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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Facile synthesis and docking studies of 7-hydroxyflavanone isoxazoles and acrylates as potential anti-microbial agents

P. Asha Bhanu[1] · B. China Raju[2] · Y. Jayavardhana Rao[3] · G. Narasimha[3] · B. Kesava Rao[1]

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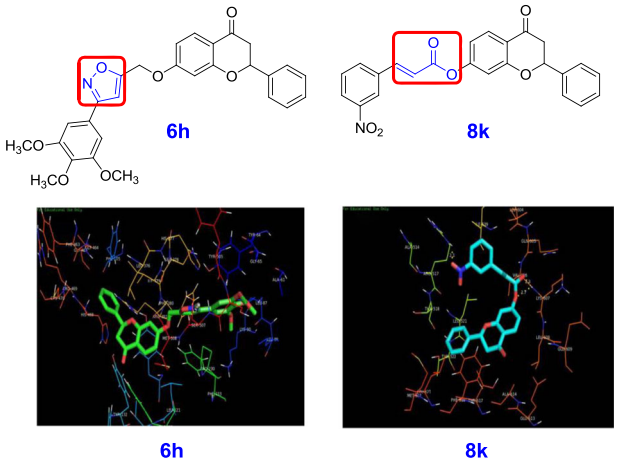
Abstract

The present study is aimed to synthesize the novel 7-hydroxyflavanone derived compounds and to assess their biological activity. Two series of compounds such as 2-phenyl-7-((3-phenylisoxazol-5-yl)methoxy)chroman-4-ones (**6a–h**) and 4-oxo-2-phenylchroman-7-yl acrylates (**8a–k**) were synthesized from 7-hydroxyflavanone. All the compounds were subjected to anti-microbial activity and molecular docking studies. The results showed that the compounds **6e, 6g–h, 8h–i** and **8k** were exhibited most potent anti-microbial activity when compared with the standard drugs. Further, the docking studies revealed that the compounds **6a** and **8h** have the highest binding affinity score of sterol 14-α demethylase and DNA gyrase B respectively. This is the first report assigning unique synthesis of 7-hydroxyflavanone derivatives and their anti-microbial activity proved with in silico studies. Furthermore, the present study is useful for constructive research to synthesize novel compounds along with their biological activity.

Graphical Abstract

Series of 7-hydroxyflavanone based novel isoxazoles **6a–h** and acrylates **8a–k** were synthesized. Isoxazole compounds **6e, 6g–h** and acrylates **8h–i** and **8k** were identified as most potent anti-microbial agents.



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✉ B. Kesava Rao
krbhattiprolu@gmail.com

[1] Department of Chemistry, University College of Sciences, Acharya Nagarjuna University, Nagarjunanagar, Guntur Dt., Andhra Pradesh 522510, India

[2] Department of Organic Synthesis & Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderbad, Telangana 500007, India

[3] Department of Virology, Sri Venkateswara University, Tirupathi, Andhra Pradesh 517502, India

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Keyword 7-Hydroxyflavanone · Isoxazoles · Acrylates · Anti-microbial activity · DNA gyrase

Introduction

Flavanones (Harborne and Williams 1995) are important natural products owing to their interesting pharmacological properties such as antioxidant (Pietta 2000), anti-microbial (Wächter et al. 1999), anti-inflammatory (Njamen et al. 2004, Domínguez-Villegas et al. 2013), antihypertensive (Oh et al. 2016, Chanet et al. 2012), antitumor (Bracke et al. 1999) and antiviral (Paredes et al. 2003). The preparations of flavanones have been achieved by synthetic approaches or enzymatic modification of chalcones (Jurd 1962). 7-Hydroxyflavanone is the major component isolated from various plants and *Syzygium samarangense* is one of the important medicinal plants to produce this compound in major quantity. The literature reports have been dealt that 7-hydroxyflavanone has been used for the preparation of few heterocyclic compounds such as 4-triazolylflavans (Yahiaoui et al. 2004), tricyclic fused pyridines (Zheng et al. 2016) and 4-imadazolylflavans (Pouget et al. 2002). There is an opportunity to prepare novel heterocyclic compounds by using this important natural compound.

Isoxazole (Pinho e Melo 2005) has two heteroatoms such as oxygen and nitrogen at the adjacent position and C–C and C–N double bonds are responsible for displaying the biological properties (Zhu et al. 2018) which includes anti-microbial (Kang et al. 2000), anticancer (Bargiotti et al. 2012), antiviral (Lee and Kim 2002), anti-TB (Mao et al. 2009) and anti-inflammatory (Pedada et al. 2016). Similarly, cinnamates (α-β unsaturated esters) (Clifford 2000) are natural products and important organic compounds belongs to the family of phenyl propanoids. Ferulic acid, Cumaric acid, Caffeic acid and Sinapic acid are natural products and bioactive compounds, which are precursors of the cinnamates. Further, cinnamates are important industrial products used as graphics, lubricants and perfumes (Shu and Hongjun 2012). Moreover, cinnamates have been explored as potential anxiolytic compounds, which act as GABA transaminase inhibitors (Awad et al. 2009). Several acryl cinnamates have been used as intermediates for the synthesis of flavanones (Moghaddam and Abdi-Oskoui 1999), chromones (Pinto et al. 1999), dihydrocoumarins (Aoki et al. 2005), benzofuranones (Shankaran et al. 1985) and pyrazoles (Li et al. 2005).

As part of our ongoing research work on isolation of natural products (Kesava et al. 1983, 1984, Rao et al. 1984, 1986, Hanumaiah et al. 1985), we have isolated 7-hydroxyflavanone, Ellagic acid and Gallic acid as major compounds from important medicinal plant *Syzygium samarangense*. Owing to the importance of 7-hydroxyflavanone, there is an opportunity to prepare useful heterocyclic compounds by chemical modification. The present manuscript describes the preparation of 2-phenyl-7-((3-phenylisoxazol-5-yl)methoxy)chroman-4-ones (**6a–h**) and 4-oxo-2-phenylchroman-7-yl cinnamates (**8a–k**) starting from 7-hydroxyflavanone. The prepared compounds were screened for their anti-microbial activity and explained the structure activity relationships (SARs). Further, the compounds were studied for their molecular modelling using DNA gyrase B and sterol-14α-demethylase.

Results and discussion

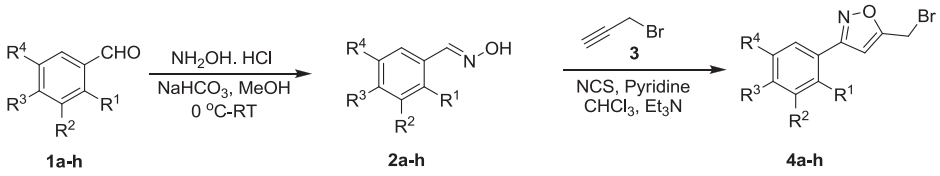
Chemistry

To achieve these objectives, the target compounds 2-phenyl-7-((3-phenylisoxazol-5-yl)methoxy)chroman-4-ones **(6a–h)** and 4-oxo-2-phenylchroman-7-yl acrylates (**8a–k**) have been prepared starting from 7-hydroxyflavanone (**5**, Schemes 1–3). Initially, we have prepared the oxime derivatives (**2a-h**) by the condensation of benzaldehydes **(1a–h)** with hydroxylamine hydrochloride in presence of sodium bicarbonate in methanol at room temperature. The intermolecular cycloaddition reaction of **2a–h** with propargyl bromide (**3**) with *N*-chlorosuccinimide in the presence of base (Liu et al. 2009) provided the compounds 5-(bromomethyl)-3-phenylisoxazoles (**4a–h**, Scheme 1).

