings, rosuvastatin also caused improvements in the status of laboratory variables in CVD patients. In the study by Sexton et al. enrolling 54 patients with ACS assigning them into intervention (receiving 40 mg rosuvastatin) and placebo groups, they found that this drug can lead to decrease troponin and CK-MB levels in patients with ACS [20]. Likewise, in the study by Luo et al., it was found that the use of high dose, in comparison to conventional-dose of this drug, could have a greater effect on improving blood lipid metabolism and reduce the blood lipid metabolism [21]. It is in line with the results of this study regarding improvement of laboratory markers following use of rosuvastatin. Meanwhile, in the study by Hearps et al., it was revealed that rosuvastatin had no significant effect on improving interleukin 6, CXCL10, and monocyte subsets. The reasons of this difference can be differences in the type of laboratory variables examined; in this study, triglyceride, cholesterol, ALT, AST, ALP, LDH, and LDL were explored, while in the study by Hearps, the other variables had been examined [22]. According to the results, both rosuvastatin and atorvastatin led to improvements in the blood markers of the patients; however, the extent of improvement and mean difference were greater for rosuvastatin than for atorvastatin. In the study by Umrani et al., who had examined atorvastatin and rosuvastatin on the status of blood markers of patients with ACS, they observed that rosuvastatin could lower the hs-CRP and ESR of patients more considerably than atorvastatin [23]. It is in line with the results of this study regarding the greater effect of rosuvastatin drug compared to atorvastatin in

improving the blood biomarkers of CVD patients. Meanwhile, findings of some studies have not accorded with the present study results; in the metaanalysis by Pratiwi et al., studying 687 patients in four papers with the aim of comparing these two drugs on the status of CRP of ACS patients, it was found that although atorvastatin and rosuvastatin both resulted in reduced CRP of patients, no significant difference was found between these two drugs regarding CRP reduction [24]. In the study by Kumar et al., examining both atorvastatin and rosuvastatin on the status of blood biomarkers of patients with ATS, it was found that in the rosuvastatin group, the hs-CRP and ESR levels were lower compared to the atorvastatin group [25]. Meanwhile, in the study by Umrani et al. investigating both atorvastatin and rosuvastatin on the status of blood biomarkers of patients with ACS, it was indicated that rosuvastatin could lower hs-CRP and ESR more considerably than atorvastatin did [23].

Conclusion

Regarding the greater effect of rosuvastatin compared to atorvastatin on improving the laboratory variables, prescription of this drug is suggested for improving the status of CVD patients.

Acknowledgements

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Chemical synthesis of various composites of chromen-2-one: A review

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A B S T R A C T

Chromen-2-one composites are a type of heterocycles that has a wide range of uses in healthcare technology, biological research, and a variety of commercial fields. Many attempts are being made to create the innovative and more realistic ways of manufacturing such molecules in order to achieve this goal. Several chromen-2-one composite synthesis procedures are described in this study, including Von Pechmann condensation, Knoevenagel condensation, Kostanecki reaction, Baylis-Hillman retort, Michael addition, electrophilic reaction mediated by vinyl phosphonium salt, and the reaction of Heck-lactonization.

KEYWORDS Chromen-2-one composites; chemical synthesis;pharmacological properties.

INTRODUCTION

Chromen-2-one composites are of high significance due to their important biological activities [1]. These composites, as bioactive agents, can activities exhibit diverse biological which include antiviral [2], antibacterial [3], antimicrobial [4], anticoagulant [5], anti-inflammatory [6], anticancer [7], anticonvulsant [8], antioxidant [9], anti-fungal [10], and anti-HIV [11]. They also have features such as platelet aggregation inhibition [12] and steroid 5α-reductase inhibition. In addition, chemists are quite

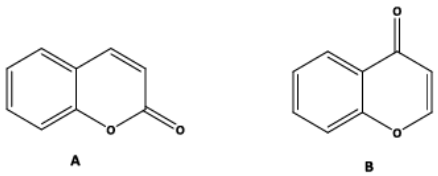


FIGURE 1 Two general types of benzopyrones

interested in them due to their huge range of applications along with photosensitizers [13] and optically fluorescent dyes and components in nutrition, fragrance, skincare, and medications. A family of heterocyclic molecules known as benzopyrone is formed when the pyrone ring and the benzene nucleus fuse. As displayed in Figure 1, there are two varieties of benzopyrones. They are benzo-α-pyrone (A), also known as coumarin, and benzo-γpyrone (B), also known as chromones, and they merely differ in the location of the pyrone ring's carbonyl group [13].

Chromen-2-ones, as depicted in Figure 2, are categorized according to their molecular constitution: the simple chromen-2-ones with the benzene ring hydroxylated, alkylated, or alkoxylated (e.g., Umbelliferone). The linear

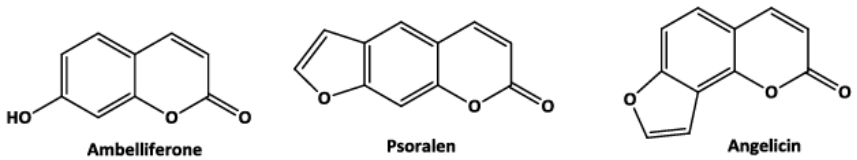


FIGURE 2 The classic examples of different types of chromen-2-ones

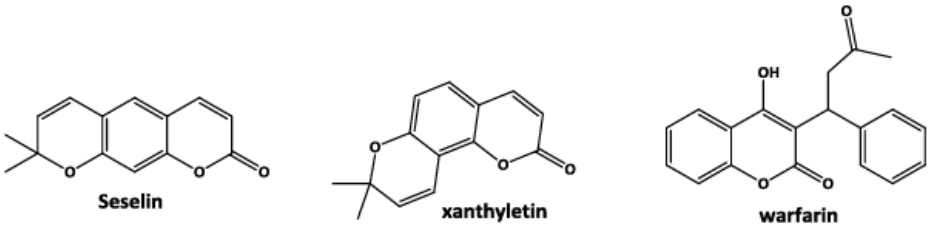


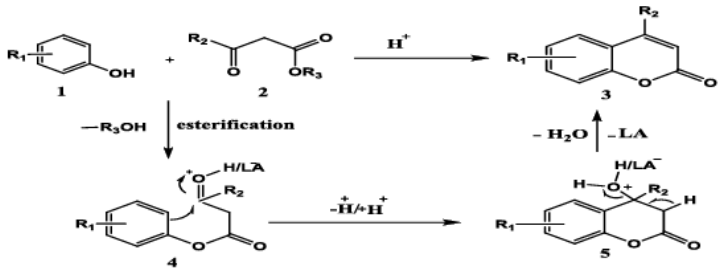
FIGURE 3 The classic examples of pyrano chromen-2-ones

Synthetic chemists are developing new to isolate chromen-2-one composites in the light of these diverse activities of chromen-2-ones. The most extensively used technique for chromen-2one synthesis is the Pechmann reaction [15], which includes the condensing of phenols with β-keto esters using acid as a catalyst. This approach involves both homogeneous catalysts, including concentrate sulphoric acid [15], F3CCOOH [16], aluminum chloride [17], zinc chloride, titanium (IV) chloride [18], and many others. Nafion resin/silica composites [19], cation-exchange resins [20], and the other solid acids are some examples of heterogeneous catalysts furanochromen-2-ones (e.g., psoralen) and the angular furanochromen-2-ones (e.g., Angelicin) are furanochromen-2-ones which have a five-membered furan ring attached to the chromen-2-one group [14] Xanthyletin and Seselin). Chromen-2-ones have pyrone ring substitutes (e.g., Warfarin) [14].

