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by Hariyanti Uploded By Wieda

Submission date: 06-Apr-2022 10:03AM (UTC+0700)

Submission ID: 1803017504

File name: HARIYANTI_FARMASI_JAPS1_-_Monev_2021_Dr_appt_Hariyanti_M.Si..pdf (347.03K)

Word count: 4384

Character count: 22059



Synthesis and *in vitro* cytotoxic activity of novel indazole analogues of curcumin against MCF-7, HeLa, WiDr, and vero cell lines

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ARTICLE INFO

Received on: 01/08/2021
 Accepted on: 01/12/2021
 Available Online: 05/04/2022

Keywords:

Curcumin indazole analogs, cytotoxicity, selectivity, MCF-7, HeLa, WiDr, vero.

ABSTRACT

We prepared six novel curcumin indazole analogs and confirmed their structures by Fourier transform infrared, nuclear magnetic resonance, and mass spectra. Subsequently, their cytotoxicity was tested using the Michigan Cancer Foundation (MCF-7) proliferation assay against the Michigan Cancer Foundation (MCF-7), HeLa, WiDr, and vero cell lines. This study found that the compounds we prepared were more active against WiDr than HeLa and MCF-7. The activity of 3b, 3c, 3d, and 5a against WiDr (colorectal carcinoma) cells was higher than curcumin and tamoxifen. Their selectivity index (SI) indicated that several synthesized compounds showed more selectivity (SI value > 2) than positive controls tamoxifen and doxorubicin (SI value < 2.00). Three compounds (3a, 3b, and 3c) showed high SI against WiDr cells (3.74, 5.27, and 4.39, respectively). Compound 3b produced the highest cytotoxic activity, especially against WiDr cells (IC₅₀ = 27.20 μM) with excellent selectivity (SI = 5.27). Therefore, the compound should be further developed as an anticancer agent for colorectal carcinoma.

INTRODUCTION

The annual report in 2020 indicated a high prevalence of breast cancer, cervical cancer, and colorectal cancer worldwide (American Cancer Society, 2020). The development of monocarbonyl analogs of curcumin to be tetrahydro-indazole structures showed good antioxidant and antitumor against Michigan Cancer Foundation (MCF-7), WI38, Hep G2, and vero cells (Bayomi *et al.*, 2015; Bayomi *et al.*, 2013). Indazole compounds are scarcely found in nature, generally prepared by organic synthesis. The formation of the indazole ring significantly improved the biological activity of the molecules (Gaikwad *et al.*, 2015; Plescia *et al.*, 2010; Shrivastava *et al.*, 2016; Thangadurai *et al.*, 2012; Thirupalu *et al.*, 2014; Zhang *et al.*, 2018). Recently, *in silico* studies using pharmacophore modeling and docking methods indicated that several asymmetric hexahydro-2H-

indazoles were potentially active as ERα inhibitors (Hariyanti *et al.*, 2021). Therefore, we prepared six novel curcumin indazole analogs and evaluated them for their cytotoxicity against breast (MCF-7), cervical (HeLa), and colorectal (WiDr) cancer cells. To evaluate their selectivity, the compounds' cytotoxicity was also tested against normal vero cells.

MATERIALS AND METHODS

General procedures

All chemicals (E. Merck, Germany, or Sigma-Aldrich, USA) were obtained commercially. Purity tests and reactions monitoring were carried out using the thin layer chromatography procedure. Melting points (m.p.) were assessed by the melting point instrument (Bibby Sterilin, UK) and were not corrected. Infrared (IR) spectra were scanned in a Kalium Bromide mixture on the Shimadzu FTIR-8400S Spectrometer (Japan). Nuclear magnetic resonance (NMR) spectra were run in a CDCl₃ solution on a JEOL JNM 500 Spectrometer (Peabody, USA). Mass spectra were found using electrospray ionization (+) mode UNIFI-Waters Liquid Chromatography-Mass Spectrometry (MS/MS) (USA). 3-(4-Methoxyphenyl)/3,4-dimethoxyphenyl)-3,3a,4,5,6,7-

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hexahydro-2H-indazole (**1a-b**), cyclovalone (**4a**), and 2,6-bis-[(E)-4-hydroxybenzylidene]cyclohexanone (**4b**) used as starting materials were prepared according to the reported method (Hayun *et al.*, 2017; Minu *et al.*, 2009; Rahmawati *et al.*, 2020).

