Science & Technology Development Journal, 24(4):2141-2145

Open Access Full Text Article

Research article

Synthesis of New Isoxazole Analogs of Curcuminoid

Vo Thi Nga, Le Thanh Huy, Hoang Minh Hao*

Use your smartphone to scan this QR code and download this article

ABSTRACT

Introduction: Structure-activity relationship analysis demonstrated that the β-diketone moiety present in the curcumin skeleton is necessary for biological activities. Structural modifications on the pharmacophores can be envisioned as a strategy to afford novel analogs possessing promising biological activities. Curcumin-based analogs containing an isoxazole ring have been synthesized and showed inhibitory activity against cancer cell lines. **Methods:** In this respect, an isoxazole cyclization of the free 1,3-diketone group in curcuminoids (**1**-**7**) bearing -OH/-OCH_3/-F groups in aromatic rings with hydroxylamine hydrochloride was performed in acetic acid as solvent and catalyst to afford isoxazole-containing curcuminoids. NMR and MS measurements were used to interpret the chemical structures of synthesized compounds. **Results:** Seven isoxazole analogs of curcuminoids (**1a**-**7a**) were synthesized in yields of 30-61%, and their chemical structures were elucidated by NMR and MS spectra. Five new compounds (**3a-7a**) were reported for the first time among synthesized structures. **Conclusion:** This work demonstrated the synthesis of five novel isoxazole-containing curcuminoids (**3a**-**7a**), along with two known ones (**1a**, **2a**).

Key words: Curcuminoid, isoxazole curcuminoid, β-diketone, isoxazole cyclization

INTRODUCTION

Natural products, secondary metabolites derived from natural sources have been demonstrated as a source of potential drug leads[1,2]. Curcumin (**1**), a major constituent of *Curcuma longa* L. exhibited several interesting biological activities[3]. Therefore, curcumin has been found to be a natural lead for the development of potentially new drug candidates. However, the clinical application of curcumin has been limited in the body due to its poor solubility and rapid metabolism[4]. Structure-activity relationship (SAR) studies reported that the substituents in the aromatic ring and the β-diketone moiety present in curcumin are responsible for biological responses and kinetic stability. In this respect, several curcumin analogs have been developed from the curcumin skeleton through chemical modifications on the 1,3-diketone group to optimize the curcumin scaffold[5–12].

Among numerous curcumin-based analogs, isoxazole curcuminoid constituting a five-membered heterocycle with one nitrogen atom and one oxygen atom at adjacent position exhibited a highly potent multidrug-resistant anti-mycobacterial activity[5], increased growth inhibitory activity against cancer cell lines, and anti-tumor activity[8–14]. In the present work, we report the synthesis of isoxazole curcuminoids by converting the β-diketone moiety into its corresponding isoxazole framework (Scheme 1).

MATERIALS AND METHODS

Chemicals

Curcuminoids (**1**-**7**) were synthesized according to our previous work, and their NMR/MS data have been described in our early report[7]. The free 1,3-dicarbonyl curcuminoids were used as starting materials for isoxazole cyclization. Hydroxylamine hydrochloride ($NH_2OH.HCl$, 99%, ACROS Organics), acetic acid (100%, Merck), dichloromethane (DCM, 99.8%, JTBaker, USA), *n*-hexane (CH, 98.5%, JTBaker, USA) and ethyl acetate (EA, 98.5%, JTBaker, USA) were used as received without further purification.

General synthetic procedure for isoxazole curcuminoids (1a-7a)

Isoxazole curcuminoids (**1a**-**7a**) were synthesized by following a procedure published in the literature[13,14]. Curcuminoid (0.6 mmol) from our previous work and hydroxylamine hydrochloride (1.2 mmol) was transferred into a 50 mL round-bottom flask and dissolved in 10 mL glacial acetic acid. The solution was stirred at 80 ^oC for 8-24 h. Careful monitoring via thin-layer chromatography (TLC) was necessary to stop the reaction in time. The resulting product was neutralized by 20.0 mL saturated $NaHCO_3$ and extracted with DCM (3 × 40 mL). The combined organic phase was dried over anhydrous Na_2SO_4. Solvent was removed

Faculty of Chemical and Food Technology, Ho Chi Minh City University of Technology and Education, 01 Vo Van Ngan, Linh Chieu Ward, Thu Duc City, Ho Chi Minh City, Vietnam

