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Research Article

SYNTHESIS OF NEW COUMARIN DERIVATIVES AND EVALUATION OF THEIR ANTI-CANCER ACTIVITY

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ABSTRACT

*A fragment-based approach has been applied to derive 2-(7-hydroxy-2-oxo-2H-chromen-4-yl)acetic acid **1** into 4 new coumarin derivatives **2a-d** through amide bonds. The compounds were screened for their anticancer activity using MTT assay on MCF-7 and HepG2 cell lines. The results showed that compounds **2a-c** significantly inhibited MCF-7 cells at 40 µM (29-38%) while compound **2d** is a strong HepG2 inhibitor with IC_{50} of 21 µM. Docking studies of the most potent compound **2d** suggest its HepG2 antiproliferative activity could be mediated through multikinase inhibition of p38α, VEGFR2 and FGFR-1. Further optimisation should lead to a more potent compound.*

***Keywords*:** 2-(7-hydroxy-2-oxo-2H-chromen-4-yl)acetic acid; amide coupling; anticancer; MCF-7; HepG2; molecular docking

1. Introduction

Fragment-based drug discovery is an established field for discovering new drug candidates. Over the past 20 years, 40 clinical candidates and four drugs have been discovered using this strategy (Denis et al., 2021). Typically, fragment with molecular weight < 250 will be grown and optimised into more extensive drug-like compounds, using chemical reactions, as drug candidates for clinical studies. On the other hand, coumarin is a class of compounds present in both natural and synthetic compounds and has a wide range of biological activities such as anticancer, antibacterial, antiviral, etc. (Rawat & Reddy, 2022). Drugs containing coumarin are known, such as 4-methylumbelliferone (choleretic

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and antispasmodic), warfarin (anticoagulant), and novobiocin (antibiotic). Moreover, amide bond is the most common chemical synthesis used for drug discovery and development (Boström et al., 2018). Some amide derivatives of substituted benzylamines have previously shown excellent anticancer activity (Pham & Truong, 2022).

Thus, in this report, using fragment-based drug discovery strategy, the fragment 2-(7-hydroxy-2-oxo-2H-chromen-4-yl)acetic acid **1** (MW = 220), a derivative of 4-methylumbelliferone, was grown into bigger drug-like molecules of MW around 350 (4 new coumarin derivatives) using amide coupling between the acid group of **1** with various substituted benzylamine derivatives and studied their anticancer activity as well as their mechanism of action via molecular docking.

2. Materials and methods

2.1. Instrumentation

NMR spectroscopic data were acquired on a Bruker Avance III at 600 MHz for ^{1}H–NMR and 150 MHz for ^{13}C–NMR. HRMS spectra were recorded on an LCMS-IT-TOP (Shimadzu).

2.2. Material

Reagents and solvents were obtained from commercial suppliers and were used without further purification. Column chromatography was carried out using Merck Kieselgel 60 silica gel (particle size: 32-63 Å). Analytical TLC was performed using Merck precoated silica gel 60 F-254 sheets.

2.3. Synthesis

*2-(7-Hydroxy-2-oxo-2H-chromen-4-yl)-N-(2-chlorophenyl)acetamide **2a***

The mixture of **1** (44.0 mg, 0.2 mmol), HATU (91.2 mg, 0.24 mmol), and Et_3N (0.2 mL, 1.4 mmol) was added to the solution of 2-chlorobenzylamine (33.8 mg, 0.24 mmol) in THF (0.2 mL) at room temperature. The reaction was stirred at room temperature for 2 hrs. The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to produce a residue purified by recrystallisation (dichloromethane) to afford the desired product **2a**. Yield: 52.4 mg (white solid, 76%). ^{1}H-NMR δ_H (600 MHz, DMSO-d_6, δ ppm): 10.54 (1H, *br*), 8.71 (1H, *t*, J = 6.0 Hz), 7.63 (1H, *d*, J = 9.0 Hz), 7.45-7.43 (1H, *m*), 7.33-7.28 (3H, *m*), 6.79 (1H, *dd*, J = 8.4 Hz, J = 2.4 Hz), 6.73 (1H, *d*, J = 2.4 Hz), 6.20 (1H, *s*), 4.35 (2H, *d*, J = 6.0 Hz), 3.76 (2H, *s*). ^{13}C-NMR δ_C (150 MHz, DMSO-d_6, δ ppm): 167.9, 161.2, 160.2, 155.0, 151.0, 135.9, 132.2, 129.2, 129.2, 128.8, 127.1, 126.7, 112.8, 111.9, 111.4, 102.3, 40.4, 38.6 ppm. HRMS calcd $C_{18}H_{15}ClNO_4^+$ ($[M+H]^+$): 344.0690, found: 344.0697.

