Fe₃O₄-supported sulfonated graphene oxide as a green and magnetically separable nanocatalyst for synthesis of 2-amino-3-cyano-4H-chromene derivatives and their in-silico studies

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ABSTRACT
Under ultrasound irradiation, 17 examples of 2-Amino-3-cyano-4H-chromene derivatives were prepared via one-pot three components domino Knoevenagel–Michael condensation reaction of aliphatic/ aromatic/heterocyclic aldehydes, malononitrile, and α-naphthol/β-naphthol/resorcinol in the presence of Fe₃O₄-supported sulfonated graphene oxide as a green and magnetically separable nanocatalyst in H₂O: EtOH (1:1) solvent system. FT-IR, TGA, SEM, and XRD were used to evaluate the catalyst. The current protocol is appealing because of high atom economy (95%), excellent yields (88-95%), its short reaction time, waste-free conditions, cost-effectiveness, use of a nontoxic solvent, lack of high temperature for reflux, non-chromatographic purification of products, recyclability of catalyst, etc. In-silico studies were conducted on the selected proteins DNA gyrase (1KZN) and CYP51 (4WMZ) to study the docking interactions with highest docking scores 4h (−8.8 kcal/mol) and 4e (−10.1 kcal/mol), respectively. ADME and Toxicity analysis of docked compounds and reference drugs were also done.

HIGHLIGHTS
- Room temperature and ultrasound assisted three-component synthesis
- Synthesis of biological important 4H-chromene derivatives in H₂O: EtOH (1:1) solvent
- High yields of products (88–95%) within rapid reaction time (10–15 min).
- High atom economy 95%.
- Avoid of column chromatography
- In-silico studies
- Easy and fast work up
- Magnetically separable and reusable catalyst.

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Introduction

Due to rising environmental concerns, environmentally friendly techniques such as selectivity, high efficiency, high yield, and easy reaction procedures have become the most significant goals to achieve in organic chemistry field. Multicomponent reactions (MCRs) have recently emerged as the most powerful tools to achieve these goals, providing better yield than multistep synthesis of organic compounds and chemotherapeutic drugs using a one-pot procedure, due to atom economy, operational simplicity, convergent character, labor, structural diversity, complexity of the resultant products, less reaction time, simple separation steps, and cost-effectiveness.[1–6]

As a result, green chemistry has become a hot topic, with the development of heterogeneous catalysts with a wide range of applications as recoverable and ecologically friendly materials generating a lot of desire in using it in a variety of industrial and organic transformations as well as synthesis.[7]

Different nanoparticles (NPs) have sparked a lot of interest among heterogeneous catalysts because of their strong catalytic activity and unique chemical and physical features, including as good selectivity, long-term stability, nontoxicity, reusability, and a high surface area to volume ratio that enables high catalyst loading capacity.[8–15] Furthermore, nanoparticles are simply dispersed and create stable suspensions.[16,17] Nanostructured carbon materials have sparked a lot of interest among the well-documented nanomaterials because of their intriguing qualities like excellent low cost, air stability, and the ability to resist corrosion for usage in a variety of chemical and industrial processes.[18–23]

Carbon based nanomaterials present in various allotropic forms such as fullerene, carbon nanotubes (CNTs), graphene, diamond, and porous carbon on zero-, one-, two-, and three-dimensional nanoscales. Graphene is a well-known carbon allotrope that consists of one atom thick planar sheets of sp²-bonded carbon atoms packed densely in a
two-dimensional hexagonal honeycomb crystal lattice. Graphitic materials have become the most widely used carbon materials in various fields due to outstanding characteristics such as appropriate suitable transparency, electrical conductivity, high mechanical strength, high surface area, and proper biocompatibility.\textsuperscript{[24–29]}

Graphene oxide (GO) has recently been discovered to have oxidative catalytic activity, significant mechanical strength, remarkable thermal stability, and unique structural and surface properties and has found a wide range of applications as an air-stable heterogeneous metal-free catalyst for use in a variety of reactions.\textsuperscript{[30–32]} GO with a two-dimensional sheet-like structure has a huge surface area that is easily accessible to the reactants and has negligible mass transfer barrier, in contrast to typical porous materials. The presence of multiple oxygen-containing functionalities on the surface of GO sheets, such as epoxide and hydroxyl groups, allows for easy functionalization by various functional groups.\textsuperscript{[33–36]}

Sulfonated graphene oxide, an effective heterogeneous catalyst employed in organic reactions, is featured in this series. For the manufacture of sulfonated graphene oxide, a variety of techniques for sulfonation of graphene oxide are known.\textsuperscript{[37–42]}

Despite these advantages, such small particles necessitate time-consuming recycling and separation through the reaction mixture via filtration or costly ultracentrifugation, limiting their application.\textsuperscript{[43–48]} To overcome these drawbacks, Heterogeneous catalysts assisted by MNP offer a wide range of applications in organo catalysis and industrial catalytic processes.\textsuperscript{[49,50]}

Due to their high surface area, high catalyst loading ability, conductivity, magnetic susceptibility, catalytic activity, and striking stability, \( \text{Fe}_2\text{O}_3 \) and \( \text{Fe}_3\text{O}_4 \) nanoparticles are the most widely researched core magnetic supports in this context.\textsuperscript{[51–53]}

Chromenes represent as significant category of chemical entities being the main elements of numerous naturally accessible products.\textsuperscript{[54–56]} (Fig. 1).