Correspondence

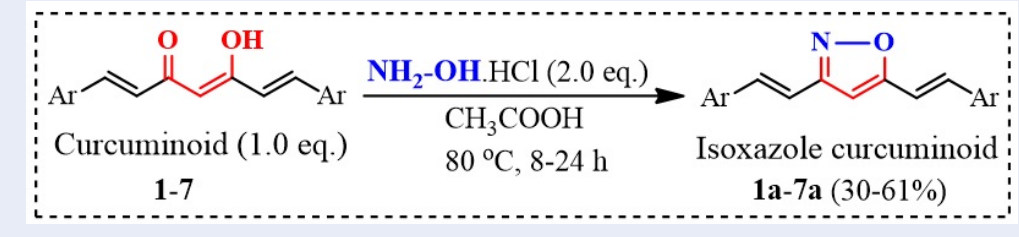
Hoang Minh Hao, Email: haohm@hcmute.edu.vn

History

- Received: 2021-09-09
- Accepted: 2021-12-08
- Published: 2021-12-18

DOI : 10.32508/stdj.v24i4.3824

Cite this article : Nga V T, Huy L T, Hao H M. **Synthesis of New Isoxazole Analogs of Curcuminoid**. *Sci. Tech. Dev. J.;* 24(4):2141-2145.



Scheme 1: Synthesis of isoxazole-containing curcuminoids (**1a-7a**) from free 1,3-dicarbonyl curcuminoids (**1-7**).

by using a rotary evaporator. The pure isoxazole curcuminoids were obtained by using flash column chromatography (CC) (SiO_2, using a gradient of CH/EA = 1:0*7:3).

Analytical method

CC was performed on Merck silica gel (0.040-0.063 mm). TLC was carried out on precoated silica gel 60 F254 plates from Merck (Germany), and sample spots on TLC were detected by UV light at λ = 254 and 365 nm. Melting points (m.p) of pure products were determined by the M5000 melting point meter (Germany) with a heating rate of 2.0 ^{o}C/min. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance (500, 600 MHz (^{1}H), 125, 150 MHz (^{13}C)). Mass spectrometry (MS) measurements were performed on an Agilent 1200 series LC-MSD.

RESULTS

The isoxazole cyclization of the β-diketone group afforded five new isoxazole-containing curcuminoids (**3a-7a**), along with two known analogs (**1a**, **2a**) [15,16] in a 30-61% yield. Chemical structures of synthesized compounds (Figure 1) were assigned by NMR and MS spectra.

4,4'-((1*E*,1'*E*)-isoxazole-3,5-diylbis(ethene-2,1-diyl))bis(2-methoxyphenol) (1a): Yield 44% (96.4 mg), white solid, $C_{21}H_{19}NO_5$ [365.13 g/mol]; R_f = 0.34 (CH/EA = 1:1); m.p. 163.6 ^{o}C (lit.[15] 162 °C) ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): δ = 3.95 (s, OCH_3, 3H), 3.96 (s, OCH_3, 3H), 5.76 (s, Ar-OH, 1H), 5.79 (s, Ar-OH, 1H), 6.41 (s, H_4, 1H), 6.79 (d, H_6, ^3J (H,H) = 16.0 Hz, 1H), 6.91 (d, $H_{5''}$, ^3J (H,H) = 8.0 Hz, 1H), 6.92 (d, $H_{5'}$, ^3J (H,H) = 8.0 Hz, 1H), 6.96 (d, H_2, ^3J (H,H) = 16.5 Hz, 1H), 7.01 (d, $H_{2''}$, ^4J (H,H) = 2.0 Hz, 1H), 7.02 (d, $H_{2'}$, ^4J (H,H) = 2.0 Hz, 1H), 7.06-7.08 (dd, $H_{6'',6'}$, ^3J (H,H) = 8.0 Hz, ^4J (H,H) = 2.0 Hz, 2H), 7.08 (d, H_7, ^3J (H,H) = 16.5 Hz, 1H), 7.26 (d, H_1, ^3J (H,H) = 16.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$, ppm): δ = 55.9 (OCH_3), 55.9 (OCH_3), 97.6 (C_4), 108.2 ($C_{2''}$), 108.8 ($C_{2'}$), 110.9 ($C_{5''}$), 113.8 ($C_{5'}$), 114.6 ($C_{6''}$), 114.8 ($C_{6'}$), 121.5 (C_2), 121.6 (C_6), 128.2 ($C_{1''}$), 128.5 ($C_{1'}$), 134.8 (C_1), 135.6 (C_7), 146.7-147.0 ($C_{4',4''}$, $C_{3',3''}$, 4C), 162.2 (C_5), 168.5 (C_3). ESI-MS *m/z* calc for $[M+H]^+$: 366.14; found: 366.00.