*2-(7-Hydroxy-2-oxo-2H-chromen-4-yl)-N-(3-chlorophenyl)acetamide **2b***

The mixture of **1** (44.0 mg, 0.2 mmol), HATU (91.2 mg, 0.24 mmol), and Et_3N (0.2 mL, 1.4 mmol) was added to the solution of 2-chlorobenzylamine (33.8 mg, 0.24 mmol) in THF (0.2 mL) at room temperature. The reaction was stirred at room temperature for 2 hrs.

The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give a residue purified by recrystallisation (dichloromethane) to afford the desired product **2b**. Yield: 40.3 mg (white solid, 59%). ^{1}H-NMR δ_H (600 MHz, DMSO-*d*$_6$, δ ppm): 10.55 (1H, *br*), 8.70 (1H, *t*, J = 6.0 Hz), 7.59 (1H, *d*, J = 9.0 Hz), 7.34-7.29 (2H, *m*), 7.25-7.24 (1H, *m*), 7.19 (1H, *d*, J = 7.2 Hz), 6.78 (1H, *dd*, J = 9.0 Hz, J = 2.4 Hz), 6.72 (1H, *d*, J = 2.4 Hz), 6.19 (1H, *s*), 4.29 (2H, *d*, J = 6.0 Hz), 3.73 (2H, *s*). ^{13}C-NMR δ_C (150 MHz, DMSO-*d*$_6$, δ ppm): 167.9, 161.2, 160.2, 155.0, 150.9, 141.8, 133.0, 130.1, 126.9, 126.7, 126.6, 125.9, 112.9, 112.0, 111.4, 102.3, 41.8, 38.8 ppm. HRMS calcd $C_{18}H_{15}ClNO_4^+$ ($[M+H]^+$): 344.0690, found: 344.0686.

2-(7-Hydroxy-2-oxo-2H-chromen-4-yl)-N-(4-chlorophenyl)acetamide ***2c***

The mixture of **1** (44.0 mg, 0.2 mmol), HATU (91.2 mg, 0.24 mmol), and Et_3N (0.2 mL, 1.4 mmol) was added to the solution of 2-chlorobenzylamine (33.8 mg, 0.24 mmol) in THF (0.2 mL) at room temperature. The reaction was stirred at room temperature for 2 hrs. The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give a residue that was purified by recrystallisation (dichloromethane) to afford the desired product **2c**. Yield: 37.3 mg (white solid, 54%). ^{1}H-NMR δ_H (600 MHz, DMSO-*d*$_6$, δ ppm): 10.57 (1H, *br*), 8.69 (1H, *t*, J = 6.0 Hz), 7.58 (1H, *d*, J = 9.0 Hz), 7.36 (2H, *d*, J = 8.4 Hz), 7.25 (2H, *d*, J = 8.4 Hz), 6.78 (1H, *dd*, J = 8.4 Hz, J = 2.4 Hz), 6.71 (1H, *d*, J = 2.4 Hz), 6.18 (1H, *s*), 4.27 (2H, *d*, J = 6.0 Hz), 3.71 (2H, *s*). ^{13}C-NMR δ_C (150 MHz, DMSO-*d*$_6$, δ ppm): 167.7, 161.3, 160.2, 155.0, 150.9, 138.2, 131.4, 129.1, 128.2, 126.6, 112.8, 111.8, 111.3, 102.3, 41.7, 38.7 ppm. HRMS calcd $C_{18}H_{15}ClNO_4^+$ ($[M+H]^+$): 344.0690, found: 344.0687.

