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Synthesis and biological evaluation of (3-arylisoxazol-5-yl)methyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylates as antioxidant and antimicrobial agents

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Abstract: A series of novel (3-arylisoxazol-5-yl)methyl 6-fluoro-4-oxo-4*H*--chromene-2-carboxylate derivatives (**C_1**–**C_{12}**) were synthesized by the Cu(I)--catalyzed reaction of *in situ* generated nitrile oxides with prop-2-ynyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylate in good yields and their antioxidant and antimicrobial activities were investigated. Among all the synthesized compounds, **C_1** (IC_{50}: 16.43±0.57 μM) and **C_{12}** (IC_{50}:15.98±0.72 μM) registered good antioxidant activity as compared to the standard drug trolox. Compounds **C_1**, **C_3** and **C_6** registered very good inhibition against all the tested Gram-positive and Gram-negative bacterial strains with *MIC* values ranging from 9.375 to 37.5 μg mL^{-1}. Compounds **C_7**–**C_{11}** registered good inhibition against *Bacillus subtilis* and *Staphylococcus aureus* with *MIC* values ranging from 18.75 to 37.5 μg mL^{-1}. Compounds **C_{10}** and **C_{11}** against *Pseudomonas aeroginosa* showed more prominent activity than the standard drug penicillin (*MIC*: 12.5 μg mL^{-1}) with an *MIC* value of 9.375 μg mL^{-1} (≈1.33-fold more potent than penicillin). Compounds **C_7**–**C_9** registered good to moderate antifungal activity against the four tested fungal strains with *MIC* values ranging from 18.75 to 37.5 μg mL^{-1}.

Keywords: isoxazole; chromene; antioxidant; antimicrobial activity.

INTRODUCTION

Isoxazole and its derivatives have attracted much awareness because of their unique structure and applications.[1] The isoxazole ring system is a five-membered heterocyclic ring structure composed of nitrogen and oxygen atoms at the 1,2 positions and is used in the synthesis of pharmaceuticals.[2,3] The isoxazole moiety is a versatile lead molecule in pharmaceutical development and has a wide range

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of biological activities. In the past few years, the therapeutic interest of isoxazole derivatives in the pharmaceutical and medicinal fields has been given great attention by medicinal chemist.[4,5] A literature survey revealed that isoxazole derivatives are well known to exhibit antibacterial,[6] $GABA_A$ antagonist,[7] anti-cancer,[8] antidiabetic[9] and anti-HIV activities.[10] The synthesis of isoxazole derivatives is obviously an important assignment in modern medicinal chemistry research. Isoxazole is the basic moiety for several drugs, such as zonisamide (**Z**, an anti-convulsant), leflunomide (**L**, a disease-modifying antirheumatic drug, DMARD) and valdecoxib (**V**, a COX-2 inhibitor), Fig. 1. Although a number of synthetic methods are available,[11] the copper(I)-catalyzed union of terminal alkynes and oximes to give 3,5-disubstituted isoxazole exhibits a remarkably broad scope and exquisite selectivity.[12] In recent years, extensive studies have been focused on isoxazole derivatives because of their diverse chemical reactivity, accessibility and wide range of biological activities.

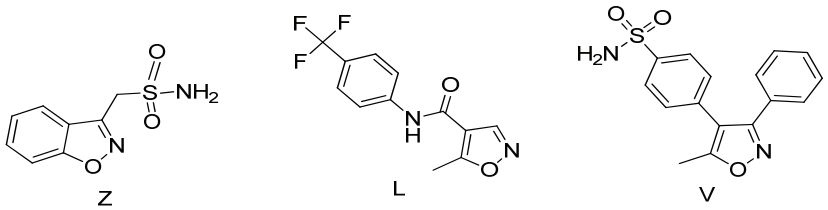


Fig. 1. Structures of isoxazole-congaing drugs.

Chromone and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases. Chromone derivatives are a broad class of chemical compounds with many important pharmacological properties.[13,14] Substituted chromone derivatives play a significant role in the medical field with many pharmacological activities, such as anti-HIV,[15] antimicrobial,[16] anticancer,[17,18] antiviral,[19] antioxidant,[20] cytotoxic activities[21] and anti-inflammatory activity.[22] Based on the above considerations and in continuation of ongoing research on biologically potent azole derivatives,[23–31] herein, the synthesis of (3-arylisoxazol-5-yl)methyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylate hybrids and their antioxidant and antimicrobial activities are reported.