3,5-di((*E*)-styryl)isoxazole (2a): Yield 56% (91.7 mg), white solid, $C_{19}H_{15}NO$ [273.12 g/mol]; R_f = 0.43 (CH/EA = 9:1); m.p. 168.3 ^{o}C ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): 7.03 (s, H_4, 1H), 7.23 (d, H_6, ^3J (H,H) = 16.5 Hz, 1H), 7.26 (d, H_2, ^3J (H,H) = 16.5 Hz, 2H), 7.30 – 7.38 (m, $H_{2',2''}$, 2H), 7.38 – 7.46 (m, $H_{1,7,6',6'',4',4''}$, 6H), 7.67 (dd, $H_{3',3'',5',5''}$, ^{3} J (H,H) = 7.5 Hz, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$, ppm): 99.2 (C_4), 113.3 (C_6), 115.6 (C_2), 127.1 ($C_{2',6'}$, 2C), 127.2 ($C_{2'',6''}$, 2C), 128.8 ($C_{4'}$), 128.8 ($C_{4''}$), 128.9 ($C_{3',5'}$, 2C), 129.1 ($C_{3'',5''}$, 2C), 134.4 ($C_{1'}$), 135.3 ($C_{1''}$), 135.6 (C_1), 136.2 (C_7), 161.9 (C_5), 168.0 (C_3). ESI-MS *m/z* calc for $[M+H]^+$: 274.13; found: 273.90.

3,5-bis((*E*)-4-methoxystyryl)isoxazole (3a): Yield 48% (95.9 mg), yellow solid, $C_{21}H_{19}NO_3$ [333.14 g/mol]; R_f = 0.28 (CH/EA = 4:1); m.p. 172.2 ^{o}C ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): 3.83 (s, OCH_3, 3H), 3.84 (s, OCH_3, 3H), 6.41 (s, H_4, 1H), 6.80 (d, H_6, ^3J (H,H) = 16.5 Hz, 1H), 6.90 (d, $H_{3',3'',5',5''}$, ^3J (H,H) = 8.0 Hz, 4H), 6.97 (d, H_2, ^3J (H,H) = 17.0 Hz, 1H), 7.10 (d, H_7,^3J (H,H) = 16.5 Hz, 1H), 7.28 (d, H_1,^3J (H,H) = 16.0 Hz, 1H), 7.45 (d, $H_{2',2'',6',6''}$, ^{3} J (H,H) = 9.0 Hz, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$, ppm): 55.3 (OCH_3), 55.4 (OCH_3), 97.7 (C_4), 111.0 (C_6), 114.0 (C_2), 114.3 ($C_{3',5'}$, 2C), 114.4 ($C_{3'',5''}$, 2C), 128.3 ($C_{2',6'}$, 2C), 128.4 ($C_{1'}$), 128.5 ($C_{2'',6''}$, 2C), 128.7 ($C_{1''}$), 134.4 (C_1), 135.2 (C_7), 160.2 ($C_{4'}$), 160.5 ($C_{4''}$), 162.2 (C_5), 168.6 (C_3). ESI-MS *m/z* calc for $[M+H]^+$: 334.15 found: 333.90.

3,5-bis((*E*)-2-fluorostyryl)isoxazole (4a): Yield 61% (113.1 mg), yellow solid, $C_{19}H_{13}F_2NO$ [309.10 g/mol]; R_f = 0.59 (CH/EA = 9/1); m.p. 120.1 ^{o}C ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): 6.57 (s, H_4, 1H), 7.07 (d, H_6, ^3J (H,H) = 16.5 Hz, 1H), 7.07-7.12 (m, $H_{3',3''}$,