Thus obtained 5-(bromomethyl)-3-phenylisoxazole (**4a**) was reacted with 7-hydroxyflavanone (**5**) in the presence of potassium carbonate in acetonitrile at room temperature. This provided the target compound 2-phenyl-7-((3-phenylisoxazol-5-yl)methoxy)chroman-4-one (**6a**). The result has encouraged us to prepare series of target compounds **6b–h**, which were prepared by the reaction of 5-(bromomethyl)-3-phenylisoxazoles (**4b–h**) with **5** under our optimized conditions (Scheme 2). The compounds 5-(bromomethyl)-3-phenylisoxazoles **4a–c** and **4h** are known compounds and compared with the literature data and unknown compounds **4d–g** were well characterized by spectral data and incorporated in the supporting information. All the target compounds **6a–h** were unknown and well characterized by spectral data.

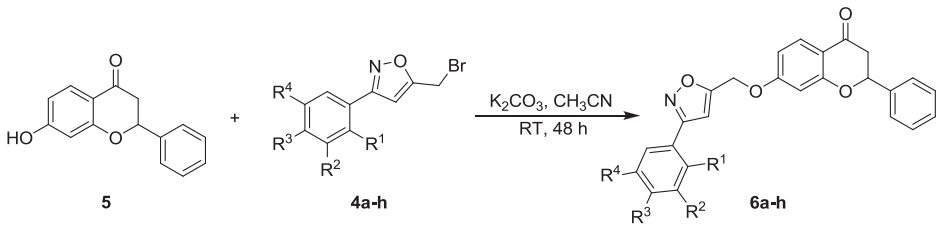
Due to the medicinal importance of acrylates, the present research work also has been designed to prepare 4-oxo-2-phenylchroman-7-yl cinnamates (Scheme 3). Accordingly, 7-hydroxflavanone (**5**) was reacted with series of cinnamic acids (**7a–k**) in the presence of DCC and DMAP at room temperature. All these reactions were preceded smoothly

Scheme 1 Preparation of 5-(bromomethyl)-3-phenylisoxazoles **(4a–h)**



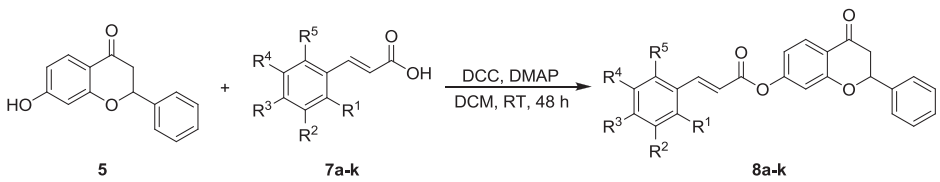
4a $R^1 = R^2 = R^3 = R^4 = H$
4b $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$,
4c $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$,
4d $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$,
4e $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$,
4f $R^1 = R^3 = OCH_3$, $R^2 = R^4 = H$,
4g $R^1 = R^3 = R^4 = OCH_3$, $R^2 = H$,
4h $R^1 = H$, $R^2 = R^3 = R^4 = OCH_3$,

Scheme 2 Preparation of 2-phenyl-7-((3-phenylisoxazol-5-yl) methoxy) chroman-4-ones **(6a–h)**



4a $R^1 = R^2 = R^3 = R^4 = H$
4b $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$,
4c $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$,
4d $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$,
4e $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$,
4f $R^1 = R^3 = OCH_3$, $R^2 = R^4 = H$,
4g $R^1 = R^3 = R^4 = OCH_3$, $R^2 = H$,
4h $R^1 = H$, $R^2 = R^3 = R^4 = OCH_3$,

Scheme 3 Preparation of 4-oxo-2-phenylchroman-7-yl acrylates **(8a–k)**



8a $R^1 = R^2 = R^3 = R^4 = R^5 = H$
8b $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$,
8c $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = CH_3$,
8d $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = F$,
8e $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Cl$,
8f $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Cl$,
8g $R^1 = Cl$, $R^2 = R^3 = R^4 = R^5 = H$
8h $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Br$,
8i $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Br$,
8j $R^1 = Cl$, $R^2 = R^3 = R^4 = H$, $R^5 = F$
8k $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = NO_2$,

and provided the corresponding target acrylate compounds (**8a–k**). All these compounds are unknown and well characterized by spectral data.

Biological evaluation

Thus prepared compounds 2-phenyl-7-((3-phenylisoxazol-5-yl)methoxy)chroman-4-ones **(6a–h)** and 4-oxo-2-phenylchroman-7-yl cinnamates (**8a–k**) were subjected to antimicrobial activity. Further, the molecular modelling studies were also performed.

Anti-bacterial activity

The target compounds **6a–h** and **8a–k** were evaluated for their in vitro anti-bacterial activity against two Gram positive organisms i.e. *Staphylococcus aureus, Bacillus subtilis* and 2 Gram negative organisms *Escherichia coli, Pseudomonas aeruginosa* by using standard Agar well plate method and the zone of inhibition (ZOI in millimetres) values along with the standard drug Streptomycin are shown in Table 1.

The in vitro results of isoxazoles revealed that the compounds **6a**, **6b–d** and **6f** shown moderate anti-bacterial activity against representative bacterial strains. The compound **6e** exhibited equipotent activity against *B subtilis* and *E coli* (ZOI 12.33 and 12.16) and most potent activity against *P aeruginosa* (ZOI 16.82). The compounds **6g–h** exhibited equipotent activity against *S aureus*, *B subtilis* and *E coli* (ZOI **6g** 13.50, 12.80, 12.30; **6h** 13.66, 12.83, 12.53, respectively) and most potent against *P aeruginosa* (ZOI **6g** 17.80; **6h** 17.60,

Table 1 Anti-bacterial activity of compounds **6a–h** and **8a–k**

Compound	Zone of inhibition (in millimetres)			
	Gram positive bacteria		Gram negative bacteria	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
6a	10.63 ± 0.24	10.46 ± 0.04	10.63 ± 0.24	09.55 ± 0.55
6b	10.05 ± 0.02	10.86 ± 0.12	10.60 ± 0.12	11.26 ± 0.20
6c	09.73 ± 0.20	11.30 ± 0.24	11.06 ± 0.16	11.43 ± 0.32
6d	11.33 ± 0.24	11.76 ± 0.20	11.30 ± 0.24	11.70 ± 0.32
6e	12.26 ± 0.20	12.33 ± 0.28	12.16 ± 0.12	16.82 ± 0.23
6f	11.73 ± 0.20	12.03 ± 0.33	11.63 ± 0.28	12.33 ± 0.28
6g	13.50 ± 0.24	12.80 ± 0.21	12.30 ± 0.24	17.80 ± 0.24
6h	13.66 ± 0.24	12.83 ± 0.28	12.53 ± 0.20	17.60 ± 0.32
8a	09.70 ± 0.25	10.26 ± 0.25	09.73 ± 0.30	10.26 ± 0.20
8b	11.20 ± 0.20	11.30 ± 0.30	10.76 ± 0.25	12.26 ± 0.25
8c	10.70 ± 0.30	11.20 ± 0.20	10.56 ± 0.25	12.03 ± 0.15
8d	10.53 ± 0.25	10.76 ± 0.25	10.10 ± 0.36	11.36 ± 0.40
8e	12.10 ± 0.20	12.26 ± 0.25	11.26 ± 0.25	13.76 ± 0.25
8f	11.86 ± 0.15	12.00 ± 0.20	11.06 ± 0.20	13.56 ± 0.20
8g	11.33 ± 0.30	11.86 ± 0.15	11.00 ± 0.20	13.20 ± 0.20
8h	12.26 ± 0.25	13.03 ± 0.15	12.03 ± 0.25	18.02 ± 0.02
8i	12.03 ± 0.35	12.73 ± 0.25	11.86 ± 0.15	17.26 ± 0.25
8j	11.86 ± 0.15	12.50 ± 0.26	11.30 ± 0.30	14.43 ± 0.40
8k	13.43 ± 0.40	13.23 ± 0.25	12.26 ± 0.25	18.56 ± 0.30
Streptomycin	**14.26 ± 0.25**	**13.23 ± 0.25**	**12.76 ± 0.25**	**16.76 ± 0.25**

respectively) in comparison with the standard drug Streptomycin (ZOI 16.76).