EXPERIMENTAL

All the reagents and solvents were purchased from Sigma–Aldrich or S.D. Fine Chemicals and used without further purification. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} pre-coated plates (0.25 mm) and silica gel (particle size 60–120 mesh) was used for column chromatography. Melting points were determined using a Cintex apparatus and are uncorrected. FTIR spectra were recorded using a Bruker spectrometer and are reported on the frequency of absorption (cm^{-1}). Elemental analysis was performed using a

Perkin Elmer 2400 CHN elemental analyzer. The ^{1}H-NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer and the ^{13}C-NMR spectra on a Bruker 100 MHz spectrometer. $CDCl_3$ was used as the solvent. The ^{1}H-NMR spectra are reported relative to Me_4Si (δ 0.0 ppm). Coupling constants (J) values are presented in Hz and spin multiples are given as *s* (singlet), *d* (doublet), *t* (triplet), *dd* (doublet of doublets) and *m* (multiplet). The mass spectral analysis was recorded on a Bruker HCT mass spectrometer using the electrospray ionization mass spectrometry (ESI-MS) technique.

Analytical and spectral data of the synthesized compounds are given in Supplementary material to this paper.

*Synthesis of ethyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylate (**2**)*

To a stirred solution of 1-(5-fluoro-2-hydroxyphenyl)ethanone (10 g, 64.93 mmol, 1 eq) and diethyl oxalate (194.79 mmol, 3 eq) in ethanol (200 mL) was added Na metal (389.58 mmol, 6 eq) and the reaction mixture was refluxed under a nitrogen atmosphere for 4 h. After completion of the reaction (TLC), the reaction mixture was cooled, 6 M HCI (100 mL) was added and the product was extracted with CH_2CI_2 (3×200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the crude compound. Recrystallization of the crude compound from ethyl acetate and diethyl ether afforded compound **2** (13.5 g, 88 %) as a light yellow solid.

*Synthesis of 6-fluoro-4-oxo-4*H*-chromene-2-carboxylic acid (**3**)*

Ethyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylate (10 g, 42.37 mmol) was dissolved in 50 % aqueous NaOH solution and stirred at room temperature for 5 h. After completion of the reaction (TLC) the reaction mixture was neutralized with dilute HCl and extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford compound **3** (6.34 g, 72 %) as a light yellow powder.

*Synthesis of prop-2-ynyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylate (**4**)*

To a stirred solution of 6-fluoro-4-oxo-4*H*-chromene-2-carboxylic acid (**3**) (5 g, 24.03 mmol) in DMF (50 mL) was added *t*-BuOK (48.06 mmol, 2 eq) portion-wise over a 10 min period. Then, propargyl bromide (31.25 mmol, 1.3 eq) was added to the reaction mixture and stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, ice-cold water (100 mL) was added to the reaction mixture and extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford compound **4** (4.73 g, 80 % yield) as a yellow solid.

*Typical experimental procedure for synthesis of 3,5-disubstituted isoxazoles (**C$_1$**–**C$_{12}$**) as exemplified by the reaction of prop-2-ynyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylate and nicotinaldehyde*

Nicotinaldehyde (500 mg, 4.67 mmol) was added to a solution of hydroxylamine hydrochloride (322 mg, 5.14 mmol) in 10 mL of 1:1 *t*-BuOH:H_2O. To this was added NaOH (205 mg, 5.14 mmol), and after stirring for 30 min at ambient temperature, TLC analysis indicated that the oxime formation was complete. Chloramine-T trihydrate (1.47 g, 5.14 mmol) was added in small portions over 10 min, followed by CuI (44 mg, 0.233 mmol). Compound **4** (1.26 g, 5.14 mmol) was added, the pH was adjusted to 6 by the addition of a few drops of 1 M NaOH, and stirring was continued for a further 8 h. The reaction mixture was poured into cold water (50 mL), and 5 mL of dilute NH_4OH was added to remove all copper salts. Isox-

azole **C_2** was collected by filtration, redissolved, and passed through a short plug of silica gel (ethyl acetate: hexanes 1:6, *RF* = 0.5) affording 3.6 g (72 %) of [3-(pyridin-3-yl)-isoxazol--5-yl]methyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylate as an off-white solid.