Synthetic Composites Methods for Chromen-2-

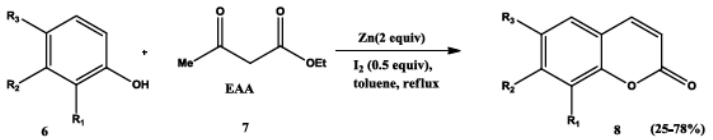
The reaction of pechmann condensation

In 1883, Pechmann & Duisburg were the first to mention the Pechmann condensation process. Because of its ease of preparation and low cost of starting material, it's been widely used in the production of chromen-2ones. In the presence of an acid catalyst, as depicted in Scheme 1, the esterification/transesterification of phenol 1 & β-keto ester 2 forming species 4, then the activated carbonyl binds to the ortho position of the aromatic ring, giving species 5. chromen-2-one composites 3 are obtained by dehydrating species 5.



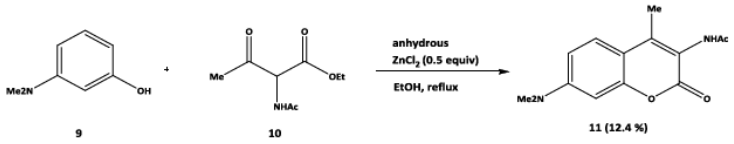
SCHEME 1 Pechmann condensation catalyzed by an acid

When substituted phenols 6 are combined with ethyl 3-oxobutanoate 7 in the presence of Zn-I2 combination, a variety of the substituted chromen-2-ones were generated in good yield, as depicted in



SCHEME 2 The reaction between various phenols and active methylene-containing group

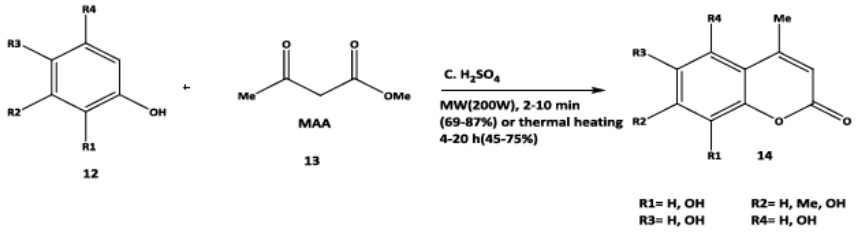
As depicted in Scheme 3, only 12.4 % of the acetamido coumarin 11 is produced when 3-(dimethylamino) phenol 9 reacts with ethyl 2-acetamido-3-oxobutanoate 10 in absolute



SCHEME 3 The synthesis of acetamido chromen-2-one composites using zinc chloride as promoter

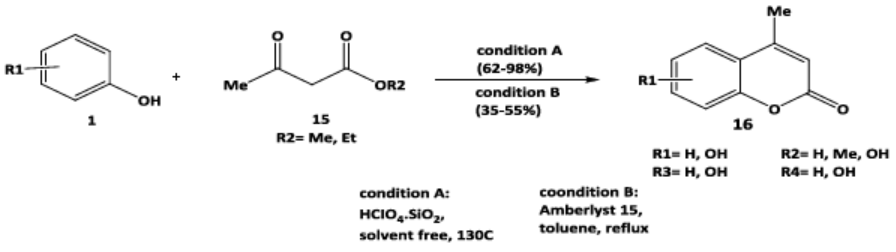
Using concentrated sulphoric acid as a catalyst under microwave and conventional heating, the substituted chromen-2-ones 14
Scheme 2 [21]. The non-substituted phenols and phenols with electron removing groups like NO2 generate lower yields than phenols with electron giving groups like -Ch3.ethanol under reflux conditions using anhydrous zinc chloride as a catalyst (Scheme 3) [22].

were produced in good yield from substituted phenols 12 and methyl 3-oxobutanoate 13, as depicted in Scheme 4 [23].



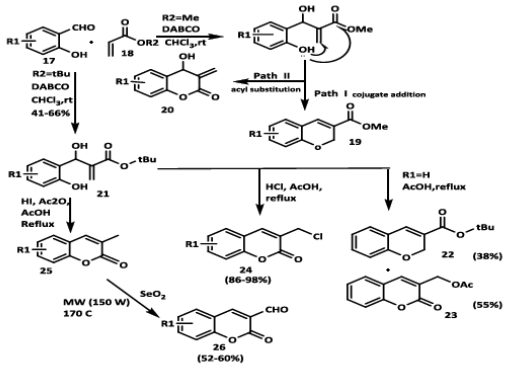
SCHEME 4 Synthesis of various substituted chromen-2-ones under different energy sources

In a liquid free environment (Scheme 5, condition A), substituted chromen-2-ones 16 were generated in good yield by reacting βketo esters 15 with substituted phenols 1 employing a heterogeneous catalyst, HClO4.SiO2 [24]. This approach uses a lowcost catalyst and produces good product

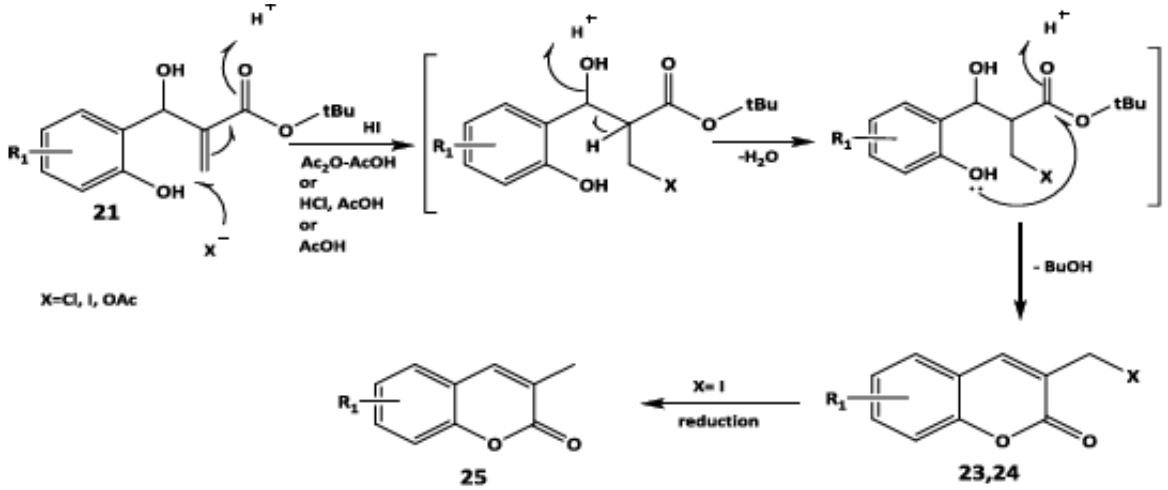


SCHEME 5 Synthesis of various substituted chromen-2-ones under a liquid free environment

Baylis-Hillman reaction Scheme 6 reveals the Baylis-Hillman technique for synthesis of substituted chromen-2-one composites s. When 1,4diazabicyclo [2.2.2] octane is presented, salicylaldehyde 17 reacts with methyl acrylate 18a to create a combination of chromen-2-one composites 19 and 20 [26]. The similar reactions of salicylaldehyde 17 with tertiary butyl acrylate 18b using the traditional approach [27] and/or irradiation via microwaves [28] generate analogous adducts of Baylis-Hillman 21, which are cyclized in acetic acid to yield a 3-substituted mixture of chromen-2-one composites 22 and 23. When adducts of Baylis-Hillman 21 are treated with strong hydrochloric acid in acetic acid reflux, the desired yields of 3(chloromethyl)-2H-chromen-2-one 24 are obtained. Furthermore, the reaction of 21 with hydrogen iodide in a combination of acetic anhydride and acetic acid under reflux yields 3-methyl-2H-chromen-2-one 25, which is then converted into the equivalent 2-oxo2H-chromen-3-carbaldehyde 26 by further reaction with selenium dioxide. Scheme 7 depicts the proposed pathway for chromen-2one composites 23, 24, and 25 synthesis.



