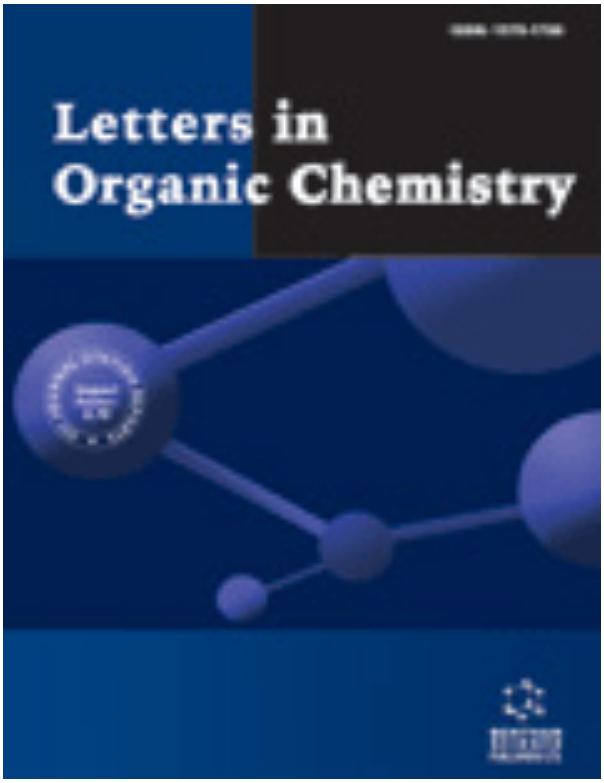
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RESEARCH ARTICLE

# Cytotoxic Prenyl and Geranyl Coumarins from the Stem Bark of *Casimiroa edulis*

Khun Nay Win Tun[1,2], Nanik Siti Aminah[3,*], Alfinda Novi Kristanti[3], Rico Ramadhan[3] and Yoshiaki Takaya[4]

[1]*Natural Science, Faculty of Science and Technology, Universitas Airlangga, Surabaya, Indonesia;* [2]*Department of Chemistry, Taunggyi University, Taunggyi, Myanmar;* [3]*Department of Chemistry, Faculty of Science and Technology, Universitas Airlangga, Surabaya, Indonesia;* [4]*Faculty of Pharmacy, Universitas Meijo, 150 Yagotoyama, Tempaku, Nagoya, 468-8503 Japan*

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**Abstract:** Phytochemical investigation of the methanolic extract of the stem bark of *Casimiroa edulis* afforded four coumarins. Various spectroscopic experiments were used to characterize the isolated coumarins. The structures were identified as auraptene (**K-1**), suberosin (**K-2**), 5-geranyloxypsoralen (bergamottin) (**K-3**), and 8-geranyloxypsoralen (**K-4**), based on the chemical and spectral analysis. Among these compounds, suberosin (**K-2**) and 5-geranyloxypsoralen (bergamottin) (**K-3**) were isolated for the first time from this genus, and auraptene (**K-1**) was isolated from this plant for the first time. Cytotoxicity of pure compound **K-4** and sub-fraction MD-3 was evaluated against HeLa and T47D cell lines and moderate activity was found with an $IC_{50}$ value in the range 17.4 to 72.33 µg/mL.

**Keywords:** *Casimiroa edulis*, coumarins, HeLa, spectroscopic experiments, stem bark, T47D.

## 1. INTRODUCTION

Nature is a good source of potential chemotherapeutic drugs [1]. The isolation process is a key step in discovering new biologically active substances from complex natural extracts [2]. A large number of bioactive compounds are isolated from research studies and screened each year, thus realizing the intrinsic therapeutic potential of natural products, and providing vast resource for further research [3]. Despite significant developments in the extraction and separation techniques, it is still a challenging task to isolate natural products from plants, animals, marine organisms or micro-organisms [4].

Coumarins (2*H*-1-benzopyran-2-ones) are a class of naturally occurring compounds found in various plants with an extensive pharmacological profile. To date, approximately 1500 coumarin derivatives have been identified from plants [5]. They have been identified as potent anti-inflammatory [6,10], anti-oxidant [7], anti-melanogenic [8], anti-bacterial [9], anti-viral [10], anti-coagulant [11], and cytotoxic agents [12].

A number of coumarins from *Casimiroa* spp. have been found by several researchers. Phellopterin, isopimpinellin, imperatorin, xanthotoxol, 8-hydroxy-5-methoxypsoralen, 8-[(6,7-dihydroxy-3,7-dimethyl-2-octen-1-yl)oxy]-5-methoxypsoralen, 8-[(4-hydroxy-3-methyl-2-buten-1-yl)oxy]psoralen, 8-[(6,7-dihydroxy-3,7-dimethyl-2-octen-1-yl)oxy]psoralen, 8-geranyloxypsoralen (**K-4**), 8-[(4-hydroxy-3-methyl-2-buten-1-yl)oxy]-5-methoxypsoralen, are reported to belong to the furanocoumarins, a class of chemical compounds produced by the roots, seeds, and leaves of *Casimiroa* spp. Another report has shown that simple coumarins (umbelliferone, esculetin, herniarin) are present in the leaves and seeds of *Casimiroa* spp. Some isolated furanocoumarins and simple coumarins have been reported to show anticoagulant and antimutagenic activity. In addition, the structure modification of some furanocoumarins was also reported [13-20].

This paper outlines the isolation and structure elucidation of compounds **K-1** to **K-4** (Figs. **1-4**) from the stem bark of *Casimiroa edulis*, as well as the cytotoxicity of sub-fraction MD-3 (section **3.3**) and pure compound **K-4**.

## 2. RESULTS AND DISCUSSION

### 2.1. Structure Elucidation

Consecutive chromatographic purification of the MeOH soluble fraction of the stem bark of *C. edulis* yielded four compounds. The molecular structures of isolated compounds were identified on the basis of their UV, IR, $^{1}$H NMR, $^{13}$C NMR, DEPT (**D**istortionless **E**nhancement by **P**olarization

*Address correspondence to this author at the Department of Chemistry, Faculty of Science and Technology, Universitas Airlangga; Tel/Fax: +62-31-5936501; Fax +62-31-5936502; E-mail: nanik-s-a@fst.unair.ac.id

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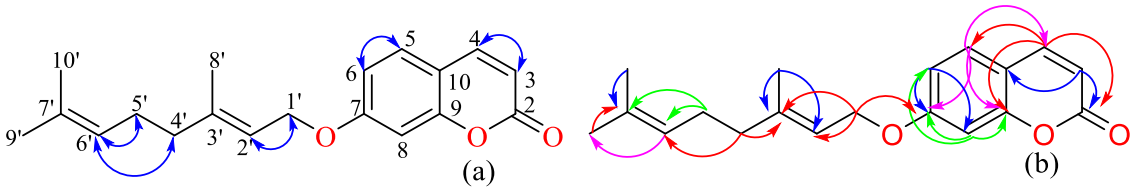


**Fig. (1).** COSY (**a**) and HMBC (**b**) key correlations in compound **K-1**.

**T**ransfer), HSQC (**H**eteronuclear **S**ingle **Q**uantum **C**oherence), HMBC (**H**eteronuclear **M**ultiple **B**ond **C**oherence), NOESY (**N**uclear **O**verhauser **E**ffect **S**pectroscop**Y**) data, and in comparison with the data reported by the literature. Detailed assignments of $^{1}H$ and $^{13}C$ NMR for compounds **K-1**, **K-2**, **K-3**, and **K-4** are summarized in Tables **1-4**.