The anti-bacterial activity of acrylate compounds **8a–k** and their ZOI values presented in Table 1. The compounds **8a–j** were shown considerable anti-bacterial inhibitory activity against tested strains. The compound **8k** shows moderate activity against *S aureus*, *B subtilis* and *E coli* (ZOI 13.43, 13.23 and 12.26, respectively) and shown potent activity against *B subtilis* (ZOI 18.02). The compounds **8h–i** (ZOI 18.02, 17.26) and **8k** (ZOI 18.56) show potential anti-bacterial activity against *P. aeruginosa* when compared with standard antibiotic (ZOI 16.76).

Anti-fungal activity

The anti-fungal activity of compounds **6a–h** and **8a–k** were studied with Agar well plate method using two representative fungal species such as *Aspergillus niger* (ATCC 1015) and *Aspergillus fumigates* (ATCC 1022) and Cycloheximide was used as standard drug. The zones of inhibition (ZOI in millimetres) values were showed in Table 2. The compounds **6e** shown moderate activity against *Aspergillus niger* (ZOI 13.53). The compounds **6g–h** have shown equipotent activity against tested strains (ZOI **6g** 14.10, 13.97; **6h** 14.26, 14.05, respectively) in comparison with standard compound Cycloheximide (ZOI 14.53).

Table 2 Anti-fungal activity of compounds **6a–h** and **8a–k**

Compound	Zone of inhibition in millimetres	
	Aspergillus niger	*Aspergillus fumigates*
6a	10.70 ± 0.20	10.83 ± 0.15
6b	11.46 ± 0.15	11.06 ± 0.20
6c	11.90 ± 0.20	11.30 ± 0.30
6d	12.30 ± 0.30	11.13 ± 0.75
6e	13.53 ± 0.25	12.50 ± 0.20
6f	12.80 ± 0.20	12.16 ± 0.25
6g	14.10 ± 0.20	13.97 ± 0.06
6h	14.26 ± 0.25	14.05 ± 0.02
8a	10.76 ± 0.25	10.26 ± 0.25
8b	11.76 ± 0.25	10.26 ± 0.25
8c	11.46 ± 0.15	10.86 ± 0.15
8d	11.06 ± 0.20	10.56 ± 0.20
8e	12.86 ± 0.15	11.86 ± 0.15
8f	12.50 ± 0.20	11.53 ± 0.25
8g	11.93 ± 0.40	11.26 ± 0.25
8h	13.76 ± 0.25	14.26 ± 0.25
8i	13.53 ± 0.25	12.50 ± 0.20
8j	13.26 ± 0.25	12.20 ± 0.20
8k	14.26 ± 0.25	14.56 ± 0.30
Cycloheximide	**14.53 ± 0.25**	**13.7 ± 0.20**

The compounds **8h–j** were showed moderate activity against *Aspergillus niger* (ZOI 13.76, 13.53, 13.26). Interestingly, compound **8h** showed most potent activity against *Aspergillus fumigates* (ZOI 14.26) and compounds **8k** (ZOI 14.26, 14.56) identified as most potent anti-fungal compound against the tested strains when compared to standard compound (ZOI 14.53, 13.70).

SAR studies

From anti-bacterial and anti-fungal results, it was observed that the compounds **6g, 6h, 8h, 8i** and **8k** showed the potent activity. Compounds **6g** and **6h** that have an electron donating methoxy groups on isoxazole ring showed the good activity on all tested bacterial strains. Compounds **8d** and **8j** having electron withdrawing fluoro and chloro groups on acrylates showed the moderate anti-microbial activity. Compounds **8h**, **8i** and **8k** having electron withdrawing bromo and nitro groups on acrylates showed the potent activity. Due to strong electro negativity nature of halogens (F and Cl) reduced the activity when compared with bromo. The SAR results suggested that the electron donating group on isoxazole and electron withdrawing groups on acrylate enhances the anti-microbial activity.

Docking studies

Docking studies were performed to evaluate the binding affinity of synthesized compounds **6a–h, 8a–k** against target enzymes DNA gyrase B and sterol 14-α demethylase and results were presented in Table 3. From the obtained results, the compound **8h** shown highest binding affinity score (−9.2 K.cal/mol) against DNA gyrase B and compound **6a** shown the highest binding affinity score (−12.2 K.cal/mol) against sterol 14-α demethylase (Table 3). The compound **8h** shows two hydrogen interactions with GLU609 and ASP610, while the compound **6a** shows no hydrogen bonding interactions. We assume that this compound might be involved in the hydrophobic and other electrostatic interactions. The interactions between the lead molecule and target enzymes are represented in Fig. 1.

Table 3 Binding affinity scores of **6a–h** and **8a–k**

Compound	Binding affinity scores	
	DNA gyrase B (PDB ID 6QTP)	Sterol 14-α demethylase (PDB ID: 5TZ1)
6a	−8.1	−12.2
6b	−8.6	−11.9
6c	−8.9	−11.3
6d	−7.8	−11.0
6e	−7.9	−10.7
6f	−7.4	−11.4
6g	−8.4	−10.4
6h	−8.3	−10.8
8a	−8.8	−10.6
8b	−8.5	−11.7
8c	−8.2	−10.8
8d	−8.1	−11.8
8e	−8.0	−11.4
8f	−8.2	−11.7
8g	−8.4	−10.9
8h	−9.2	−11.1
8i	−8.5	−11.1
8j	−8.4	−10.8
8k	−8.8	−10.8

Conclusion

In conclusion, the synthetic method has been established for the preparation of 2-phenyl-7-((3-phenylisoxazol-5-yl) methoxy)chroman-4-ones (**6a–h**) and 4-oxo-2-phenylchroman-7-yl cinnamates (**8a–k**) starting from natural product 7-hydroxyflavanone. All the titled compounds **6a–h** and **8a–k** were screened for their anti-microbial activity. Compounds **6e**, **6g–h**, **8h–i** and **8k** were identified most potent anti-microbial activity when compared with the standard drugs. Compounds **6a** and **8h** showed highest binding affinity scores. This is first report on SAR studies with respect to anti-microbial activity by isoxazoles and acrylates. The present study dealt that the isoxazoles and acrylates are most potent compounds and serve as model compounds for design and development of pharmaceutical compounds.