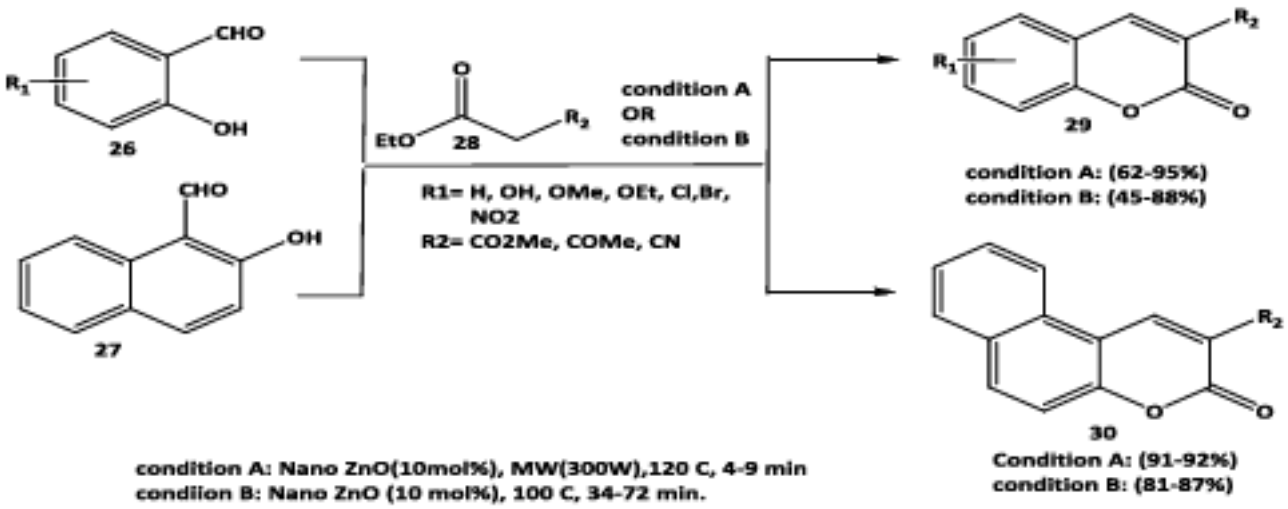
SCHEME 6 Synthesis of various 3-substituted chromen-2-ones by Baylis-Hillman technique



SCHEME 7 Synthetic mechanism of various 3-substituted chromen-2-ones utilizing a Baylis-Hillman reaction

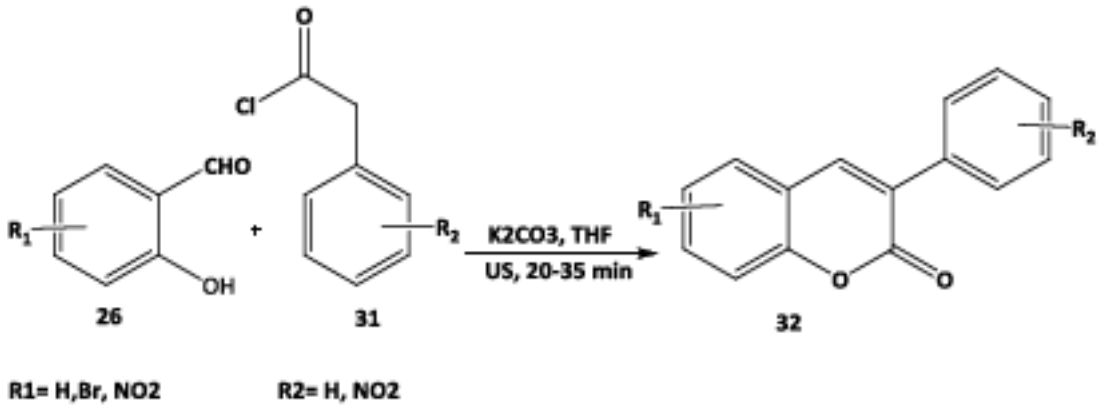
The condensation reaction of Knoevenagel

Knoevenagel condensation of different salicylaldehydes 26–27 with 1,3-dicarbonyl compounds 28 under microwave or heat conditions using zinc oxide nanoparticle catalyst has been discovered as an efficient way to synthesize 3-substituted chromen-2-one composites 29 and 30, as represented in Scheme 8 [29]. It has been proven that microwave-irradiated reactions are more efficient than thermal reactions.



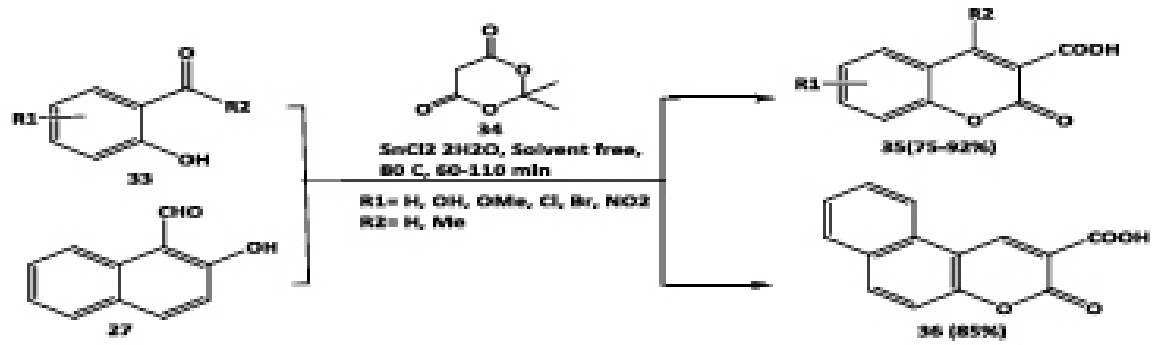
SCHEME 8 Synthesis of various 3-substituted chromen-2-ones utilizing zinc oxide nanoparticle as a promoter

The ultrasound irradiation technique was employed to make 3-aryl chromen-2-one composites. In tetrahydrofuran, the ultrasonic irradiation of salicylaldehyde 26 with acetyl chloride substituted with aryl group 31 using potassium carbonate as a catalyst results in the production of 3-aryl chromen-2-one composites 32 in good yields, as displayed in Scheme 9 [30]. This green approach looks to be a more handy and straightforward option than the traditional heating.



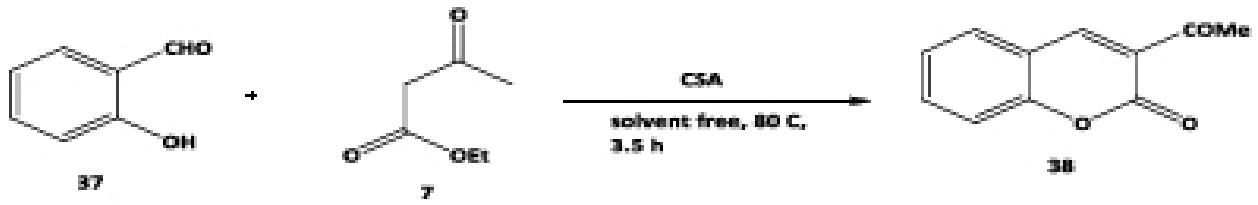
SCHEME 9 Synthesis of various 3-aryl chromen-2-ones utilizing potassium carbonate as a promoter

Under solvent-free conditions, several composites of chromen-2-one-3-carboxylic acid 35 and 36, as demonstrated in Scheme 10, have been produced in excellent yields employing catalytic quantities of stannous chloride dehydrate [31].