The isolated compound **K-1** was obtained as a crystalline solid. Its molecular formula was established as $C_{19}H_{22}O_3$ by HR-FAB-MS at m/z 299.1644 $[M + H]^+$. Its melting point was 68-76 °C and its UV spectrum exhibited the characteristic absorptions of coumarin skeleton at $\lambda_{max}$ 327, 252, and 220 nm. On the basis of the IR spectrum studied, compound **K-1** exhibited the characteristic absorption bands for C-H stretching of methine (3084 $cm^{-1}$), methylene (2972 $cm^{-1}$), methyl (2850 $cm^{-1}$), aromatic C=C (1612 and 1508 $cm^{-1}$), and α,β-unsaturated-δ-lactone (1726 $cm^{-1}$). The $^{1}H$ NMR spectrum exhibited a distinct pair of doublets at $\delta_H$ 6.24 (d, 1H, $J$ = 9.3 Hz, H-3) and $\delta_H$ 7.63 (d, 1H, $J$ = 9.5 Hz, H-4) due to the presence of coumarin skeleton. It also displayed three aromatic protons at $\delta_H$ 6.85 (dd, 1H, $J$ = 8.6 and 2.4 Hz, H-6), $\delta_H$ 6.82 (d, 1H, $J$ = 2.3 Hz, H-8) and $\delta_H$ 7.36 (d, 1H, $J$ = 8.6 Hz, H-5) revealing the presence of a trisubstituted benzene ring. The $^{1}H$-$^{1}H$ COSY (**CO**rrelated **S**pectroscop**Y**) spectrum showed a correlation between H-3 and H-4 protons, while H-5 proton had a correlation with the H-6 proton. Detailed analysis of the $^{1}H$ and $^{13}C$ NMR spectra, including COSY, HSQC, HMBC, suggested the existence of an extra $C_{10}$ moiety on the coumarin skeleton, which incorporated an oxymethylene, three methyl groups, and two carbon-carbon double bonds. In the $^{1}H$ NMR spectrum, three broad triplet signals at $\delta_H$ 2.13 (br t, 2H, $J$ = 6.8 Hz), 5.47 (br t, 1H, $J$ = 6.6 Hz), and 5.08 (br t, 1H, $J$ = 6.7 Hz) were assigned to $H_2$-5′, H-2′, and H-6′, respectively. One oxymethylene doublet signal at $\delta_H$ 4.61 (d, 2H, $J$ = 6.6 Hz) was assigned to $H_2$-1′, while another broad doublet signal at $\delta_H$ 2.10 was assigned to $H_2$-4′. The remaining three methyl singlet signals at $\delta_H$ 1.76, 1.67, and 1.60 (s, each 3H) were assigned to $H_3$-8′, $H_3$-9′, and $H_3$-10′, respectively. COSY showed that oxymethylene protons $H_2$-1' were coupled to one methine proton at $\delta_H$ 5.47 (H-2'), while another methine proton at $\delta_H$ 5.08 (H-6') was coupled to methylene protons at $\delta_H$ 2.10 ($H_2$-4') and 2.13 ($H_2$-5'). To confirm the linkage position of monoterpene moiety at C-7, $^{1}H$-$^{13}C$ HMBC correlation between H-1′ and C-7 was observed. Based on the above data and previous reports, compound **K-1** was identified as auraptene (Fig. **1**) [21, 22].

Compound **K-2** was obtained as a crystalline solid and its molecular formula was found to be $C_{15}H_{16}O_3$, based on HR-FAB-MS (m/z 245.1175 $[M + H]^+$). The typical absorption bands at 323, 251, and 218 nm in the UV spectrum exhibited a coumarin skeleton. The presence of a methoxy group, C-H in conjugation, α,β-unsaturated-δ–lactone, an ethylenic double bond and an aromatic ring was confirmed by the IR spectrum with the absorption bands at 3084, 3055, 2852-2972, 1728, 1612, 1562, and 1508 $cm^{-1}$. Initial spectral data (UV, IR, $^{1}H$ NMR, $^{13}C$ NMR) analysis showed that compound **K-2** had a coumarin skeleton with prenylated moiety. The $^{1}H$ NMR spectrum exhibited characteristic signals of the 6,7-disubstituted coumarin, with two *cis*-olefinic protons at $\delta_H$ 6.23 (d, $J$ = 9.4 Hz, H-3) and $\delta_H$ 7.62 (d, $J$ = 9.4 Hz, H-4), and two singlet aromatic protons at $\delta_H$ 7.18 (s, H-5) and $\delta_H$ 6.78 (s, H-8). Additional prenylated moiety in compound **K-2** exhibited the presence of two sharp singlet peaks at $\delta_H$ 1.71 ($H_3$-4′) and 1.77 ($H_3$-5′), a doublet peak at $\delta_H$ 3.31 (d, $J$ = 7.3 Hz, $H_2$-1′), and a broad triplet at 5.29 (br t, $J$ = 7.4 Hz, H-2′). Based on the combinational analysis of $^{13}C$ NMR and DEPT data, compound **K-2** displayed 15 carbon resonances consisting of 6 $sp^2$ quaternary carbons (including ester carbonyl carbon), 5 $sp^2$ methine carbons, 2 *gem*-dimethyl carbons, 1 $sp^3$ methylene carbon, and 1 oxygenated $sp^3$ carbon. In the $^{1}H$-$^{1}H$ COSY experiment, the cross-peaks of H-3 with H-4 and H-1′ with H-2′ were observed. The proton signals at $\delta_H$ 3.31 ($H_2$-1') were correlated with the carbon signals at $\delta_C$ 127.5 (C-6), 160.7 (C-7), 121.4 (C-2′), 133.6 (C-3′) in the HMBC spectrum. In addition, the HMBC cross-peaks of the two methyl signals at $\delta_H$ 1.71 ($H_3$-4′) and 1.77 ($H_3$-5′) were also correlated with the carbon signals at $\delta_C$ 121.4 (C-2′) and 133.6 (C-3′). A sharp singlet signal at $\delta_H$ 3.90 indicated the presence of a methoxy group on the aromatic ring. This was supported by the long-range HMBC correlation between the methoxy group ($\delta_H$ 3.90) and C-7 (160.7). In addition, the NOESY spectrum showed a correlation between the methoxy signal and H-8 proton. The above evidence indicated that compound **K-2** was suberosin (7-methoxy-6-prenylcoumarin) (Fig. **2**) [11, 23].

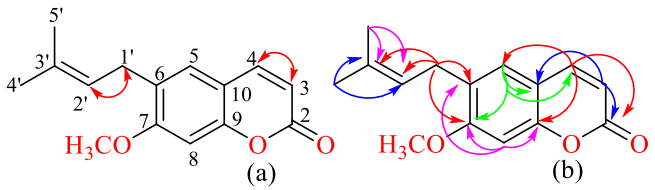


**Fig. (2).** COSY (**a**) and HMBC (**b**) key correlations in compound **K-2**.

Compound **K-3** showed a molecular ion peak at m/z 339.1595 $[M + H]^+$ in its HR-FAB-MS corresponding to the

**Table 1. $^{1}$H NMR (600 MHz) and $^{13}$C NMR (151 MHz) data of K-1 and comparison with the literature.**

| Nucleus | K-1 ($CDCl_3$) | | [19] | |
|---|---|---|---|---|
| | $\delta_H$ [m, *J* (Hz)] | $\delta_C$ | $\delta_H$ [m, *J* (Hz)] | $\delta_C$ |
| 2 | - | 161.3 | - | 161.2 |
| 3 | 6.24 (d, 9.3) | 112.9 | 6.24 (d, 9.6) | 112.9 |
| 4 | 7.63 (d, 9.5) | 143.4 | 7.63 (d, 9.6) | 143.4 |
| 5 | 7.36 (d, 8.6) | 128.6 | 7.36 (d, 7.2) | 128.6 |
| 6 | 6.85 (dd, 8.6, 2.4) | 113.2 | 6.85 (dd, 7.2, 2.0) | 113.2 |
| 7 | - | 162.2 | - | 162.1 |
| 8 | 6.82 (d, 2.3) | 101.6 | 6.82 (d, 2.0) | 101.5 |
| 9 | - | 155.9 | - | 155.8 |
| 10 | - | 112.4 | - | 112.3 |
| 1' | 4.61 (d, 6.6) | 65.5 | 4.59 (d, 7.0) | 65.4 |
| 2' | 5.47(br t, 6.6) | 118.4 | 5.47 (t, 7.0) | 118.3 |
| 3' | - | 142.3 | - | 142.3 |
| 4' | 2.10 (br d, 6.9) | 39.5 | 2.13 (m) | 39.4 |
| 5' | 2.13 (br t, 6.8) | 26.3 | 2.15 (m) | 26.4 |
| 6' | 5.08 (br t, 6.7) | 123.6 | 5.08 (q, 7.0) | 123.5 |
| 7' | - | 131.9 | - | 131.9 |
| 8' | 1.76 (s) | 16.8 | 1.75 (m) | 16.7 |
| 9' | 1.67 (s) | 25.6 | 1.65 (m) | 25.6 |
| 10' | 1.60 (s) | 17.7 | 1.59 (q, 7.0) | 17.6 |

