A microwave assisted, Fe₃O₄/Camphor-catalysed three-component synthesis of 2-amino-4H-chromenes and their antibacterial and antioxidant activity

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Abstract. The synthesis of 2-amino-4H-chromenes via Knoevenagel condensation/Michael addition/cyclization reactions under microwave irradiation is reported. Nanoparticle magnetite Fe₃O₄/camphor with nanospheres structure was developed for utilization as the heterogeneous Bronsted acid in chemical transformation. The synthesis and characterization of camphor supported on magnetic nanoparticle using FTIR, XRD and SEM-EDX are described. The three-component and one-pot synthesis of 2-amino-4H-chromenes by condensing aromatic aldehyde, malononitrile/ethyl cyanoacetate and barbituric acid/thiobarbituric in water solvent, in the presence of catalytic amount of nanoparticle Fe₃O₄/camphor under microwave irradiation was investigated. The products obtained were characterized by FTIR, UV/Vis spectrophotometer, and mass analysis. The compounds were investigated for their antibacterial activity against Escherichia coli, Bacillus cereus, Salmonella enterica ser. Typhimurium, Staphylococcus aureus, and Pseudomonas aeruginosa. Also, the antioxidant properties of the compounds were analysed using DPPH method. This method corresponding a facile synthesis of 2-amino-4H-chromenes derivatives produced shorter reaction times, good yields and selectivity. The supported catalyst could be separated from the reaction product using an external magnet and proved to be simple, efficient and environmentally friendly.

Keywords: Fe₃O₄/camphor; nanocatalyst; multicomponent reaction; chromene; 2-amino-4H-chromene

1. Introduction

Multi-component reactions (MCRs) represent a powerful tool in the fields of organic synthetic and medicinal chemistry to effectively build and complex and diverse heterocyclic molecules in a number of synthetic step by combining multiple reactants to yield the desired product carried out in the same flask [1-3]. As they require simple workup and conduct the chemical reactions without isolation of intermediates, those MCRs have generated some benefits such as being effectively simple and atom economical with the possibility of improving yields, saving chemical reagents and solvents [4]. MCRs methods lead to environment-friendly and cheaper strategies by shorter reaction time, money-savings, energy and raw materials with both economic and environmental advantages [5]. Therefore, development and enhancement of the known and unknown MCRs are interesting areas of research within the field of current synthetic organic chemistry, especially in preparing active pharmaceutical ingredients, drug discovery and library synthesis. Hence, MCRs are regarded as a crucial subject in the preparation of many important heterocyclic molecules such as chromene derivatives.
2H-chromene (2H-1-benzopyran) and 4H-chromene (4H-1-benzopyran) are heterocyclic compounds with bicyclic structure, with oxygen as a heteroatom, that results from the combination of the benzene ring with 2H-pyran or 4H-pyran rings [6]. Chromene derivatives have been appearing as a significant class of naturally occurring compounds with diverse and important biological properties such as antibacterial, anti-cancer, anti-coagulant, anti-depressant, anti-fungal, anti-influenza, anti-inflammatory, and anti-malarial activities [7]. Natural chromene derivatives are presents in plants and can be found in alkaloids, flavonoids, tocopherols, and anthocyanin [8]. The existence of chromenes has been reported in several natural extracts, such as visnadine obtained from *Annum visnaga* and Khellactone obtained from *Phlojodicarpus sibiricus* [6]. Functionalized chromenes, as one of the privileged scaffolds, have played a remarkable role in current synthetic and medicinal chemistry. Moreover, chromene derivatives with a functionality of nitrile are privileged medicinal scaffolds for preparing molecules with high biological activities as potent anti-inflammatory and anti-anaphylactic properties [9]. Due to the powerful attributes of chromene derivatives, significant observation has been focused on the improving of environmentally friendly protocols for the synthesis of 2-amino-4H-chromenes.