Antioxidant activity assay

All the synthesized compounds **C_1**–**C_{12}** were investigated for their *in vitro* antioxidant activity in terms of hydrogen donating or radical scavenging ability by the rapid and convenient 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay technique[32] using trolox and ascorbic acid as standard drugs. Methanol (95 %), DPPH solution and standard drugs were used as the blank, control and references, respectively. The absorbance was measured at 517 nm (at an absorption maximum of DPPH) after keeping a mixture of 100 mL of the synthesized compounds at a concentration 10 μg mL^{-1} (dissolved in DMSO) and 900 mL of DPPH radical solution (0.004 % solution of DPPH in methanol) in the dark for 30 min incubation. The antioxidant activity was evaluated as the IC_{50} value in μM (the effective concentration at which 50 % of the radicals were scavenged).

In vitro *antimicrobial activity assay*

All the synthesized compounds (**C_1**–**C_{12}**) were examined for their *in vitro* antibacterial activity against Gram-positive organisms, *i.e*., *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96) and *Staphylococcus epidermidis* (MTCC 2639), and Gram-negative organisms, *i.e*., *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 741) and *Klebsiella pneumoniae* (MTCC 618), using the broth dilution method.[33-37] *In vitro* antifungal activity of synthesized compounds was evaluated against the fungal strains *Candida albicans* (MTCC 227), *Saccharomyces cerevisiae* (MTCC 36), *Aspergillus niger* (MTCC 282) and *Aspergillus flavus* (MTCC 92) by the agar well diffusion method.[38] The standard pathogenic microbial cultures were procured from the Microbial Type Culture Collection (MTCC), Chandigarh, India.

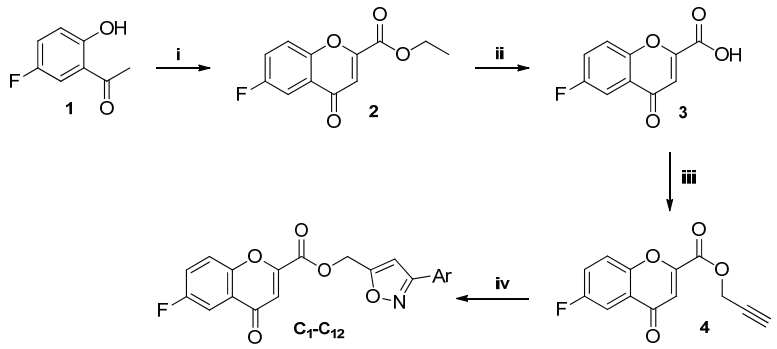
The antimicrobial activity was evaluated in terms of the minimum inhibitory concentration (*MIC*) value (which corresponds to the lowest concentration that inhibits visible microbial growth) by the broth dilution method recommended by the National Committee for Clinical Laboratory (NCCL), standard protocol in liquid medium (nutrient agar) distributed in 96-well plates. The test compounds were dissolved in dimethylformamide (DMF) and further dilutions were made at the required concentrations of 300, 150, 75, 37.5, 18.75, 9.75, 6.25, 3.125 and 1.56 μg mL^{-1}. Streptomycin and penicillin were used as reference standards for the antibacterial activity and amphotericin B was the reference standard for antifungal activity.

RESULTS AND DISCUSSION

Chemistry

In this work, a series of 3,5-disubstituted isoxazoles (**C_1**–**C_{12}**) were synthesized by employing Cu(I)-catalyzed cyclization between *in situ* generated nitrile oxide and the terminal alkyne as shown in Scheme 1. 1-(5-Fluoro-2-hydroxyphenyl)ethanone was treated with diethyl oxalate in the presence of NaOEt in EtOH under refluxing condition to afford compound **2**. The latter, on treated with 50 % NaOH solution at room temperature, afforded 6-fluoro-4-oxo-4*H*-chromene-2-carboxylic acid in good yield. In initial experiments, the outlined reaction of 6-fluoro-4-oxo-4*H*-chromene-2-carboxylic acid with propargyl bromide