**Table 2. $^{1}$H NMR (600 MHz) and $^{13}$C NMR (151 MHz) data of K-2 and comparison with the literature.**

| Nucleus | K-2 ($CDCl_3$) | | [20] | |
|---|---|---|---|---|
| | $\delta_H$ [m, *J* (Hz)] | $\delta_C$ | $\delta_H$ [m, *J* (Hz)] | $\delta_C$ |
| 2 | - | 161.5 | - | 161.5 |
| 3 | 6.23 (d, 9.4) | 112.8 | 6.24 (d, 9.6) | 112.7 |
| 4 | 7.62 (d, 9.4) | 143.6 | 7.63 (d, 9.6) | 143.6 |
| 5 | 7.18 (s) | 127.4 | 7.19 (s) | 127.4 |
| 6 | - | 127.5 | - | 127.5 |
| 7 | - | 160.7 | - | 160.6 |
| 8 | 6.78 (s) | 98.5 | 6.78 (s) | 98.5 |
| 9 | - | 154.5 | - | 155.4 |
| 10 | - | 111.9 | - | 111.9 |
| 1' | 3.31 (d, 7.3) | 27.8 | 3.31 (d, 7.2) | 27.8 |
| 2' | 5.29 (br t, 7.4) | 121.4 | 5.29 (t, 7.2) | 121.3 |
| 3' | - | 133.6 | - | 133.6 |
| 4' | 1.71 (s) | 25.8 | 1.71 (s) | 25.8 |
| 5' | 1.77 (s) | 17.8 | 1.78 (s) | 17.7 |
| 7-$OCH_3$ | 3.90 (s) | 55.9 | 3.91 (s) | 55.8 |

**Table 3.** **$^{1}$H NMR (600 MHz) and $^{13}$C NMR (151 MHz) data of K-3 and comparison with the literature.**

| Nucleus | K-3 ($CDCl_3$) | | [21] | |
|---|---|---|---|---|
| | $\delta_H$ [m, *J* (Hz)] | $\delta_C$ | $\delta_H$ [m, *J* (Hz)] | $\delta_C$ |
| 2 | - | 161.3 | - | 161.3 |
| 3 | 6.27 (d, 9.8) | 112.6 | 6.25 (d, 9.8) | 112.6 |
| 4 | 8.16 (d, 9.7, 0.5) | 139.6 | 8.14 (d, 9.8) | 139.6 |
| 5 | - | 149.0 | - | 149.0 |
| 6 | - | 114.3 | - | 114.3 |
| 7 | - | 158.1 | - | 158.2 |
| 8 | 7.16 (s) | 94.2 | 7.13 (s) | 94.3 |
| 9 | - | 152.7 | - | 152.7 |
| 10 | - | 107.6 | - | 107.6 |
| 2' | 7.59 (d, 2.4) | 144.9 | 7.57 (d, 2.5) | 144.9 |
| 3' | 6.96 (dd, 2.3, 1.0) | 105.0 | 6.94 (dd, 2.5, 0.9) | 105.0 |
| 1" | 4.95 (d, 6.7 ) | 69.8 | 4.93 (d, 6.8) | 69.8 |
| 2" | 5.54 (t, 6.9) | 118.9 | 5.51 (m) | 118.9 |
| 3" | - | 143.0 | - | 143.0 |
| 4" | 2.10 (m) | 39.5 | 2.08 (m) | 39.5 |
| 5" | 2.10 (m) | 26.2 | 2.08 (m) | 26.2 |
| 6" | 5.06 (m) | 123.5 | 5.05 (m) | 123.5 |
| 7" | - | 132.0 | - | 132.0 |
| 8" | 1.69(s) | 16.7 | 1.67 (s) | 16.7 |
| 9" | 1.68 (s) | 25.7 | 1.66 (s) | 25.7 |
| 10" | 1.60 (s) | 17.7 | 1.58 (s) | 17.7 |

molecular formula, $C_{21}H_{22}O_4$, and was obtained in an oily form. The UV signals of compound **K-3** in MeOH at 309, 258, 249 nm suggested the furanocoumarin skeleton for the molecule. Its IR spectrum exhibited absorption peaks due to the presence of an ester carbonyl group (1735 $cm^{-1}$), olefinic groups and aromatic ring (1624, 1606, 1577, and 1544 $cm^{-1}$). $^{13}$C NMR of compound **K-3** included 21 carbon signals, comprising 3 methyl carbon signals, 2 adjacent methylene carbon signals, 1 oxymethylene carbon signal, 7 methine carbon signals, and 8 quaternary carbon signals, which were classified by DEPT and HSQC experiments. Its $^{1}$H NMR spectrum had a doublet at $\delta_H$ 6.27 (d, 1H, $J$ = 9.8 Hz) and a double doublet at 8.16 (dd, 1H, $J$ = 9.7 and 0.5 Hz) assigned to H-3 and H-4, respectively, and a furan doublet at 7.59 (d, 1H, $J$ = 2.4 Hz) and double doublet at 6.96 (dd, 1H, $J$ = 2.3, 1.0 Hz) assigned to H-2' and H-3', respectively, as well as a singlet at 7.16 (s, 1H, H-8). Five-bond coupling constants ($^{5}J$) were observed for H-4 (dd, $^{3}J_{3,4}$ = 9.7, $^{5}J_{4,8}$ = 0.5 Hz) and H-3′ (dd, $^{3}J_{2',3'}$ = 2.3, $^{5}J_{3',8}$ = 1.0 Hz). The above information and previous data indicated that compound **K-3** was a furanocoumarin. Long-range HMBC correlations from H-3 to C-2,10, H-4 to C-2,9, H-8 to C-6,7,9,10, and from H-2′,3′ to C-6,7 further confirmed the presence of the furanocoumarin moiety. The $^{1}$H NMR spectrum of compound **K-3** showed an additional geranyl group on the furanocoumarin skeleton as compared with compound **K-1**. The existence of geranyl group was indicated by the presence of two multiplet signals at $\delta_H$ 2.10 ($H_2$-4",5") and 5.06 ($H_2$-6"), an oxymethylene doublet signal at $\delta_H$ 4.95 ($H_2$-1"), another triplet signal at $\delta_H$ 5.54 (H-2"), and three methyl singlet signals at $\delta_H$ 1.69, 1.68 and 1.60, assigned to $H_3$-8", $H_3$-9", and $H_3$-10", respectively. The observed $^{1}$H-$^{13}$C HMBC correlation between H-1″and C-5 confirmed the linkage position of the geranyl moiety at C-5. Detailed HMBC and COSY correlations of compound **K-3** are shown in Fig. (**3**). Therefore, the structure of compound **K-3** was determined to be 5-geranyloxypsoralen (bergamottin) [24, 25].

Compound **K-4** was obtained as a yellow crystalline solid. Its molecular formula was determined as $C_{21}H_{22}O_4$ by HR-FAB-MS (m/z 339.1590 $[M + H]^+$). The UV spectrum showed absorption maxima at 249 and 298 nm. The IR spectrum showed the characteristic absorption bands at $\nu_{max}$ 1585, 1625, 1702, and 1720 $cm^{-1}$ indicating the presence of olefinic moieties, aromatic ring, and ester carbonyl function.