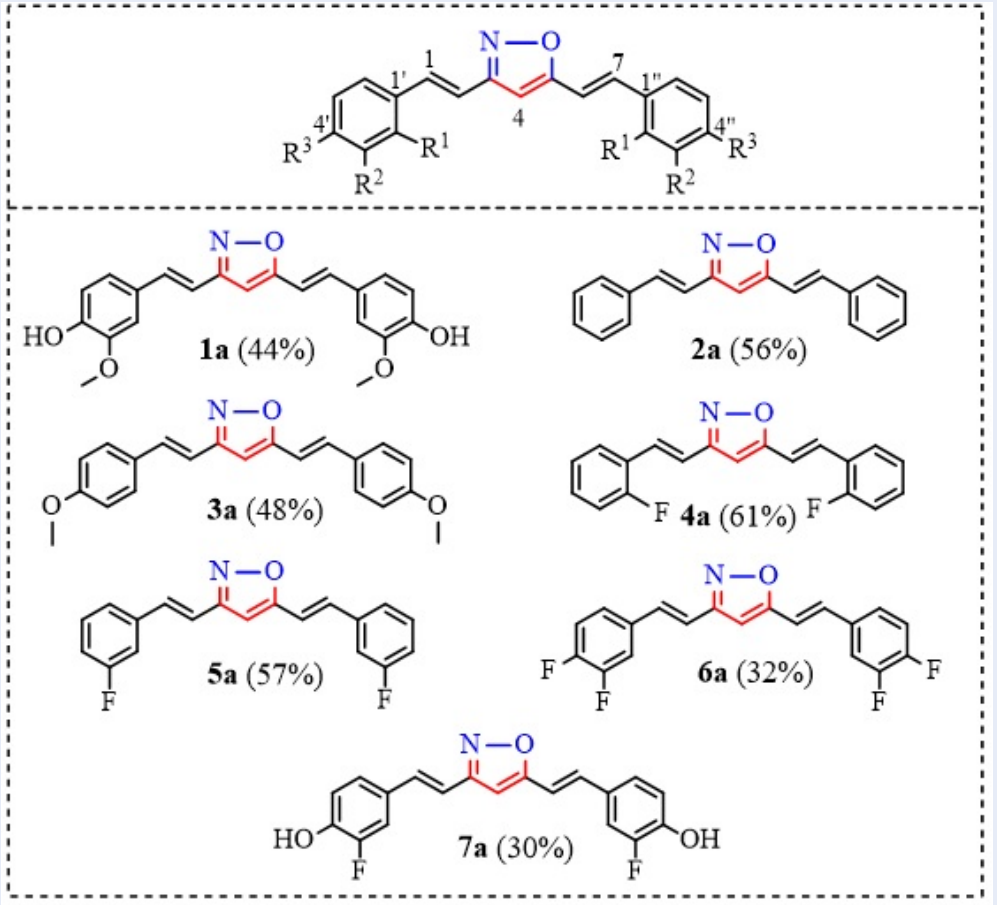


Figure 1: Chemical structures and synthesis yields of synthesized isoxazole curcuminoids (**1a**-**7a**).

2H), 7.15-7.19 (td, $H_{5',5''}$, ^3J (H,H) = 7.5 Hz,^4J (H,H) = 1.0 Hz, 2H), 7.20 (d, H_2,^3J (H,H) = 16.5 Hz, 1H); 7.28-7.32 (m, $H_{6',6''}$, 2H), 7.33 (d, H_7, ^3J (H,H) = 16.5 Hz, 1H) 7.46 (d, H_1, ^3J (H,H) = 17.0 Hz, 1H); 7.53-7.63 (td, $H_{4',4''}$, ^3J (H,H) = 7.5 Hz, ^4J (H,H) = 1.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$, ppm): 98.9 (C_4), 115.5 (C_6), 115.9 ($C_{3''}$), 116.0 ($C_{3'}$), 118.3 (C_2), 123.5 ($C_{1''}$, 123.7($C_{1'}$), 124.4 ($C_{5',5''}$), 127.4 ($C_{4'}$), 127.8 (C_1), 128.1 (C_7), 128.2 ($C_{4''}$) , 130.2 ($C_{6''}$), 130.4 ($C_{6'}$), 159.6-161.9 ($C_{2',2''}$, 2C), 162.1 (C_5), 168.3 (C_3). ESI-MS *m/z* calc for $[M+H]^+$: 310.11; found: 309.90.