The conventional syntheses of chromenes derivatives are typically time-consuming and suffer from the availability of reactants [10]. Therefore, the development of easy understood and versatile protocols is still desired for the generation of chromenes derivatives. A number of developed synthetic protocols of 2-amino-4H-chromenes have been reported via MCRs by condensation of aromatic aldehyde, methylene active compound, and enolizable of C-H activated acidic compound using different type of homogenous or heterogeneous, organic, inorganic, and nanomaterial catalysts, such as Amberlite SR1L Na [4], 1,4-diazabicyclo [2.2.2]octane (DABCO) [7], niobium pentachloride [6], nanosized ZnO [11], 2-ethyl imidazolium acetate [12], potassium phthalimide-N-oxyl (POPINO) [13] and silica gel-supportedolphosphoric acid [14]. The literature demonstrated successful the synthesis of chromene derivatives through MCRs methods but endured several limitations including prolonged reaction times, severe reaction conditions, complex reaction pathway, and expensive chemical reagents and solvents as well as the need of special apparatus. Moreover, most of the reported methods undergo expensive catalyst with lack ability to be recycled. Therefore, there is a requirement to develop better methods that can proceed under easy, methodical, and environmentally friendly reaction conditions.

While facing to the organic reaction, the catalyst holds a major role in almost all the organic transformation reactions, magnetic nanoparticle (MNP)s have been applied as support in catalyzing diverse organic transformations due to their potential features for designed surface functionalities along with preparation of several catalysts [15], the stable Fe₃O₄ MNPs exhibit excellent responsive to an external magnetic field due to their paramagnetic and insoluble properties. Maleki *et al.* [16] reported the utilization of naturally abundant biocompatible material Fe₃O₄/camphor as a heterogeneous catalyst in the preparation of β-amino carbonyl compounds. Hence, we report an easy and simple method using Fe₃O₄/camphor as a catalyst for the synthesis of 2-amino-4H-chromene derivatives in water through MCRs pathways under microwave-irradiation conditions. Microwave methods have been employed in the short-time preparation of desired products and become a useful technology in organic chemistry. By combining MCRs and microwave-assisted synthesis leads to improve the rate of reactions, increasing yields, easier reaction procedure, and in general cleaner workup in the framework of green chemistry [17]. Furthermore, the use of water, as an environment-friendly, safe, green, natural, and high abundance solvent, not only reduces the risk of organic solvents, but also strongly enhances conversion rates due to its remarkable properties of strong hydrogen bonding capacity and high polarity.

### 2. Experimental

#### 2.1. Materials

All the chemicals were obtained from Merck or Sigma-Aldrich Chemical Company as well as were used without any further purification. All reactions were performed in a Samsung microwave apparatus (Samsung Corp., South Korea). The upcoming compounds were employed as starting materials. Iron(III) nitrate nonahydrate (Merck, 98%), iron(II) chloride (Sigma-Aldrich, 98%), camphor (Sigma-
The synthesis of Fe₃O₄/camphor carried out using coprecipitation in situ method based on Maleki et al. [16] with modification. As much as 10 mmol of Fe(NO₃)₃·9H₂O and 5 mmol of FeCl₂·5H₂O were dissolved in 100 mL of deionized water in a three-necked bottom flask (250 mL) under N₂ atmosphere for 30 min. A mixture of 3 g camphor in 10 mL of ethanol absolute was added slowly into the solution with vigorous mechanical stirring. Thereafter, 2.0 M NaOH solution was dropped slowly into the mixture solution until the pH value (Schoot Instrument) was reached 11 for 150 min at 30°C under N₂ atmosphere bubbling. The black precipitate formed was separated using centrifugation at 3000 g and washed several times with deionized water until pH value declined to 7, and dried at 80°C in a vacuum oven (Spectra) for 20 h.

2.3. General procedure for the synthesis of 2-amino-4H-chromenes
A mixture of 4-hydroxybenzaldehyde (1 mmol), malononitrile/ethyl cyanoacetate (1 mmol), barbituric acid/thiobarbituric acid (1 mmol), and Fe₃O₄/camphor (0.015 g) in H₂O (3 mL) as a solvent in a flask. The mixture was subject to microwave irradiation (300 W) for 1-5 min. Completion of the reaction was monitored on TLC and catalyst was separated by the external magnetic field. The precipitate was isolated by centrifugation on 10000 g at 4°C for 3 min and washed several times with deionized water. The crude solid product was recrystallized from hot ethanol to obtain the pure product in high yield.