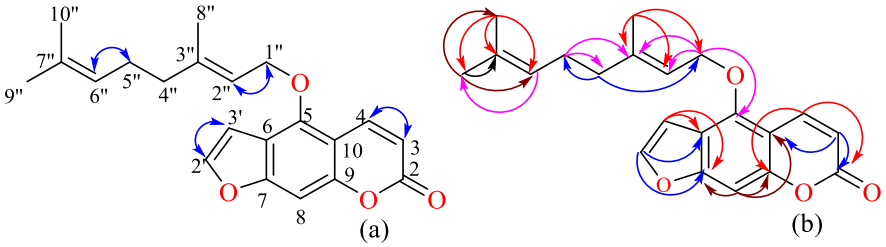


**Fig. (3).** COSY (**a**) and HMBC (**b**) key correlations in compound **K-3**.

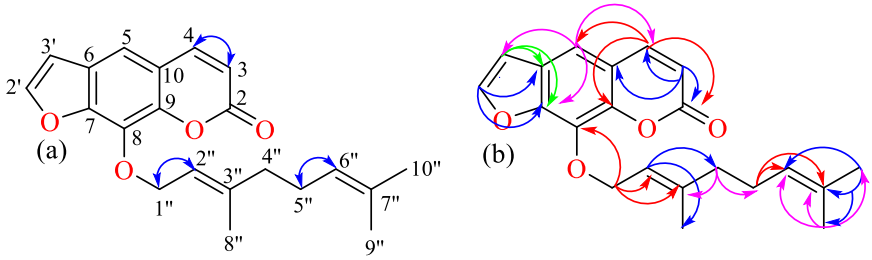


**Fig. (4).** COSY (a) and HMBC (b) key correlations in compound **K-4**.

**Table 4.** **$^{1}$H NMR (600 MHz) and $^{13}$C NMR (151 MHz) data of K-4 and comparison with the literature.**

| Nucleus | K-4 ($CDCl_3$) | | [22] | |
|---|---|---|---|---|
| | $\delta_H$ [m, *J* (Hz)] | $\delta_C$ | $\delta_H$ [m, *J* (Hz)] | $\delta_C$ |
| 2 | - | 160.5 | - | 160.5 |
| 3 | 6.37 (d, 9.3) | 114.7 | 6.34 (d, 9.6) | 114.7 |
| 4 | 7.76 (d, 9.5) | 144.3 | 7.74 (d, 9.5) | 144.3 |
| 5 | 7.36 (s) | 113.2 | 7.34 (s) | 113.2 |
| 6 | - | 125.8 | - | 125.8 |
| 7 | - | 148.8 | - | 148.7 |
| 8 | - | 131.6 | - | 131.5 |
| 9 | - | 143.9 | - | 143.9 |
| 10 | - | 116.5 | - | 116.4 |
| 2' | 7.69 (d, 2.2) | 146.6 | 7.66 (d, 2.2) | 146.6 |
| 3' | 6.81 (d, 2.2) | 106.7 | 6.79 (d, 2.3) | 106.7 |
| 1" | 5.04 (d, 7.1) | 70.1 | 5.01 (d, 7.2) | 70.1 |
| 2" | 5.60 (br t, 7.6) | 119.4 | 5.57 (t, 7.1) | 119.4 |
| 3" | - | 143.1 | - | 143.2 |
| 4" | 2.01 (s) | 39.6 | 1.98 (s) | 39.5 |
| 5" | 2.02 (s) | 26.4 | 1.99 (s) | 26.3 |
| 6" | 5.01 (m) | 123.8 | 4.98 (m) | 123.7 |
| 7" | - | 131.7 | - | 131.7 |
| 8" | 1.70 (s) | 16.5 | 1.67 (s) | 16.5 |
| 9" | 1.64 (s) | 25.6 | 1.61(s) | 25.6 |
| 10" | 1.57 (s) | 17.6 | 1.54 (s) | 17.6 |

The $^{1}H$ and $^{13}C$ NMR spectra of compound **K-4** were very similar to that of compound **K-3,** with the exception of the side-chain substitution. The $^{1}H$ NMR spectrum exhibited an easily distinguishable pair of doublets at $\delta_H$ 6.37 (d, 1H, $J$ = 9.3 Hz, H-3) and $\delta_H$ 7.76 (d, 1H, $J$ = 9.5 Hz, H-4). It also displayed two furan doublets at $\delta_H$ 7.69 and 6.81 (each d 1H, $J$ = 2.2 Hz, H-2′ and H-3′ respectively), and an aromatic singlet at $\delta_H$ 7.36 (s, 1H, H-5). The $^{1}H$-$^{1}H$ COSY showed a correlation between H-3 and H-4. Long-range HMBC correlations were observed from H-3 to C-2,4,10, H-4 to C-2,5,9, H-5 to C-3',4,7 and H-2′,3′ to C-6,7. Analysis of the $^{1}H$ and $^{13}C$ NMR spectra, including COSY, HSQC, HMBC, suggested the presence of an additional $C_{10}$ moiety (one geranyl group) on the furanocoumarin skeleton, which comprised of oxymethylene, three methyl, and two carbon-carbon double bonds. In the $^{1}H$ NMR spectrum, one multiplet signal at $\delta_H$ 5.01 (m, 1H) was assigned to H-6", and two methylene singlet protons at 2.01 and 2.02 (each s 2H) were assigned to $H_2$-4″,5″. One oxymethylene doublet signal at $\delta_H$ 5.04 (d, 2H, $J$ = 7.1 Hz) was assigned to $H_2$-1″, while one broad triplet signal at $\delta_H$ 5.60 was assigned to H-2″. The remaining three methyl singlet signals at $\delta_H$ 1.70, 1.64, and 1.57 (s, each 3H) were assigned to $H_3$-8″, $H_3$-9″, and $H_3$-10″, respectively. COSY showed that oxymethylene protons H-1" were coupled to one methine proton $\delta_H$ 5.60 (H-2"), while another methine proton at $\delta_H$ 5.04 (H-1") was coupled to two methylene protons at $\delta_H$ 2.01 and 2.02 ($H_2$-4",5"). In compound **K-4**, the position of monoterpene moiety (a geranyl group) at C-8 was confirmed by the $^{1}H$-$^{13}C$ HMBC correlation between $H_2$-1″ and C-8. All the protons and carbons were allocated with the help of 2D NMR data analysis, such as COSY, DEPT, HSQC and HMBC. Thus, the structure of compound **K-4** was determined as shown in Fig. (**4**) and identified as 8-geranyloxypsoralen [26].

### 2.2. Cytotoxicity of Compound K-4 and Sub-Fraction MD-3 against HeLa and T47D Cell Lines

Pure compound **K-4** and sub-fraction MD-3 (see section **3.3**) were evaluated for their cytotoxicity against HeLa (Henrietta Lacks cervical carcinoma) and T47D (human hormone-dependent breast cancer) cell lines by the MTT [2-(4,5-dimethyl-2-thiazolyl)-3,5-diphenyl-2H-tetrazolium bromide] method. According to Table **5**, pure compound **K-4** showed moderate activity [12, 27] against T47D cell line with the $IC_{50}$ (half maximal **I**nhibitory **C**oncentration) value of 72.33 µg/mL; sub-fraction MD-3 also showed moderate activity [10, 24] against both HeLa and T47D cell lines with $IC_{50}$ values of 56.40 and 17.40 µg/mL, respectively.

**Table 5. Cytotoxicity of pure compound K-4 and sub-fraction MD-3.**

| Sample | $IC_{50}$, µg/mL | |
|---|---|---|
| | HeLa | T47D |
| K-4 | 148.93 | 72.33 |
| MD-3 | 56.40 | 17.40 |

### 2.3. Discussion

Coumarins were originally discovered in Tonka Bean and are known to be present in around 150 species, extending to approximately 30 distinct families, including Rutaceae, Umbelliferae, Clusiaceae (Guttiferae), Oleaceae, Nyctaginaceae and Apiaceae. Natural coumarins are primarily divided into six different kinds according to the chemical compound composition. They are simple coumarins, furanocoumarins, dihydrofuranocoumarins, pyranocoumarins (linear and angular types), phenylcoumarins, and bicoumarins [28]. Natural and synthetic coumarins are known to have a wide range of pharmacological properties [29-31]. 8-Geranyloxypsoralen (**K-4**) was previously isolated from various plant sources and demonstrated nematicidal activity (against *Bursaphelenchus xylophilus* and *Panagrellus redivivus*), high anti-microbial effect (against *Staphylococcus epidermidis* and *Candida kefyr*), weak anti-oxidant activity [DPPH (**D**i**P**henyl**P**icryl **H**ydrazyl) assay], cytotoxic effect on McCoy cell line, and weak anti-fungal activity (against yeast *Malassezia globosa*) [32, 33]. Auraptene (**K-1**) was isolated from *Cleome viscosa* (L.), *Citrus junos*, *Ferula* spp., *Zosima absinthifolia*, and showed no anti-microbial activity, weak cytotoxicity, neuroprotective effects, allelopathic effects, and anti-carcinogenic properties [34-37]. Bergamottin (**K-3**), a geranyloxyfuranocoumarin, is the most abundant in nature. It showed a significant dose-dependent inhibitory effect on human liver cancer line (HepG2), human leukemia cell line (HL-60), and human gastric cancer cell line (BGC-823) [38, 39]. Suberosin (**K-2**) is a bioactive and useful secondary metabolite. It was previously isolated from *Arracacia tolucensis* var. *multifida, Ferulago* spp. and showed anti-mycobacterial, anti-coagulant, anti-diabetic, and anti-cancer activities [40-43]. This research described the isolation and identification of methoxyprenylcoumarin **K-2**, geranyloxycoumarin **K-1**, and geranyloxyfuranocoumarins **K-3,4** from Myanmar Rutaceae. Moreover, the cytotoxicity of compound **K-4** and sub-fraction MD-3 against HeLa and T47D cell lines was investigated. The results showed moderate cytotoxicity effect on the tested substances.

## 3. EXPERIMENTAL

### 3.1. General

Melting points were determined by the Fisher-Johns melting point apparatus. UV spectra were recorded on the UV-Vis Shimadzu spectrometer. FTIR-8400 spectrophotometer was used for measuring IR spectra. The NMR spectra were recorded at 600 MHz for $^{1}H$ and 151 MHz for $^{13}C$ on the Bruker Avance III spectrometer. Chemical shift values were determined on a δ (ppm) scale and tetramethylsilane (TMS) was used as an internal standard. The kind of carbon ($CH_3$, $CH_2$, and CH) was confirmed by DEPT experiments. HR-FAB-MS was measured on a JEOL JMS HX-110 mass spectrometer. Purification of the compounds was performed by using vacuum liquid chromatography (VLC) on silica gel 60 (Merck, 63–230 µm), and column chromatography (CC) on silica gel 60 (Merck, 0.043-0.063). Analytical thin-layer chromatography (TLC) was performed on pre-coated Kieselgel silica gel 60 $F_{254}$ plates (Merck, Germany). Preparative thin-layer chromatography (PTLC) was carried out on silica

gel 60 $F_{254}$ glass plates (Merck, 20 × 20 cm, 0.25 mm). The compound bands were scraped off and washed with 100% chloroform.