using K_2CO_3 in DMF at room temperature was investigated.[39] This reaction afforded prop-2-ynyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylate in low yield (23 %). Then, propargylation was performed using *t*-BuOK in DMF at room temperature for 4 h, which afforded the corresponding prop-2-ynyl 6-fluoro-4-oxo--4*H*-chromene-2-carboxylate in good yield (80 %). Further, other aldehydes were converted to the corresponding aldoximes using hydroxylammonium chloride and 1 M NaOH in *t*-BuOH:H_2O at room temperature. These aldoximes were converted to the corresponding nitrile oxide using chloramine-T trihydrate.[40] The *in situ* generated nitrile oxide and alkyne in the presence of copper(I) catalyst at room temperature yielded 3,5-disubstitued isoxazoles (**C_1–C_{12}**) in good yields, Table I.



Scheme 1. Reagents and reaction conditions: *i*) diethyl oxalate / NaOEt, EtOH, reflux, 4 h; *ii*) 50 % NaOH, r.t., 5h; *iii*) propargyl bromide / *t*-BuOK, DMF, r.t., 4h; iv) a) Ar-CHO, $NH_2OH{\cdot}HCl$, NaOH, *t*-BuOH:H_2O, r.t., 30 min. b) chloramine-T trihydrate, Cu(I), r.t., 8–10 h.

TABLE I. Synthesized 3,5-disubstituted isoxazoles C_1–C_{12} from various aldehydes

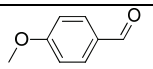
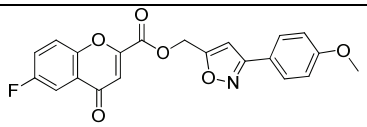
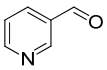
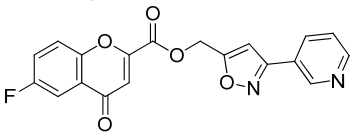
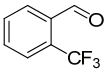
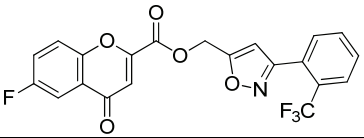
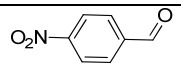
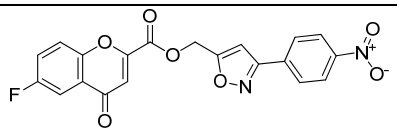
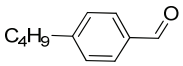
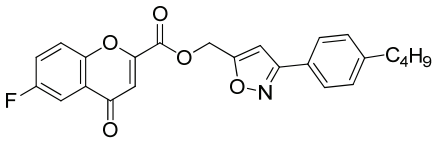
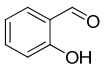
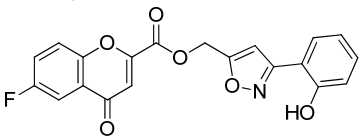
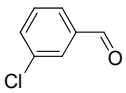
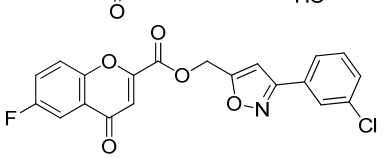
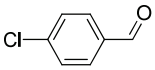
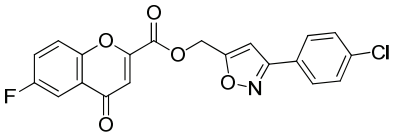
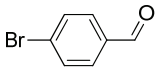
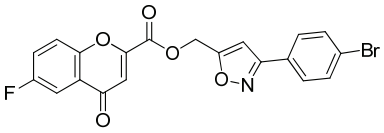
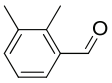
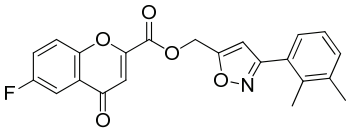
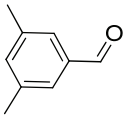
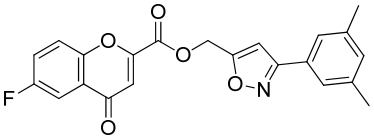
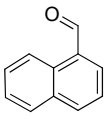
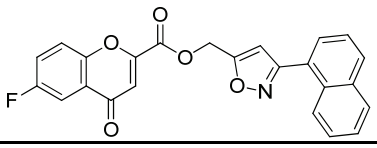
Entry	Ar-CHO	Time, h	Product	Yield, %
C_1		8.5		68
C_2		9		70
C_3		10		68