2.4. Spectral data of the representative compounds

2.4.1. 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a). White crystal solid. IR (KBr): νmax=3400, 3327, 3210, 2962, 2198, 1683, 1680, 1665, 1606, 1251, 1213, 1039. GC/MS (ESI)=m/z 295.3 (M+H)*.

2.4.2. 7-Amino-5-(4-hydroxyphenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyran-2,3-dipyrimidine-6-carbonitrile (4b). Yellow solid. IR (KBr): νmax=3280, 3201, 2820, 1721,1673, 1611, 1537, 1508, 1414,1348, 1287, 1210,1190, 1043. LC/MS-MS (ESI)=m/z 297.15.
2.5.3. 7-Amino-5-(4-hydroxyphenyl)-4-oxo-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (4c). Orange powder solid. IR (KBr): \( v_{\text{max}} = 3223, 3177, 2895, 1694, 1655, 1582, 1530, 1451, 1403, 1308, 1214, 1173, 1081 \) cm\(^{-1}\) \( \). The two peaks might be designated to the environment of the Fe-O covalent structural bond. A broad \( \text{O-H} \) stretching vibration bands at 3428 cm\(^{-1}\) was corresponding to OH group adsorbed water on the surface of the nanoparticles. The C-H stretching vibration bands at 2879 and 2962 cm\(^{-1}\) show nanospheres formed between camphor and Fe\(_3\)O\(_4\) [16].

2.5.4. Ethyl 7-amino-5-(4-hydroxyphenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate (4d). Yellow solid. IR (KBr): \( v_{\text{max}} = 3277, 3199, 2817, 1723, 1672, 1659, 1610, 1537, 1541, 1410, 1350, 1293, 1219, 1043 \) cm\(^{-1}\) \( \). LC/MS-MS (ESI)=m/z 340.17.

2.5.5. Ethyl 7-amino-5-(4-hydroxyphenyl)-4-oxo-2-thioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate (4e). Dark orange solid. IR (KBr): \( v_{\text{max}} = 3206, 3176, 2889, 1693, 1658, 1611, 1582, 1527, 1439, 1405, 1308, 1219, 1166, 1077 \) cm\(^{-1}\) \( \). LC/MS-MS (ESI)=m/z 361.37.

2.6. DPPH\(^•\) radical scavenging activity

The activity of free radical scavenging of the synthesized products was measured by 1,1-diphenyl-2-picrylhydrazyl (DPPH\(^•\)) according to Subbareddy and Sumathi [7]. In a typical procedure, different concentration of the sample, 9.8, 19.5, 39.0, 78.0, 156.0, and 312.0 \( \mu \text{g/mL} \) were prepared by dissolving stock solution (1 mg compound in 2 mL methanol) in 2 mL methanol. Then, 1 mL of the test sample and 1 mL of DPPH\(^•\) 0.1 mM solution were mixed and incubated in the dark place for 30 min at 37°C. Moreover, incubated sample solutions and negative control (without sample) was evaluated the absorbance at 517 nm using a UV-Vis light spectrophotometer. The experiments were carried out thrice, with ascorbic acid and butylated hydroxytoluene (BHT) was used as the standards. Each test sample as well as the standard were determined their IC\(_{50}\) values. The free radical scavenging activity was determined from the equation:

\[
\% \text{ Inhibition} = \frac{|AB - AA|}{AB} \times 100
\]

Where AB is the absorption of DPPH solution and AA is the absorption of the sample solutions.

