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Evaluating the effect of dopamine-geldanamycin hybrids on anticancer activity

Thongchai Taechowisan[1*], Tipparat Samsawat[1], Chanjira Jaramornburapong[2], Weerachai Phutdhawong[3], Waya S. Phutdhawong[2]

[1]Department of Microbiology, Silpakorn University, Nakhon Pathom, Thailand.
[2]Department of Chemistry, Faculty of Science, Silpakorn University, Nakhon Pathom, Thailand.
[3]Department of Chemistry, Faculty of Liberal Arts and Science, Kasetsart University, Nakhon Pathom, Thailand.

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ABSTRACT

Geldanamycin (GDM) is an antibiotic isolated from *Streptomyces zerumbet* W14 that specifically targets and deactivates heat shock protein 90 (Hsp90), directed to the functional protein deficiency. The utilization management of GDM has been *limited* by its poor water solubility and hepatotoxicity. Five new dopamine-geldanamycin hybrids (DGH), compounds **2** to **6**, were synthesized from GDM (**1**). Solubility, cytotoxicity, anticancer activity, molecular docking, and ADMET analyses were carried out. The solubility of DGH in water was 0.386–5.464 mM, higher than that of compound **1**. These compounds showed weak cytotoxic activity against Vero cells and LLC-MK2, with IC_{50} values in the range of 104.52–496.31 µg/ml. Compounds **2**, **3**, and **6** were also active against MDA-MB231 cells with IC_{50} values of 41.88, 52.12, and 70.93 µg/ml, respectively. They interacted positively with Hsp90, showing binding free energy (ΔG) of −97.03 to −101.06 kcal/mol, which indicated lower Hsp90 affinity compared with that of GDM (−133.06 kcal/mol) and 17-dimethylamino ethylamino-17-demethoxygeldanamycin (−136.55 kcal/mol), despite being partly bound in the active site (compounds **2**, **3**, and **6**) or outside the active site (compound **4**). Since compound **4** bound outside the active side and compound **5** did not bind to any part of Hsp90, they were not active on cytotoxicity against both normal cells and cancer cells. The predicted results showed that the ADMET parameters of DGH were similar to those of GDM. Furthermore, the experimental results are associated with a theoretical basis by molecular docking and ADMET analysis. The study findings revealed, through molecular docking and ADMET analysis, that the development of DGH improved the pharmacokinetic profiles of solubility, cytotoxicity, and anticancer activities. We, therefore, recommend DGH as a potential alternative treatment agent for some cancers.

INTRODUCTION

Geldanamycin (GDM) is a benzoquinone ansamycin antibiotic. Recently, GDM was isolated from *Streptomyces zerumbet* W14 (Taechowisan *et al*., 2019). It interacts with heat shock protein 90 (Hsp90), which *inhibits* the *growth of* cancers (Mimnaugh *et al*., 1996; Whitesell *et al*., 1994). However, the utilization management of this compound has been *limited* by its poor water solubility and hepatotoxicity (Fukuyo *et al*., 2009; Supko *et al*., 1995). Therefore, the development of GDM derivatives with increased pharmacokinetic properties has been attempted. Various synthetic GDM derivatives that will generate new types of Hsp90 inhibitors with weak toxicity and high efficiency have been sought (Kitson *et al*., 2013; Lin *et al*., 2015; Modi *et al*., 2011; Tian *et al*., 2004; Wrona *et al*., 2010). Several GDM derivatives have been synthesized, for example, 17-N-allylamino-17-demethoxygeldanamycin, and 17-dimethylamino ethylamino-17-demethoxygeldanamycin; however, their water solubility was limited (Smith *et al*., 2005). Recently, tryptamine-geldanamycin hybrids have been synthesized. These compounds showed moderate cytotoxic activity against normal cells and strong cytotoxic activity against various cancer cell lines. Their water solubility was increased above that of GDM (Taechowisan *et al*., 2020).