Preparation of curcumin tetrahydro-indazole analogs (**3a-d**)

The preparation of **3a** with a yield of 61.0% has been reported previously (Hariyanti *et al.*, 2020). Preparation of compounds **3b-d** was carried out according to the procedures of compound **3a** by reacting **1b** that replaced **1a** with *p*-methoxybenzaldehyde, vanillin, or 3,4-dimethoxybenzaldehyde (**2a-c**).

4-[(7E)-3-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydro-3aH-indazol-7-ylidene]methyl-2-methoxyphenol (**3b**)

Pale yellow powder, yield 35.2%, and m.p. 240°C–242°C. FT-IR, ν/cm^{-1} : 3,217 (OH), 3,059 (C-H Ar stretch), 2,956 (C-H Al stretch), 1,582 (C=N), 1,519 (C=C ring Ar stretch), 1,460 (C-H Al bend), 1,253 (C-O-Ar asymmetrical stretch), and 1,162 (C-O-Ar symmetrical stretch). ¹H-NMR, δ/ppm : 7.24 (d, 1H, *J* 3 Hz), 6.94 (d, 0.2H, *J* 8 Hz), 7.17 (dd, 0.1H, *J* 8 Hz), 6.89 (dd, 0.2H, *J* 8 Hz), 3.85 (t, 0.1H), 3.91 (d, 6H), 3.92 (s, 3H), 2.81 (m, 0.4H), 1.97 (m, 0.2H). ¹³C-NMR, δ/ppm : 149.35 (1C), 149.21 (1C), 148.64 (1C), 148.36 (1C), 145.53 (1C), 144.13 (1C); 129.9 and 114.8 (C=C_{ethylene}), 1,122.4 (2C_{Ar}); 123.9, 119.9, 112.8, 0, 111.1, 0, 110.9, and 110.2 (1C_{Ar}, respectively); 56.0, 55.1, and 55.06 (1C_{O-Me}, respectively); 227.2, 31.2, 24.2, and 22.2 (1C_{Ar}, respectively). HR-MS: *m/z* 393.18003 [M+H]⁺; calculated for C₂₃H₂₄N₂O₄ = 392.17361 [M]; Error = - 2.3 ppm.

(7E)-3-(3,4-dimethoxyphenyl)-7-(4-methoxybenzylidene)-4,5,6,7-tetrahydro-3aH-indazole (**3c**)

Pale yellow powder, yield 74.3%, and m.p. 244°C–246°C. FT-IR, ν/cm^{-1} : 3,020 (C-H Ar stretch), 2,920 (C-H Al stretch), 1,561 (C=N), 1,519 (C=C ring Ar stretch), 1,460 (C-H Al bend), 1,261 (C-O-Ar asymmetrical stretch), and 1,136 (C-O-Ar symmetrical stretch). ¹H-NMR, δ/ppm : 7.23 (d, 1H, *J* 1.5 Hz), 6.89 (d, 2H, *J* 9 Hz), 7.17 (dd, 1H, *J* 8 Hz), 6.97 (s, 1H), 6.94 (dd, 1H, *J* 8 Hz), 6.87 (d, 1H, *J* 8.5 Hz), 0.392 (s, 3H), 0.391 (d, 0.6H), 0.281 (m, 4H), 1.88 (m, 0.2H). ¹³C-NMR, δ/ppm : 149.22 (1C), 148.65 (1C), 148.29 (1C), 145.73 (1C), 144.02 (1C); 129.6 and 122.4 (C=C_{ethylene}); 126.2, 123.9, 119.9, 114.8, 112.8, 0, 111.2, 0, 111.1, 110.95, and 110.92 (1C_{Ar}, respectively); 56.1, 56.05, and 55.0 (1C_{O-Me}, respectively); 27.2, 31.2, 0.247, and 22.3 (1C_{Ar}, respectively). HR-MS: *m/z* 409.21152 [M+CH₃OH+H]⁺; calculated for C₂₃H₂₄N₂O₃ = 376.17896 [M]; Error = 0.3 ppm.