2-Aminochromenes is a vital class of heterocyclic compounds possessing substantial biological activities. Many organic chemists are interested in 4H-chromenes rings and their derivatives. In addition, substituted chromenes have become increasingly important in the development of synthetic approaches to promising molecules in medicinal chemistry, such as anticancer,\textsuperscript{[57]} antimicrobial,\textsuperscript{[58,59]} antiviral,\textsuperscript{[60,61]} aldose reductase inhibitors,\textsuperscript{[62]} apoptosis-inducing,\textsuperscript{[63]} molluscicidal,\textsuperscript{[64]} antileishmanicidal,\textsuperscript{[65]} antitumor,\textsuperscript{[66]} antioxidant,\textsuperscript{[67]} anticonvulsant,\textsuperscript{[68]} as well as treatment of Alzheimer’s disease\textsuperscript{[69]} and Schizophrenia disorder.\textsuperscript{[70]} Fused chromene ring systems display blood platelet anti-aggregating,\textsuperscript{[71]} hypolipidemic,\textsuperscript{[72]} analgesic,\textsuperscript{[73]} vascular-disrupting activity,\textsuperscript{[74]} DNA breaking activities, mutagenicity activities.\textsuperscript{[75,76]} Antiproliferative,\textsuperscript{[77]} sex hormone,\textsuperscript{[78]} as well as central nervous system activities.\textsuperscript{[79]} (Fig. 2).

Chromenes revealed new applications in the field rather than numerous pharmacological activities, including pigments, beauty items, potentially biodegradable agrochemicals,\textsuperscript{[80]} photo-spiriting matters,\textsuperscript{[81]} and building unit of many regular crops.\textsuperscript{[82]} Chromene derivatives also operate as a precursor in a variety of processes. We have already used chromenes as starting materials to make a variety of physiologically active scaffolds.\textsuperscript{[83–85]}

Keeping all of this in mind, We have created a simple synthetic procedure of 17 examples of 2-amino-3-cyano-4H-chromene derivatives (4a–q) from one-pot three components domino Knoevenagel–Michael condensation reaction of aliphatic and aromatic...
Figure 1. Structure and biological activity of selected chromene derivatives isolated from natural sources.

Figure 2. Some drugs containing chromene motifs.
aldehydes, malononitrile and α-naphthol/β-naphthol/resorcinol in the presence of catalytic amount of Fe₃O₄-supported sulfonated graphene oxide as a green and magnetically separable nanocatalyst in H₂O: EtOH (1:1) solvent system under ultrasound irradiation (Scheme 1).

In addition, docking interactions of the produced compounds were studied in silico on the selected DNA gyrase (1KZN) and human lanosterol 14 alpha-demethylase CYP51 (4WMZ).

Scheme 1. General reaction for the synthesis of chromenes.

Scheme 2. Synthesis of Fe₃O₄@sulfonated GO nanoparticles
Result and discussion

Chemistry

Synthesis and characterization of Fe₃O₄@sulfonated GO nanoparticles

Starting from graphite, we have synthesized graphene oxide by hummer’s method. GO suspension was ultrasonicated. Then, sulfanilic acid was added to the mixture and allowed to keep for 24 h. Finally, sample was washed to obtain SGO multiple times and dried for 8 h at 60°C (Scheme 2).

FTIR technique is used for functional group determination. The spectra of GO, SGO, and F-SGO are shown in the (Fig. 3). Because of the enolic, carboxylic, and hydroxy groups in GO, the O–H stretching vibration is detected in the region of 3224 cm⁻¹. The stretching vibrations of the C=O, C=C, and C–O groups are ascribed to the peaks at 1710, 1590, and 1219 cm⁻¹ in the GO spectrum, respectively, which were in good agreement with previous findings. For SGO spectrum, O–H stretching vibration is observed at 3740 cm⁻¹, C=O, C=C, and C–O groups at 1700 cm⁻¹, 1520 cm⁻¹, 1190 cm⁻¹, respectively, and additional peak at 855 cm⁻¹ is attributed to S–O bond in sulfonic acid group. For F-SGO spectrum, the O–H stretching vibration is observed at 3264 cm⁻¹, C=O, C=C, and C–O peaks at 1750, 1571, and 1223 cm⁻¹. The result confirms successful stretching vibrations of Fe–O bond at 630 cm⁻¹.

For the determination of structure and interlayer spacing XRD is used. The X-ray diffraction (XRD) spectrum is used for characterization of crystalline nature of GO, SGOs and F-SGO. Reflection peaks of GO was observed at 2θ = 9.95°, 25.0°. The larger interlayer spacing of GO sheets is due to more oxygenated functional groups. The XRD pattern of SGO shows peak at 24.79°, 45.24°. The XRD pattern of F-SGO shows the positions and relative intensities of the peaks seen at 2θ = 26.39°, 29.74°, 42.36°, 59.31°, and 62.93° (Fig. 4).