Materials and methods

Chemistry

All the chemicals and reagents of analytical grade were purchased from Aldrich (Sigma-Aldrich, USA), AVRA Chemicals Pvt. Ltd (Hyderabad, India) and were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F_{254} (mesh); spots were visualized under UV light. Column chromatography has been carried out by using Merck silica gel (60–120 mesh). Melting points were determined in open glass capillary tubes on a Mettler–Temp apparatus and are uncorrected. An IR spectrum was recorded with a Thermo Nicolet Nexus 670 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 300, 400 and 500 MHz spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane as internal

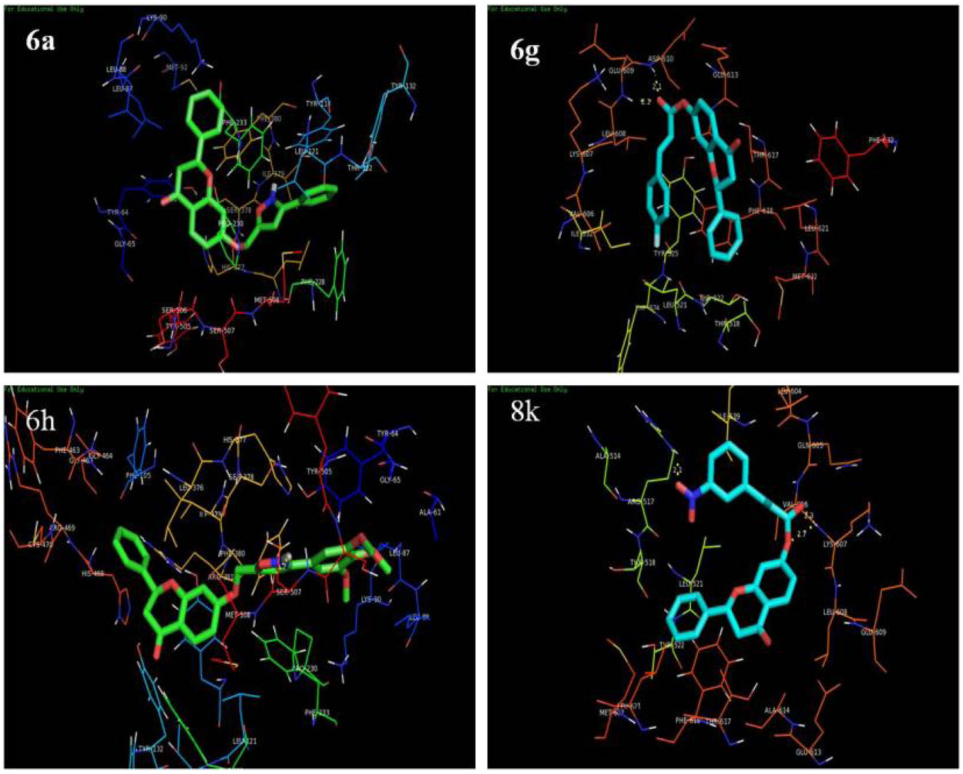


Fig. 1 3D Model interaction of compounds **6a, 6g, 6h** and **8k**

standard. ESI-MS obtained on 7070H spectrometer operating at 0 ev using a direct inlet system. HRMS were carried out on Agilent 6510, Q-TOFLC/MS instrument ESI-Technique.

General procedure for the preparation of 5-(bromomethyl)-3-phenylisoxazoles (4a–h)

$NaHCO_3$ (5.6 mmol) was added portion wise at 0 °C to a stirred solution of hydroxylamine hydrochloride (3.7 mmol) in water (7 ml) at room temperature and the mixture was stirred for 30 min. The benzaldehyde (**1a**, 3.1 mmol) has dissolved in methanol (5 ml) and added to the above reaction mixture and stirring was continued for an additional 6 h. Methanol was removed under reduced pressure and the residue was extracted with diethyl ether. The organic extract was washed with brine, dried over Na_2SO_4 and solvent has removed under reduced pressure gave **2a** as colourless solid in 85% yield. The crude oxime was taken for further reaction without purification. *N*-Chlorosuccinimide (1.3 mmol) and pyridine (2 drops) were added to a stirred solution of oxime **2a** (1.3 mmol) in anhydrous $CHCl_3$ (15 ml) at room temperature. The reaction mixture was stirred for 1 h at 50–60 °C. The Propargyl bromide (1.4 mmol) was added to the reaction mixture and followed by triethylamine (1.95 mmol) in $CHCl_3$ (5 ml) and the reaction mixture was stirred at room temperature for 2 h and water was added (10 ml), the organic layer was separated, and washed with 2.5% HCl (15 ml) and followed by water (15 ml) and with brine solution (15 ml). After the completion of the reaction solvent was removed under reduced pressure and the residue was purified by column chromatography using silica gel (ethyl acetate/hexane 5:95) afforded 5-(bromomethyl)-3-phenylisoxazole **4a**. The remaining oxime compounds **2b–h** were prepared from corresponding benzaldehydes with hydroxylamine hydrochloride. Similarly, the remaining isoxazole compounds **4b–h** were prepared from corresponding benzaldehyde oximes.

5-(bromomethyl)-3-p-tolylisoxazole (4b)

Pedada et al. (2016).

5-(bromomethyl)-3-(4-methoxyphenyl)isoxazole (4c)

Liu et al. (2009).

5-(bromomethyl)-3-(2,3-dimethoxyphenyl)isoxazole (4d)

Colourless solid; mp: 85–90 °C, Yield 52%, FT-IR ν_{max}/cm^{-1}: 3014, 1583, 1481, 1409, 1304, 1264, 1223, 1177, 1096, 1051, 1002, 935. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.39 (m, 1H, Ar-H), 7.22–7.10 (m, 1H, Ar-H), 7.02 (dd, $J = 8.2$, 1.4 Hz, 1H, Ar-H), 6.84 (s, 1H), 4.68–4.53 (m, 2H), 3.92–3.80 (m, 6H). ESI-MS: *m/z* 298 $[M+H]^+$.

5-(bromomethyl)-3-(3,4-dimethoxyphenyl)isoxazole (4e)

Colourless solid; mp: 90–98 °C, Yield 68%, FT-IR ν_{max}/cm^{-1}: 3007, 2949, 2839, 1600, 1526, 1466, 1426, 1383, 1243, 1145, 1074, 1021, 930. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, $J = 2.0$ Hz, 2H, Ar-H), 7.07–7.05 (m, 1H, Ar-H), 6.87 (d, $J = 8.3$ Hz, 1H), 4.99 (dd, $J = 6.3$, 4.2 Hz, 2H), 3.92 (s, 6H). ESI-MS: *m/z* 298 $[M+H]^+$.

5-(bromomethyl)-3-(2,4-dimethoxyphenyl)isoxazole (4f)

Colourless solid; mp: 94–96 °C, Yield 72%, FT-IR ν_{max}/cm^{-1}: 2945, 2837, 1580, 1479, 1407, 1304, 1263, 1228, 1174, 1094, 1049, 1001, 935. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, $J = 8.5$, 2.2 Hz, 1H, Ar-H), 6.82–6.76 (m, 1H, Ar-H), 6.59–6.53 (m, 2H, Ar-H), 4.66–4.50 (m, 2H), 3.89–3.85 (m, 6H). ESI-MS: *m/z* 298 $[M+H]^+$.

5-(bromomethyl)-3-(2,4,5-trimethoxyphenyl)isoxazole (4g)

Colourless solid; mp: 108–116 °C, Yield 78%, FT-IR ν_{max}/cm^{-1}: 2945, 1672, 1611, 1525, 1470, 1363, 1280, 1220, 1035, 817. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, $J =$ 1.7 Hz, 1H, Ar-H), 6.86 (s, 1H, Ar-H), 6.59 (d, $J = 1.5$ Hz, 1H, Ar-H), 4.59 (d, $J = 58.2$ Hz, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H). ESI-MS: *m/z* 328 $[M+H]^+$.

5-(bromomethyl)-3-(3,4,5-trimethoxyphenyl)isoxazole (4h)

Suman et al. (2015).

General procedure for the preparation of 2-phenyl-7-((3-phenylisoxazol-5-yl) methoxy) chroman-4-one (6a)

7-Hydroxyflavanone (**5**, 1 eq.) in acetonitrile was added to the stirred solution of K_2CO_3 (1.2 eq) and stirred for 30 min. Then isoxazole (**4a**, 1.2 eq) in acetonitrile was added at room temperature to the reaction mixture and stirring continued for 48 h. After completion of the reaction (TLC), the reaction mixture was filtered through sintered funnel and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using silica gel (hexane/ethyl acetate 5%) afforded **6a**.