(7E)-3-(3,4-dimethoxyphenyl)-7-(3,4-dimethoxybenzylidene)-4,5,6,7-tetrahydro-3aH-indazole (**3d**)

Pale yellow powder, yield 56.1%, and m.p. 236°C–238°C. FT-IR, ν/cm^{-1} : 3,020 (C-H Ar stretch), 2,947 (C-H Al stretch), 1,591 (C=N), 1,514 (C=C ring Ar stretch), 1,450 (C-H Al bend), 1,255 (C-O-Ar asymmetrical stretch), and 1,142 (C-O-Ar symmetrical stretch). ¹H-NMR, δ/ppm : 6.88 (s, 2H), 7.19 (dd, 0.1H, *J* 8 Hz), 6.91 (s, 2H), 6.87 (s, 0.1H), 6.94 (dd, 2H, *J* 8 Hz), 2.93 (s, 3H), 0.392 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 2.81 (m, 4H), 1.88 (m, 2H). ¹³C-NMR, δ/ppm : 149.27 (1C), 148.94 (1C), 148.71 (1C), 148.16 (1C), 0.129.85 (1C), 0.128.0 (1C); 122.12 and 121.3

(C=C_{ethylene}); 119.42, 109.92, and 111.04 (2C_{Ar}, respectively); 112.66 and 111.28 (1C_{Ar}, respectively); 56.08 and 56.04 (2C_{O-Me}, respectively); 31.15, 27.24, 0.24, 8.1, and 22.38 (1C_{Ar}, respectively). HR-MS: *m/z* 407.19619 [M+H]⁺; calculated for C₂₄H₂₆N₂O₃ = 406.18926 [M]; Error = - 0.7 ppm.

Preparation of curcumin hexahydro-indazole analogs (**5a-b**)

Preparation of **5a-b** was carried out by mixing 10 mmol of the synthesized cyclovalone (**4a**) for **5a** and its *p*-hydroxy analog (**4b**) for **5b**, with 100 mmol hydrazine monohydrate in 10 ml of glacial acetic acid, refluxed at 120°C for 3 hours until completed reaction, added to crushed ice, filtered off till the suspension was obtained, and washed using cold water to afford the solid product. Recrystallization was done from a suitable solvent to provide the pure compound **5a-b**.

1-[(7E)-3-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxy-3-methoxybenzylidene)-3,3a,4,5,6,7-hexahydro-2H-indazol-2-yl]-ethan-1-one (**5a**)

Pale yellow powder, yield 23.7%, and m.p. 105°C–107°C. FT-IR, ν/cm^{-1} : 3,200–3,525 (OH), 3,059 (C-H Ar stretch), 2,956 (C-H Al stretch), 1,635 (C=O), 1,599 (C=N), 1,518 (C=C ring Ar stretch), 1,450 (C-H Al bend), 1,273 (C-O-Ar asymmetrical stretch), and 1,121 (C-O-Ar symmetrical stretch). ¹H-NMR, δ/ppm : 7.14 (s, 1H), 6.92 (d, 2H, *J* 2-Hz), 6.75 (d, 0.1H, *J* 2 Hz), 6.86 (s, 0.1H), 6.78 (dd, 1.1, *J* 8 Hz), 6.88 (d, 1H, *J* 8 Hz), 3.90 (d, 6H), 2.19 (s, 3H), 4.83 (d, 1H), 3.06 (d, 3.33), 2.39 (s, 2H), 2.32 (m, 1H), 2.43 (m, 1H), 2.96 (m, 1H), 1.94 (m, 2H). ¹³C-NMR, δ/ppm : 170.64 (1C_{C=O}), 159.08 (1C_{C=N}); 0.146.82, 0.146.38, 145.61, 145.06 (1C_{Ar-O}, respectively); 0.128.98 and 128.19 (C=C_{ethylene}); 134.11, 128.64, 123.47, 118.63, 114.86, 114.46, 112.38, and 108.48 (1C_{Ar}, respectively); 67.99 (1C_{C=N}); 57.43 and 56.08 (1C_{O-Me}, respectively); 38.96, 30.15, 29.06, 0.24, 49, and 22.49 (1C_{Ar}, respectively). HR-MS: *m/z* 423.19132 [M+H]⁺; calculated for C₂₄H₂₆N₂O₅ = 422.18417 [M]; Error = - 0.2 ppm.