*Corresponding Author
Thongchai Taechowisan, Department of Microbiology, Silpakorn University, Nakhon Pathom, Thailand.
E-mail: tewson84 @ hotmail.com

Dopamine is a neurotransmitter responsible for transmitting signals between nerve cells. It is used in the treatment of severe hypotension, bradycardia, circulatory shock, and cardiac arrest (Bhatt-Mehta and Nahata, 1989). Dopamine is polar a covalent compound that is soluble in polar molecules such as water. In this study, it is a useful tool for the development of dopamine-geldanamycin hybrids (DGH) with improved solubility and biological activities. The C17-methoxy group of the GDM molecule can allow the introduction of various nucleophiles. Thus, GDM has been a precursor for synthesizing its derivatives (Modi *et al*., 2011; Tian *et al*., 2004; Wrona *et al*., 2010). Furthermore, another report showed that, compared with GDM, some of the GDM derivatives exhibited greater activity against myeloma cells (Jurczyszyn *et al*., 2014; Mielczarek-Lewandowska *et al*., 2019).

In this study, the novel DGH was synthesized. Molecular docking was performed to determine the hydrogen-bonding interaction, the binding energy, and the orientation of inhibitors bound in the active site of Hsp90. The ADMET of the compounds was predicted via *in silico* methods. Their anticancer activity was then evaluated on three cancer cell lines, MDA-MB-231, HeLa, and human hepatocellular carcinoma (HepG2) cells, using an MTT colorimetric assay. The water solubility was also carried out.

MATERIALS AND METHODS

Cultivation of actinomycetes and product isolation

Streptomyces zerumbet W14 was obtained from *Zingiber zerumbet* (L.) Smith using the surface-sterilization technique (Taechowisan *et al*., 2019). The bacterium was cultured on ISP-2 agar at 30ºC for 14 days. The initial steps of antibiotic isolation and purification were as previously described (Taechowisan *et al*., 2020). The isolated compound was subjected to investigation by NMR spectroscopy. The spectral data for this compound *identified it as* geldanamycin ($C_{29}H_{40}N_2O_9$) (**1**).

Chemical reagents and materials

The chemicals were purchased from Sigma-Aldrich (*Darmstadt*, *Germany*), Tokyo Chemical Industry (Tokyo, Japan), and Fluka Chemical (Buchs, Switzerland) Companies. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 spectrometer (Bruker, MA). Mass spectra were determined with a micrOTOF (Bruker, MA). Melting points were measured with a Stuart Scientific SMP 2 (Cole-Parmer Ltd., Staffordshire, UK) and are uncorrected. The reaction was monitored by TLC, performed on aluminum sheets precoated with silica gel 60 (*Darmstadt*, *Germany*). Column chromatography was carried out using a Merck Kieselgel 60 column chromatography (*Darmstadt*, *Germany*).

Synthesis of DGH

The synthesis of DGH has been described by Taechowisan *et al*. (2021). The spectral data of the synthesized compounds are described as follows:

(4E,6Z,8S,9S,10E,12S,13R,14S,16R)-19-((3,4-dihydroxyphenethyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1] docosa-1(21),4,6,10,18-pentaen-9-yl carbamate (**2**): 0.0167 g (21% yield using 1:2 hexane:EtOAc as a mobile phase); m.p. 114ºC–116ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, J = 6.2 Hz, 3H, CH_3), 1.00 (d, J = 6.9 Hz, 3H, CH_3), 1.60–1.78 (m, 3H, hydrocarbon), 1.80 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 2.35–2.43 (m, 1H, CH), 2.62–2.83 (m, 4H, hydrocarbon), 3.27 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.46 (m, 1H, CH), 3.59–3.73 (m, 3H, hydrocarbon), 4.33 (d, J = 9.7 Hz, 1H, CH), 4.97 (br, 2H, NH_2), 5.18 (s, 1H, CH), 5.83–5.90 (m, 2H, 2CH), 6.41 (br, 1H, NH), 6.54–6.61 (m, 2H, 2CH), 6.73 (d, J = 1.8 Hz, 1H, ArH), 6.81 (d, J = 8.0 Hz, 1H, ArH), 6.94 (d, J = 11.5 Hz, 1H, CH), 7.21 (s, 1H, CH), 9.18 (br, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.5, 12.6, 12.8, 22.8, 28.6, 29.7, 32.3, 34.3, 35.0, 35.2, 47.0, 56.7, 57.1, 72.8, 81.1, 81.4, 81.9, 108.5, 108.7, 115.6, 115.7, 120.8, 126.6, 127.0, 129.6, 132.8, 133.6, 134.9, 141.3, 143.1, 144.3, 144.9, 156.3, 168.5, 180.4, 183.9; HMS calculated for $C_{36}H_{47}N_3O_{10}$ $(M+Na)^+$ 704.3154, found 704.3157.