Table I. Continued

Entry	Ar-CHO	Time, h	Product	Yield, %
C4		10		65
C5		8.5		70
C6		9		65
C7		8.5		66
C8		8.5		68
C9		8.5		66
C10		9		65
C11		10		62
C12		9		68

Spectral analysis

All the synthesized compounds were well characterized by spectral and analytical studies, such as ^{1}H-NMR, ^{13}C-NMR, FTIR, ESI-MS and elemental

analysis. For convenience, compound **C1** is discussed for spectral analysis. The presence of absorption bands at 3061 (C–H, Ar), 1740 (C=O, ester), 1657 (C=O, chromene), 1608 (C=N, isoxazole) and 1220, 1130 cm^{-1} (Ar-C–O–CH_3) in the FTIR spectrum confirmed the required functional groups present in compound **C1**. From its ^{1}H-NMR spectrum, the presence of three multiplet signals (ppm) in the region δ 7.46–7.86 (3H, Ar-H), two doublet signals at δ 7.37 (2H, Ar-H) and δ 7.12 (2H, Ar-H), two singlet signals at δ 7.15 (1H, chromene-H) and δ 6.82 (1H, isoxazole CH), and two singlet signals at δ 5.62 (2H, O–CH_2) and 3.82 (3H, O–CH_3) confirmed the formation of compound **C1**. Similarly, from the ^{13}C--NMR spectrum, the presence of characteristic carbon peaks at (ppm) 178.6 (C=O, ester), 168.7, (C=N, isoxazole), 162.3 (O–**C**=C), 162.1 (C=O, chromene), 100.1 (C–H, isoxazole), 61.9 (O–CH_3) and 58.8 (CH_2, ester) confirmed the presence of the characteristic carbon peaks in compound **C1**.

The presence of the fluorine atom was confirmed by the additional carbon splitting pattern in the C-NMR spectra of **C1** with a doublet coupling constant, *J*, values 245.6, 29.3, 10.5, and 9.2 Hz, respectively. In addition, the molecular ion peak [396.0 (M+H)] from the ESI-MS spectrum and elemental analysis (CHN) data (C, 63.88 %; H, 3.50 %; N, 3.57 %) were further evidence for the formation of compound **C1**.

Antioxidant activity

The evaluation of antioxidant activity results (Table II) revealed that some of the tested compounds exhibited good to moderate antioxidant activity as compared with the positive controls trolox and ascorbic acid. Among them, compounds possessing the 4-methoxyphenyl and 1-napthyl group on the isoxazole ring (**C1** and **C12**, respectively) registered very good antioxidant activity with IC_{50} values of 16.43±0.57 and 15.98±0.72 μM, respectively.

Compounds bearing 4-butylphenyl, 2,3-dimethylphenyl and 3,5-dimethylphenyl groups on the isoxazole ring (**C5**, **C10** and **C11**, respectively) exhibited a moderate scavenging ability with IC_{50} values of 23.78±1.42, 27.15±1.47 and 18.87±0.82 μM, respectively. The remaining compounds exhibited moderate to poor antioxidant activity with IC_{50} values ranging from 34.66±2.10 to 82.31±3.02 μM. The potential scavenging ability may be attributed to the presence of pharmacologically active groups, such as 4-methoxyphenyl and 1-napthyl groups on the isoxazole ring.

In vitro *antibacterial activity*

The antibacterial screening results (Table III) revealed that some of the synthesized compounds exhibited excellent to moderate inhibition against the tested bacterial strains. Compounds bearing 4-methoxyphenyl (**C1**), 2-(trifluoromethyl)-phenyl (**C3**) and 2-hydroxyphenyl (**C6**) groups on the isoxazole core registered pro-

TABLE II. Antioxidant activity of (3-arylisoxazol-5-yl)methyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylates (**C_1**–**C_{12}**) determined by the DPPH method

Product	IC_{50} / μM
C_1	16.43±0.57
C_2	82.31±3.02
C_3	54.62±1.37
C_4	66.17±2.21
C_5	23.78±1.42
C_6	45.30±1.31
C_7	34.66±2.10
C_8	77.40±1.88
C_9	68.02±1.54
C_{10}	27.15±1.47
C_{11}	18.87±0.82
C_{12}	15.98±0.72
Trolox	13.24±0.80
Ascorbic acid	3.54±0.40