The TGA is a tool for comparing the weight loss of materials as temperature rises. The evaporation of trapped water molecules between GO sheets causes the weight loss (22%) in GO below 100°C. The emission of carbon monoxide (CO), carbon dioxide (CO₂), and residual water molecules causes a 97% weight loss at 200°C. At 400°C, the weight reduction (98%) could be attributable to more stable oxygen functions. The TGA thermogram of SGO revealed a typical thermal deterioration, with a small weight loss (18%) below 100°C and an 88% weight loss around 500°C and the F-SGO graph revealed a weight loss (18%) below 100°C and a 93% weight loss around 500°C (Fig. 5).

SEM photographs of GO, SGO and, F-SGO indicates that the nanosheets have a homogenous surface, with crystalline structures ranging from 100 to 500 μm to few microns in the lateral dimension. Images of the GO indicated buds on smooth surface. However, the SGO shows solid crumbs on porous surface and FSGO displayed scattered and rough surface with full of macropores (Fig. 6).

Catalytic performance of Fe₃O₄@sulfonated GO

Earlier the reactions of chromene with dehydrogenating agents’ irradiation have been studied by our group. Herein we report efficient protocol for the reaction of multiple
aliphatic, aromatic and heteroaryl aldehyde analogs (1a–1p) which contains both electron donating and withdrawing substitutes, malononitrile 2 and other activated phenols derivatives (3a–c) such as resorcinol, \( \alpha \)-naphthol and \( \beta \)-naphthol were reacted using green tools to form chromenes in good to high yield c.f. (Table 2). To examine the catalytic efficiency of Fe\(_3\)O\(_4\)@sulfonated GO nanoparticles, condensation reaction of aldehyde 1a and malononitrile 2 with \( \alpha \)-naphthol 3a to provide 4a was taken as the model reaction for achieving optimized reaction conditions viz; catalyst and solvent of the reaction (Table 1). For this, the reactants were taken in 50 mL

![Figure 3. FTIR spectra of (a) GO, (b) sulfonated GO, and (c) Fe\(_3\)O\(_4\)@sulfonated GO.](image-url)
Erlenmeyer flask with 15 mg of catalyst in EtOH: H₂O (1:1) and agitated for an adequate amount of time at room temperature under ultrasonic irradiation (Table 2). TLC was used to track the reaction’s progress; it took 10–15 min to complete the reaction, with yields ranging from 88 to 95%.

Selection of solvents elucidated that reaction can take place in various solvents. Results are given below c.f. (Table 1), reaction carried out when no catalyst was used in H₂O as well ethanol as a solvent gives no yield. At room temperature, when 10 mg of catalyst was taken no reaction was seen in solvent free condition. However, when same amount of catalyst was taken in presence of EtOH 45% yield, in THF 35% yield, in 1-4DiOxane 45% yield, in DMSO 55% yield was seen. Results obtained were different when reaction condition was changed to ultrasonication at room temperature. When solvent was THF 40% yield was obtained, in 1-4DiOxane 65% yield, DMSO 70% yield, ethanol gives 90% yield. Solvent EtOH: H₂O gives different yields at different concentration.

The results showed that 95% yield was obtained when reaction was performed under ultrasonication for 15 min using 10 mg of nanocatalyst in EtOH: H₂O (1:1).

Table 1. Screening reaction parameters for modal synthesis of chromenes derivatives.a

| Entry | Catalyst loading (mg) | Solvent           | Reaction condition | Time (min.) | Yieldb (%) |
|-------|-----------------------|-------------------|--------------------|-------------|------------|
| 1     | No catalyst           | H₂O               | RT                 | 480         | No reaction|
| 2     | No catalyst           | EtOH              | RT                 | 480         | No reaction|
| 3     | 10                    | Solvent free      | RT                 | 120         | No reaction|
| 4     | 10                    | EtOH              | RT                 | 180         | 45         |
| 5     | 10                    | THF               | RT                 | 180         | 35         |
| 6     | 10                    | 1-4DiOxane        | RT                 | 180         | 45         |
| 7     | 10                    | DMSO              | RT                 | 180         | 55         |
| 8     | 10                    | THF               | Ultrasound         | 60          | 40         |
| 9     | 10                    | 1-4DiOxane        | Ultrasound         | 60          | 65         |
| 10    | 10                    | DMSO              | Ultrasound         | 60          | 70         |
| 11    | 15                    | H₂O               | Ultrasound         | 60          | 52         |
| 12    | 10                    | EtOH              | Ultrasound         | 60          | 90         |
| 13    | 10                    | EtOH: H₂O (1:1)   | RT                 | 60          | 75         |
| 14    | 10                    | EtOH: H₂O (1:1)   | Ultrasound         | 15          | 95         |
| 15    | 10                    | EtOH: H₂O (1:2)   | Ultrasound         | 15          | 90         |
| 16    | 10                    | EtOH: H₂O (1:3)   | Ultrasound         | 15          | 85         |
| 17    | 5                     | EtOH: H₂O (1:1)   | Ultrasound         | 15          | 80         |
| 18    | 15                    | EtOH: H₂O (1:1)   | Ultrasound         | 15          | 82         |
| 19    | 20                    | EtOH: H₂O (1:1)   | Ultrasound         | 15          | 84         |
| 20    | 30                    | EtOH: H₂O (1:1)   | Ultrasound         | 15          | 87         |

*aAll the reactions were carried out using 1.0 equiv. of aldehyde 1a, 1.0 equiv. of malononitrile 2, 1.0 equiv. of α-naphthol in appropriate catalyst and solvent.