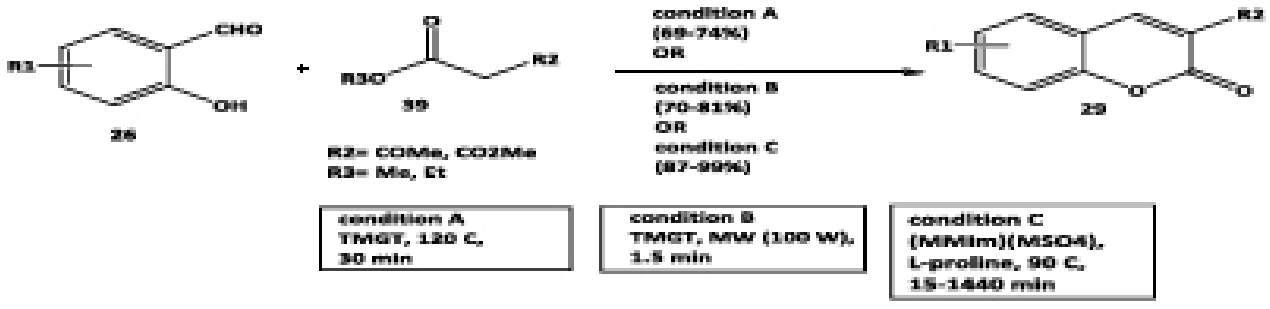
SCHEME 10 Synthesis of different chromen-2-one-3-carboxylic acid composites under solvent-free conditions

The Knoevenagel condensation process uses cellulose sulfonic acid as a promoter to produce chromen-2-one substituted at 3-position, as depicted in Scheme 11. In the presence of CSA, 3-acetyl chromen-2-one 38 is produced in a yield of 88 % under solvent-free conditions, in a reaction involving salicylaldehyde 37 and ethyl 3-oxobutanoate 7 [32].



SCHEME 11 Synthesis of chromen-2-one-3-substituted composite using cellulose sulfonic acid as a promoter

Through Knoevenagel condensation of salicylaldehyde 26 with dicarbonyl compounds 39 in the presence of 1,1,3,3-tetramethylguanidinium trifluoroacetate (TMGT) (33) under thermal heating (Scheme 12, condition A) and/or microwave irradiation conditions, 3-substituted chromen-2-ones 29 were produced in desired yields. Under heating conditions (Scheme 12, condition B), 3-substituted chromen-2-ones 29 are similarly generated from identical starting precursors using the 1,3-dimethyl-1*H*-imidazol-3-ium methyl sulfate ionic liquid in the presence of L-proline as an additional promoter (Scheme 12, condition C).

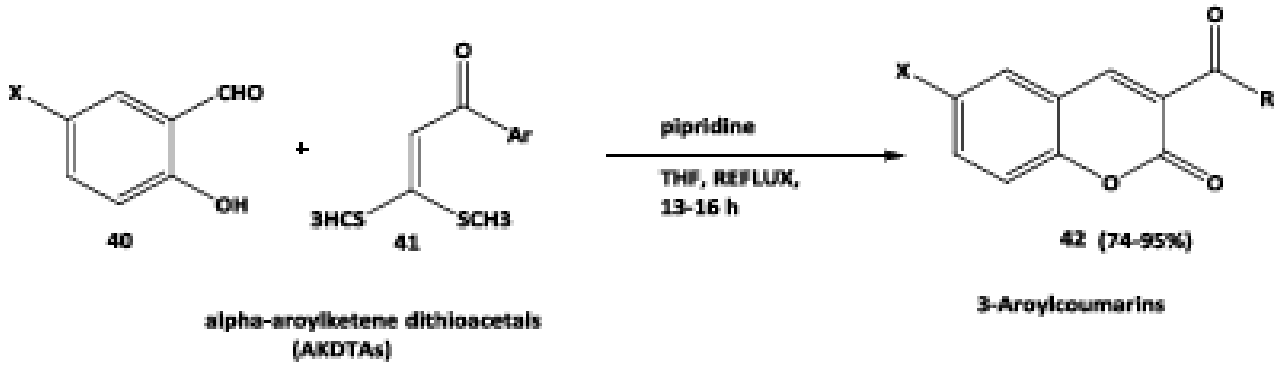


SCHEME 12 Synthesis of chromen-2-one-3-substituted composites using L-proline as a promoter in different reaction conditions

Michael addition reaction

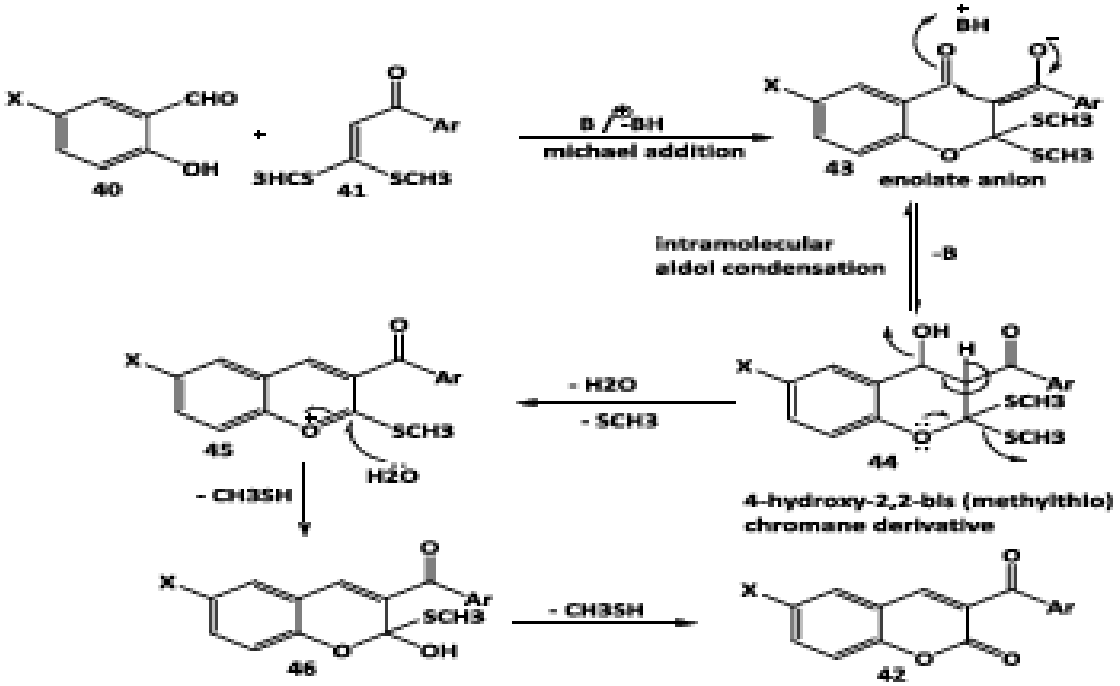
Michael addition, as depicted in Scheme 13, was used to synthesize 3-aroyl-chromen-2-

one composites 42 in excellent yields from salicylaldehyde 40 and dithioacetals of α-aroylketene 41 in a refluxing condition in the tetrahydrofuran solvent system using piperidine as a promoter [34].



