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One pot two-step borylation/fluorination reaction of dysobinin from *Chisocheton macrophyllus* and its cytotoxicity against cancer cell

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Abstract

Dysobinin is a naturally occurred limonoid, which is a specific form of triterpenoid, mostly found in certain plants, particularly the Meliaceae family. Overall, it has been found that limonoids have a wide range of biological functions. Typically, the compound comprises anticancer, antimicrobial, and anti-inflammatory properties. Even though dysobinin has shown some effectiveness, its potential in pharmacology, so far, is found limited. This study, therefore, aims to enhance the pharmacological properties of dysobinin through the addition of fluorine. To do this, a one-pot, two-step reaction comprising C-H borylation and selectfluor was used to turn dysobinin into two new compounds: 1,2-dihydro-6α-acetoxyazadirone (**5**) and 1β-fluorodysobinin (**6**). After the transformation, various spectroscopic methods, including UV (Ultraviolet), IR (infrared), MS (mass spectra), as well as NMR (1D and 2D) were applied to figure out the structures of the new compounds. Accordingly, of the derived compounds, 1β-fluorodysobinin showed significantly higher cytotoxicity against A549 lung cancer cells when compared to dysobinin.

Keywords: Fluorine; boron; selecflour; cancer cell; dysobinin; limonoid

1. Introduction

Cancer is a common term for various types of malignant tumors [1] that are known for uncontrolled cell growth, abnormal cell movement, and the unwanted spread to nearby tissues and organs [2]. Research has demonstrated that several variables are capable of transforming a healthy cell into a cancerous cell by disrupting its signal transduction, regulatory, and apoptotic pathways. Carcinogenic cell is a common example of a cancerous cell, widely known for its rapid and uncontrolled growth [3-4].

To reduce the death rate from this disease, investigators have examined an organic compound called as limonoid, which seems to have some important potentials. One of the secondary metabolites, limonoid, is mostly found in plant families such as Meliaceae, Rutaceae, and Rutales [5]. This compound, especially the one from the Meliaceae family, has a variety of biological properties. It has been noted for its antifeedant, anticancer, antimalarial, antibacterial, and cytotoxic effects [6-13]. Nevertheless, it is crucial to clarify that the chemical compound has several inherent limitations. This observation emphasized the need to develop an effective strategy, specifically designed to enhance the potential of limonoid, and a profound solution introduced as a result is the mixture of fluorine with the compound. The utilization of fluorine-containing molecules in organic synthesis has made great progress, especially in the manufacturing of medications and pesticides [14,15]. Previous research has shown that fluorine has a number of particular physical properties, including high electronegativity, short atomic size, and low polarizability in the C-F bond. These qualities enable fluorine to imitate hydrogen or hydroxy group [16-20].

Several studies have shown the effect of fluorine in limonoids or triterpenoids. 11β-fluorogedunin has twofold the activity of gedunin against leukaemia P-388 [21]. Fluorination of dammaran-type triterpenoids also showed increased activity against various cancer cells of MGC-803, SGC-7901, MCF-7, PC-3 cells [22]. In addition, the majority of synthesized fluorine-containing lupane triterpenoid acid derivatives exhibited several significant anti-inflammatory and antioxidant effects [23]. Based on the considerations, this

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present study aims to fluorinate dysobinin, a type of limonoid from *Chisocheton macrophyllus* through a one-pot, two-step reaction process comprising borylation and selectfluor. The novelty of this study lies in the fact that it is the first to report the fluorination of dysobinin using the previously mentioned method. Dysobinin was fluoridated since its mass is larger compared to other three compounds. It is also a major compound in *C. macrophyllus*. During the inquiry, two synthesized compounds and four isolated compounds were assessed for their capacity to constrain the growth of cancer cells.

2. Materials and Methods

2.1. General experimental procedures

The research involved the determination of optical rotations using a Perkin Elmer 341 Polarimeter (Waltham, MA, USA) and record of Ultraviolet (UV) spectra in methanol using a TECAN Infinite M200 pro spectrophotometer. The infrared (IR) spectra, furthermore, were acquired using a PerkinElmer Spectrum-100 FT-IR spectrometer with samples positioned in KBr pellets, while the HR-TOF-MS were obtained by using a Waters Xevo QTOF MS instrument. NMR spectra were gained by Bruker Ascend operating at certain frequencies: 700 MHz for ^{1}H, 175 MHz for ^{13}C, and 470 MHz for 19F. The internal standard used was tetramethylsilane (TMS); as a consequence, the process of separating substances using silica gel 60 (with the particle sizes of 70–230 and 230–400 mesh, manufactured by Merck) was carried out. A study was performed utilizing GF_{254} silica gel plates (Merck, 0.25 mm thickness) to undertake thin layer chromatography (TLC) examination with various solvent systems. The plates in this particular situation were examined using UV-visible light at (λ 254 & 365 nm), and a Vilber Lourmat lamp. The reagent used for additional characterisation and detection was Ehrlich's reagent, also known as *p*-Dimethylaminobenzaldehyde. It was diluted with ethanol after being mixed with 10% H_2SO_4. The resulting solution was then sprayed over the heated silica gel plates.