*bIsolated yield.

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Table 2. Synthesis of chromenes derivatives catalyzed by Fe$_3$O$_4$@sulfonated GO nanoparticles.

| S.N. | Substrate | Phenol Derivatives | Product | Time (min) | Yield$^a$ (%) |
|------|-----------|--------------------|---------|------------|---------------|
| 1    | $\text{CHO}$ | $\text{OH}$ | $\text{NH}_2$ | 10 | 95 |
| 2    | $\text{CHO}$ | $\text{OH}$ | $\text{NH}_2$ | 10 | 91 |
| 3    | $\text{CHO}$ | $\text{OH}$ | $\text{NH}_2$ | 12 | 90 |
| 4    | $\text{CHO}$ | $\text{OH}$ | $\text{NH}_2$ | 11 | 95 |

(continued)
|   |     |     |     |   |   |
|---|-----|-----|-----|---|---|
| 5 | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | 10 | 94 |
| 6 | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | 14 | 89 |
| 7 | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | 12 | 92 |
| 8 | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | 13 | 90 |
| 9 | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | 13 | 90 |
| 10| ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | ![Image](https://via.placeholder.com/150) | 14 | 92 |

(continued)
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 11| ![1k](image) | ![3a](image) | ![4k](image) | 15 | 90 |
| 12| ![1l](image) | ![3a](image) | ![4l](image) | 12 | 92 |
| 13| ![1m](image) | ![3b](image) | ![4m](image) | 15 | 88 |
| 14| ![1n](image) | ![3b](image) | ![4n](image) | 12 | 90 |
| 15| ![1o](image) | ![3b](image) | ![4o](image) | 15 | 89 |
| 16| ![1p](image) | ![3b](image) | ![4p](image) | 11 | 90 |
Substrates containing \( \alpha \)-napthol fused ring gives chromene compounds in high yields in short reaction time (4a-q). Chromene 4a (entry 1) derived from 3, 4 di-methoxy benzaldehyde gives 95% yield in 10 min. Chromene that contains 4b where two 2 methoxy groups at 2, 4 position of the phenyl ring gives 95% yield (entry 2) in 10 min. Chromene 4c gives 90% yield (entry 3). Aldehyde 1d that gives chromene 4d with 95% yields in 11 min (entry 4). While aldehyde 1e underwent smooth Knoevenagel reaction to give product chromene 4e with 94% yield in 10 min (entry 5). Chromene comprising of cyclohexyl group 4f (entry 6) was isolated with 89% yield. Synthesis of chromene 4g gives yield 92%. Chromene (4h-l) (entries 10–12) obtained in 90–92% yields. Chromene 4m gives 88% yield (entry 13). The reaction went good with chromene 4n (entry 14) with yield 90% and we also obtained chromenes (4o–q) (entries 15–17) gives high yields 88–90%.

Comparison of various literature findings on nanocatalysts for the synthesis of 2-amino-3-cyano-4 H-chromene derivatives, demonstrating the model reaction was contrasted with the previously published protocols to determine the suitability of this process (Table 3).

**Mechanistic pathway**

A plausible mechanistic justification for the reaction is shown in Scheme 3. This shows that active methylene compound, malononitrile 2, undergoes tautomerization in the presence of Fe\(_3\)O\(_4\)@sulfonated GO catalyst which gives Knoevenagel condensation with aldehyde derivative 1 that takes place in ethanol solvent with the loss of water molecule and subsequently the formation of arylidene malononitrile P in quantitative yield. Afterward, ortho C-alkylation of \( \alpha \)-napthol 3 produces Q. Later Q undergoes tautomerization to produce R. Then, nucleophilic addition of hydroxyl group of R toward CN moiety for intramolecular cyclization to produce 2-imino-chromenes S. The subsequent intramolecular proton transfer gives substituted 2-Amino-2H-chromene-3-carbonitrile 4. The catalyst Fe\(_3\)O\(_4\)@sulfonated GO was recycled again. For chromenes obtained from \( \beta \)-napthol would be not easy because of steric crowding of the aryl groups.