2-Phenyl-7-((3-phenylisoxazol-5-yl) methoxy) chroman-4-one (6a)

Colourless solid, mp: 132–136 °C; Yield 75%, FT-IR ν_{max}/cm^{-1}: 3020, 2353, 1609, 1436, 1215, 1012, 922. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.83–7.78 (m, 2H, Ar-H), 7.50–7.46 (m, 3H, Ar-H), 7.46–7.36 (m, 5H, Ar-H), 6.72 (dd, $J = 8.8$, 2.4 Hz, 1H, Ar-H), 6.67 (s, 1H, Ar-H), 6.60 (d, $J = 2.4$ Hz, 1H, Ar-H), 5.49 (dd, $J = 13.3$, 2.9 Hz, 1H), 5.24 (s, 2H), 3.06 (dd, $J =$ 16.9, 13.3 Hz, 1H), 2.86 (dd, $J = 16.9$, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.53, 167.30, 164.03, 163.86, 163.43, 162.96, 162.62, 142.0, 138.61, 130.29, 129.13, 128.91, 128.59, 126.89, 126.22, 121.42, 115.74, 114.16, 110.42, 105.54, 102.06, 101.84, 80.12, 61.39, 44.32. ESI-MS: m/z 398 $[M+H]^+$, ESI-HRMS: *m/z* 398.1391 $[M+H]^+$ (calcd for $C_{25}H_{19}NO_4$ 398.1392).

2-Phenyl-7-((3-(p-tolylisoxazol-5-yl) methoxy) chroman-4-one (6b)

Colourless solid, mp: 140–144 °C; Yield 62%, FT-IR ν_{max}/cm^{-1}: 2952, 2838, 1605, 1513, 1460, 1421, 1353, 1271, 1215, 1159, 1030, 955. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.76–7.65 (m, 2H, Ar-H), 7.54–7.41 (m, 5H, Ar-H), 7.41–7.37 (m, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 6.71 (dd, $J = 8.8$, 2.4 Hz, 1H, Ar-H), 6.64 (s, 1H, Ar-H), 6.60 (d, $J = 2.4$ Hz, 1H, Ar-H), 5.49 (dd, $J =$ 13.3, 2.9 Hz, 1H), 5.23 (s, 2H), 3.06 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.86 (dd, $J = 16.9$, 2.9 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.53, 167.08, 164.06, 163.84, 163.43, 162.95, 162.56, 140.47, 138.62, 129.70, 129.12, 128.90, 126.77, 126.21, 125.74, 115.71, 112.24, 110.43, 109.29, 102.29, 102.05, 101.77, 80.12, 61.40, 44.32, 21.48. ESI-MS: *m/z* 412 $[M+H]^+$, ESI-HRMS: *m/z*, 412.1552 $[M+H]^+$ (calcd for $C_{26}H_{21}NO_4$ 412.1548).

7-((3-(4-methoxyphenyl) isoxazol-5-yl) methoxy)-2-Phenylchroman-4-one (6c)

Colourless solid, mp: 123–126 °C; Yield 60%, FT-IR ν_{max}/cm^{-1}: 2947, 2837, 1581, 1480, 1407, 1304, 1264, 1227, 1177, 1095, 1050, 1002, 934. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.81–7.70 (m, 2H, Ar-H), 7.50–7.36 (m, 5H, Ar-H), 7.02–6.93 (m, 2H, Ar-H), 6.71 (dd, $J = 8.8$, 2.4 Hz, 1H, Ar-H), 6.64–6.56 (m, 2H, Ar-H), 5.49 (dd, $J = 13.3$, 2.9 Hz, 1H), 5.22 (s, 2H), 3.85 (s, 3H), 3.06 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.86 (dd, $J = 16.9$, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.55, 166.99, 164.85, 164.07, 163.70, 163.43, 162.22, 161.20, 142.36, 138.60, 129.13, 128.90, 128.30, 126.20, 124.25, 121.07, 115.71, 114.40, 110.44, 102.04, 101.58, 80.13, 61.42, 55.40, 53.46, 44.33. ESI-MS: *m/z* 428 $[M+H]^+$, ESI-HRMS: *m/z* 428.1484 $[M+H]^+$ (calcd for $C_{26}H_{21}NO_5$ 428.1497).

7-((3-(2,3-dimethoxyphenyl) isoxazol-5-yl) methoxy)-2-Phenylchroman-4-one (6d)

Colourless solid; mp: 123–127 °C, Yield 57%, FT-IR ν_{max}/cm^{-1}: 3014, 1583, 1481, 1409, 1304, 1264, 1223, 1177,

1096, 1051, 1002, 935. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.47–7.42 (m, 5H, Ar-H), 7.40 (d, $J = 3.0$ Hz, 1H, Ar-H), 7.29 (dd, $J = 8.3$, 2.0 Hz, 1H, Ar-H), 6.92 (d, $J = 8.4$ Hz, 1H, Ar-H), 6.72 (dd, $J = 8.8$, 2.4 Hz, 1H, Ar-H), 6.63–6.60 (m, 2H, Ar-H), 5.49 (dd, $J = 13.2$, 2.9 Hz, 1H), 5.23 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.06 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.86 (dd, $J = 16.9$, 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.52, 167.09, 164.04, 163.43, 162.34, 152.80, 150.83, 149.39, 141.98, 138.59, 129.14, 128.90, 126.20, 121.28, 120.07, 115.74, 111.08, 110.43, 109.32, 102.04, 101.62, 99.59, 80.14, 61.43, 56.04, 56.0, 44.33. ESI-MS: *m/z* 458 $[M+H]^+$, ESI-HRMS: *m/z* 458.1602 $[M+H]^+$ (calcd for $C_{27}H_{23}NO_6$ 458.1603).

7-((3-(3, 4-dimethoxyphenyl) isoxazol-5-yl) methoxy)-2-Phenylchroman-4-one (6e)

Colourless solid; mp: 118–124 °C, Yield 58%, FT-IR ν_{max}/cm^{-1}: 3007, 2949, 2839, 1600, 1526, 1466, 1426, 1383, 1243, 1145, 1074, 1021, 930. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.46 (dd, $J = 16.4$, 11.9, 5.1 Hz, 5H, Ar-H), 7.41–7.33 (m, 1H, Ar-H), 7.29 (dd, $J =$ 8.3, 2.0 Hz, 2H, Ar-H), 6.93 (d, $J = 8.4$ Hz, 1H, Ar-H), 6.72 (dd, $J = 8.8$, 2.4 Hz, 1H, Ar-H), 6.66–6.53 (m, 1H, Ar-H), 5.49 (dd, $J = 13.2$, 2.9 Hz, 1H), 5.23 (s, 2H), 3.94 (d, $J =$ 8.0 Hz, 6H), 3.06 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.86 (dd, $J =$ 16.9, 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.52, 167.10, 164.04, 163.42, 163.13, 162.34, 161.05, 150.83, 150.60, 149.39, 138.59, 129.13, 128.90, 126.20, 121.28, 120.07, 115.73, 111.09, 110.43, 109.32, 102.04, 101.63, 80.14, 61.42, 56.07, 56.0, 44.32. ESI-MS: *m/z* 458 $[M+H]^+$, ESI-HRMS: *m/z* 458.1604 $[M+H]^+$ (calcd for $C_{27}H_{23}NO_6$ 458.1603).