2.2. Biological material

The *C. macrophyllus* seeds utilized in this investigation were gathered from the Bogor Botanical Garden, located in Bogor, West Java Province, Indonesia. Furthermore, a voucher specimen (No. Bo-1295453) was stored in the Herbarium Bogoriense, Bogor.

2.3. Extraction and isolation

The dry *C. macrophyllus* seeds (3.5 kg) were soaked in methanol for 6 days. After the solvent was evaporated, the resultant mixture was extracted, producing a crude extract weighing 414.0 g. The extract was further separated into several fractions using *n*-hexane, ethyl acetate, and *n*-butanol, resulting in 197.0 g, 41.7 g, and 15.0 g of concentrated extract, respectively. Consequently, the n-hexane extract was separated using VLC (Vacuum liquid chromatography) on silica gel G_{60} with a gradient elution system consisting of *n*-hexane, ethyl acetate, and methanol (beginning with a 10% concentration of ethyl acetate). From this technique, 9 fractions were obtained and classified into A to I. Fraction D (50 mg) underwent recrystallization using chloroform-methanol, resulting in the formation of compound **1** (500 mg). Fraction E (2.04 g) underwent additional purification using column chromatography (CC) on silica gel (70-230 mesh) using a gradient system with a mixture of 2.5% ethyl acetate in *n*-hexane. Continuing from the previous procedure, fraction E9 (289.4 mg), obtained from the initial chromatography on silica gel CC (70-230 mesh), underwent additional purification on a silica gel column. This was followed by recrystallization with chloroform, resulting in the separation of compound **2** (200 mg). Furthermore, Fractions E2 to E5 were mixed (142.5 mg) and separated using a silica gel column; it resulted in compound **3** (16.1 mg). Similarly, Fractions E9 to E12 (96 mg) were combined and submitted to chromatography on a silica gel column, resulting in the isolation of compound **4** (18.0 mg) [24].

2.4. Procedure for borylation and selectflour

In a glovebox, $[Ir(cod)OMe]_2$ (5.0 mg, 0.0075 mmol), dtbpy (4.0 mg, 0.015 mmol), B_2pin_2 (127.0 mg, 0.500 mmol), and dysobinin (123.0 mg, 0.25 mmol) were added to a Schlenk flask that was equipped with a stirring bar. The flask subsequently was capped and taken out of the glovebox. THF (4.0 mL) was added under a nitrogen atmosphere using a Schlenk vacuum line. The flask was then sealed and subjected to heating at a temperature of 50°C for 20 hours. Afterward, the reaction mixture was cooled to the ambient temperature, and any easily evaporating substances were eliminated by means of a vacuum. Later on, selectflour (0.25 mmol, 0.25 equiv), acetonitrile (2.0 mL), and methanol (2.0 mL) were added consecutively to the mixture. The resulting mixture was sealed and stirred at room temperature for 20 hours (Fig. 1.). It was then subjected to chromatography on a column of silica gel, using *n*-hexane: EtOAc (8:2) as the eluent. This process yielded product **5** (72 mg, 56%) and product **6** (28.0 mg, 21.8%) [25].

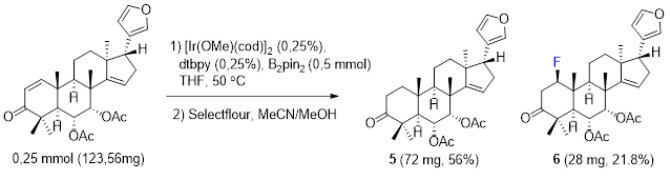

Fig. 1. One pot two-step borylation/fluorination reaction of Dysobinin

*2.4.1. 1β-fluorodysobinin **(6)***

White needle crystals; mp: 169-172°C; $[\alpha]^{27}_{D}$ -30^{o} (*c* 0.2, $CHCl_3$); UV (MeOH) λ_{max} 208 nm; IR (KBr) ν_{max} 2950, 1739, 1382, 1366, 1248 cm^{-1}; HR-TOFMS *m/z* 515.2808 $[M+H]^+$, (calcd. for $C_{30}H_{40}O_6F$ *m/z* 515.2809); ^{1}H-NMR ($CDCl_3$, 700 MHz) and ^{13}C-NMR ($CDCl_3$, 175 MHz) (see Table 1). ^{19}F-NMR ($CDCl_3$, 470 MHz): δ -175.4 (m, 1F).