**Green chemistry matrix**

Series of green matrices were calculated, it was found that reaction possess low environment-factor (E-factor = 0.059), high atom economy (AE = 95.30%), process mass
| S. no | Catalyst | Catalyst loading | Solvent | Condition | Time | Yield (%) | Ref. |
|-------|----------|-----------------|---------|-----------|------|-----------|------|
| 1     | Fe₃O₄@Sal@Cu | 8 mg | EtOH | Ultrasonic at RT | 5–25 min | 78–97 | [94] |
| 2     | Fe(ClO₄)₃/SiO₂ | 10 mol% | CH₃CN | Reflux | 72–135 min | 85–95 | [95] |
| 3     | CuSO₄.5H₂O | 5 mol% | H₂O | Reflux | 30–185 min | 80–95 | [96] |
| 4     | L-Proline | 10 mol% | EtOH | Reflux | 60–150 min | 65–93 | [97] |
| 5     | L-Proline | 10 mol% | EtOH | Reflux | 240–360 min | 88–98 | [98] |
| 6     | Fe₃O₄ NPs@GO@C₄H₈SO₃H | 100 mg | EtOH | Reflux | 5–15 min | 82–98 | [99] |
| 7     | Fe₃O₄@L-proline@SO₃H | 100 mg | Solvent free | Ultrasonic at RT | 5–90 min | 65–91 | [100] |
| 8     | Fe₃O₄@SiO₂@((CH₂)₂ NHCO-adenine sulfonic acid | 40 mg | Solvent free | Heat 110°C | 120–170 min | 70–90 | [101] |
| 9     | c-Fe₃O₄@Si-(CH₂)₃ melamine@butyl sulfonic acid | 4 mg | EtOH | Heat 60°C | 10–45 min | 80–92 | [102] |
| 10    | Fe₃O₄@sulfonated GO nanoparticles | 1 equiv. | EtOH:H₂O (1:1) | Ultrasound at RT | 10–15 min | 88–95 | Present work |
intensity (PMI = 1.05), reaction mass efficiency (RME = 94.0%), eco-score (72.5) indicated that this method is efficient and follows the green synthesis protocol as shown in SI.

**Molecular docking**

To discover the key protein–ligand interactions, molecular docking was done on a set of test compounds, namely (4a-q), against DNA gyrase (1KZN) and CYP51 (4WMZ). All of the produced admixtures had potential for interaction with one or more amino acids in the active site of the individual receptors, according to the docking scores for the tested ligands. The results of the molecular docking study by CB-Dock which uses AutoDock algorithm revealed the minimum binding energy (kcal/mol) of the tested compounds and reference drugs summarized in Table 4. The whole synthesized compounds had moderate to good docking scores, with binding energies ranging from −7.1 to −10.1 kcal/mol to the specified protein target. The anti-bacterial reference drug ciprofloxacin binds to the active site of DNA gyrase (1KZN) with the binding energy of −7.2 kcal/mol, while the tested compound 4h showed the lowest binding energy of −8.8 kcal/mol (Figs. 7 and 8).

The anti-fungal reference drug ketoconazole binds to the active site of CYP51 (4WMZ) with the binding energy of −10.7 kcal/mol, while the tested compound 4e showed the lowest binding energy of −10.1 kcal/mol (Figs. 9 and 10).
To qualify for a drug candidate the ligand should not only have a lot of promise, but also a good ADME profile. To reduce the number of safety issues it’s recommended that computational ADME properties of the ligands should be studied as early as possible in drug discovery process. One of the most widely accepted rule set for describing the molecular properties of a drug candidate is Lipinski’s rule of five, which evaluates the important pharmacokinetic properties.

### Table 4. Minimum binding energy (kcal/mol) by molecular docking study of selected molecules and reference drugs with DNA gyrase (1KZN) and CYP51 (4WMZ).

| Molecule | 1KZN  | 4WMZ  |
|----------|-------|-------|
| 4a       | -8.1  | -9.7  |
| 4b       | -8.3  | -8.9  |
| 4c       | -7.4  | -9.2  |
| 4d       | -8.3  | -9.7  |
| 4e       | -8.3  | -10.1 |
| 4f       | -8.8  | -9.6  |
| 4g       | -8.8  | -9.7  |
| 4h       | -8.8  | -9.6  |
| 4i       | -8.6  | -9.4  |
| 4j       | -8.4  | -9.5  |
| 4k       | -8.4  | -9.5  |
| 4l       | -8.4  | -9.6  |
| 4m       | -7.1  | -8.9  |
| 4n       | -7.3  | -8.4  |
| 4o       | -7.6  | -10.1 |
| 4p       | -7.3  | -9    |
| 4q       | -7.2  | NA    |
| Ciprofloxacin | -7.2 | NA |
| Ketoconazole | NA | -10.7 |

**Figure 4.** Spectra of XRD (a) GO, (b) sulfonated GO, and (c) Fe₃O₄@sulfonated GO.[89,90]

**Figure 5.** TGA spectra of (a) GO, (b) sulfonated GO, and (c) Fe₃O₄@sulfonated GO.[91,92]

**ADMET analysis**

To qualify for a drug candidate the ligand should not only have a lot of promise, but also a good ADME profile. To reduce the number of safety issues it’s recommended that computational ADME properties of the ligands should be studied as early as possible in drug discovery process. One of the most widely accepted rule set for describing the molecular properties of a drug candidate is Lipinski’s rule of five, which evaluates the important pharmacokinetic properties.
parameters such as ADME. The ADME study was carried out using SwissADME\textsuperscript{[103]}, Aqueous solubility (log S), skin permeability (log Kp), synthetic accessibility score (SA), percentage absorption, pharmacokinetics, drug-likeness, and medicinal chemistry friendly qualities of small compounds are all evaluated using this free web application. For this investigation, the following criteria were used: molecular weight 500, 5 hydrogen bond donors (HBDs), 10 hydrogen bond acceptors (HBAs), and 10 rotatable bonds (RBs).