1-[(7E)-3-(4-hydroxyphenyl)-7-(4-hydroxybenzylidene)-3,3a,4,5,6,7-hexahydro-2H-indazol-2-yl]-ethan-1-one (**5b**)

Pale yellow powder, yield 42.2%, and m.p. 146°C–148°C. FT-IR, ν/cm^{-1} : 3,200–3,500 (OH), 3,012 (C-H Ar stretch), 2,943 (C-H Al stretch), 1,647 (C=O), 1,579 (C=N), 1,512 (C=C ring Ar stretch), 1,450 (C-H Al bend), and 1,263 (C_{Ar}-O stretch). ¹H-NMR, δ/ppm : 6.74 (m, 0.1H, *J* 2 Hz), 7.19 (d, 0.1H, *J* 8 Hz), 6.91 (s, 0.1H), 6.84 (dd, 0.1H, *J* 6 Hz), 7.05 (m, 0.1H, *J* 8 Hz), 6.78 (dd, 2H, *J* 8 Hz), 2.13 (s, 3H), 4.07 (m, 0.1H), 3.06 (d, 0.1H), 2.72 (m, 0.2H), 2.0 (s, 0.1H), 1.8 (m, 0.1H), 1.21 (m, 2H). ¹³C-NMR, δ/ppm : 170.6 (1C_{C=O}), 159.97 (1C_{C=N}); 156.63 and 155.55 (1C_{Ar-O}, respectively); 0.114.16 and 0.115.20 (C=C_{ethylene}); 131.36, 130.71, 128.88, 128.12, 126.99, 121.35, 115.70, 115.63, 115.28 and 115.20 (1C_{Ar}, respectively); 67.43 (1C_{C=N}); 30.05, 29.76, 29.13, 27.20 and 24.67 (1C_{Ar}, respectively). HR-MS: *m/z* 363.17051 [M+H]⁺; calculated for C₂₃H₂₂N₂O₃ = 362.16304 [M]; Error = +0.8 ppm.

In vitro cytotoxicity

The prepared compounds were tested for cytotoxicity against MCF-7, HeLa, WiDr, and vero cell lines (American Type

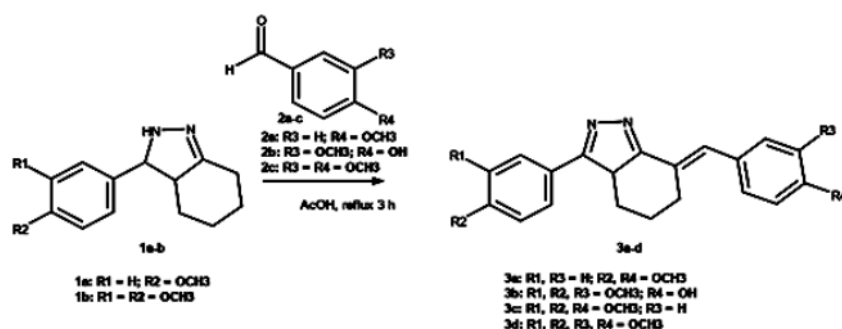


Figure 1. Preparation reaction of compounds 3a-d.

Culture Collection ([ATCC 15 TB-22, ATCC CCL-2, ATCC CCL-218, and ATCC CCL-81] using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay procedure (ATCC, 2020). Fetal bovine serum (5%), penicillin (100 U/ml), and streptomycin (100 µg/ml) were added to the 96-well plates containing cultivated cells in suitable growth media (Dulbecco's Modified Eagle's medium for WiDr and vero and Roswell Park Memorial Institute 1640 medium for MCF-7 and HeLa) and incubated for 24 hours until the culture reached 60% confluence. After replacing the growth media with new media, a series of concentrations (3.125–200 µg/ml) of test compounds were added. The cells were reincubated for 48 hours (the growth media were replaced every day with new media). After that, a 10 µl MTT solution was added and incubated for 4 hours; the media were discarded and the formazan formed in 700 µl ethanol was dissolved. Finally, the dissolved formazan was measured using an Enzyme-Linked Immunosorbent Assay reader at λ 595 nm (Bahuguna *et al.*, 2017). The IC_{50} values were determined from the curve of concentrations versus inhibitions (%). GraphPad Prism 8 v. 8.02 (www.graphpad.com) was used for analysis.

RESULTS AND DISCUSSION

Chemistry

Compounds 3b-d were prepared by condensation 1b-and-benzaldehyde derivatives-2a-c in a yield of 35.2%, 56.1%, and 74.3% (Fig 1), while compounds 5a-b were prepared by condensation symmetrical bis-benzylidene-cyclohexanone 4a-b and hydrazine monohydrate in a yield of 23.7% and 42.2% (Fig 2). The reactions were carried out in glacial acetic acid and

reflux temperature to afford novel products 4,5,6,7-tetrahydro-3aH-indazole (3b-d) and 2-acetylated-3,3a,4,5,6,7-hexahydro-2H-indazole (5a-b). The high temperature applied in the reaction most likely lowered the stability of the starting materials (Weerawatanakorn *et al.*, 2015), causing low yields. The application of mild conditions resulted in a higher yield; however, the products were different from those above (Bayomi *et al.*, 2015; Nuriev *et al.*, 2016; Raut *et al.*, 2020).