N-((1H-benzo[d]imidazol-2-yl)methyl)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl)acetamide ***2d***

The mixture of **1** (220.0 mg, 1.0 mmol), HATU (760 mg, 2.0 mmol), and Et_3N (3.0 mL) was added to the solution of 1H-benzimidazole-2-methanamine (147.0 mg, 1.0 mmol) in DMF (1.0 mL) at room temperature. The reaction was stirred at room temperature for 12 hrs. The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give a residue that was purified by silica gel column chromatography using ethyl acetate: ethanol (5:0.1) to afford the desired product **2d**. Yield: 111.0 mg (white solid, 32%). ^{1}H-NMR δ_H (600 MHz, DMSO-*d*$_6$, δ ppm): 12.25 (1H, *s*), 10.53 (1H, *s*), 8.91 (1H, *t*, J = 6.0 Hz), 7.67 (1H, *d*, J = 8.4 Hz), 7.57 (1H, *d*, J = 7.8 Hz), 7.45 (1H, *d*, J = 7.8 Hz), 7.16-7.14 (2H, *m*), 6.78 (1H, *dd*, J = 8.4 Hz, J = 2.4 Hz), 6.71 (1H, *d*, J = 2.4 Hz), 6.25 (1H, *s*), 4.51 (2H, *d*, J = 6.0 Hz), 3.77 (2H, *s*). ^{13}C-NMR δ_C (150 MHz, DMSO-*d*$_6$, δ ppm): 168.1, 161.2, 160.2, 155.0, 151.8, 151.0, 143.0, 136.9, 134.9, 134.1, 126.9, 121.8, 117.9, 112.8, 111.8, 111.4, 102.2, 38.6, 37.3 ppm.

2.4. Cell culture and MTT assay

The MCF7 or HepG2 cells were cultured at a density of 7000 cells in a volume of 100 µL per well in a 96-well plate. Following cell adhesion to the surface, a new environment containing compounds at single or varying concentrations was substituted for the old medium, and the cells were further incubated for 48 hours. Subsequently, a medium containing MTT at a concentration of 5 mg/mL was employed to incubate the cells for 4 hours. The medium was then removed, and 100 microliters of DMSO were added to dissolve the formazan crystals. Optical density (OD) values were measured using a Multiscan spectrophotometer at a wavelength of 570 nm (Le et al., 2023). The IC_{50} value was calculated using GraphPad Prism 5.0 software with a logarithmic concentration function.

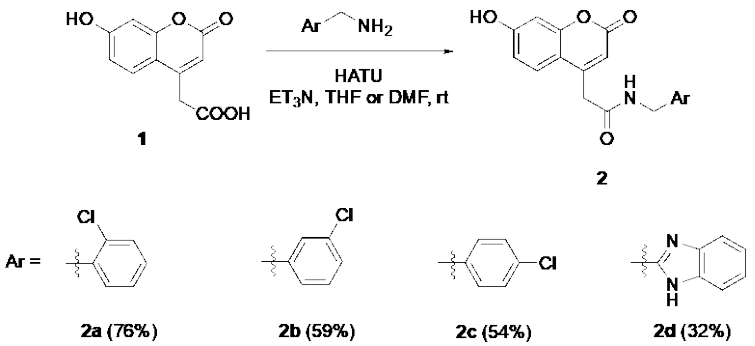
2.5. Molecular docking

Molecular modelling and docking studies were carried out using the Schrödinger Suites software, focusing on the Maestro graphical interface. Crystal structures of VEGFR2 (PDB: 3WZE), FGFR-1 (PDB: 5ZV2), and p38alpha (PDB: 3HEG) were prepared using Protein Preparation, while the compound of interest was optimised with Ligprep for subsequent docking simulations. Docking was conducted to predict the binding modes of the compound with the protein targets, employing the Glide module with the XP docking protocol, and the binding affinities were analysed using the MM-GBSA method. The resulting docked poses were then scored and analysed to identify critical protein-ligand interactions (Le et al., 2023).