### 3.2. Plant Material

The fresh stem bark of *C. edulis* Llave et Lex was collected in August 2016 from Taunggyi (Shan State), Myanmar and identified by Prof. Dr. Aye Aye Win Kyi, Department of Botany, University of Taunggyi. A voucher specimen (BT001289) has been deposited at the Department of Chemistry, University of Taunggyi.

### 3.3. Extraction and Isolation

The stem bark of *C. edulis* was cut into small pieces and air-dried at room temperature. The dried samples (1000 g) were extracted with MeOH (3000 mL) for 28 days. The whole extract was filtered and the solution was evaporated under vacuum. MeOH crude extract (250 g) was obtained. After that, the MeOH extract was partitioned successively with hexane and MeOH. The hexane soluble fraction (13 g) and MeOH soluble fraction (50 g) were obtained. Each fraction was evaporated under pressure by using a rotary evaporator. The MeOH extract (50 g) was subjected to VLC eluting with a gradient solvent system hexane/EtOAc (100:0-60:40, 0:100, v/v) to give fractions, A to F. Fraction B (300 mg) was separated by silica gel CC with hexane/EtOAc (100:0 to 96:4) to give compound **K-3** (9.1 mg) and sub-fraction MD-3. MD-3 (120 mg) was further purified by PTLC using 80% chloroform in hexane as an eluent to yield compounds **K-1** (7.2 mg) and **K-2** (2.3 mg). Fraction C (1 g) was separated by in silica gel CC using a gradient solvent of hexane/EtOAc (9:1 − 7:3) to obtain compound **K-4** (30 mg).

### 3.4. MTT Assay

The cytotoxicity of the isolated compound **K-4** and fraction MD-3 on HeLa and T47D cells was measured by using the MTT assay *in vitro*. The isolated samples were dissolved in DMSO (100 µL) to obtain various concentrations. Each sample was prepared in triplicate. The final DMSO concentration was adjusted to <0.1 %. Doxorubicin was used as a positive control. The media control solution consisted of the media culture and the cell control solutions consisted of the culture and cell media. The cells were prepared by following the method for cell subculture. Enough amount of HeLa cell and T47D cell ($213.4 \times 10^4$ cells / well and $167 \times 10^4$ cell/well) solution was prepared and 100 µL was placed in each 96-well plate. The plates containing the cancer cells were treated with species under study and incubated for 24 h. After 24 h incubation, the cells were washed and treated with 100 µL of MTT per well. Plates were incubated at 37 °C in a 5% $CO_2$ atmosphere for 4 h, and 0.1 mL of the extraction buffer (10% sodium dodecyl sulfate in 0.01% HCl) was added. After overnight incubation at 37 °C, the absorbance was measured at 595 nm using an ELISA (**E**nzyme-**L**inked **I**mmuno **S**orbent **A**ssay) reader and was compared with the control cultures without compound. To determine cell viability, percent viability was calculated by the formula

$$\% \text{ Viability } = \frac{A_t - A_{mc}}{A_{ng} - A_{mc}} \times 100$$

where $A_t$ = absorbance of treatment, $A_{mc}$ = absorbance of media control, $A_{nc}$ = absorbance of the negative control. $IC_{50}$ values of the tested sample were calculated from the concentration v/s percentage of cell viability inhibition curves.

## CONCLUSION

Four coumarins, auraptene (**K-1**), suberosin (**K-2**), bergamottin (**K-3**), and 8-geranyloxypsoralen (**K-4**), were obtained from the stem bark of *C. edulis*. Among these compounds, suberosin (**K-2**) and bergamottin (**K-3**) were isolated for the first time from this genus and auraptene (**K-1**) was isolated from this plant for the first time. 8-Geranyloxypsoralen (**K-4**) and sub-fraction MD-3 were tested for their cytotoxicity against HeLa and T47D cell lines. The results demonstrated that they had moderate activity against HeLa and T47D cell lines with $IC_{50}$ values in the range of 17.4 to 72.33 µg/mL.

## CONSENT FOR PUBLICATION

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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## SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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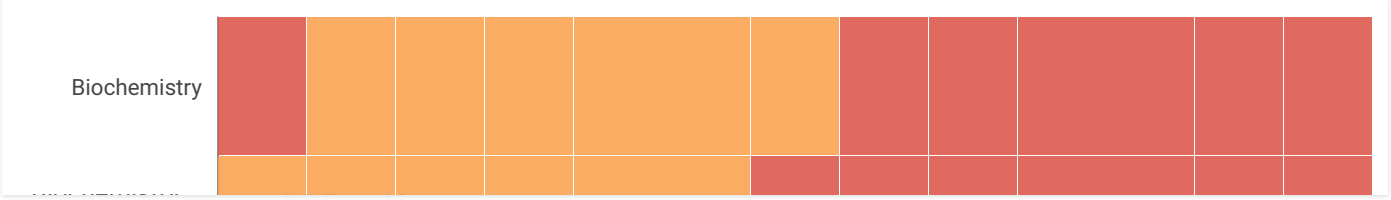


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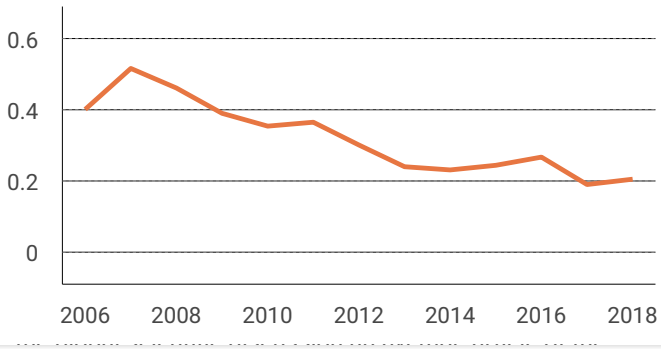


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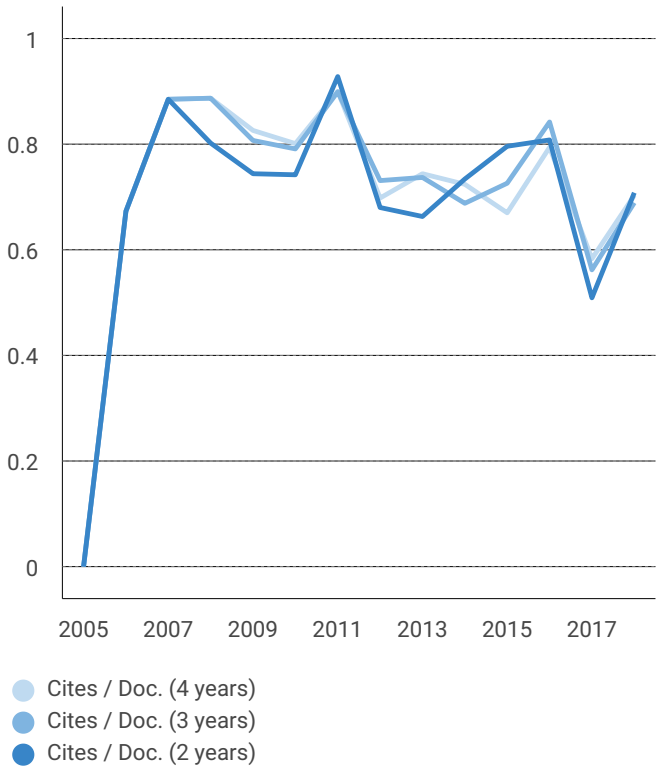


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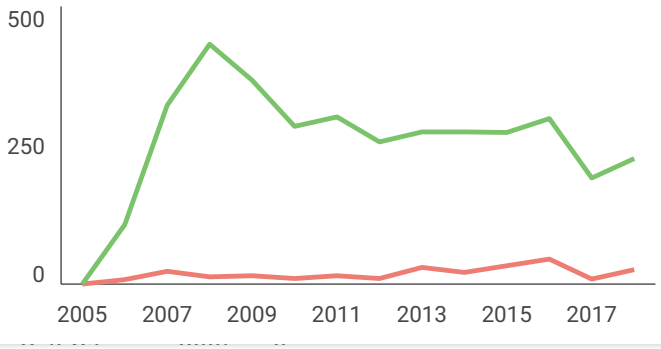


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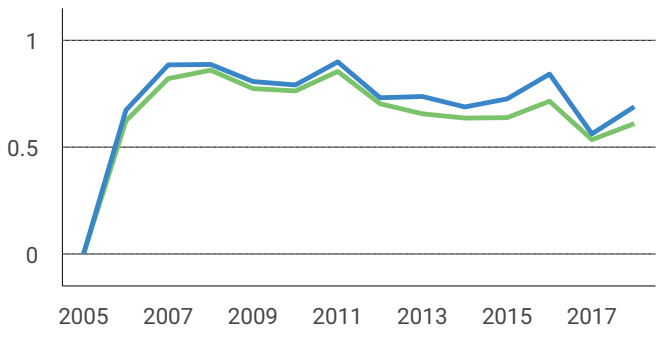