TABLE III. *In vitro* antibacterial activity (*MIC* / μg mL^{-1}) of (3-arylisoxazol-5-yl)methyl 6--fluoro-4-oxo-4*H*-chromene-2-carboxylates (**C_1**–**C_{12}**) against various bacterial strains

Compound	Bacteria					
	B. subtilis	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
C_1	9.375	18.75	18.75	37.5	18.75	37.5
C_2	75	75	150	75	75	150
C_3	9.375	37.5	18.75	37.5	18.75	18.75
C_4	75	75	75	150	75	150
C_5	37.5	37.5	75	75	18.75	18.75
C_6	9.375	18.75	18.75	37.5	18.75	37.5
C_7	37.5	37.5	75	75	75	75
C_8	18.75	37.5	75	75	75	75
C_9	37.5	18.75	150	75	75	75
C_{10}	37.5	37.5	75	75	9.375	37.5
C_{11}	18.75	37.5	75	75	9.375	18.75
C_{12}	37.5	75	75	75	18.75	75
Penicillin	1.562	1.562	3.125	12.5	12.5	6.25
Streptomycin	6.25	6.25	3.125	6.25	1.562	3.125

minent inhibition against all the tested Gram-positive and Gram-negative microorganisms with *MIC* values ranging from 9.375 to 37.5 μg mL^{-1}, as compared with the standard drugs penicillin and streptomycin. Compounds possessing 4-butylphenyl (**C_5**), 3-chlorophenyl (**C_7**), 4-chlorophenyl (**C_8**), 4-bromophenyl (**C_9**), 2,3-dimethylphenyl (**C_{10}**) and 3,5-dimethylphenyl (**C_{11}**) groups on the isoxazole core registered good inhibition against *B. subtilis* and *S. aureus* bacterial strains, with *MIC* values ranging from 18.75 to 37.5 μg mL^{-1}. Compounds **C_{10}** and **C_{11}** showed prominent activity against *P. aeruginosa*, greater than the stan-

dard drug penicillin (*MIC*: 12.5 μg mL^{-1}) with an *MIC* value of 9.375 μg mL^{-1} (≈1.33 fold more potent than penicillin).

Compounds **C$_{10}$** and **C$_{11}$** also showed moderate inhibition against *K. pneumoniae*, with *MIC* values of 37.5 and 18.75 μg mL^{-1}, respectively. Similarly, compound **C$_5$** also registered moderate inhibition against *P. aeruginosa* and *K. pneumoniae*, with an *MIC* value 18.75 μg mL^{-1}. Compound **C$_{12}$** registered moderate inhibition against *B. subtilis* and *P. aeruginosa*, with MIC values of 37.5 and 18.75 μg mL^{-1}, respectively. The remaining compounds (**C$_2$** and **C$_4$**) showed poor activity against all the bacterial strains.

From the above observations, it is obvious that the presence of pharmacologically active moieties, such as 4-methoxyphenyl, 2-(trifluoromethyl)phenyl, 2-hydroxyphenyl, 2,3-dimethylphenyl and 3,5-dimethylphenyl groups, on the isoxazole core increased the antibacterial activity.

In vitro *antifungal activity*

The antifungal activity screening results (Table IV) revealed that some of the synthesized compounds registered good to moderate activity against the tested microorganisms. Compound **C$_7$**, **C$_8$**, and **C$_9$** showed better antifungal activity than the other synthesized compounds against the four fungal strains with *MIC* values ranging from 18.75 and 37.5 μg mL^{-1}. Compounds **C$_2$** and **C$_5$** showed moderate activity against *C. albicans* and *S. cerevisiae*, with an *MIC* value of 37.5 μg mL^{-1}. Compound **C$_{10}$** and **C$_{11}$** showed moderate antifungal activity against *C. albicans* and *A. flavus*, with *MIC* values ranging from 18.75 to 37.5 μg mL^{-1}. The remaining compounds (**C$_1$**, **C$_3$**, **C$_4$**, **C$_6$** and **C$_{12}$**) exhibited poor inhibition against all the tested fungal strains. From the above observations, it is obvious that the presence