3,5-bis((*E*)-3-fluorostyryl)isoxazole (5a): Yield 57% (105.7 mg), yellow solid, $C_{19}H_{13}F_2NO$ [309.10 g/mol]; R_f = 0.26 (CH/EA = 9:1); m.p. 157.8 ^oC ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): 6.50 (s, H_4, 1H), 6.94 (d, H_6, ^3J(H,H) = 16.5 Hz, 1H), 7.01 (m, $H_{4',4''}$, 2H), 7.13 (d, H_2, ^3J(H,H) = 16.5 Hz, 1H), 7.14 (d, H_7, ^3J(H,H) = 16.5 Hz, 1H), 7.21 (d, $H_{2''}$, ^4J (H,H) = 1.5 Hz, 1H), 7.23 (d, $H_{2'}$,^4J (H,H) = 1.5 Hz, 1H), 7.28 (d, $H_{6',6''}$, ^3J (H,H) = 8.0 Hz, 2H), 7.31 (d, H_1, ^3J(H,H) = 17.0 Hz, 1H), 7.33 (m, $H_{5',5''}$, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$, ppm): 99.1 (C_4), 113.3 – 113.5 ($C_{2',2''}$, 2C), 114.1 (C_6), 115.7 – 116.1 ($C_{4',4''}$, 2C), 117.4 (C_2), 122.8 – 123.2 ($C_{6',6''}$, 2C), 130.3 – 130.4 ($C_{5',5''}$, 2C), 133.8 (C_7), 134.6 (C_1), 138.1 ($C_{1',1''}$, 2C), 161.7 ($C_{3''}$), 162.2 ($C_{3'}$), 164.1 (C_5), 167.9 (C_3). ESI-MS *m/z* calc for $[M+H]^+$: 310.11; found: 309.90.

3,5-bis((*E*)-3,4-difluorostyryl)isoxazole (6a): Yield 32% (66.3 mg), yellow solid, $C_{19}H_{11}F_4NO$ [345.08 g/mol]; R_f = 0.45 (CH/EA = 9:1); m.p. 164.7 ^oC ^{1}H-NMR (500 MHz, $CDCl_3$, ppm): 6.47 (s, H_4, 1H), 6.85 (d, H_6, ^3J(H,H) = 16.5 Hz, 1H), 7.01 (d, H_2, ^3J(H,H) = 16.5 Hz, 1H), 7.08 (d, H_7, ^3J(H,H) = 16.5 Hz, 1H), 7.17-7.23 (m, $H_{2',2'',5',5''}$, 4H), 7.29 (d, H_1, ^3J(H,H) = 15.5 Hz, 1H), 7.32 (m, $H_{6',6''}$,2H); ^{13}C-NMR (125 MHz, $CDCl_3$, ppm): 99.1 (C_4), 113.8 (C_6), 115.2 – 115.4 ($C_{6',6''}$, 2C), 117.1 (C_2), 117.7 – 117.9 ($C_{2',2''}$, 2C), 123.3 ($C_{5''}$), 123.8 ($C_{5'}$), 124.8 ($C_{1',1''}$, 2C), 132.8 (C_1), 133.6 (C_7), 149.6 ($C_{3',3''}$), 151.7 ($C_{4',4''}$), 161.5 (C_5), 167.8 (C_3). ESI-MS *m/z* calc for $[M+H]^+$: 346.09; found: 345.80.

4,4'-((1*E*,1'*E*)-isoxazole-3,5-diylbis(ethene-2,1-diyl))bis(2-fluorophenol) (7a): Yield 30% (61.4 mg), yellow solid, $C_{19}H_{13}F_2NO_3$ [341.09 g/mol]; R_f = 0.25 (CH/EA = 7:3); m.p. 214.3 ^oC ^{1}H-NMR (600 MHz, $CDCl_3$, ppm): 6.37 (s, H_4, 1H), 6.71 (d, H_6, ^3J(H,H) = 16.2 Hz, 1H), 6.85 (d, H_2, ^3J(H,H) = 16.2 Hz, 1H), 6.91 (m, $H_{2',2''}$, 2H), 6.99 (d, H_7, ^3J(H,H) = 16.2 Hz, 1H), 7.07 (d, $H_{5',5''}$, ^3J(H,H) = 8.4 Hz, 2H), 7.15 (d, H_1, ^3J(H,H) = 16.8 Hz, 1H), 7.17 (m, $H_{6',6''}$, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$, ppm): 97.9 (C_4), 111.3 (C_6), 113.9 – 114.0 ($C_{6',6''}$, 2C), 114.2 (C_2), 118.1 – 118.2 ($C_{2',2''}$, 2C), 123.7 ($C_{5''}$), 124.0 ($C_{5'}$), 128.7-130.9 ($C_{1',1''}$, 2C), 133.9 (C_1), 134.7 (C_7), 145.8 ($C_{3',3''}$), 150.9 ($C_{4''}$), 152.5 ($C_{4'}$), 162.0 (C_5), 168.3 (C_3). ESI-MS *m/z* calc for $[M+H]^+$: 342.10; found: 341.90.