3. Results and discussion

3.1. Synthesis

Amide coupling reaction could be realised by using coupling reagents such as 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate - HATU (Pikul et al., 2013), 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate - TBTU (Le et al., 2023, 2021), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide - EDC (Seavill & Wilden, 2020), etc. In this report, amides **2a-d** (32-76%) were synthesised by coupling reactions between acid **1** and benzylamine derivatives (*o*-chlorobenzylamine, *m*-chlorobenzylamine, *p*-chlorobenzylamine), or 1H-benzimidazole-2-methanamine using HATU in solvent THF/or DMF for 2hrs or 12 hrs at room temperature (Scheme 1). Amine 1H-benzimidazole-2-methanamine were synthesised by *o*-phenylendiamie and glycine in HCl (Yaqia et al., 2019). NMR confirmed all the structures of these compounds.



Scheme 1. *Synthesis of amides **2a-d***

3.2. Anticancer activity screening

The synthesised amides **2a-d** have been screened for anticancer activity on MCF-7 and HepG2 cell lines using MTT assay as previously described [Le at al. 2023] at 40 µM for 48 hrs in comparison with starting material **1** and the reference 5FU as a positive control.

Table 1. *Antiproliferative activity (% inhibition at 40 µM) of the compounds on MCF-7 and HepG2 cell lines using MTT assay. The biological assay was repeated two to four times for the concentration. The data is presented as mean ± SD*

Compound	MCF-7	HepG2
1	12.9 ± 4.1	0
2a	28.7 ± 5.8	2.0 ± 2.1
2b	34.4 ± 1.9	9.0 ± 5.0
2c	38.4 ± 7.7	0
2d	0	75.1 ± 5.3
5FU	18.7 ± 2.5	36.0 ± 2.0

The results (Table 1) showed that, except coumarin-benzimidazole hybrid **2d** (no inhibition), the chloro-substituted compounds **2a-c** significantly inhibited MCF-7 cell growth at the percentage of 29-38%, being better than fragment **1** (13%) and 5FU (19%). On the other hand, **2a-c** showed insignificant inhibition of HepG2 cell growth (0-9%) while **2d** showed potent inhibition (75%) as compared to **1** (0%) and 5FU (36%). Dose-dependent inhibition measurement of **2d** (Figure 2) showed an IC_{50} of 21 µM.

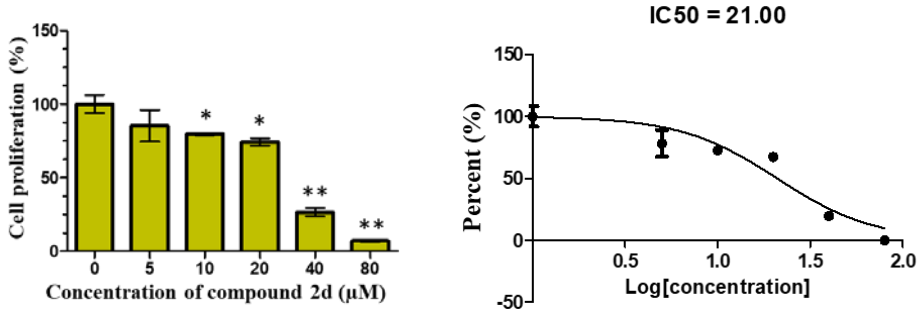


Figure 2. *Effect of compound 2**d** on cell proliferation and the logarithm for determining the IC50 value on HepG2 cell. The biological assay was repeated four times for each concentration. The data is presented as mean ± SD*

3.3. Physical-chemical properties of 2d

The physical chemical properties of a compound are essential to predict its drug likeliness property. We calculated five properties in Lipinski's rule of five, including AlogP (Ghose-Crippen-Viswanadhan octanol-water partition coefficient), PSA (polar surface area), MW (molecular weight), HBD (H bond donor) and HBA (H bond acceptor) for compound **2d** and the result is shown in Figure 3. All five parameters are within the allowable value of Lipinski's rule of five, and a good MPO (multiparameter optimisation) score is observed.