2.7. In vitro antibacterial studies

All synthesized compounds were employed for in vitro antibacterial studies against Gram-positive bacteria including Staphylococcus aureus ATCC 25923 and Bacillus cereus, and Gram-negative bacteria including Salmonella enterica ser. Typhimurium ATCC 14028, Escherichia coli ATCC 25922, and Pseudomonas aeruginosa ATCC 27853 using the disc diffusion method according to Nawaz et al. [18]. Each compounds solution with a concentration of 10 mg/mL was prepared in pure DMSO. Bacterial cells suspension of 0.5 MacFarland standard were spread on Mueller-Hinton agar plate. Each disc (6 mm) was impregnated with 50 \( \mu \text{L} \) of test solutions and place on the inoculated agar surface. All the plates and controls (DMSO) were incubated at 37°C for 24 h. Inhibition zones were measured and the diameters were calculated in millimeters.

3. Results and discussion

3.1. Characterization of the catalyst Fe\(_3\)O\(_4\)/camphor

Experimental evidence in support of the formation nanospheres of camphor and Fe\(_3\)O\(_4\) was obtained through the FT-IR spectrum. The preparation of the expected product was verified by the FT-IR spectrum (Fig. 1). The spectrum represents the common characteristic absorption peaks of Fe\(_3\)O\(_4\) at approximately 555 and 410 cm\(^{-1}\), due to the Fe\(_{\alpha}\)-O and Fe\(_{\beta}\)-O stretching vibrations, respectively [19-23]. The two peaks might be designated to the environment of the Fe\(_3\)O\(_4\) nanoparticle of the tetrahedral and octahedral Fe-O covalent structural bond. A broad O-H stretching mode around 3428 cm\(^{-1}\) was corresponding to OH group adsorbed water on the surface of the nanoparticles. The C-H stretching vibration bands at 2879 and 2962 cm\(^{-1}\) show nanospheres formed between camphor and Fe\(_3\)O\(_4\) [16].
Energy-dispersive X-ray spectroscopy (EDX) was employed to evaluate the elemental composition of Fe$_3$O$_4$/camphor nanoparticles. From Fig. 2a, it is clear that the EDX spectrum indicates iron, oxygen and carbon in synthesized Fe$_3$O$_4$/camphor nanocatalyst. The EDX elemental map images showing the distribution of iron, oxygen and carbon are illustrated in Fig. 2b. The results reveal the expected distribution of all the elements present in the sample.

Fig. 2a and 2b illustrate the X-ray diffraction patterns of the camphor, synthesized Fe$_3$O$_4$ and Fe$_3$O$_4$/camphor nanoparticle. We could assume that the peaks of the prepared Fe$_3$O$_4$ nanoparticles showed the following crystal plane: (2 2 0), (3 1 1), (2 2 2), (4 0 0), (4 2 2), (5 1 1), (4 4 0) and (5 3 3) indicating the formation of magnetite with cubic inverse spinel structure (2b). The magnetite nanoparticles are very close to the literature reference Joint Committee on Powder Diffraction Standards (JCPDS) No. 46-0943 of Fe$_3$O$_4$ XRD spectrum. Moreover, additional peaks around $2\theta$=10–20° showed the formation of the mixture of Fe$_3$O$_4$ with camphor. The Debye-Scherrer equation ($Dhkl$$1/4$k$kl/\beta \cos \theta$) was employed to calculate the estimated average crystallite size from the XRD patterns, where $D$ is the
size of the axis parallel to the \((hkl)\) plane, \(k\) is a constant of 0.89 typical value of spherical particles, \(l\) is the radiation wavelength, \(\beta\) is the full width at half maximum (FWHM) in radians, and \(\theta\) is the position of the diffraction peak maximum or Bragg angle [24]. The average of crystalline sizes of Fe\(_3\)O\(_4\)/camphor nanoparticles was determined to be 45.75 nm by employing peak widths of the X-ray diffraction patterns.

![XRD patterns of champhor (a) and comparative XRD patterns of Fe\(_3\)O\(_4\) and Fe\(_3\)O\(_4\)/camphor (b).](image)

**Figure 3.** XRD patterns of champhor (a) and comparative XRD patterns of Fe\(_3\)O\(_4\) and Fe\(_3\)O\(_4\)/camphor (b).