The prepared compound structures were elucidated based on spectral analysis. No sharp peak at 3,290–3,300 cm^{-1} appeared in the FT-IR spectra, indicating the disappearance of the amine group. The bands at 3,012–3,059 and 2,920–2,956 cm^{-1} confirmed the presence of C-H aromatic and aliphatic bonds. The C=N azole, C=C aromatic ring, and C-O-C ether bonds were observed at 1,732–1,734, 1,447–1,665, and 1,140–1,265 cm^{-1} , respectively. Broad peaks at 3,217 and 3,200–3,500 cm^{-1} indicated a hydroxyl group's presence in the 3b and 5a-b compounds, while a strong peak at 1,635–1,647 cm^{-1} confirmed the C=O of acetamide in the 5a and 5b compounds. In the 1H -NMR spectra, 7–9 protons for the two aromatic rings and one ethenyl chain appeared at 6–7 ppm, and a typical proton OCH_3 group appeared at around 3.8 ppm. Structural analysis was also supported by ^{13}C -NMR and the mass spectral data, which confirmed the suitability to the targeted compounds (MarvinSketch 20.8.0, 2020; Silverstein *et al.*, 2005).

In vitro cytotoxicity

The prepared compounds (3a-d and 5a-b) were evaluated for their cytotoxicity against four cell lines (MCF-7, HeLa, WiDr, and vero) using an MTT assay procedure. Curcumin, tamoxifen, and doxorubicin were used as a comparable compound

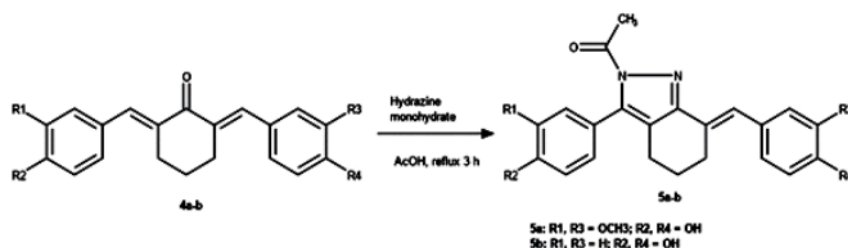


Figure 2. Preparation reaction of compounds 5a-b.

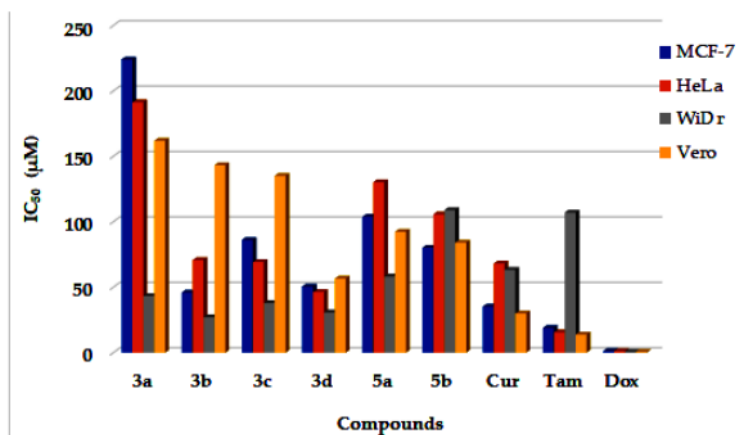


Figure 3. Cytotoxic activity (IC_{50} , μM) values for the prepared compounds, curcumin, tamoxifen, and doxorubicin on MCF-7, HeLa, WiDr, and vero cells, respectively.

Table 1. IC_{50} and SI values of the prepared compounds, curcumin, tamoxifen, and doxorubicin against MCF-7, HeLa, WiDr, and vero cell lines.