DISCUSSION

The isoxazole analogs (**1a**-**7a**) were prepared by treatment of free β-diketone curcuminoids (**1**-**7**) with hydroxylamine hydrochloride in acetic acid at 80 ^oC. Acetic acid here plays dual roles: as a solvent to dissolve reactants and catalysts for isoxazole cyclization. First, under acidic conditions, an oxime is generated via an acid-catalyzed mechanism, similar to the imine formation between a carbonyl group reacting with a primary amine[6,7]. Then, the protonation of the second carbonyl group is occurred rendering it more electrophilic. Then, the oxygen atom is sufficiently nucleophilic to attack a protonated carbonyl group directly to give an isoxazole ring.

The structures of the synthesized compounds were elucidated by ^{1}H- and ^{13}C-NMR, MS spectra. The ^{1}H-NMR spectra of isoxazole curcuminoids (**1a**-**7a**) exhibited a singlet (s, 1H) at δ ~ 5.8-6.5 ppm, which was assigned to the signal of proton bonded to the central carbon of a three-carbon pattern in isoxazole ring. The doublet signal ($^3J_{H-H}$ ~16.0 Hz) at 6.5-7.8 ppm is characteristic of *trans*-configuration in the seven-carbon chain of isoxazole analogs. Compared to respective mother structures, curcuminoids (**1**-**7**), the signal for carbonyl carbon (δ ~ 183 ppm)[7] disappeared and the imine bond (>C=N) formation was inferred from an incoming peak at δ ~ 167 ppm observed at ^{13}C NMR spectra, which confirmed the presence of isoxazole ring.

CONCLUSIONS

In summary, we reported a synthetic procedure that enables access to isoxazole-containing curcuminoids. Curcuminoids possessing a free 1,3-dicarbonyl group underwent an isoxazole cyclization with hydroxylamine hydrochloride using acetic acid as solvent and catalyst to yield seven isoxazole curcuminoids (**1a**-**7a**). The isolated yields of the isoxazole cyclization are in the range of 30 to 61%. NMR spectra assigned the synthesized structures in combination with ESI-MS measurements. With the results shown above, we could, for the first time, demonstrate the synthesis of five novel isoxazole curcuminoids (**3a**-**7a**), along with two known compounds (**1a**, **2a**).

LIST OF ABBREVIATIONS

CC: Column chromatography
CH: *n*-Hexane
DCM: Dichloromethane
d: Doublet
dd: Doublet-doublet
EA: Ethyl acetate
HSQC: Heteronuclear single quantum correlation
lit: Literature
m: multiplet
m.p: melting point
MS: Mass spectrometry
NMR: Nuclear magnetic resonance
td: Triplet-doublet
TLC: Thin layer chromatography
UV: Ultraviolet

COMPETING INTERESTS

The authors declare that they have no competing interests.

SUPPORTING INFORMATION

Supporting Information contains ^{1}H, ^{13}C-NMR, HSQC, and MS spectra of the isoxazole containing curcuminoids (**1a**-**7a**).

ACKNOWLEDGMENT

This work belongs to the project grant No: B2020-SPK-05 funded by the Ministry of Education and Training and hosted by Ho Chi Minh City University of Technology and Education, Vietnam.