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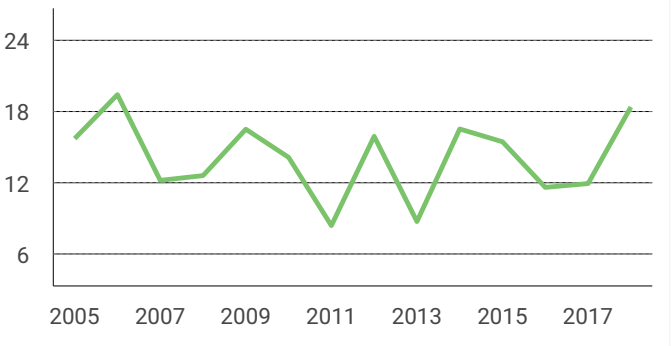


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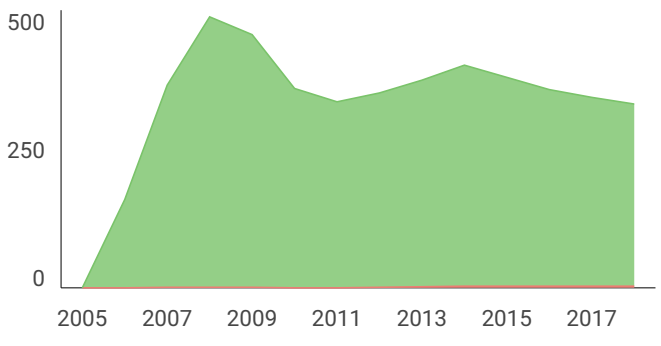


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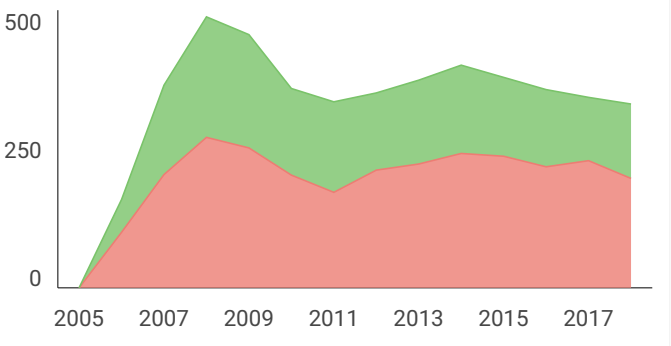


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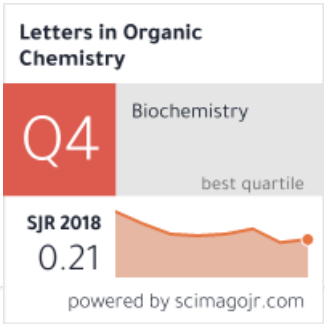


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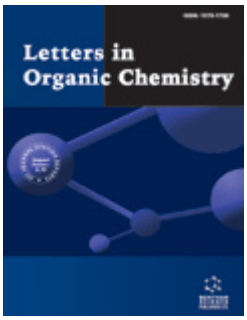




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**Computational Study on the Mechanism of Cycloaddition Reactions of Bissulfonyl-1,3-butadiene with Some Alkenes (http://dx.doi.org/10.2174/1570178617666200210112307)**
*Sepideh Masoumifar, Mina Haghdadi* and Hassan Ghasemnejad Bosra*
DOI: **10.2174/1570178617666200210112307**
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**Synthesis, Design and Biological Evaluation of Antibacterial Activity of Novel Mixed Metal Complexes Derived from Benzoimidazolphenylethanamine and 6-Amino-N,N-dimethyluracil (http://dx.doi.org/10.2174/1570178617666200210111442)**
*Fahad M. Alminderej**
DOI: **10.2174/1570178617666200210111442**
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**An Effective Assembling of Novel Derivatives Containing Both Benzo[d]thiazole and Benzo[d]oxazole Rings (http://dx.doi.org/10.2174/1570178617666200207104912)**
*Nguyen Thi Ngoc Mai, Duong Quoc Hoan*, Vu Thi Anh Tuyet, Tran Thi Thu Trang, Duong Khanh Linh and Trinh Thi Huan*
DOI: **10.2174/1570178617666200207104912**
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**A Simple Synthesis of the Anticancer Drug Altretamine (http://dx.doi.org/10.2174/1570178617666200210111041)**
*Vu Binh Duong, Pham Van Hien, Tran Thai Ngoc, Phan Dinh Chau and Tran Khac Vu**
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**A Rationale for the Ortho Effect in Electrophilic Aromatic Substitutions (http://dx.doi.org/10.2174/1570178617666200207103755)**
*Timothy Eckert*, Grace Harmeyer, Steven Legate and Steven Mathe*
DOI: **10.2174/1570178617666200207103755 (http://dx.doi.org/10.2174/1570178617666200207103755)**

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**Facile One-Pot Synthesis and Crystal Structure of 2:1 Adducts of Myrcene (or Ocimene) with Benzoquinones (http://dx.doi.org/10.2174/1570178617666200227110001)**
*Sujata V. Bhat*, Rohan S. Pawar and DU Rajakannu*
DOI: **10.2174/1570178617666200227110001 (http://dx.doi.org/10.2174/1570178617666200227110001)**

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**Synthesis of TFA-protected α-Amino Acid Chloride via a Vilsmeier Reagent for Friedel–Crafts acylation (http://dx.doi.org/10.2174/1570178617666200207111127)**
*Zetryana Puteri Tachrim, Kazuhiro Oida, Fumina Ohashi, Natsumi Kurokawa, Lei Wang, Takeyuki Suzuki and Makoto Hashimoto **
DOI: **10.2174/1570178617666200207111127 (http://dx.doi.org/10.2174/1570178617666200207111127)**

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**Synthesis of (E)-1,2-Bis[4-[di(1H-pyrrol-2-yl)methyl]phenyl]ethene as a New Bis(dipyrromethane) Building Block (http://dx.doi.org/10.2174/1570178617666200207102604)**
*Faride Ranjbari, Salar Hemmati* and Mohammad Reza Rashidi**
DOI: **10.2174/1570178617666200207102604 (http://dx.doi.org/10.2174/1570178617666200207102604)**

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**Application of Amine-based Ru Compounds in the Olefin Metathesis of Methyl Eugenol: A Comparison with Grubbs Catalysts (http://dx.doi.org/10.2174/1570178617666191127102552)**
*Denise A. Sousa, Paulo S. Meneses, Patrik D. S. Gois, Eliada A. Silva, Valdemiro P. C. Junior, Benedito S. Lima-Neto and José L. Silva Sá**
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**Synthesis, Antibacterial and Antioxidant Activities of Some New Nsubstituted Azachalcone, Schiff base and Pyrazole Derivatives (http://dx.doi.org/10.2174/1570178617666200108111211)**
*Nedime Çalışkan, Asu Usta*, Fatih Şaban Beriş, Nimet Baltaş and Efsun Çelik*
DOI: **10.2174/1570178617666200108111211 (http://dx.doi.org/10.2174/1570178617666200108111211)**

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**A Computational Study of the Conformational Behavior of 2,5-Dimethyl- 1,4-dithiane-2,5-diol and Analogous S and Se: DFT and NBO Study (http://dx.doi.org/10.2174/1570178617666200129144750)**
*Elmira Danaie, Shiva Masoudi* and Nasrin Masnabadi*
DOI: **10.2174/1570178617666200129144750 (http://dx.doi.org/10.2174/1570178617666200129144750)**

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**Trihaloisocyanuric Acids: Useful Reagents for Conversion of Benzaldehydes into Benzylidene Dihalides under Appel Conditions (http://dx.doi.org/10.2174/1570178617666200121110618)**
*Haryadylla da C. Sindra, Carlos Vinícius P. dos Santos and Marcio C. S. de Mattos**
DOI: **10.2174/1570178617666200121110618 (http://dx.doi.org/10.2174/1570178617666200121110618)**

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**Chiral Catalysts Utilized in the Nucleophilic Addition of Dialkyl-zinc Reagents to Carbonyl Compounds (http://dx.doi.org/10.2174/1570178617666191220145038)**
*Adnan Cetin**
DOI: **10.2174/1570178617666191220145038 (http://dx.doi.org/10.2174/1570178617666191220145038)**