2.5. Cytotoxic activity

The PrestoBlue® test was utilized to assess the cytotoxicity

of compounds **1** to **6** by conducting a cell viability test. The cells used were cultured in Roswell Park Memorial Institute (RPMI) medium supplemented with 10% (v/v) fetal bovine serum (FBS) and 1μL/mL antibiotics. The cultures were then kept at a temperature of 37°C in a humid environment with 5% CO_2. A549, MCF-7, B-16-F10 and CV-1 cells were then placed into 96-well culture plates with a density of 1.7 × 104 cells per well. After a 24-hour incubation period, the old media was replaced with fresh one, which contained a number of different samples at various concentrations (7.81, 15.63, 31.25, 62.50, 125.00, 250.00, 500.00, and 1000.00μg/mL) and a control. The samples and cells were cultured for 24 hours prior to the application of the PrestoBlue® reagent (resazurin dye) to the wells. The data were subsequently assessed using a multimode reader at a wavelength of 570 nm. Finally, the IC_{50} values, which indicated the concentration of chemicals that caused a 50% decrease in cell viability, were calculated using the linear regression method in Microsoft Excel software. Within this particular setting, the absorbance seen in the control wells directly indicated a cell viability of 100%.

2.6. Methods for NMR Calculation

The conformational distribution searches at Molecular Mechanics MMFF were conducted by the help of Spartan 14.0 software developed by Wavefunction Inc. The initial stable conformers were optimized using the Boltzmann distribution method with a minimum energy threshold of 2%, in the Gaussian 09 program (Gaussian Inc., Wallingford, CT, USA). The conformers were also optimized using the Density Functional Theory (DFT) approach at the B3LYP/6-31g(d) level. The optimized conformers were then analysed using the NMR GIAO method at MPW1PW91/6-311+g(d,p) level of theory, (IEFPCM=chloroform). They were further utilized for NMR computation [26-27].

3. Results and Discussion

3.1. Synthesis dysobinin derivatives

The isolated compounds **1-4** were gained from the *n*-hexane extract of *C. macrophyllus* seeds (Fig. 2). Dysobinin **(1)**, obtained from *C. macrophyllus* [25], was treated with C-H borylation and selectflour in one-pot two-step reaction, 1,2-dihydro-6*α*-acetoxyazadirone **(5)** and 1*β*-fluorodysobinin **(6)** were obtained at 56% and 21.8% yields, respectively. Compound 5 is a derivative of the dysobinin compound that has been carried out by [28], identified by comparing spectroscopic data with previously reported values.

The fluorination of heteroarenes was conducted using a two-step one-pot reaction method via Ir-catalyzed C-H borylation, followed by fluorination with selectflour. This was related to the instability of heteroaryl pinacol boronate. The reaction must take place under inert atmospheric conditions if there is oxygen heteroaryl pinacol boronate that would return to the starting compound (dysobinin) [19]. Compound **6** was found as white crystals in which its chemical formula, $C_{30}H_{39}O_6F$, was shown by HR-TOF-MS experiment with the positive ion peak at m/z 515.2808 $[M+H]^+$ (calcd, 515.2809), which indicated twelve DBEs. The IR spectrum of **6** revealed the existence of ether (1248 cm^{-1}), gem-dimethyl (1366 and 1382 cm^{-1}), C=O (1739 cm^{-1}), and CH aliphatic (2930 cm^{-1}) groups.