SCHEME 13 Synthesis of 3-aroyl-chromen-2-one composites using a Michael addition reaction

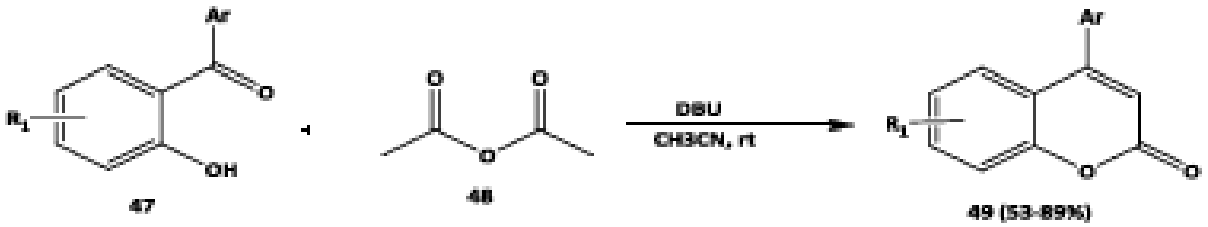
As presented in Scheme 14, the reaction mechanism of the aforementioned composites starts with a Michael addition, and then enhances to an intramolecular aldol condensation process [34].



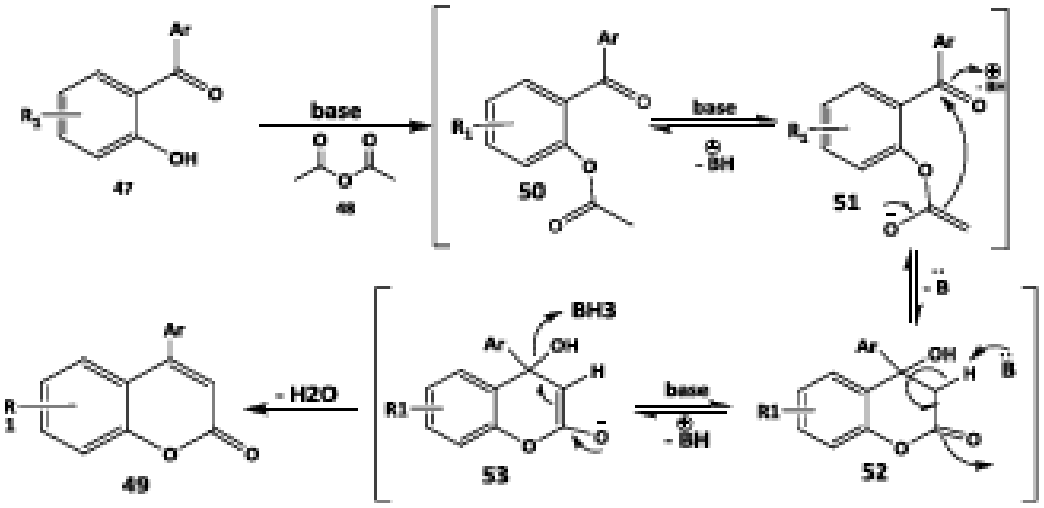
SCHEME 14 Synthetic mechanism of the 3-aroyl-chromen-2-one composites 42

Kostanecki reaction

Under relatively mild conditions, the Kostanecki reaction of 2-benzoylphenol 47 with acetic anhydride 48 under the catalytic influence of DBU yielded 4-arylchromen-2-one composites 49 in excellent yields, as depicted in Scheme 15. Also, the mechanistic steps concerning this reaction are illustrated in Scheme 16 [35].



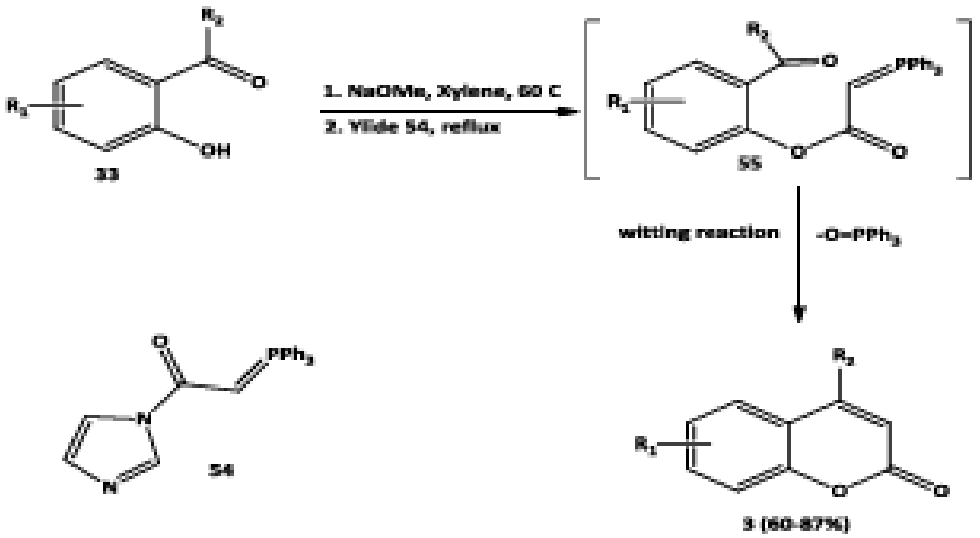
SCHEME 15 Synthesis of 4-arylchromen-2-one composites under Kostanecki reaction conditions



SCHEME 16 The kostanecki reaction mechanism

Wittig reaction

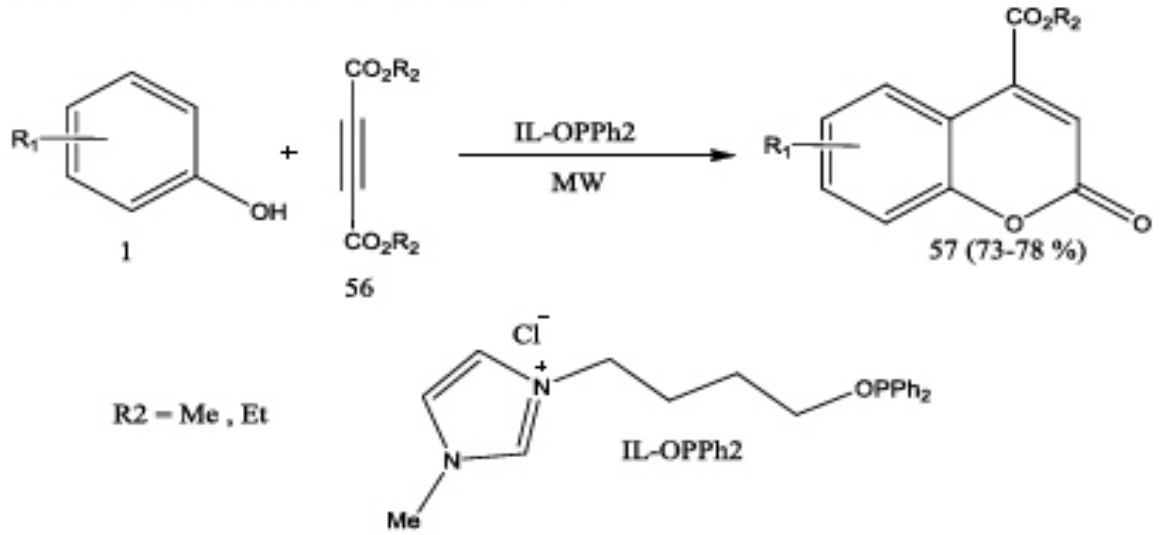
Kumar and colleagues used the intramolecular Wittig cyclization to effectively synthesize substituted chromen-2-one composites 3 from ortho carbonyl group substituted phenolic compounds 33 and imidazole triphenyl phosphorane ylide 54, as depicted in Scheme 17. As determined by spectroscopic data, all of the reactions take place via the production of phosphorane intermediates 55 [35].