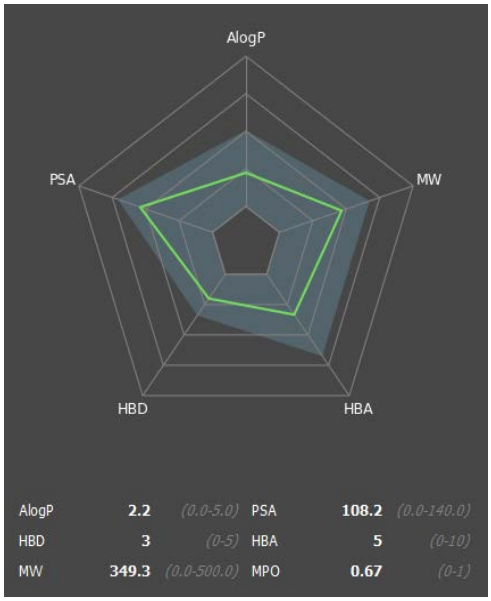


Figure 3. *Multi-Parameter about ADME of* ***2d***

3.4. Docking studies of 2d

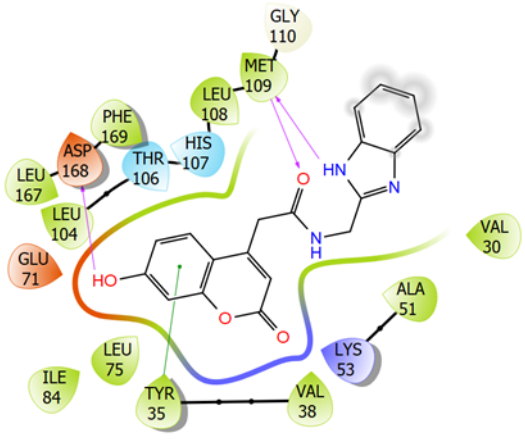
Multitargeted tyrosine kinase inhibitor drugs, such as Lenvatinib and Sorafenib, exhibit significant promise in cancer therapy by targeting various receptors involved in tumour growth and angiogenesis. While Lenvatinib primarily targets vascular endothelial growth factor receptors (VEGFR) and fibroblast growth factor receptors (FGFR), Sorafenib extends its inhibition to VEGFR, FGFR, platelet-derived growth factor receptor (PDGFR), and RAF kinase. Through their ability to disrupt tumour angiogenesis and curb tumour cell proliferation, these inhibitors have emerged as pivotal treatment options for various cancers, notably hepatocellular carcinoma, and renal cell carcinoma. By emulating the inhibition mechanisms of Lenvatinib and Sorafenib, which target crucial protein kinases such as VEGFR2, FGFR-1, and Protein Kinase p38alpha, we propose that leveraging similar inhibitory actions could lay a promising foundation for developing novel multikinase inhibitors.

Molecular modelling and docking studies were carried out using the Schrödinger Suites software, focusing on the Maestro (Schrödinger, 2021a) graphical interface. Crystal structures of VEGFR2 (PDB: 3WZE) (Okamoto et al., 2015), FGFR-1 (PDB: 5ZV2)

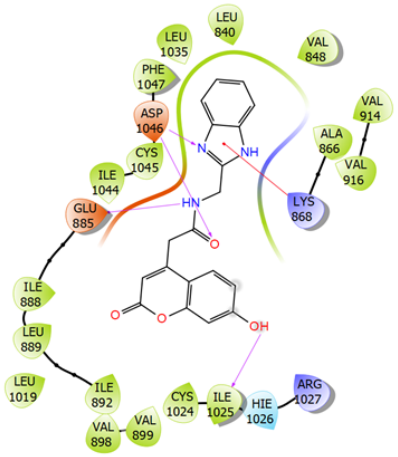
(Matsuki et al., 2018), and p38alpha (PDB: 3HEG) (Namboodiri et al., 2010) were prepared using Protein Preparation (Schrödinger, 2021b), while the compound of interest was optimised with Ligprep (Schrödinger, 2021c) for subsequent docking simulations. Docking was conducted to predict the binding modes of the compound with the protein targets, employing the Glide (Schrödinger, 2021d) module with the XP docking protocol, and the binding affinities were analysed using the MM-GBSA (Knight et al., 2014) method. The resulting docked poses were then scored and analysed to identify key protein-ligand interactions. Table 2 shows good values of −10.426, -8.395, and −8.395 kcal/mol of glide xp docking scores were observed for p38α, VEGFR2, and FGFR-1, respectively. The best docking poses of compound **2d** revealed key interaction with residues met109, asp168 and tyr35 with p38α (Figure 4A); asp1046, lys868, glu885 and ile1025 with VEGFR2 (Figure 4B); ala564 and glu571 with FGFR-1 (Figure 4C).