ADMETlab\textsuperscript{[104]} 2.096 was used to investigate the toxicity profile. Toxicological endpoints (Hepatotoxicity, Carcinogenicity, Immunotoxicity, Mutagenicity) and levels of toxicity (LD50, mg/kg); toxicity profiles—hERG potassium channel inhibition (cardiotoxicity), H-HT (human hepatotoxicity), AMES (Ames Mutagenicity), and SkinSen (skin sensitization); Drug-induced liver injury (DILI); mitochondrial membrane potential
MMP ADMETlab 2.0 was used to predict the toxicity and cytotoxicity parameters of the chromene compounds examined. Except for compound 4l, which has MLOGP > 4.15, the results of in-silico investigations clearly show that most of the compounds exhibited drug-like candidate qualities with no

![Figure 8](image)

**Figure 8.** Molecular docking of compound 4h with DNA gyrase (1KZN). (a) 2D interaction, (b) 3D interaction of the compound 4h with 1KZN, and (c) complex 3D ribbon structure.

![Figure 9](image)

**Figure 9.** Molecular docking of ketoconazole with CYP51 (4WMZ). (a) 2D interaction, (b) 3D interaction of the drug with 4WMZ, and (c) complex 3D ribbon structure.
violation of any of the drug-likeness rules stated above. The Swiss ADME predictor values of log P, molar refractivity, and total polar surface area in these compounds were found to be in excellent accord with the most essential rules of drug-likeness. All of the substances in the study had an excellent hydrophilic-lipophilic balance, the same indicated bioavailability (score 0.55), and high GI absorption. Because the studied compounds had a total polar surface area (TPSA) of less than 140, they should have a high oral bioavailability.

Figure 10. Molecular docking of compound 4e with CYP51 (4WMZ). (a) 2D interaction, (b) 3D interaction of the compound 4e with 4WMZ, and (c) complex 3D ribbon structure.

Figure 11. Graphical illustration of ADME features of chemicals (4a–q), ciprofloxacin, and ketoconazole—anticipate GI absorption and brain penetration of small molecules.
The findings obtained from Swiss ADME engine are summarized in SI Table S1, while the toxicological endpoints and toxicity profiles—hERG potassium channel inhibition (cardiotoxicity), H-HT (human hepatotoxicity), AMES (Ames Mutagenicity), and SkinSen (skin sensitization); drug-induced liver injury (DILI) are summarized in SI Table S2.

The boiled-egg diagram shows that the derivatives were within the acceptable range of typical medications, according to the analysis (Fig. 11). Compounds found in the yellow zone have the ability to cross the blood-brain barrier (BBB). The gastrointestinal tract may easily absorb all of the chemicals found in the white area (GIT). The tested chromene derivatives were found to be in good agreement with the provided parameters and to have good oral bioavailability in this investigation.

**Physicochemical characteristics and drug-likeness evaluation**

All of the 17 chromene derivatives tested did not violate Lipinski’s rule of five for oral bioavailability, demonstrating that the compounds have drug-like molecular nature (Table 1) as shown in SI. It is important to note that Lipinski’s rule of five is essential for rational drug design and it has been suggested that the low permeability or poor absorption for a given compound results when it violates Lipinski’s rule. Molecular weight, LogP, number of hydrogen bond acceptors (NBHA), number of hydrogen bond donors (NBHD) of all other chromene derivative under study were found to be within recognized values.

**Conclusion**

In conclusion, we have developed a green procedure for the synthesis of 2-amino-3-cyano-4H-chromene derivatives using a magnetically separable Fe₃O₄@sulfonated GO catalyst for the synthesis of chromene derivatives in good yields using a one-pot multicomponents condensation process of aliphatic and aromatic aldehydes, malononitrile and α-naphthol/β-naphthol/resorcinol in H₂O: EtOH (1:1) solvent system under ultrasound irradiation. FT-IR, XRD, TGA, and SEM techniques were used to describe the structure of the prepared Fe₃O₄@sulfonated GO catalyst and obtained products were identified using FT-IR, ¹H-NMR, ¹³C-NMR spectra, elemental data analysis. The excellent yields (88–95%) under ambient reaction conditions in just 10–15 min made this protocol for easy and fast scale production of chromene derivatives. The prepared catalyst was easily recovered and reused for successive five cycles.