SCHEME 17 Synthesis of substituted chromen-2-one composites via an intramolecular Wittig cyclization methodology

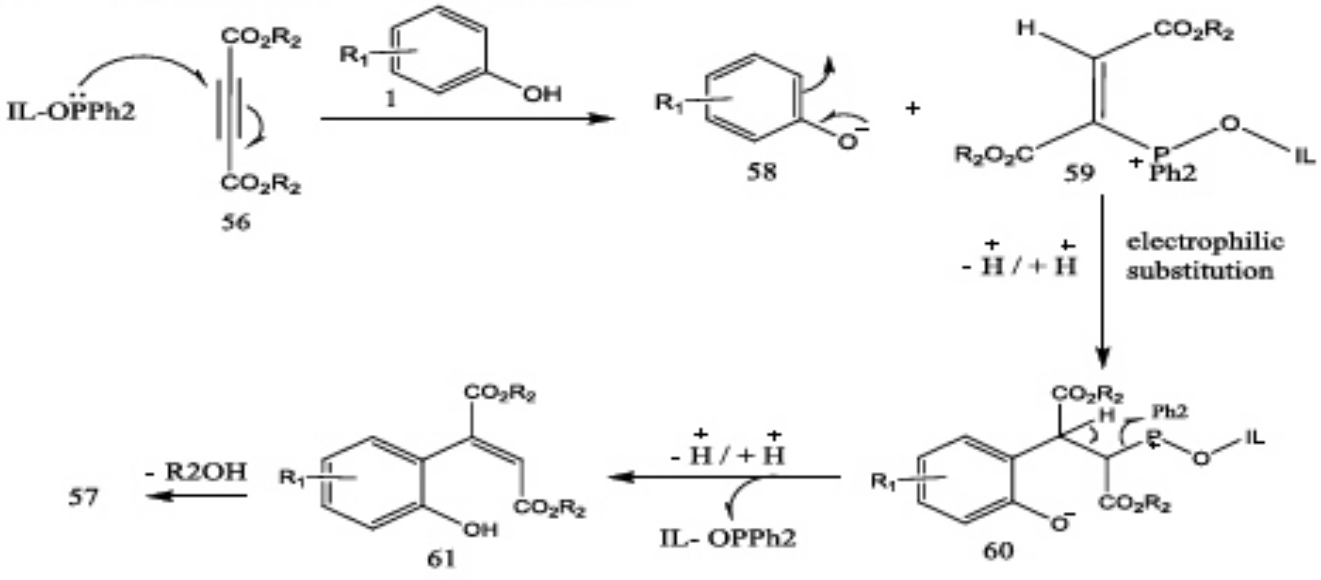
Electrophilic substitution process mediated by vinyl phosphonium salt

Under solvent-free microwave conditions, a number of 4-carboxy (methyl/ethyl) chromen-2-one composites 57 were produced in excellent yields from substituted phenols 1 and di(methyl/ethyl) 2-butynedioate 56 in the presence of phosphinite alkaline solution, as illustrated in Scheme 18. The process exceeded through the ionic liquid of diphenylphosphine group [37].



SCHEME 18 Synthesis of 4-functionalized chromen-2-one composites via an electrophilic substitution reaction

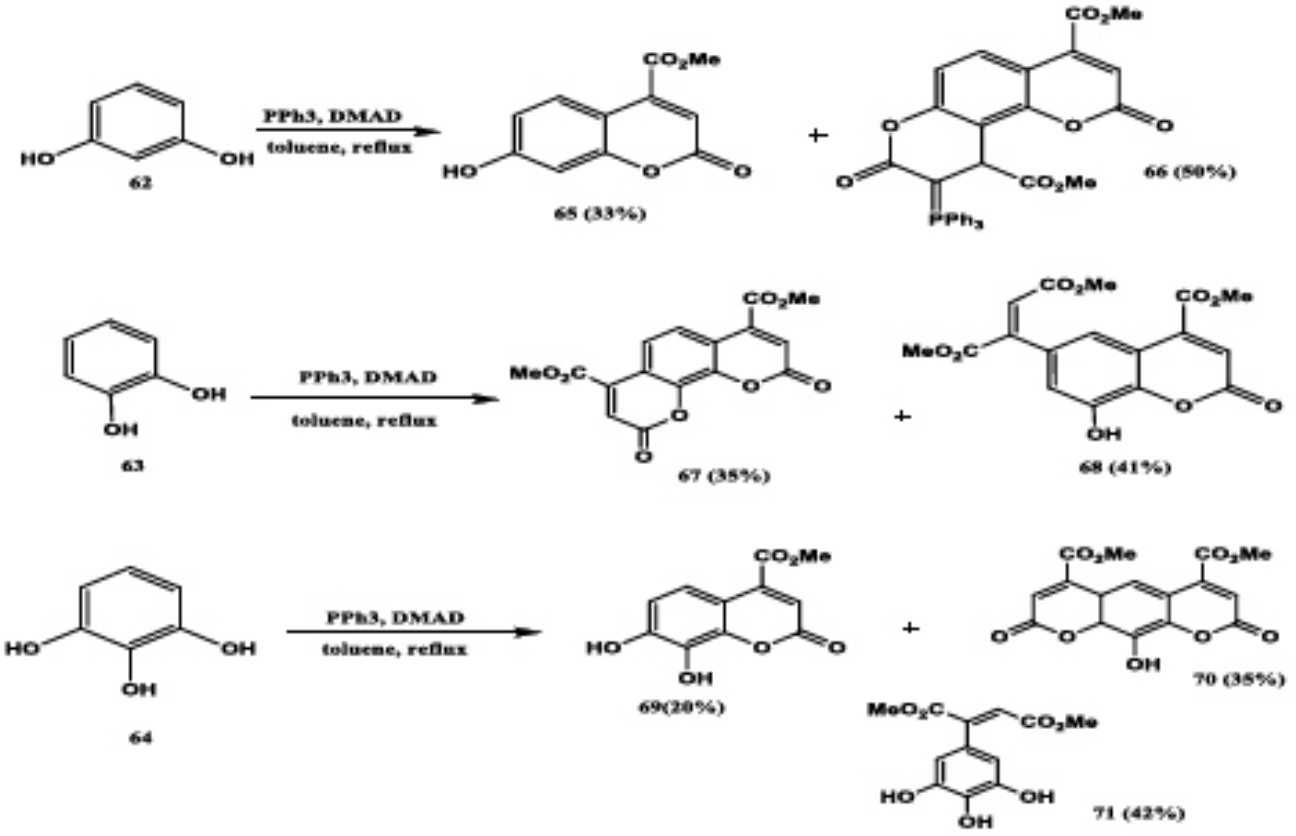
Scheme 19 depicts the suggested mechanistic steps involved in the generation of 4-functionalized chromen-2-one composites 57 by electrophilic substitution mediated by vinyl phosphonium salts.



SCHEME 19 Synthetic mechanism of 4-functionalized chromen-2-one composites via an electrophilic substitution reaction

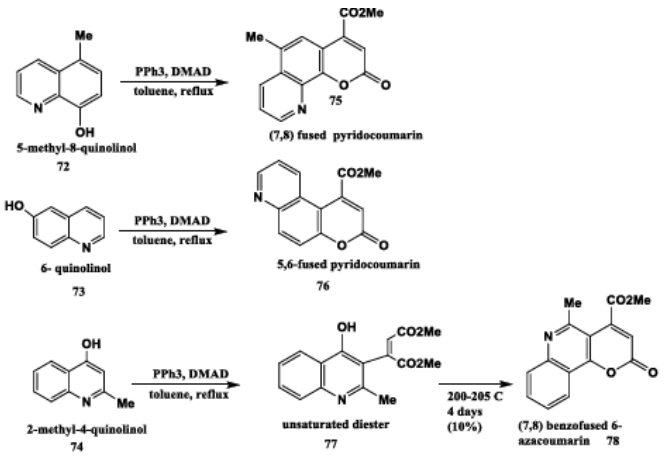
By reacting di-or tri-phenols with dimethyl 2-butynedioate under refluxing conditions in toluene as a solubilizing medium and with the presence of

triphenylphosphine, polyfunctionalized chromen-2-one composites are produced with a considerable number of the unwanted by-products, as displayed in Scheme 20 [38].