The morphology and surface of Fe\(_3\)O\(_4\) (Fig. 4a) and Fe\(_3\)O\(_4\)/camphor (Fig. 4b) nanoparticles were investigated by scanning electron microscopy (SEM). Fig. 4 of the SEM images reveals the change of morphology of magnetite nanoparticle after addition of camphor. The Fe\(_3\)O\(_4\) magnetic nanospheres were near-monodispersed with uniform size—the smooth surface of the magnetite nanoparticle altered to be rough and inconsistent, due to the configuration of Fe\(_3\)O\(_4\) and camphor mixture. It seems that some agglomeration in particle size occurred. However, it is very difficult to find out the particle size of the prepared magnetite catalyst from the SEM micrographs.

![SEM image of Fe\(_3\)O\(_4\) (a) and Fe\(_3\)O\(_4\)/camphor (b) nanoparticles.](image)

**Figure 4.** SEM image of Fe\(_3\)O\(_4\) (a) and Fe\(_3\)O\(_4\)/camphor (b) nanoparticles.

### 3.2. Catalytic application of Fe\(_3\)O\(_4\)/camphor in the synthesis of 2-amino-4H-chromenes compounds

Initially, the parameter of catalyst amount on the reaction yield to optimize the reaction conditions for the synthesis of 2-amino-4H-compounds on the reaction of benzaldehyde (1 mmol), malononitrile (2 mmol) and dimedone (1 mmol) as a pilot test under microwave irradiation were examined (table 1). It was revealed that employing 0.015 g of the Fe\(_3\)O\(_4\)/camphor nanoparticle was adequate to complete reaction in 1.5 min and gives in 83.20% in yield in 3 mL of water as environment-friendly, safe, and green solvent to obtain the desired product 4a. It is found that no increasing yield was observed when the reaction was carried out in a higher amount of catalyst with more than 15 mg. Fe\(_3\)O\(_4\)/camphor is considered to be an efficient and promising catalyst in terms of organic reactions.
After optimization of the reaction conditions and in order to investigate the scope of this method, the condensation of 4-hydroxy benzaldehyde (1 mmol), malononitrile/ethyl cyanoacetate (1.2 mmol), and barbituric acid/thiobarbituric acid (1 mmol) in the presence of Fe₃O₄/camphor were observed (table 2). The studied reactions yielded the desired product 4b, 4c, 4d, and 4g during the very short time (3-5 min) in excellent yields. The influence of electron-withdrawing groups on benzaldehyde and barbituric acid derivatives upon the reaction times and yields revealed the changing of substituents had a significant effect on the reaction results.

**Table 1.** Optimization of the amount of catalyst for the reaction conditions.

| Entry | Fe₃O₄/camphor (mg) | Time (min) | Yield (%) |
|-------|------------------|------------|-----------|
| 1     | 0                | 3          | 39.92     |
| 2     | 15               | 1.5        | 83.20     |
| 3     | 30               | 1          | 73.79     |
| 4     | 45               | 1          | 58.33     |

**Table 2.** Fe₃O₄/camphor nanoparticles-catalyzed synthesis of 2-amino-4H-chromene compounds.

| No. | Aromatic aldehyde | Active methylene | Enol | Product | Yield (%) |
|-----|-------------------|------------------|------|---------|-----------|
| 1   | 4-Hydroxy benzaldehyde | Malononitrile | Barbituric acid | ![Image](image1.png) | 81.85     |
| 2   | 4-Hydroxy benzaldehyde | Malononitrile | Thiobarbituric acid | ![Image](image2.png) | 77.32     |
| 3   | 4-Hydroxy benzaldehyde | Ethyl cyanoacetate | Barbituric acid | ![Image](image3.png) | 87.43     |
| 4   | 4-Hydroxy benzaldehyde | Ethyl cyanoacetate | Thiobarbituric acid | ![Image](image4.png) | 86.42     |

Here, the presence of acidic nanoparticle plays a significant role in the rearrangement and cyclization process of the intermediate. In a plausible mechanism, aromatic aldehyde (1a & 1b) is firstly activated by the acidic Fe₃O₄/camphor nanoparticles. The carbonyl carbon is attacked by a nucleophilic compound of nitriles or barbituric acid derivatives to produce the Knoevenagel products. Then, subsequent of
enolizable compounds to Knoevenagel intermediates gives rise to the in situ configuration of the Michael adducts via Michael-type addition, which becoming tautomerized in the presence of an acidic catalyst of Fe\(_3\)O\(_4\)/camphor to produce intermediate. It proceeds forward intramolecular nucleophilic cyclization (Thorpe-Ziegler type reaction) and tautomerizes to obtain the final products [25, 26].