In addition, in-silico studies of the docking contacts of the synthesized compounds were conducted on the selected DNA gyrase (1KZN) and human lanosterol 14 alpha-demethylase CYP51 (4WMZ). It can be concluded from the docking results of both computations that 4h and 4e usually create stable binding contacts with DNA gyrase and CYP51 enzymes. The docked molecules in both enzymes are capable of creating important H-bonding and other hydrophobic interactions. As a result, we can deduce that these molecules 4h and 4e may have inhibitory effect against the proteins in question.
**Experimental**

Merck Sigma Aldrich, Alfa-Aesar, Loba Chemie chemical firm (synthetic grade) provided natural flake graphite (325 mesh, 99.95 percent) which was utilized as received. FT-IR spectra were acquired in cm⁻¹ from KBr pellets using a Bruker/OPUS 7.5.18 FT-IR spectrometer. On a Bruker Avance NEO 400 MHz spectrometer, the ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra of produced compounds were scanned using tetramethysilane (TMS) as an internal standard and DMSO as a solvent. The chemical shifts and J values were measured in Hertz (Hz) and ppm (d), respectively. Various analytical methods were used to characterize the catalyst, including scanning electron microscopy (SEM) studies using Hitachi-PU, with a 5.0 kV accelerating voltage, X-newon Bruker/OPUS 7.5.18, and thermogravimetric analysis (TGA) studies using TG/DTA 6200, SII Exstar6000, with a heating rate of 5 °C/min. The element analysis (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. 

The process of ultrasonication was used in a 2200 ETH-SONICA ultrasound cleaner at frequency of 45 kHz. Thin-layer chromatography (TLC) on Silica Gel as an adsorbent with UV irradiation was used to track the progress of the reaction.

**Synthesis of graphene oxide**

The modified Hummers method was used to make graphene oxide.²⁵ 250 mL H₂SO₄ was first added to 5 g graphite powder, and the mixture was then agitated for 24 h. Following that, 30 g KMnO₄ was added to the reaction mixture, which was then agitated continuously for 72 h at 50 °C. The resultant liquid was then placed into a beaker containing 500 mL of ice, and 50 mL H₂O₂ (30%) in 500 mL deionized (DI) water was added. As a result, the color of the combination changed from brown to bright yellow. Centrifugation was used to separate the reaction product, which was then washed with DI water and a 10% HCl solution several times before being dried at 60 °C.

**Synthesis of sulfonated graphene oxide**

For the preparation of SGO, GO (200 mg) was dispersed in 100 mL distilled water using ultrasonication technique. Then, the mixture was kept for stirring in the oil bath at 60 °C. Later, sulfanilic acid (50 mg) was added to the mixture.³⁰ After 12 h, the samples were washed three times using distilled water and then, dried at 60 °C for 8 h.

**Synthesis of Fe₃O₄@sulfonated GO nanoparticles nano magnetization of sulfonated graphene oxide**

Fe₃O₄ supported sulfonated graphene oxide was prepared by co-precipitation of FeSO₄.4H₂O and FeCl₃.6H₂O in presence of sulfonated graphene oxide. An aqueous solution of FeSO₄.4H₂O and FeCl₃.6H₂O was made using the molar ratio of 1:2. Nano magnetization of sulfonated graphene oxide was carried out following a modified approach reported.³¹ First, 40 mg of already prepared sulfonated graphene oxide in 40 mL DI water was ultrasonicated for 30 min. Then, in the resulting mixture 50 mL solution of FeCl₃ (800 mg) and FeSO₄ (380 mg) in DI water (40 mL) was added. After
that, a 30% aqueous solution of ammonia (15 mL) was added to the mixture to raise the pH to 11, and the mixture was agitated at 75°C for 30 min. The resultant mixture was then allowed to cool to room temperature before being centrifuged and washed six times with DI water before being dried at 70°C to yield pure Fe₃O₄@sulfonated GO nanoparticles.

**General procedure for synthesis of 2-amino-3-cyano-4H-chromenes using Fe₃O₄@sulfonated GO nanoparticles**

Aldehyde (1 mmol), α-naphthol/β-naphthol/Resorcinol (0.14 g, 1 mmol) and malononitrile (0.066 g, 1 mmol) were added to Fe₃O₄@sulfonated GO (0.004 g) in 10 mL of EtOH: H₂O (1:1). The mixture was kept at 50°C in ultrasound for an appropriate time and TLC was used to monitor the reaction until no more progress could be seen. The reaction mixture was then allowed to cool at room temperature before the catalyst was isolated with an external magnet and re-used for another run under the same reaction conditions. The combined organic layer’s solvent was evaporated at reduced pressure to yield a residue, which was then recrystallized in EtOH to yield the pure product. Physical characteristics and spectral (FT-IR, ¹H NMR, ¹³C NMR, elemental data analysis) studies were used to characterize the synthesized products (4a–q).

**Methodology of molecular docking**

The evaluation of computational docking of 17 chromene derivatives for DNA gyrase and CYP51 protein was performed using CB-Dock,[108] an online server that uses Autodock Vina algorithm[109] to comprehend the interaction of the drug molecule with the protein, the probable binding mechanism, and the energy.

The crystal structure of E. coli 24 kDa domain in complex with clorobiocin (PDB ID:1KZN, with a resolution 2.30 Å, R-value free 0.267, R-value work 0.239) and S. cerevisiae complexed with fluconazole (PDB ID: 4WMZ, with a resolution 2.05 Å, R-value free 0.232, R-value work 0.199) both of which were retrieved from PDB databank (https://www.rcsb.org). The entire structure was prepared by eliminating water molecules, adding hydrogen, and assigning partial charges for both proteins, and the binding sites were found after deleting the co-crystallized ligands, and the structures were saved in PDB format for future docking procedures using the AutoDock Tools (ADT) v1.5.4 protein preparation parameters using Kollman and Gasteiger.