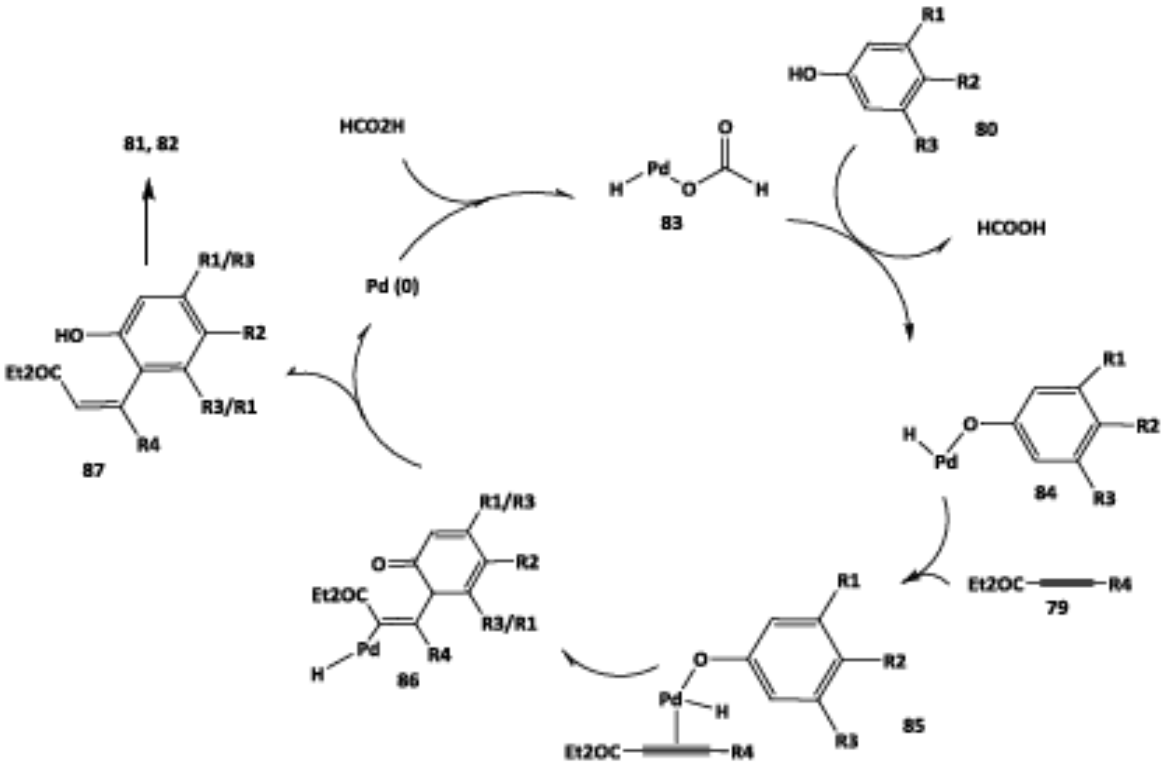


SCHEME 20 Synthesis of polyfunctionalized chromen-2-one composites employing triphenylphosphine as a promoter

This method has also been utilized to make the angular pyridochromen-2-one composites 75, 76, and benzo-fused 6-azachromen-2-one 78, as demonstrated in Scheme 21 [38].

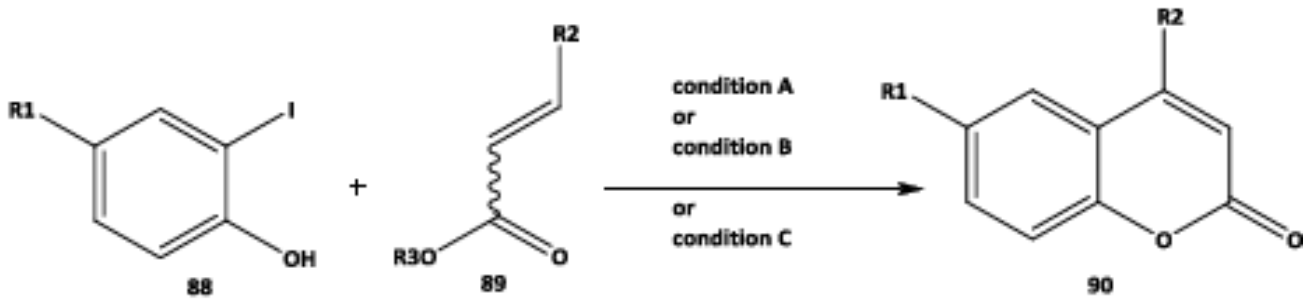


SCHEME 21 Synthetic of pyridochromen-2-one and benzo-fused azacohromen-2-one composites via an electrophilic substitution reaction



SCHEME 23 Synthetic mechanism of polysubstituted chromen-2-one composites 81 and 82

Heck-lactonization using palladium catalysis of *E*- or *Z*-enoates 89 with 2-iodophenols 88 yielded 4,6-disubstituted chromen-2-one composites s 90, as presented in Scheme 24 [39].

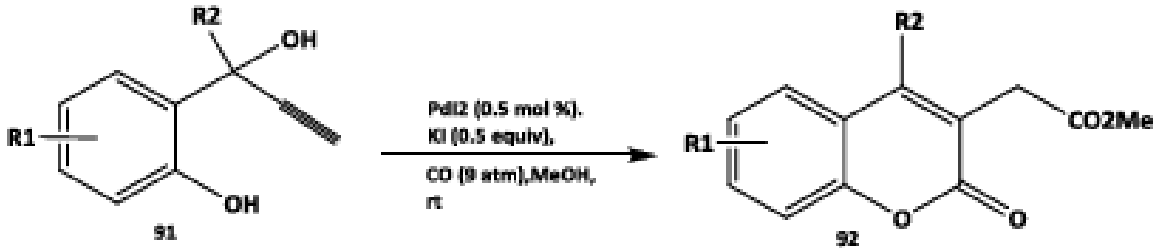


R1 = H, Cl, NO2, CO2Me R2 = CH2CHMe2, Me R3 = Et, Me, tBu

condition A : 10 mol% of Pd(OAc)2,3 equiv Et3N, H2O, 80 C, 40 h
condition B : 10 mol % of PdCl2, 3 equiv Et3N, H2O, 80 C, 40 h
condition C : 10 mol% of Pd(OAc)2, in the presence or absence of 20 mol % of pph3, 3 equiv AgCO3, acetone, reflux, 40 h

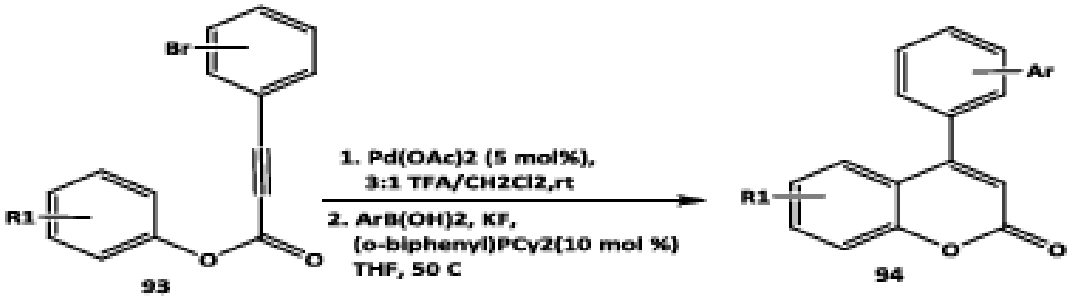
SCHEME 24 Synthesis of 4,6-disubstituted chromen-2-one composites via a palladium catalysis methodology

Furthermore, dicarbonylation of accessible 2-(1-hydroxyprop-2-yn-1-yl) phenols 91 catalyzed by palladium in methanol at room temperature gives polyfunctionalized chromen-2-ones 92 in good quantities, as displayed in Scheme 25 [39].