AUTHOR CONTRIBUTIONS

Vo Thi Nga: ^{1}H-, ^{13}C-NMR and MS analysis, writing-original draft preparation; Le Thanh Huy: laboratory work-up, writing-original draft preparation. Hoang Minh Hao: conceptualization, supervision, writing-review and editing. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Dias DA, Urban S, Roessner U. A Historical Overview of Natural Products in Drug Discovery. Metabolites 2012;2:303-36;Available from: https://doi.org/10.3390/metabo2020303.
2. Bernardini S, Tiezzi A, Laghezza Masci V, Ovidi E. Natural products for human health: an historical overview of the drug discovery approaches. Nat Prod Res 2018;32:1926-50;Available from: https://doi.org/10.1080/14786419.2017.1356838.
3. Amalraj A, Pius A, Gopi S, Gopi S. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives - A review. J Tradit Complement Med 2017;7:205-33;Available from: https://doi.org/10.1016/j.jtcme.2016.05.005.
4. Nagahama K, Utsumi T, Kumano T, Maekawa S, Oyama N, Kawakami J. Discovery of a new function of curcumin which enhances its anticancer therapeutic potency. Sci Rep 2016;6;Available from: https://doi.org/10.1038/srep30962.
5. Changtam C, Hongmanee P, Suksamrarn A. Isoxazole analogs of curcuminoids with highly potent multidrug-resistant anti-mycobacterial activity. Eur J Med Chem 2010;45:4446-57;Available from: https://doi.org/10.1016/j.ejmech.2010.07.003.
6. Theppawong A, Van de Walle T, Grootaert C, Van Hecke K, Catry N, Desmet T, et al. Synthesis of Non-Symmetrical Nitrogen-Containing Curcuminoids in the Pursuit of New Anticancer Candidates. ChemistryOpen 2019;8:236-47;Available from: https://doi.org/10.1002/open.201800287.
7. Pham VTB, Nguyen TV, Nguyen HV, Nguyen TT, Hoang HM. Curcuminoids versus Pyrazole-Modified Analogues: Synthesis and Cytotoxicity against HepG2 Cancer Cell Line. ChemistrySelect 2020;5:11681-4;Available from: https://doi.org/10.1002/slct.202003003.
8. Das J, Pany S, Panchal S, Majhi A, Rahman GM. Binding of isoxazole and pyrazole derivatives of curcumin with the activator binding domain of novel protein kinase C. Bioorg Med Chem 2011;19:6196-202;Available from: https://doi.org/10.1016/j.bmc.2011.09.011.
9. Simoni D, Rizzi M, Rondanin R, Baruchello R, Marchetti P, Invidiata FP, et al. Anti-tumor effects of curcumin and structurally β-diketone modified analogs on multidrug resistant cancer cells. Bioorg Med Chem Lett 2008;18:845-9;Available from: https://doi.org/10.1016/j.bmcl.2007.11.021.
10. Amolins MW, Peterson LB, Blagg BSJ. Synthesis and evaluation of electron-rich curcumin analogs. Bioorg Med Chem 2009;17:360-7;Available from: https://doi.org/10.1016/j.bmc.2008.10.057.
11. Phan THA, Lê XT, Trần TVH, Trần VS. Tổng hợp và xác định hoạt tính sinh học của các dẫn xuất isoxazol, pyrazol và phenylpyrazol curcumin. Vietnam J Chem 2009;47:1-6;.
12. Phan THA, Lê XT, Trần TVH, Trần VS. Synthesis and biological activities of two novel curcumin derivatives: 2-hydrozinobenzothiazolcurcumin and 2,4-difluorophenylhydrazinocurcumin. Vietnam J Sci Technol 2010;48:192-299;.
13. Shim JS, Kim DH, Jung HJ, Kim JH, Lim D, Lee S-K, et al. Hydrazinocurcumin, a novel synthetic curcumin derivative, is a potent inhibitor of endothelial cell proliferation. Bioorg Med Chem 2002;10:2987-92;Available from: https://doi.org/10.1016/S0968-0896(02)00129-3.
14. Selvam C, Jachak SM, Thilagavathi R, Chakraborti AsitK. Design, synthesis, biological evaluation and molecular docking of curcumin analogs as antioxidant, cyclooxygenase inhibitory and anti-inflammatory agents. Bioorg Med Chem Lett 2005;15:1793-7;Available from: https://doi.org/10.1016/j.bmcl.2005.02.039.
15. Mishra S, Karmodiya K, Surolia N, Surolia A. Synthesis and exploration of novel curcumin analogs as anti-malarial agents. Bioorg Med Chem 2008;16:2894-902;Available from: https://doi.org/10.1016/j.bmc.2007.12.054.
16. Hahnvajanawong V. Reductive ring opening of 3,5-bis(2-arylethenyl)isoxazoles with molybdenum hexacarbonyl: A novel route to symmetrical and unsymmetrical curcumin derivatives. Orient J Chem 2016;32:127-35;Available from: https://doi.org/10.13005/ojc/320113.