7-((3-(2, 4-dimethoxyphenyl) isoxazol-5-yl) methoxy)-2-Phenylchroman-4-one (6f)

Colourless solid; mp: 119–126 °C, Yield 55%, FT-IR ν_{max}/cm^{-1}: 2945, 2837, 1580, 1479, 1407, 1304, 1263, 1228, 1174, 1094, 1049, 1001, 935. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.52–7.42 (m, 5H, Ar-H), 7.40 (d, $J = 6.9$ Hz, 1H, Ar-H), 7.29 (dd, $J = 8.3$, 2.0 Hz, 1H, Ar-H), 6.92 (d, $J = 8.4$ Hz, 1H, Ar-H), 6.71 (dd, $J =$ 8.8, 2.4 Hz, 1H, Ar-H), 6.67–6.54 (m, 2H, Ar-H), 5.49 (dd, $J = 13.2$, 2.9 Hz, 1H), 5.22 (s, 2H), 3.94 (d, $J = 8.0$ Hz, 6H), 3.06 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.86 (dd, $J = 16.9$, 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.52, 167.10, 164.77, 164.04, 163.42, 162.34, 160.83, 150.83, 149.39, 138.59, 129.13, 127.62, 126.20, 126.20, 125.69, 121.28, 120.07, 111.09, 110.42, 109.32, 102.04, 101.63, 80.13, 61.42, 56.07, 55.99, 44.32. ESI-MS: *m/z* 458 $[M+H]^+$, ESI-HRMS: *m/z* 458.1603 $[M+H]^+$ (calcd for $C_{27}H_{23}NO_6$ 458.1603).

2-Phenyl-7-((3-(2,4,5-trimethoxyphenyl)isoxazol-5-yl) methoxy) chroman-4-one (6g)

Colourless solid; mp: 132–140 °C, Yield 54%, FT-IR νmax/cm^{-1}: 2945, 1672, 1611, 1525, 1470, 1363, 1280, 1220, 1035. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.50–7.42 (m, 5H, Ar-H), 7.42–7.36 (m, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 6.72 (dd, $J = 8.8$, 2.4 Hz, 1H, Ar-H), 6.67–6.54 (m, 2H, Ar-H), 5.49 (dd, $J = 13.2$, 2.9 Hz, 1H), 5.22 (s, 2H), 3.90 (dd, $J = 15.1$, 10.8 Hz, 9H), 3.06 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.85 (dd, $J = 16.9$, 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.57, 165.81, 164.24, 163.42, 159.93, 152.28, 151.52, 143.45, 138.64, 135.29, 129.03, 128.89, 128.86, 128.42, 126.20, 115.61, 111.50, 110.51, 108.76, 105.28, 102.06, 97.46, 80.10, 61.34, 56.49, 56.44, 56.10, 44.33. ESI-MS: *m/z* 488 $[M+H]^+$, ESI-HRMS: *m/z* 488.1708 $[M+H]^+$ (calcd for $C_{28}H_{25}NO_7$ 488.1709).

2-Phenyl-7-((3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl) methoxy) chroman-4-one (6h)

Colourless solid; mp: 117–120 °C, Yield 60%, FT-IR νmax/cm^{-1}: 2951, 1667, 1609, 1523, 1469, 1363, 1278, 1218, 1034.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.46 (dtd, $J = 7.4$, 5.7, 1.9 Hz, 5H, Ar-H), 7.40 (dd, $J = 5.0$, 3.6 Hz, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 6.72 (dd, $J = 8.8$, 2.4 Hz, 1H, Ar-H), 6.66–6.57 (m, 2H, Ar-H), 5.49 (dd, $J = 13.2$, 2.9 Hz, 1H), 5.22 (s, 2H), 3.90 (dd, $J =$ 15.1, 10.8 Hz, 9H), 3.06 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.85 (dd, $J = 16.9$, 3.0 Hz, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 190.57, 165.81, 164.24, 163.42, 162.07, 159.93, 154.09, 152.28, 151.52, 143.45, 138.64, 129.03, 128.89, 128.86, 126.20, 115.61, 111.50, 110.51, 108.76, 105.28, 102.06, 97.46, 80.10, 61.34, 56.49, 56.44, 56.10, 44.33. ESI-MS: *m/z* 488 $[M+H]^+$, ESI-HRMS: *m/z* 488.1710 $[M+H]^+$ (calcd for $C_{28}H_{25}NO_7$ 488.1709).

General procedure for the preparation of 4-oxo-2-phenylchroman-7-yl cinnamate (8a)

7-Hydroxyflavanone (**5**, 1eq) was added to the stirred solution of cinnamic acid (**7a**, 1.2 eq.), *N,N′*-dicyclohexylcarbodiimide (DCC, 1.2 eq), and 4-dimethylamin opyridine (DMAP, 0.2 eq.) in dry dichloromethane at room temperature and continued for 48 h. After completion of the reaction (TLC), water was added and extracted with dichloromethane. The organic layer was washed with brine solution and separate organic layer, dried over Na_2SO_4 and the solvent was removed under reduced pressure and the residue was purified by column chromatography using silica gel (hexane/ethyl acetate 5%) afforded to **8a**.

4-Oxo-2-phenylchroman-7-yl cinnamate (8a)

Colourless solid; mp: 117–120 °C, Yield 63%; FT-IR ν_{max}/cm^{-1}: 3026, 2930, 2859, 1735, 1695, 1645, 1614, 1529, 1445, 1369, 1297, 1232, 1132, 1068, 989. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.88 (d, $J = 16.0$ Hz, 1H, Ar-H), 7.59 (dd, $J = 6.5$, 2.9 Hz, 2H, Ar-H), 7.50–7.46 (m, 3H, Ar-H), 7.43 (dd, $J = 4.7$, 2.6 Hz, 5H, Ar-H), 6.99–6.87 (m, 2H, Ar-H), 6.61 (d, $J = 16.0$ Hz, 1H), 5.52 (dd, $J = 13.3$, 2.8 Hz, 1H), 3.09 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.96–2.83 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.91, 166.54, 166.05, 164.51, 162.53, 156.88, 154.08, 147.54, 143.35, 131.03, 130.06, 129.09, 128.91, 128.53, 128.46, 127.96, 126.19, 119.48, 118.81, 116.63, 115.78, 111.23, 80.04, 44.48. ESI-MS: *m/z* 371 $[M+H]^+$, ESI-HRMS: *m/z* 371.1258 $[M+H]^+$ (calcd for $C_{24}H_{18}O_4$ 371.1283).

(E)-4-Oxo-2-phenylchroman-7-yl 3-p-tolylacrylate (8b)

Colourless solid; mp: 113–117 °C, Yield 60%; FT-IR νmax/cm^{-1}: 3023, 2927, 2859, 1731, 1692, 1611, 1515, 1442, 1366, 1317, 1231, 1126, 1067, 989. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.85 (d, $J = 16.0$ Hz, 1H, Ar-H), 7.50 (s, 1H, Ar-H), 7.48–7.36 (m, 6H, Ar-H), 7.23 (d, $J = 8.0$ Hz, 2H, Ar-H), 6.95–6.86 (m, 2H, Ar-H), 6.56 (d, $J = 16.0$ Hz, 1H), 5.52 (dd, $J = 13.3$, 2.8 Hz, 1H), 3.09 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.90 (dd, $J = 16.9$, 2.9 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.92, 164.69, 162.53, 156.98, 154.19, 147.57, 143.45, 141.61, 140.44, 138.55, 129.83, 128.90, 128.49, 126.18, 118.76, 118.41, 115.82, 115.47, 111.23, 80.02, 68.18, 56.11, 49.91, 44.48, 21.60. ESI-MS: *m/z* 385 $[M+H]^+$, ESI-HRMS: *m/z* 385.1441 $[M+H]^+$ (calcd for $C_{25}H_{20}O_4$ 385.1439).