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**The Study on Chlorination by Sulfuryl Chloride of Benzene/Pyridine Carboxamides and Carbonitriles (http://dx.doi.org/10.2174/1570178617666191203101254)**
*Weiqing Yang, Yongjing Cao, Hongrui Cheng, Qingrong Sun and Menglin Ma**
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**Metal-Free Synthesis of Pyrimidinone Derivatives via Biginelli Reaction Using Aqueous NaICl2 (http://dx.doi.org/10.2174/1570178617666191126095808)**
*Navnath T. Hatvate, Shrikant M. Ghodse, Krishna N. Mundlod and Vikas N. Telvekar**
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**Thiazolidine-2, 4-Diones as Non-Hepatotoxic Tri-action Drug Candidates: Design, Synthesis, Characterization, Biological Evaluation and Docking Studies (http://dx.doi.org/10.2174/1570178617666191220142852)**
*Karuna S. Shukla, Shailendra Pandey and Pooja A. Chawla**
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**Synthesis of C3-Quaternary 2H-Pyrrolines by [3+2] Cycloaddition of Isocyanoacetates and 1,1-Disubstituted Alkenes (http://dx.doi.org/10.2174/1570178617666191218104959)**
*Yi Cheng, Runmei Zhang, Tianhao Lu, Yong Shen, Min Wang and Chunsong Xie**
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**MoO3 Nanoparticles as an Efficient Catalyst for the Synthesis of Pyrazoles in Aqueous-alcoholic Medium at Room Temperature (http://dx.doi.org/10.2174/1570178617666191127103433)**
*Sonatai Patil*, Ananda Mane and Savita Dhongade-Desai*
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**Synthesis of New C2-Symmetric Chiral Benzimidazole Derivatives Having Norbornene/Dibenzobarrelene Skeletons (http://dx.doi.org/10.2174/1570178616666190731105327)**
*Irfan Capan and Suleyman Servi**
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**A Novel Copper-Catalyzed Synthesis of N-Monosubstituted 2-Alkynimidamides from 1-Alkynes and Trichloroacetamidines (http://dx.doi.org/10.2174/1570178616666191023142821)**
*Hossein Fasihi Dastjerdi, Manijeh Nematpour, Elham Rezaee, Mehdi Jahani and Sayyed Abbas Tabatabai**
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**Cytotoxic Prenyl and Geranyl Coumarins from the Stem Bark of Casimiroa edulis (http://dx.doi.org/10.2174/1570178616666191019121437)**
*Khun Nay Win Tun, Nanik Siti Aminah, Alfinda Novi Kristanti, Rico Ramadhan and Yoshiaki Takaya*
DOI: **10.2174/1570178616666191019121437**
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**Synthesis of Highly Functionalized Quinazoline-2, 4 (1H, 3H)-diones from Isocyanides, Aniline and Isocyanate via Cu-Catalyzed Intermolecular C-H Activation Reactions (http://dx.doi.org/10.2174/1570178616666190905142545)**
*Manijeh Nematpour, Hossein Fasihi Dastjerdi, Mehdi Jahani and Sayyed Abbas Tabatabai**
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**4-Anilidopiperidine Derivatives for in vivo Imaging of μ-Opioid Receptors (http://dx.doi.org/10.2174/1570178616666190905144136)**
*János Marton*, Attila Sipos, Sándor Berényi, Brita Glaenzel and Gjermund Henriksen**
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**Chiral Mn(III) Salen Complex Immobilized on CuFe2O4@SiO2-NH2 NPs: A Cheap and Efficient Catalyst for N-arylation of Aryl Halides and Phenylboronic Acid Under Mild Conditions (http://dx.doi.org/10.2174/1570178616666190919110639)**
*Mohammad Ali Nasseri , Seyyedeh Ameneh Alavi, Milad Kazemnejadi and Ali Allahresani*
DOI: **10.2174/1570178616666190919110639**
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**Asymmetric Reactions in Water Catalyzed by L-Proline Tethered on Thermoresponsive Ionic Copolymers (http://dx.doi.org/10.2174/1570178616666190819141307)**
*Noriyuki Suzuki*, Daisuke Mizuno, Armoando M. Guidote Jr., Shun Koyama, Yoshiro Masuyama and Masahiro Rikukawa*
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**Squaramide-Catalyzed Enantioselective Michael Addition of Pyrazol-3- ones to ortho-Quinone Methides (http://dx.doi.org/10.2174/1876402911666190806105543)**
*Laura Carceller Ferrer, Gonzalo Blay, José R Pedro* and Carlos Vila*
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**One-pot Pseudo-Domino Three-Component Knoevenagel Condensation Reaction in Water Enabled by Micellar Catalyst: Mechanism and Reactivity (http://dx.doi.org/10.2174/1570178616666190701102542)**
*Dini Ahanthem, Devi Prasan Ojha, Francis A.S. Chipem and Warjeet S. Laitonjam*
DOI: **10.2174/1570178616666190701102542**
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**PEG1000 as a Low Melting and Ecofriendly Solvent for Air Oxidative and Catalyst Free 2,4-Disubstitute Quinazoline Synthesis (http://dx.doi.org/10.2174/1570178616666190417122005)**
*Ebrahim Saeedian Moghadam, Shahrzad Ghafary and Mohsen Amini**
DOI: **10.2174/1570178616666190417122005**
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**nanik siti aminah <nanik-s-a@fst.unair.ac.id>**

# Online Abstract Submission -Letters in Organic Chemistry

1 message

**Letters in Organic Chemistry LOC** <loc@benthamscience.net> Tue, Jun 11, 2019 at 2:10 PM
To: nanik-s-a@fst.unair.ac.id

Dear Dr. Aminah,

With the reference to your abstract entitled “Prenyl and Geranyl Coumarins from the Stem Bark of Casimiroa edulis and their Cytotoxicity against HeLa and T47D cell lines” submitted in the journal Letters in Organic Chemistry. This is pleased to inform you that your abstract has been accepted by EIC of the Journal. Therefore you are kindly requested to please submit your complete manuscript via our online system https://benthammanuscriptpoint.com

Thanks and regards,

***Zubia Aleem Khan***

*Manager Publications*

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# Submission Acknowledgement | BMS-LOC-2019-118

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Cc: loc@benthamscience.net, zubia.aleem@benthamscience.net

**Reference#: BMS-LOC-2019-118**

Submission Title: Prenyl and Geranyl Coumarins from the Stem Bark of Casimiroa edulis with Cytotoxicity

Dear Dr. Aminah,

Thank you for your submission to "Letters in Organic Chemistry(LOC)". It will be sent to the Editor in Chief for his initial provisional approval, and once this is obtained for peer-reviewing, on the understanding that the manuscript contains original work that has neither been published earlier nor has simultaneously been submitted elsewhere. In case this is not so, please let us know immediately.

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To: nanik-s-a@fst.unair.ac.id
Cc: sobiaahmed@benthamscience.net

Reference#: BMS-LOC-2019-118

Submission Title: Prenyl and Geranyl Coumarins from the Stem Bark of Casimiroa edulis with Cytotoxicity

Dear Dr. Nanik Siti Aminah,

Thanks for submitting the manuscript to "Letters in Organic Chemistry". Your manuscript has been reviewed by experts in the field, and the consensus is that it needs significant revision keeping in consideration the comments given below. You are encouraged to address the comments of the reviewers and carefully revise the manuscript, highlighting the exact changes made in the manuscript.

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REVIEWER A:

Four prenyl and geranyl coumarins (K-1 to K-4) were isolated from the stem bark of Casimiroa edulis. Cytotoxicity of pure compound K-4 and sub-fraction MD-3 was evaluated against HeLa and T47D cell lines and displayed moderate activity with IC50 value in the range 17.4 to 72.33 mg/ml. Accept with minor revision. Comment 1: The “Extraction and Isolation” section, the weight of compounds K-1 to K-4 should be supplied. Comment 2: Compounds K-1 - K-4 are coumarins. Why only compound K-4 were determined for their cytotoxicity? Especially compounds K-1 and K-2, which are isolated from sub-fraction MD-3 and had more cytotoxicity.

REVIEWER B:

1. In paragraph one: The statement “A research was carried out from which a large number of the bioactive compounds were isolated and screened each year, thus realizing the intrinsic therapeutic potential of natural products, building on a vast resource to further research”. The statement sounds like a description of results. It should be reframed. 2. In paragraph two: The statement “To date, approximately 1500 coumarin derivatives have been identified from plant” was wrongly referenced. Authors should do well to correct this anomaly. Authors are also advised to ensure that this does not occur any where in the write-up as this was observed to recur most of the time. Eg. Reference [6] and [10} meant for anti-inflammatory and antiviral activities. 3. In results and discussion-structure elucidation: the statement In The molecular structure of isolated compounds were identified on the basic; the word basic should be replaced with “basis”. 4. Figure 2 a and b were absent 5. The statement “Natural and synthesis coumarins are well-known for their pharmacological properties” is not ambiguous . Authors should rephrase it. 6. Authors should avoid personalizing statements like “We have….” 7. The methanol extract (50 g) was subjected to vacuum liquid. Authors should indicate yield obtained before mentioning the quantity. 8. Under MTT assay: The isolated compounds were dissolved in DMSO. Authors should indicate the concentration of DMSO that was used in the dissolution of compounds. 9. Authors should mention how data on cytotoxicity was analyzed to obtain IC 50 Values. 10. The statement” auraptene was the first study in this plant” should be deleted as it is not linked it any objective.