SCHEME 25 Synthesis of polyfunctionalized chromen-2-one composites via a palladium catalysis methodology

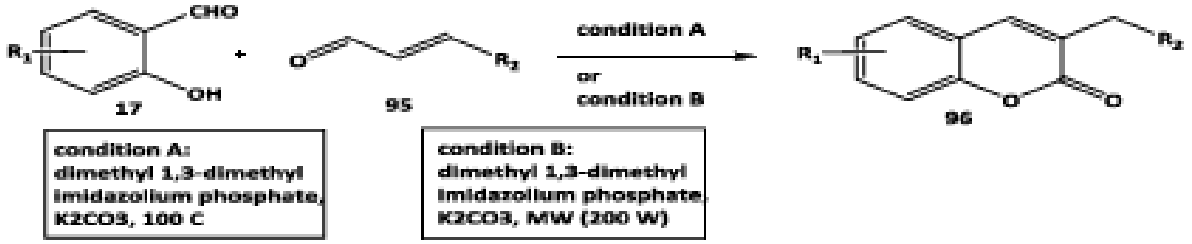
Moreover, the 4-arylchromen-2-one composites 94 are obtained in moderate to fair yields via cycloisomerization mediated by electrophilic palladium of brominated aryl propynoate 93 performed by Suzuki–Miyaura reaction using Ar-B(OH)$_2$, as depicted in Scheme 26 [39].



SCHEME 26 Synthesis of 4-arylchromen-2-one composites via a palladium catalysis methodology

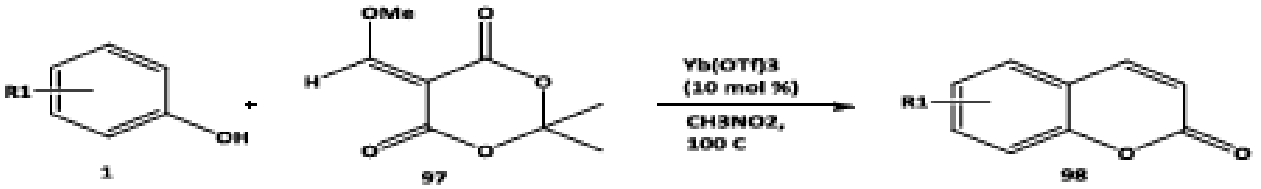
Other methods

By generating N-heterocyclic carbine intermediates under conventional heating (Scheme 27, condition A) or microwave irradiation (Scheme 27, condition B), a variety of 3-alkylchromen-2-one composites 96 are afforded in high quantities from salicylaldehyde 17 and α,β-unsaturated aldehydes 95 [40].



SCHEME 27 Synthesis of 3-alkylchromen-2-one composites under various energy sources

The substituted phenols 1 reaction with 5-(methoxymethylene)-isopropylidene malonate 97 in nitromethane at 100 °C promoted by Ytterbium (III) triflate create the substituted chromen-2-one composites s 98 in good yields, as illustrated in Scheme 28 [40].



SCHEME 28 Synthesis of monosubstituted chromen-2-one composites utilizing Ytterbium (III) triflate as a promoter

Conclusion

The benefits and/or drawbacks of chromen2-one composite synthesis in one pot compared to the other techniques were explored in this review. The ionic liquids and/or solid acids catalyze reactions under microwave and/or the ultrasonic irradiation conditions. Both the Pechmann and Knoevenagel condensation reactions have several advantages, including high product yields, the simplicity of the product separation, short reaction times, and the environmental benefits by preventing hazardous precursors and solvents. Chemo- and regioselective synthesis of 3-substituted chromen-2-ones was accomplished using Baylis-Hillman reactions under the mild conditions. Under neutral circumstances, however, the electrophilic substitution reactions of phenols mediated by vinyl phosphonium salts give 4-carboxyalkyl chromen-2-one composites in high yields. For the production of chromen-2-ones with acidsensitive functional groups, this approach has a lot of benefits. Furthermore, the regioselective synthesis of chromen-2-one composites from 2-iodophenols and enoates has been achieved using a palladiumcatalyzed Heck lactonization technique. This reaction is demonstrated to be sensitive to steric hindrance in the enoates surrounding the double bond. The Kostanecki reaction conditions can improve the yields of chromen-2-one composites, particularly those which are highly functionalized 4arylchromen-2-one composites structural variety. Acknowledgements with structural variety.

Acknowledgements

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Ethical issues1

The scientific committee of the Pharmaceutical Chemistry Department was approved this work Competing interests We have no conflicts of interest to disclose. Authors' contributions All authors contributed toward data analysis, drafting and revising the paper and agreed to responsible for all the aspects of this work.

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2 Conference papers may only be submitted if the paper has been completely re-written (taken to mean more than 50%) and the author has cleared any necessary permission with the copyright owner if it has been previously copyrighted.

3 All our articles are refereed through a double-blind process.

4 All authors must declare they have read and agreed to the content of the submitted article and must sign a declaration correspond to the originality of the article.

Submission Process

All articles for this journal must be submitted using our online submissions system. http://enrichedpub.com/ . Please use the Submit Your Article link in the Author Service area.

Manuscript Guidelines

The instructions to authors about the article preparation for publication in the Manuscripts are submitted online, through the e-Ur (Electronic editing) system, developed by **Enriched Publications Pvt. Ltd**. The article should contain the abstract with keywords, introduction, body, conclusion, references and the summary in English language (without heading and subheading enumeration). The article length should not exceed 16 pages of A4 paper format.

Title

The title should be informative. It is in both Journal's and author's best interest to use terms suitable. For indexing and word search. If there are no such terms in the title, the author is strongly advised to add a subtitle. The title should be given in English as well. The titles precede the abstract and the summary in an appropriate language.

Letterhead Title

The letterhead title is given at a top of each page for easier identification of article copies in an Electronic form in particular. It contains the author's surname and first name initial .article title, journal title and collation (year, volume, and issue, first and last page). The journal and article titles can be given in a shortened form.

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1. Original scientific paper (giving the previously unpublished results of the author's own research based on management methods).

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The article should be in English. The grammar and style of the article should be of good quality. The systematized text should be without abbreviations (except standard ones). All measurements must be in SI units. The sequence of formulae is denoted in Arabic numerals in parentheses on the right-hand side.

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An abstract is a concise informative presentation of the article content for fast and accurate Evaluation of its relevance. It is both in the Editorial Office's and the author's best interest for an abstract to contain terms often used for indexing and article search. The abstract describes the purpose of the study and the methods, outlines the findings and state the conclusions. A 100- to 250-Word abstract should be placed between the title and the keywords with the body text to follow. Besides an abstract are advised to have a summary in English, at the end of the article, after the Reference list. The summary should be structured and long up to 1/10 of the article length (it is more extensive than the abstract).

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Acknowledgements

The name and the number of the project or programmed within which the article was realized is given in a separate note at the bottom of the first page together with the name of the institution which financially supported the project or programmed.

Tables and Illustrations

All the captions should be in the original language as well as in English, together with the texts in illustrations if possible. Tables are typed in the same style as the text and are denoted by numerals at the top. Photographs and drawings, placed appropriately in the text, should be clear, precise and suitable for reproduction. Drawings should be created in Word or Corel.

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