(E)-4-Oxo-2-phenylchroman-7-yl 3-m-tolylacrylate (8c)

Colourless solid; mp: 118–124 °C, Yield 76%; FT-IR νmax/cm^{-1}: 3025, 2927, 2855, 1734, 1694, 1615, 1442, 1370, 1314, 1224, 1131, 1070, 991. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.86 (d, $J = 16.0$ Hz, 1H, Ar-H), 7.45 (dd, $J = 20.8$, 8.9 Hz, 5H, Ar-H), 7.39 (d, $J = 3.0$ Hz, 2H, Ar-H), 7.31 (dd, $J = 13.7$, 5.5 Hz, 2H, Ar-H), 6.99–6.84 (m, 2H, Ar-H), 6.60 (d, $J = 16.0$ Hz, 1H), 5.53 (dd, $J = 13.3$, 2.8 Hz, 1H), 3.10 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.90 (dd, $J = 16.9$, 2.9 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.89, 163.53, 161.48, 155.87, 146.70, 137.73, 137.47, 132.86, 130.83, 129.88, 128.05, 127.91, 127.85, 127.48, 125.13, 124.60, 117.74, 115.31, 114.75, 110.17, 78.99, 43.44, 29.96, 25.30, 20.31. ESI-MS: *m/z* 385 $[M+H]^+$, ESI-HRMS: *m/z* 385.1433, $[M+H]^+$ (calcd for $C_{25}H_{20}O_4$385.1439).

(E)-4-Oxo-2-phenylchroman-7-yl 3-(4-fluorophenyl) acrylate (8d)

Colourless solid; mp: 132–138 °C, Yield 85%; FT-IR νmax/cm^{-1}: 3054, 2932, 2859, 1734, 1692, 1607, 1512, 1443, 1368, 1322, 1229, 1131, 1064, 989. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.84 (d, $J = 16.0$ Hz, 1H, Ar-H), 7.62–7.57 (m, 2H, Ar-H), 7.50–7.39 (m, 5H, Ar-H), 7.12 (t, $J = 8.6$ Hz, 2H, Ar-H), 6.96–6.86 (m, 2H, Ar-H), 6.54 (d, $J = 15.9$ Hz, 1H), 5.53 (dd, $J = 13.3$, 2.8 Hz, 1H), 3.10 (dd, $J = 16.9$, 13.4 Hz, 1H), 2.91 (dd, $J = 16.9$, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.91, 165.33, 164.39, 162.52, 156.81, 154.04, 146.16, 142.06, 138.49, 130.45, 130.38, 128.91, 128.55, 126.18, 119.20, 118.83, 116.38, 116.21, 116.16, 115.98, 115.74, 111.20, 80.06, 44.46. ESI-MS: *m/z* 389 $[M+H]^+$, ESI-HRMS: *m/z*, 389.1182 $[M+H]^+$ (calcd for $C_{24}H_{17}FO_4$ 389.1188).

(E)-4-Oxo-2-phenylchroman-7-yl 3-(4-chlorophenyl) acrylate (8e)

Colourless solid; mp: 116–125 °C; Yield 85%; FT-IR νmax/cm^{-1}: 3019, 2357, 2290, 2100, 1893, 1737, 1695, 1641, 1581, 1528, 1490, 1423, 1319, 1225, 1137, 1098, 1053, 985. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.83 (d, $J = 16.0$ Hz, 1H, Ar-H), 7.55–7.51 (m, 4H, Ar-H), 7.50–7.46 (m, 5H, Ar-H), 6.97–6.83 (d, 2H, Ar-H), 6.58 (d, $J = 16.0$ Hz, 1H), 5.53 (dd, $J = 13.3$, 2.9 Hz, 1H), 3.10 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.91 (dd, $J = 16.9$, 2.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.90, 166.20, 164.27, 162.52, 156.75, 153.98, 146.01, 138.47, 132.43, 129.59, 129.40, 129.21, 129.09, 128.91, 128.58, 126.18, 120.01, 118.86, 117.22, 115.71, 111.19, 80.07, 44.47, 31.02. ESI-MS: *m/z* 405 $[M+H]^+$, ESI-HRMS: *m/z* 405.0895, $[M+H]^+$ (calcd for $C_{24}H_{17}ClO_4$ 405.0893).

(E)-4-Oxo-2-phenylchroman-7-yl 3-(3-chlorophenyl) acrylate (8f)

Colourless solid; mp: 129–132 °C; Yield 80%; FT-IR νmax/cm^{-1}: 3023, 2928, 1736, 1692, 1611, 1483, 1439, 1303, 1229, 1134, 1068, 990. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.81 (d, $J = 16.0$ Hz, 1H, Ar-H), 7.58 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.54–7.43 (m, 5H, Ar-H), 7.42–7.33 (m, 3H, Ar-H), 7.00–6.78 (m, 2H, Ar-H), 6.61 (d, $J = 16.0$ Hz, 1H), 5.53 (dd, $J = 13.3$, 2.9 Hz, 1H), 3.10 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.91 (dd, $J = 16.9$, 2.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.90, 164.10, 162.52, 156.69, 145.81, 141.67, 138.47, 135.74, 135.13, 130.85, 130.33, 128.92, 128.59, 128.13, 127.69, 126.60, 126.19, 120.92, 118.89, 118.15, 115.69, 111.18, 80.07, 44.47. ESI-MS: *m/z* 405 $[M+H]^+$, ESI-HRMS: *m/z* 405.0889 $[M+H]^+$ (calcd for $C_{24}H_{17}ClO_4$ 405.0893).

(E)-4-Oxo-2-phenylchroman-7-yl 3-(2-chlorophenyl) acrylate (8g)

Colourless solid; mp: 128–131 °C; Yield 84%; FT-IR νmax/cm^{-1}: 3023, 2930, 1735, 1691, 1611, 1440, 1368, 1316, 1276, 1223, 1130, 1053. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, $J = 16.0$ Hz, 1H, Ar-H), 8.00 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.70 (dd, $J = 7.6$, 1.8 Hz, 1H, Ar-H), 7.47 (ddd, $J =$ 7.0, 4.8, 3.8 Hz, 5H, Ar-H), 7.42–7.31 (m, 3H, Ar-H), 6.95 (d, $J = 2.1$ Hz, 2H, Ar-H), 6.61 (d, $J = 16.0$ Hz, 1H), 5.53 (dd, $J = 13.3$, 2.8 Hz, 1H), 3.10 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.91 (dd, $J = 16.9$, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.90, 166.20, 164.27, 162.52, 156.75, 153.98, 146.01, 138.47, 132.43, 129.59, 129.40, 129.21, 129.09, 128.91, 128.58, 126.18, 120.01, 118.86, 117.22, 115.71, 111.19, 80.07, 56.06, 44.47. ESI-MS: *m/z* 405 $[M+H]^+$, ESI-HRMS: *m/z* 405.0892 $[M+H]^+$ (calcd for $C_{24}H_{17}ClO_4$ 405.0893).