Table 2. *The docking score and MM-GBSA binding free energies estimations (kcal/mol) of* ***2d*** *with 3 target proteins.*

Targets	Glide XP (kcal/mol)	MM-GBSA (kcal/mol)
Protein kinases p38alpha (PDB: 3HEG)	-10.426	-68.03
Vascular endothelial growth factor receptor 2 (VEGFR2) (PDB: 3WZE)	-8.395	-68.32
Fibroblast growth factor receptor1 (FGFR-1) (PDB: 5ZV2)	-8.395	-58.54



A



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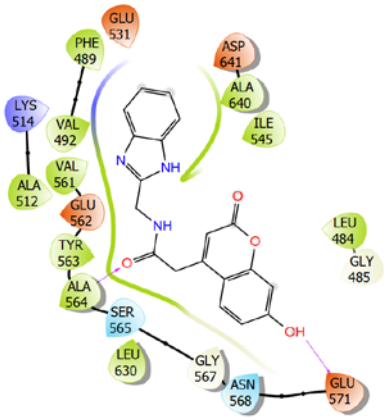

C

Figure 4. *2D docking poses of* ***(2d)*** *with protein kinases p38alpha (**A**, PDB ID 3HEG), vascular endothelial growth factor receptor 2 (VEGFR2) (**B**, PDB ID 3WZE), and fibroblast growth factor receptor 1 (FGFR-1) (**C**, PDB ID 5ZV2)*

4. Conclusions

We report a fragment growing of 2-(7-hydroxy-2-oxo-2H-chromen-4-yl)acetic acid into 4 new derivatives through amide bond with different chloro-substituted benzylamines and (1H-benzo[d]imidazol-2-yl)methanamine. The results showed that chloro-substituted compounds **2a-c** significantly inhibited MCF-7 cell growth, while coumarin-benzimidazole hybrid **2d** is a specific HepG2 inhibitor. Docking studies of the most potent compound **2d** suggest its HepG2 antiproliferative activity could be mediated through multikinase inhibition of p38α, VEGFR2, and FGFR-1. This paves the way for discovering more potent compounds and mechanistic studies.

- ***Conflict of Interest:*** *Authors have no conflict of interest to declare.*
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TỔNG HỢP MỘT SỐ DẪN XUẤT COUMARIN MỚI VÀ ĐÁNH GIÁ HOẠT TÍNH CHỐNG UNG THƯ CỦA CHÚNG

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TÓM TẮT

2-(7-Hydroxy-2-oxo-2H-chromen-4-yl)acetic acid ***1*** *được chuyển hoá thành 4 dẫn xuất coumarin* ***2a-d*** *mới thông qua phản ứng ghép cặp amide. Các hợp chất amide này được sàng lọc hoạt tính chống ung thư bằng phương pháp MTT trên hai dòng tế bào ung thư MCF-7 và HepG2. Kết quả cho thấy hợp chất* ***2a-c*** *ức chế đáng kể tế bào MCF-7 ở nồng độ 40 µM (29-38%) trong khi hợp chất* ***2d*** *là chất ức chế HepG2 mạnh với giá trị* IC_{50} *là 21 µM. Thí nghiệm in silico của hợp chất tiềm năng* ***2d*** *cho thấy khả năng chống tăng sinh tế bào HepG2 có thể được thực hiện thông qua sự ức chế đồng loạt nhiều men kinase p38α, VEGFR2 và FGFR-1.*

Từ khoá**:** 2-(7-hydroxy-2-oxo-2H-chromen-4-yl)acetic acid; phản ứng ghép cặp amide; hoạt tính chống ung thư; MCF-7; HepG2; molecular docking