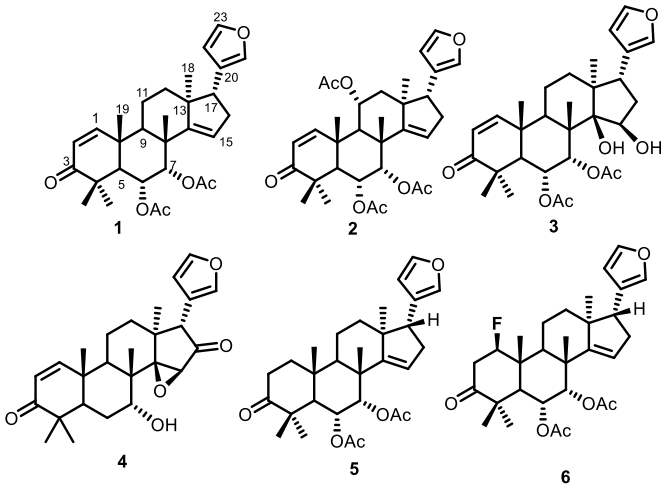

Fig. 2. Structures of compounds 1-6

The ^{1}H NMR data of **6** implied was similar to dysobinin [24,29] with the only difference regarding the proton location close to the fluorinated carbon. In this study, H-1 and H-2 comprised $J_{H,F}$-coupling [δ_H 4.91 (1H, ddd, $J_{H,F}$ = 50.2 Hz, $J_{H,H}$ = 7.0, 4.7 Hz, H-1) and 2.30 (2H, dd, $J_{H,F}$ = 49, $J_{H,H}$ = 7.0 Hz, H-2)], respectively. The ^{13}C NMR (Table 1), DEPT 135, and (HSQC) spectra were similar to dysobinin. The presence of $J_{C\text{-}F}$ coupling is the distinguishing data with dysobinin. Compound **6** had a carbonyl, which comprised $^3J_{C,F}$-coupling at δ_C 210.2 (d, J = 15.8 Hz, C-3), one methylene carbon which constituted $^2J_{C,F}$-coupling 46.6 (d, J = 21.1 Hz, C-2), and one sp^3 methine, which had $^1J_{C,F}$-coupling δC 90.7 (d, J = 177 Hz, C-1).

The position of C-1 fluorination and the presence of a furan ring were elucidated through (HMBC) and (^{1}H-^{1}H COSY) experiments (Fig. 3). Furthermore, correlations were found between *sp*^{3} methine protons, which had $^2J_{C,F}$-coupling at δ_H 4.91 (1H, ddd, $J_{H,F}$ = 50.2 Hz, $J_{H,H}$ = 7.0, 4.7 Hz, H-1) to δ_C 38.24 (d, J = 5.2 Hz, C-10), allowing for the identification of C-1 fluorination. It was also observed that methyl singlet at δ_H 0.87 (CH_3-18) to δ_C 51.6 (C-17), and a methine proton at δ_H 2.79 (H-17) to δ_C 34.4 (C-16) as well as δ_C 124.7 (C-20) allowed for the identification of the furan ring attached at C-17.

In accordance with previous studies, NOESY experiments of compound **6**, as shown in Fig. 4, were found to have similarities with compound dysobinin [24,29]. Meanwhile, the unambiguous fluor in C-1 was determined using NMR DP4+ calculation, and the obtained result was shown as 1*R* (referring to Fig. 5) [26-27]. The optical rotation of **6**, $[\alpha]^{27}_D$ 30° (c 0.05, $CHCl_3$) is of similar sign as found in the previous compound, dysobinin (1) ($[\alpha]^{20}_D$+150°) but the skeleton has been identified to be a novel havanensin-type limonoid derivative, designated as 1*β*-fluorodysobinin. The comparison of previous NMR data was performed to identify other compounds. Here, four known compounds were identified as dysobinin **(1)**, 11*α*-acetoxydysobinin **(2)**, dysobinol **(3)**, and 7-deacetylepoxyazadiradione **(4)** [24].

Table 1. 1β-fluorodysobinin ($C_{30}H_{39}FO_6$) ^{1}H-NMR and ^{13}C-NMR

1β-fluorodysobinin	
^{1}H-NMR (700 MHz)	^{13}C-NMR (175 MHz)
δ_H ppm (ΣH; mult; J=Hz)	δC ppm (mult; J=Hz)
4.91 (1H; ddd; 50.2; 7.0; 4.7)	90.7 (d; 177)
2.30 (2H; dd; 49; 7.0)	46.6 (d; 21.12)
-	210.2 (d; 15.84)
-	47.1
2.72 (1H; d; 12.0)	48.2
5.44 (1H; dd; 12.0; 1.9)	69.9
5.42 (1H; d; 2.7)	74.7
-	42.8
2.14 (1H; m)	42.2
-	38.2 (d; 5.2)
1.70 (2H; m)	16.4
2.34 (2H; dd; 7.3; 3.5)	32.6
-	46.5
-	158.1
5.37 (1H; m)	119.8
1.90 (2H; t)	34.4
2.79 (1H; dd; 10.9; 7.3)	51.6
0.80 (3H; s)	20.5
1.04 (3H; s)	18.2
-	124.5
7.24 (1H; s)	139.7
6.24 (1H; d; 1.45)	111.0
7.37 (1H; d; 1.6)	142.6
1.13 (3H; s)	20.8
1.29 (3H; s)	29.6
1.26 (3H; s)	26.2
2.02 (3H; s)	21.0
-	170.1
2.04 (3H; s)	21.3
-	170.2