Compounds	IC_{50} (μM) ^a				SI ^b		
	HeLa	MCF-7	WiDr	Vero	HeLa	MCF-7	WiDr
3a	>100	>100	43.28	>100	<2	<2	3.74
3b	70.80	45.97	27.20	>100	2.02	3.12	5.27
3c	69.30	86.24	37.96	>100	<2	<2	4.39
3d	46.36	50.56	30.77	56.68	<2	<2	<2
5a	>100	>100	58.19	92.47	<2	<2	<2
5b	>100	80.26	>100	84.12	<2	<2	<2
Curcumin	68.09	35.30	63.41	30.01	<2	<2	<2
Tamoxifen	15.62	19.01	>100	13.91	<2	<2	<2
Doxorubicin	1.27	1.40	0.66	0.75	<2	<2	<2

^a: Mean of triplicate experiments; ^b: SI value = ratio between IC_{50} of vero (normal) cell and IC_{50} of cancer cell.

and positive control. Tamoxifen is a drug commonly used in breast cancer treatment, while doxorubicin is most useful for treating broad cancers such as leukemia, neuroblastoma, and ovary, lung, and breast cancer (Thorn *et al.*, 2011).

The results indicated that the prepared compounds had low to medium cytotoxic activity (Table 1 and Fig. 3). The IC_{50} values against MCF-7 cells were between 45.97 and 86.24 μM . Compound 3b had the highest cytotoxicity against MCF-7, but its activity was lower than curcumin. In contrast, tamoxifen and doxorubicin exhibited high cytotoxicity against MCF-7. The IC_{50} values against HeLa cells were between 46.36 and 100 μM . Compound 3d had the highest cytotoxicity against HeLa cells. The cytotoxicity of 3d was higher than that of curcumin but lower than tamoxifen and doxorubicin. The IC_{50} values against WiDr cells were between 27.20 and 58.19 μM . These results indicated that the synthesized compounds were more cytotoxic against WiDr than against HeLa and MCF-7 cells. -Compound 3b had the highest cytotoxicity against WiDr cells. This activity was better than curcumin and tamoxifen but lower than doxorubicin.

The cytotoxicity of compounds 3b, 3c, and 3d containing three and four methoxy groups was higher than compounds 3a, 5a, and 5b containing less than three methoxy groups. The results were in line with the finding previously reported in asymmetrical analogs of curcumin and 4-amino chalcone derivatives that the methoxy group's number and position influence cytotoxic activity (Prasetyaningrum *et al.*, 2018; Novilla *et al.*, 2019).

The IC_{50} values against vero cells were between 56.68 and >100 μM . These data indicated that most synthesized compounds had low toxicity against normal cells (Burger *et al.*, 2004; Schmitz *et al.*, 1993). Compound 3b showed high selectivity against MCF-7, HeLa, and WiDr cells [selectivity index, (SI) = 3.12, 2.02, and 5.27]. In contrast, compounds 3a and 3c only showed selectivity against WiDr cells (SI = 3.74 and 4.39). The selectivity of these compounds was higher than curcumin and the positive controls (tamoxifen and doxorubicin). The compound with an SI less than two indicates general toxicity. The higher the SI, the more selective the compound (Burger *et al.*, 2004; Badisa *et al.*,

2009; Kurnia *et al.*, 2019). The IC_{50} value of curcumin against MCF-7 cells was 35.03 μ M, whereas in a previous study it was 8.62 μ M (Li *et al.*, 2015). This difference may be due to the different methods used for the testing or different laboratory conditions. The resistance factor also affects the sensitivity of the drug to cells.

CONCLUSION

A series of six curcumin indazole analogs have been prepared. All the compounds showed low to moderate cytotoxicity against MCF-7, HeLa, and WiDr cells. Compounds **3b** exhibited the greatest cytotoxicity, especially against WiDr cells with excellent selectivity. The compound should be further developed as a cytotoxic agent for colorectal adenocarcinoma.

ACKNOWLEDGMENTS

The authors are grateful to the Chemical Research Center, LIPI, Tangerang, Indonesia, for NMR and MS measurements.

CONFLICT OF INTEREST

The authors confirm no conflicts of interest between the authors.

FUNDING

This research and APC were supported by the Ministry of Research and Technology/ BRIN, RI, 2020 (Assignment Agreement No. NKB-0373/UN2.RST/HKP.05.00/2020).

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

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How to cite this article:

Hariyanti H, Yanuar A, Kusmardi K, Hayun H. Synthesis and in vitro cytotoxic activity of novel indazole analogues of curcumin against MCF-7, HeLa, WiDr, and vero cell lines. *J Appl Pharm Sci*, 2022; 12(04):179–184.

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