(4E,6Z,8S,9S,10E,12S,13R,14S,16R)-19-((3,4-dimethoxyphenethyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1] docosa-1(21),4,6,10,18-pentaen-9-yl carbamate (**3**): 0.0508 g (50% yield using 1:1 Hexane:EtOAc as a mobile phase); m.p. 127ºC–129ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.95 (d, J = 6.4 Hz, 3H, CH_3), 1.00 (d, J = 6.9 Hz, 3H, CH_3), 1.62–1.78 (m, 3H, hydrocarbon), 1.80 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.39–2.46 (m, 1H, CH), 2.67–2.93 (m, 4H, hydrocarbon), 3.27 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.45 (m, 1H, CH), 3.57 (dd, J = 1.8, 9.0 Hz, 1H, CH), 3.62–3.85 (m, 1H, CH), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.31 (d, J = 9.8 Hz, 1H, CH), 4.86 (br, 2H, NH_2), 5.19 (s, 1H, CH), 5.83–5.92 (m, 2H, 2CH), 6.38 (br, 1H, NH), 6.58 (t, J = 11.5 Hz, 1H, CH), 6.71–6.91 (m, 3H, 3ArH), 6.95 (d, J = 11.4 Hz, 1H, CH), 7.26 (s, 1H, CH), 9.17 (br, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.3, 12.6, 12.8, 22.9, 28.5, 32.3, 34.4, 35.1, 35.5, 47.1, 55.9, 56.7, 57.1, 72.65, 81.2, 81.4, 81.6, 108.6, 108.7, 111.6, 111.7, 120.7, 126.5, 126.9, 129.6, 132.7, 133.7, 134.9, 135.8, 141.3, 144.7, 148.2, 149.3, 156.0, 168.4, 180.7, 183.8; HMS calculated for $C_{38}H_{51}N_3O_{10}$ $(M+Na)^+$ 732.3467, found 732.3469.

(4E,6Z,8S,9S,10E,12S,13R,14S,16R)-19-((3,4-bis(benzyloxy)phenethyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1] docosa-1(21),4,6,10,18-pentaen-9-yl carbamate (**4**): 0.0501 g (14% yield using 5:2 CH_2Cl_2:EtOAc as a mobile phase); m.p. 92ºC–94ºC; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, J = 6.4 Hz, 3H, CH_3), 1.00 (d, J = 6.9 Hz, 3H, CH_3), 1.62–1.78 (m, 3H, hydrocarbon), 1.79 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.34–2.42 (m, 1H, CH), 2.64–2.77 (m, 1H, CH), 2.84 (t, J = 6.9 Hz, 2H, CH_2), 3.26 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.43–3.46 (m, 1H, CH), 3.58 (dd, J = 1.7, 8.9 Hz, 1H, CH), 3.62–3.82 (m, 2H, CH_2), 4.31 (d, J = 9.9 Hz, 1H, CH), 4.96 (br, 2H, NH_2), 5.14 (s, 2H, OCH_2), 5.16 (s, 2H, OCH_2), 5.18 (s, 1H, CH), 5.82–5.91 (m, 2H, 2CH), 6.32 (br, 1H, NH), 6.58 (t, J = 11.5 Hz, 1H, CH), 6.73 (dd, J = 2.0, 8.1 Hz, 1H, ArH), 6.79 (d, J = 2.0 Hz, 1H, ArH), 6.91 (d, J = 8.2 Hz, 1H, ArH), 6.95 (d, J = 10.8 Hz, 1H, CH), 7.26 (s, 1H, CH), 7.29–7.40 (m, 6H, 6ArH), 7.40–7.55 (m, 4H, 4ArH), 9.17 (br, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.3, 12.6, 12.7, 22.9, 28.5, 32.3, 34.4, 35.0, 35.4, 46.9, 56.7, 57.1, 71.4, 71.5, 72.6, 81.2, 81.4, 81.6, 108.6, 108.7, 115.4, 115.6, 121.6, 126.5, 126.9, 127.3, 127.8, 128.5, 130.4, 132.7, 133.7, 134.9, 135.8, 137.1, 137.2, 141.3, 144.7, 148.2, 149.3, 156.1, 168.3, 180.6, 183.7; HMS calculated for $C_{50}H_{59}N_3O_{10}$ $(M+Na)^+$ 884.4093, found 884.4094.