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Authors must comply with all referees' requests. Moreover the drawing up of the manuscript often appears rather approximate and hasty. For this I enclose here the file "revAminah" where my corrections/suggestions are highlighted in yellow while in red there are the parts requiring author intervention (my comments in brackets). The file containing "SUPPLEMENTARY MATERIAL" must be updated in accordance with the manuscript.

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**nanik siti aminah** <nanik-s-a@fst.unair.ac.id> Mon, Sep 30, 2019 at 12:40 PM
To: Letters in Organic Chemistry <loc@benthamscience.net>

# COMMENT FOR REVEIWER

Reference#: BMS-LOC-2019-118

Submission Title: Prenyl and Geranyl Coumarins from the Stem Bark of Casimiroa edulis with Cytotoxicity

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Mehwish Akhter
Sr. Manager Publications
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Have been done in the revised of manuscript

REVIEWER A:
Four prenyl and geranyl coumarins (K-1 to K-4) were isolated from the stem bark of Casimiroa edulis. Cytotoxicity of pure compound K-4 and sub-fraction MD-3 was evaluated against HeLa and T47D cell lines and displayed moderate activity with IC50 value in the range 17.4 to 72.33 mg/ml. Accept with minor revision.

Comment 1: The "Extraction and Isolation" section, the weight of compounds K-1 to K-4 should be supplied.

The "Extraction and Isolation" section, the weight of the compounds K-1 to K-4 was assigned (page 7 in yellow colour).

Comment 2: Compounds K-1 - K-4 are coumarins. Why only compound K-4 were determined for their cytotoxicity? Especially compounds K-1 and K-2, which are isolated from sub-fraction MD-3 and had more cytotoxicity.

Due to inadequate samples for biological studies, pure compounds K-1, K-2 and K-3 have not been tested for their cytotoxicity. So, only compound K-4 was determined for cytotoxicity.

REVIEWER B:
1. In paragraph one: The statement "A research was carried out from which a large number of the bioactive compounds were isolated and screened each year, thus realizing the intrinsic therapeutic potential of natural products, building on a vast resource to further research". The statement sounds like a description of results. It should be reframed.

This statement has reframed by the Editor (page 1).

2. In paragraph two: The statement "To date, approximately 1500 coumarin derivatives have been identified from plant" was wrongly referenced. Authors should do well to correct this anomaly. Authors are also advised to ensure that this does not occur anywhere in the write-up as this was observed to recur most of the time. Eg. Reference [6] and [10] meant for anti-inflammatory and antiviral activities.

The above statement was accurately referenced. (page 1 and 7 in yellow colour)

3. In results and discussion-structure elucidation: the statement In The molecular structure of isolated compounds were identified on the basic; the word basic should be replaced with "basis".

The Editor replaced the word "basic" by basis (page 2).

4. Figure 2 a and b were absent

Figure 2a and b were shown in page 3.

5. The statement "Natural and synthesis coumarins are well-known for their pharmacological properties" is not ambiguous . Authors should rephrase it.

The statement "Natural and synthesis……." has rephrased (page 6).

6. Authors should avoid personalizing statements like "We have…."

Personalizing statements like "We have…." has rephrased (page 6).

7. The methanol extract (50 g) was subjected to vacuum liquid. Authors should indicate yield obtained before mentioning the quantity.

The yield amount of sample indicated in the text (page 6 and 7 in yellow colour).

8. Under MTT assay: The isolated compounds were dissolved in DMSO. Authors should indicate the concentration of DMSO that was used in the dissolution of compounds.

The concentration of DMSO mentioned in the text (page 7 in yellow colour).

9. Authors should mention how data on cytotoxicity was analyzed to obtain IC 50 Values.

Cytototoxicity index ($IC_{50}$) is provided by the plot of percent of cell viability against tested sample concentration (page 7 in the last pharagraf).

10. The statement" auraptene was the first study in this plant" should be deleted as it is not linked it any objective.

The statement" auraptene was the……" has rephrased (page 1 and 7).

EDITORIAL COMMENTS:
Authors must comply with all referees' requests. Moreover the drawing up of the manuscript often appears rather approximate and hasty. For this I enclose here the file "revAminah" where my corrections/suggestions are highlighted in yellow while in red there are the parts requiring author intervention (my comments in brackets). The file containing "SUPPLEMENTARY MATERIAL" must be updated in accordance with the manuscript.

Have been done

Thank for your kind help and cooperation.

Wuth best regard,

[Quoted text hidden]

--
Dr. Nanik Siti Aminah

Assoc. Professor on Natural Product Chemistry
Dept. of Chemistry
Fac. of Science and Technology
Universitas Airlangga

Vice Dean on Research and Partnership
Faculty of Science and Technology
Universitas Airlangga
Komplek Kampu C UNAIR
Jl. Ir. Soekarno
Surabaya-East Java
Indonesia
email address : nanik-s-a@fst.unair.ac.id

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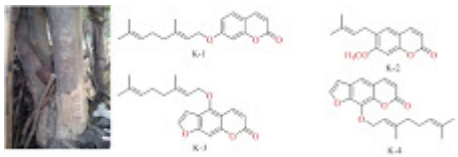

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**Letters in Organic Chemistry LOC** <loc@benthamscience.net> Tue, Oct 1, 2019 at 2:26 AM
To: nanik siti aminah <nanik-s-a@fst.unair.ac.id>

Dear Dr. Aminah,

Thank you very much for your email, your revised files has been sent for editor evaluation, I will tell you the editor's decision soon.

Please feel free to contact me if you have any questions.

Thanks and regards,

**Sobia Ahmed**

Assistant Manager Publications

**Note:**

Please reply to this email at loc@benthamscience.net otherwise your email will not reach me.

[Quoted text hidden]

nanik siti aminah <nanik-s-a@fst.unair.ac.id>

# Manuscript Acceptance letter | BMS-LOC-2019-118

6 messages

**Letters in Organic Chemistry** <admin@bentham.manuscriptpoint.com> Thu, Oct 17, 2019 at 4:34 PM
Reply-To: Letters in Organic Chemistry <loc@benthamscience.net>
To: nanik-s-a@fst.unair.ac.id
Cc: loc@benthamscience.net, qasit@benthamscience.net, sobiaahmed@benthamscience.net, sobiaahmed@benthamscinece.net

**Reference#:** BMS-LOC-2019-118

**Submission Title:** Cytotoxic Prenyl and Geranyl Coumarins from the Stem Bark of Casimiroa edulis

Dear Dr. Nanik Siti Aminah,

I am pleased to inform you that your article entitled **"Cytotoxic Prenyl and Geranyl Coumarins from the Stem Bark of Casimiroa edulis"** has been accepted for publication in "**Letters in Organic Chemistry**" after independent peer review.

We recommend you to publish your **Animated Abstract**, along with the article abstract, to extend the coverage of your article. Bentham Science has collaborated with Focus Medica, one of the world's largest publishers of expert animated atlases and videos in medicine and science, to create an **Animated Abstract** of your article. **Animated Abstract** will be published as open access (free-to-view) and help summarise the essential discoveries/key findings of your research, highlight the importance of the article for further research and utilization in the relevant industry. Each professionally produced, full-coloured animated abstract, in video format (length 3 – 5 minutes) is accompanied by an english or foreign language commentary. You can avail this service against a fee to get the **Animated Abstract** published with your textual / graphical abstract on the Journal's homepage (for reference, please visit: http://www.eurekaselect.com/video.html).

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We wish to thank you for submission of the manuscript to Letters in Organic Chemistry and look forward to continued collaboration in future.

With warm regards,

Mehwish Akhter
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**nanik siti aminah** <nanik-s-a@fst.unair.ac.id> Mon, Oct 21, 2019 at 10:39 AM
To: khun nay <khun.nay.win-2017@fst.unair.ac.id>, Khun Nay Win Tun <nkhun87@yahoo.com>

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Dr. Nanik Siti Aminah

Assoc. Professor on Natural Product Chemistry
Dept. of Chemistry
Fac. of Science and Technology
Universitas Airlangga

Vice Dean on Research and Partnership
Faculty of Science and Technology
Universitas Airlangga
Komplek Kampu C UNAIR
Jl. Ir. Soekarno
Surabaya-East Java