2D structures of chromene derivatives were drawn in ChemDraw and saved in SDF format. To validate the molecular docking protocol for anti-bacterial properties with DNA gyrase (1KZN), an already approved anti-bacterial drug ciprofloxacin (DrugBank Accession Number DB00537) was selected and was saved in SDF format. Similarly, for validation of the molecular docking protocol for anti-fungal properties with CYP51 (4WMZ), an already approved anti-bacterial drug ketoconazole (PubChem CID 456201) was selected and was saved in SDF format.

All the 17 ligand structures (17 chromene derivatives, ciprofloxacin, ketoconazole) were converted into PDB using Open Babel software[110] after energy minimization.
The coordinates of the co-crystallized ligand in the original target protein grids were used to define the active sites. Although CB-Dock performs blind docking using automated cavity detection and enhance accuracy by employing a curvature-based cavity detection technique to anticipate target protein binding locations. (CurPocket), but the active binding sites were also confirmed using computed atlas for surface topography of proteins (CASTp).[111]

The CB-Dock server[108] was used for cavity detection and molecular docking and was accessed via webserver (http://clab.labshare.cn/cb-dock/php/index.php, accessed on 06 Jan 2022). The grid center for DNA gyrase (1KZN) was determined to be X = 20, Y = 24, Z = 36 and the maximum grid box size was 27 x 27 x 27; while the grid center for CYP51 (4WMZ) was determined to be X = 19, Y = 9, Z = 17 and the maximum grid box size was 35 x 26 x 26.

Vina Scores, cavity sizes, docking centers, and anticipated cavity sizes were all provided in the result table. The structure in the interactive 3D images is visualized after a ligand in the table is selected. The 3D and 2D interaction of ligand–protein complexes was further analyzed with Biovia Discovery Studio 2021.[112] This technique generates a graphical representation of the hydrophobic and hydrogen bonds, as well as their lengths, in each docking pose.

Molecular docking is one of the most valuable techniques in computational chemistry that helps in analyzing ligand recognition. It has resulted in significant advances in drug discovery and design in the field of medicinal chemistry in recent years. It investigates the binding mechanism and affinity of a tiny chemical within the receptor target protein’s binding region. The docked ligands were sorted by their propensity for binding to receptor–ligand complexes.

**Recyclability of the catalyst**

Catalyst was separated from reaction medium by using an external magnet. The recovered catalyst was then washed with hot ethanol and dried in oven. As shown in Table 5 and Fig. 12, catalyst was recycled and reused for four times consecutively without showing any significant loss in its efficacy.

**Spectral characterization of synthesized 2-amino-3-cyano-4H-chromene derivatives**

**2-amino-4-(3,4-dimethoxyphenyl)-2H-benzo[h]chromene-3-carbonitrile (4a)**

Pale yellow solid; 95% Yield; mp 240-242 °C; IR max/cm⁻¹ 3310 (sym. stretching of NH₂), 2200 (CN), 1586 (C=C aromatic), 1230 (C-O-C ether stretching); ¹H NMR (400 MHz, CDCl₃): δ 8.16 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.59 – 7.48 (m, 3H), 7.02 (d, J = 8.5 Hz, 1H), 6.82 – 6.70 (m, 3H), 4.81 (s, 1H), 4.75 (brs, 2H, NH₂),

| Entry | Catalyst cycle | Time (min.) | Isolated yield (%) |
|-------|----------------|-------------|--------------------|
| 1     | Fresh          | 15          | 95                 |
| 2     | I              | 15          | 94                 |
| 3     | II             | 15          | 92                 |
| 4     | III            | 15          | 90                 |
| 5     | IV             | 15          | 89                 |
3.83 (s, 3H), 3.79 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$+ DMSO-d$_6$); δ 41.1, 55.8, 55.9, 60.0, 111.1, 117.3, 120.4, 120.9, 123.2, 124.3, 126.2, 126.5, 126.7, 127.7, 133.2, 137.4, 143.2, 148.1, 149.1, 159.4; Anal. for C$_{22}$H$_{18}$N$_2$O$_3$: C, 73.73; H, 5.06; N, 7.82; found: C, 73.81; H, 5.10; N, 7.74%

The supporting section includes full experimental details of FT-IR, for all of the synthesized compounds given in the study.

Full experimental details of FT-IR, $^1$H NMR, $^{13}$C NMR spectra and elemental data analysis of all the synthesized compounds (4a–q) associated with this article have been provided in supporting information. Supporting information also includes 2D and 3D docked structures of compounds and standard drugs (ciprofloxacin and ketoconazole) with protein 1KZN, 4WMZ, green chemistry matrix calculation, eco-score, ADME parameter and toxicity profile.

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**Figure 12.** Reusability and recyclability of Fe$_3$O$_4$@sulfonated GO nanoparticles.
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