TABLE IV. *In vitro* anti-fungal activity (*MIC* / μg mL^{-1}) of (3-arylisoxazol-5-yl)methyl 6--fluoro-4-oxo-4*H*-chromene-2-carboxylates (**C$_1$**–**C$_{12}$**) against various fungal strains

Compound	Fungi			
	C. albicans	*S. cerevisiae*	*A. niger*	*A. flavus*
C$_1$	150	75	150	75
C$_2$	37.5	37.5	75	75
C$_3$	75	150	75	75
C$_4$	75	75	150	150
C$_5$	37.5	37.5	75	75
C$_6$	75	75	150	150
C$_7$	18.75	37.5	18.75	37.5
C$_8$	37.5	18.75	37.5	37.5
C$_9$	37.5	37.5	37.5	37.5
C$_{10}$	37.5	75	75	37.5
C$_{11}$	18.75	75	75	37.5
C$_{12}$	150	150	150	150
Amphotericin B	6.25	6.25	1.562	6.25

of 3-chlorophenyl, 4-chlorophenyl, and 4-bromophenyl groups on the isoxazole core influenced the antifungal activity of the synthesized compounds.

CONCLUSIONS

In conclusion, a series of novel (3-arylisoxazol-5-yl)methyl 6-fluoro-4--oxo-4*H*-chromene-2-carboxylates was synthesized by the Cu(I)-catalyzed reaction between *in situ* generated nitrile oxides and prop-2-ynyl 6-fluoro-4-oxo--4*H*-chromene-2-carboxylate in good yields. All the synthesized compounds were investigated for their antioxidant and antimicrobial activities. Compounds **C$_1$** and **C$_{12}$** exhibited very good antioxidant activity. Compounds **C$_1$**, **C$_3$** and **C$_6$** registered marked antibacterial activity against all bacterial strains, and **C$_{10}$** and **C$_{11}$** against *P. aeroginosa*. Similarly, compounds **C$_7$**, **C$_8$** and **C$_9$** showed better antifungal activity than remaining synthesized compounds. The biological activity of these compounds suggests that the synthesized compounds could be good candidates for future investigations.

SUPPLEMENTARY MATERIAL

Analytical and spectral data for the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding authors on request.

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ИЗВОД

СИНТЕЗА (3-АРИЛИЗОКСАЗОЛ-5-ИЛ)МЕТИЛ-6-ФЛУОР-4-ОКСО-4*H*-ХРОМЕН-2--КАРБОКСИЛАТА И ИСПИТИВАЊЕ ЊИХОВЕ АНТИОКСИДАТИВНЕ И АНТИМИКРОБНЕ АКТИВНОСТИ

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Синтетисана је серија (3-арилизоксазол-5-ил)метил-6-флуор-4-оксо-4*H*-хромен--2-карбоксилата (**C$_1$**–**C$_{12}$**) у добром приносу, у реакцији *in situ* формираног нитрил-оксида са проп-2-инил-6-флуор-4-оксо-4*H*-хромен-2-карбоксилатом у присуству Cu(I) као катализатора. Испитана је антіоксидативна и антимикробна активност синтетисаних једињења. Од свих синтетисаних једињења, **C$_1$** (IC_{50}: 16,43±0,57 μM) и **C$_{12}$** (IC_{50}: 15,98±0,72 μM) имају добру антиоксидативну активност у поређењу са тролоксом, стандардним леком. Једињења **C$_1$**, **C$_3$** и **C$_6$** имају добру инхибиторну активност према свим грам-позитивним и грам-негативним бактеријама, са *MIC* вредностима у опсегу од 9,375 до 37,5 μg mL^{-1}. Једињења **C$_7$**–**C$_{11}$** имају добру инхибиторну активност према *Bacillus subtilis* и *Staphylococus. aureus* са *MIC* вредностима у опсегу од 18,75 до 37,5 μg mL^{-1}. Једињења **C$_{10}$** и **C$_{11}$** показују истакнуту активност према *Pseudomonas aeruginosa* у поређењу са пеницилином, као стандардним леком: *MIC*, 12,5 μg mL^{-1} према 9,375 μg mL^{-1} (~1,33 активније од пеницилина). Једињења **C$_7$**–**C$_9$**

имају добре до умерене антифунгалне активности према четири испитивана соја гљива са *MIC* вредностима у опсегу од 18,75 до 37,5 μg mL^{-1}.

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