3.3. DPPH radical scavenging activity
The radicals scavenging activity of 2-amino-4\(H\)-chromene derivatives was carried out using the 2,2-diphenyl-1-picrylhydrazyl (DPPH•) assay. DPPH is widely employed to determine the antioxidant activity of extracts as well as synthetic organic compounds. Absorbance at 517 nm was measured to evaluate the reduction of DPPH• radicals. The activity of the compounds (4b-4c) was compared with other antioxidants such as ascorbic acid and butylated hydroxytoluene (BHT). The IC\(_{50}\) values were calculated for each compound and standard which are shown in Fig. 5. The results showed that all compound 4b-e possessed good antioxidant activity, although the IC\(_{50}\) values was higher compared to the standards. It also demonstrated that barbituric derivatives compounds 4b and 4d showed better antioxidant activity with lower IC\(_{50}\) values compared to thiobarbituric acid derivatives compounds 4c and 4e. Compound 4d showed the largest antioxidant activity against DPPH radical as compare with other compounds. We assume that the sulphur and OH groups affected the antioxidant activity of the synthetic compounds.

3.4. In vitro antibacterial studies
2-Amino-4\(H\)-chromene derivatives were evaluated their biological activities as an antibacterial agent against different type of Gram-positive and Gram-negative bacteria by employing agar disc diffusion method. All the tested compounds exhibited varied response against a variety of bacteria. The antibacterial activity of 2-amino-4\(H\)-chromene compounds is shown in table 3. Compound 4e showed the largest zone (15 mm) of inhibition against \textit{Pseudomonas aeruginosa} as compared with other compounds at 10 mg/mL. Barbituric acid derivatives including 4b and 4d observed ineffective against \textit{Salmonella enterica ser. Typhimurium} and exhibited no zone of inhibition, while thiobarbituric acid derivatives of 4c and 4d showed a large zone of inhibition. The sulfur and OH group in the compounds may actively participate in their antibacterial activity.
Table 3. Antibacterial activity of 2-amino-4H-chromene compounds.

| Compounds | Zone of inhibition in mm |
|-----------|--------------------------|
|           | B. cereus | S. aureus | Salmonella enterica ser. Typhimurium | P. aeruginosa | E. coli |
| 4b        | 8.79      | 6.63      | 0                                    | 9.40         | 7.22    |
| 4c        | 12.25     | 9.98      | 11.46                                | 12.98        | 13.00   |
| 4d        | 13.89     | 14.91     | 0                                    | 13.35        | 12.82   |
| 4e        | 15.24     | 10.17     | 14.19                                | 15.64        | 10.68   |

4. Conclusions
A simple and efficient method using Fe₂O₃-camphor as a catalyst in the multicomponent reaction of an aromatic aldehyde, methylene active, and enols, 2-amino-4H-chromene derivatives, have been reported. This method provides an efficient protocol and easy work-up in the preparation of highly functionalized 2-amino-4H-chromene derivatives at microwave-irradiation condition in good yields. The present methodology offers good yields compared to the reaction without catalyst, simple reaction conditions, and easy isolation of the desired products without further complex purification. Moreover, among the screened 2-amino-4H-chromene derivatives, compound 4d and 4e were considerably promising and recognized as lead compounds showing good antioxidant activity with IC₅₀ of 118.23 and 144.25 ppm, respectively; and antibacterial activity with inhibition zone of 14.91 mm against S. aureus for compound 4d and 15.64 mm against P. aeruginosa for compound 4e, respectively.

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