(E)-4-Oxo-2-phenylchroman-7-yl 3-(4-bromophenyl) acrylate (8h)

Colourless solid; mp:148–153 °C; Yield 71%; FT-IR νmax/cm^{-1}: 2931, 2858, 1734, 1696, 1645, 1614, 1529, 1489, 1443, 1370, 1313, 1231, 1137, 1071.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.81 (d, $J =$ 16.0 Hz, 1H, Ar-H), 7.60–7.47 (m, 5H, Ar-H), 7.46–7.35 (m, 4H, Ar-H), 6.96–6.84 (m, 2H, Ar-H), 6.60 (d, $J =$ 16.0 Hz, 1H), 5.52 (dd, $J = 13.2$, 2.9 Hz, 1H), 3.10 (dd, $J =$ 16.9, 13.3 Hz, 1H), 2.90 (dd, $J = 16.9$, 3.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.90, 164.26, 162.52, 156.74, 146.09, 141.95, 138.47, 133.67, 132.85, 132.36, 132.17, 129.77, 129.29, 128.91, 128.58, 126.18, 125.41, 120.09, 118.87, 117.33, 115.70, 111.18, 80.07, 44.47. ESI-MS: *m/z* 449 $[M+H]^+$, ESI-HRMS: *m/z* 451.0367 $[M+H]^+$ (calcd for $C_{24}H_{17}BrO_4$ 449.0388).

(E)-4-Oxo-2-phenylchroman-7-yl 3-(3-bromophenyl) acrylate (8i)

Colourless solid; mp:112–118 °C; Yield 76%; FT-IR νmax/cm^{-1}: 3024, 2920, 1736, 1691, 1611, 1574, 1475, 1439, 1302, 1228, 1133, 1067, 990.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.86–7.71 (m, 2H, Ar-H), 7.58–7.50 (m, 2H, Ar-H), 7.50–7.36 (m, 5H, Ar-H), 7.31 (t, $J = 7.9$ Hz, 1H, Ar-H), 7.00–6.80 (m, 2H, Ar-H), 6.61 (d, $J = 16.0$ Hz, 1H), 5.53 (dd, $J = 13.3$, 2.9 Hz, 1H), 3.10 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.91 (dd, $J = 16.9$, 2.9 Hz, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 191.63, 190.90, 176.04, 164.07, 162.52, 156.69, 147.19, 145.71, 138.47, 136.01, 133.76, 131.08, 130.58, 128.92, 128.60, 127.03, 126.19, 123.21, 118.89, 118.17, 115.69, 111.18, 80.07, 44.47. ESI-MS: *m/z* 449 $[M+H]^+$, ESI-HRMS: *m/z* 451.0368, $[M+H]^+$ (calcd for $C_{24}H_{17}BrO_4$ 449.0388).

(E)-4-Oxo-2-phenylchroman-7-yl 3-(2-chloro-6-fluorophenyl) acrylate (8j)

Colourless solid; mp: 130–134 °C; Yield 60%; FT-IR νmax/cm^{-1}: 3021, 2935, 2859, 1738, 1693, 1609, 1527, 1447, 1368, 1311, 1220, 1135, 1065, 988. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, $J = 16.4$ Hz, 1H, Ar-H), 8.00 (d, $J =$ 8.6 Hz, 1H, Ar-H), 7.47 (dt, $J = 8.7$, 1.7 Hz, 5H, Ar-H), 7.10 (dd, $J = 13.1$, 5.2 Hz, 3H, Ar-H), 6.96 (d, $J = 2.1$ Hz, 1H, Ar-H), 6.92 (dd, $J = 8.7$, 2.1 Hz, 2H, Ar-H), 5.54 (dd, $J =$ 13.3, 2.8 Hz, 1H), 3.10 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.91 (dd, $J = 16.9$, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.90, 166.20, 164.27, 162.52, 156.75, 153.98, 146.01, 141.91, 138.47, 132.43, 129.59, 129.40, 129.21, 129.09, 128.91, 128.58, 126.18, 120.01, 118.86, 117.22, 115.71, 111.19, 80.07, 44.47. ESI-MS: *m/z* 423 $[M+H]^+$, ESI-HRMS: *m/z* 423.0798, $[M+H]^+$ (calcd for: $C_{24}H_{16}ClFO_4$ 423.0799).

(E)-4-Oxo-2-phenylchroman-7-yl 3-(3-nitrophenyl) acrylate (8k)

Colourless solid; mp: 146–150 °C; Yield 60%; FT-IR νmax/cm^{-1}: 3078, 2930, 2858, 1735, 1687, 1609, 1533, 1445, 1348, 1283, 1234, 1137, 1067, 992. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H, Ar-H), 8.29 (d, $J = 8.1$ Hz, 1H, Ar-H), 8.01 (d, $J = 8.6$ Hz, 1H, Ar-H), 7.92 (d, $J = 15.8$ Hz, 2H, Ar-H), 7.64 (t, $J = 8.0$ Hz, 2H, Ar-H), 7.46 (dd, $J =$ 12.9, 6.2 Hz, 5H, Ar-H), 6.99–6.87 (m, 1H, Ar-H), 6.75 (d, $J = 16.0$ Hz, 1H), 5.54 (dd, $J = 13.3$, 2.7 Hz, 1H), 3.11 (dd, $J = 16.9$, 13.3 Hz, 1H), 2.90 (d, $J = 2.9$ Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.00, 163.73, 162.56, 156.53, 148.79, 144.49, 138.38, 135.64, 133.91, 130.20, 129.28, 128.93, 128.83, 128.68, 126.18, 125.18, 122.75, 119.90, 118.99, 115.60, 110.87, 103.41, 80.12, 44.45. ESI-MS: *m/z* 416 $[M+H]^+$, ESI-HRMS: *m/z* 416.1139 $[M+H]^+$, (calcd for: $C_{24}H_{17}NO_6$ 416.1133).

Biological activity

Chemicals and kits

Test microbial strains include *Staphylococcus aureus (*ATCC 25923), *Bacillus subtilis* (ATCC 23857), *Escherichia coli (*ATCC 25922), *Pseudomonas aeruginosa* (ATCC 10145), *Aspergillus niger* (ATCC 1015) and *Aspergillus fumigates* (ATCC 1022) were obtained American Type Culture Collection (ATCC, Manassas, USA). Nutrient agar medium and Potato dextrose agar medium,

petridishes were purchased from Hi- media chemicals (Mumbai, India).

Anti-microbial assay

Agar well diffusion method was used to determine the anti-microbial activity of synthesized compounds. Totally four bacterial and two fungal strains were used in the present study viz. *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Aspergillus niger* and *Aspergillus fumigates*, respectively. Further, Streptomycin and Cycloheximide were used as a standard references for bacteria and fungi, respectively. Nutrient agar and potato dextrose agar plates were prepared and allowed for solidification. Followed by the wells were created using sterile cork borer and bottom of the wells was sealed with respective media to prevent the leakage of compounds. A total of 50 µl of bacterial and fungal strains were spread over the surface of agar plate using sterile swab. Then the wells were labelled and filled with 100 µl of DMSO soluble synthesized compounds **6a–h, 8a–k**. Agar plates were incubated at 37 °C and 25 °C for the growth of bacteria and fungi, respectively. After incubation period, anti-microbial activity for synthesized compounds was assessed by measuring the zone of inhibition around the wells using calibrated scale (Prakash et al. 2011).

Molecular docking studies

The structures for synthesized compounds were drawn using Chem Draw Ultra V6.0 and then followed by 3D coordinates were prepared using Dundee PRODRG2 (http://davapc1.bioch.dundee.ac.uk/prodrg/). X-ray crystal structures of sterol 14-α demethylase (CYP51) from *Candida albicans* (PDB ID: 5TZ1) and DNA gyrase B (PDB ID: 6QTP) from *Staphylococcus aureus* were downloaded from PDB (www.rcsb.org/pdb). Then the synthesized compounds were subjected to molecular docking against sterol 14-α demethylase and DNA gyrase B using Autodock 4.2 module in PyRx 0.8. After docking, the binding affinities were noted and the interactions between protein–ligand complexes were analyzed by PyMol viewer 1.5.4 (Jones et al. 1997).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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