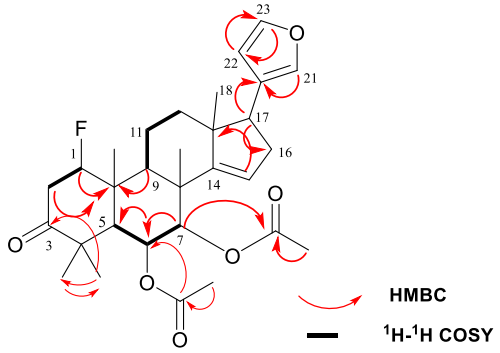

Fig. 3. Selected HMBC and ^{1}H-^{1}H COSY correlations for **6**

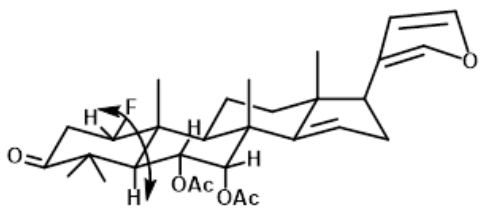

Fig. 4. Selected HMBC and ^{1}H-^{1}H COSY correlations for **6**

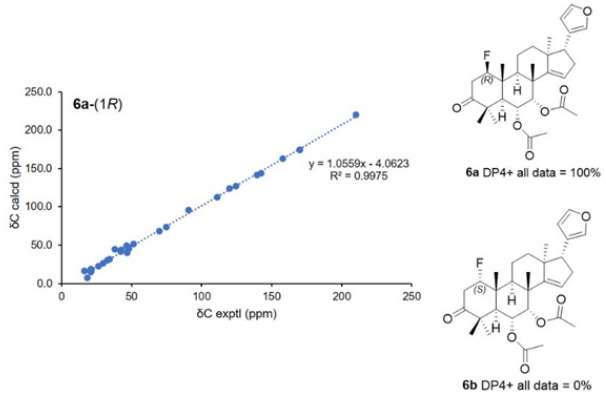

Fig. 5. Calculation and experiment of NMR calculation (DP4+ analysis) of **6**

3.2. Cytotoxic activity

All compounds were assessed for cytotoxic activity against A549, MCF-7, B-16-F10 and CV-1 cell line using the previously described approach [30-32]. The positive controls used were doxorubicin and cisplatin. The results of these assessments, aspresented in Table 2, indicated that compound **6** displayed the highest level of effectiveness against A549 lung cancer cells with IC_{50} (inhibitory concentration, 50%) values of 57.00 µg/mL. This is attributed to the presence of fluorine at C-1 that improved its cytotoxic activity. Alternatively, compound **5**, lacking *α,β*-unsaturation, showed weak activity, suggesting that the absence of *α,β*-unsaturation can reduce the effectiveness.

Based on the activity of fluorine in dysobinin, modulating biological activity or pharmaceutical profile is deemed useful. Fluorine has strong electronegativity, small atomic size, and low polarization of C-F bonds, and can mimic hydrogen or hydroxyl groups. The incorporation of fluorine into molecules is an important medicinal chemistry approach in drug discovery. The antiproliferative activity of fluorinated derivatives against a panel of human tumour cell lines is related to the beneficial effects of atom on conformation, pKa, intrinsic potential, membrane permeability, metabolic pathways, and pharmacokinetic properties [33].

Table 2. Cytotoxicity of compounds **1–6** against cancer cell.

Compound	IC_{50} (µg/mL)			
	A549	MCF-7	B16-F10	CV-1
Dysobinin (1)	>100	66.7	71.5	>100
11 *α*-acetoxydysobinin (2)	>100	>100	>100	>100
Dysobinol (3)	>250	96.4	40.3	>100
7-deacetylepoxyazadiradione (4)	>100	>100	>100	>100
1,2-dihydro-6*α*-acetoxyazadirone (5)	>100	>100	77.4	>100
1*β*-fluorodysobinin (6)	57.0	>100	90.3	>100
Doxorubicin (positive control)	1.77	-	-	-
Cisplatin	-	43.8	51.8	39.5

4. Conclusion

Dysobinin was treated with C-H borylation and selectflour in one-pot two-step reaction, and 1,2-dihydro-6*α*-acetoxyazadirone **(5)** and 1*β*-fluorodysobinin **(6)** were

obtained with the yield of 56% and 21.8%, respectively. Compound 6 displayed the highest level of effectiveness against A549 lung cancer cells with IC_{50} (inhibitory concentration, 50%) values of 57.00µg/mL.

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