(4E,6Z,8S,9S,10E,12S,13R,14S,16R)-19-((3,4-bis((2-bromobenzyl)oxy)phenethyl) amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]do-cosa-1(21),4,6,10,18-pentaen-9-yl carbamate (**5**): 0.0757 g (53% yield using 2:1 CH_2Cl_2:EtOAc as a mobile phase); m.p. 174°C–176°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.94 (d, *J* = 6.4 Hz, 3H, CH_3), 1.00 (d, *J* = 6.9 Hz, 3H, CH_3), 1.62–1.79 (m, 3H, hydrocarbon), 1.80 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.36–2.44 (m, 1H, CH), 2.65–2.80 (m, 1H, CH), 2.88 (t, *J* = 6.9 Hz, 2H, CH_2), 3.26 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.43–3.46 (m, 1H, CH), 3.57 (dd, *J* = 1.4, 8.6 Hz, 1H, CH), 3.60–3.85 (m, 2H, CH_2), 4.31 (d, *J* = 9.9 Hz, 1H, CH), 5.06 (br, 2H, NH_2), 5.18 (s, 1H, CH), 5.20 (s, 2H, OCH_2), 5.22 (s, 2H, OCH_2), 5.82–5.91 (m, 2H, 2CH), 6.33 (br, 1H, NH), 6.58 (t, *J* = 11.6 Hz, 1H, CH), 6.77–6.86 (m, 2H, 2ArH), 6.93 (d, *J* = 8.1 Hz, 1H, ArH), 6.95 (d, *J* = 11.6 Hz, 1H, CH), 7.17 (td, *J* = 0.5, 7.4 Hz, 2H, 2ArH), 7.26 (s, 1H, CH), 7.31 (td, *J* = 0.6, 7.5 Hz, 2H, 2ArH), 7.56 (d, *J* = 7.9 Hz, 2H, ArH), 7.61 (ddd, *J* = 1.8, 2.3, 7.7 Hz, 2H, 2ArH), 9.17 (br, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.3, 12.5, 12.7, 22.9, 28.4, 32.3, 34.4, 35.0, 35.3, 46.8, 56.7, 57.0, 70.6, 72.5, 81.2, 81.4, 81.5, 108.6, 108.7, 115.1, 115.2, 121.9, 122.0, 122.1, 126.5, 126.9, 127.5, 127.6, 128.8, 128.9, 129.1, 129.2, 130.7, 130.8, 132.4, 132.8, 133.6, 134.9, 135.8, 136.3, 136.4, 141.2, 144.7, 147.7, 147.8, 148.8, 148.9, 156.2, 168.3, 180.6, 183.6; HMS calculated for $C_{50}H_{57}Br_2N_3O_{10}$ $(M+Na)^+$ 1040.2303, found 1040.2323.

(4E,6Z,8S,9S,10E,12S,13R, 14S,16R)-19-((3,4-dibutoxyphenethyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo [16.3.1] docosa-1(21),4,6,10,18-pentaen-9-yl carbamate (**6**): 0.0097 g (25.8% yield using 10:7 CH_2Cl_2:EtOAc as the mobile phase); m.p. 178°C–181°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.98–1.01 (m, 12H, $4CH_3$), 1.41–1.60 (m, 4H, $2CH_2$), 1.61–1.89 (m, 10H, hydrocarbon), 2.02 (s, 3H, CH_3), 2.38–2.46 (m, 1H, CH), 2.65–2.80 (m, 2H, hydrocarbon), 2.88 (t, *J* = 7.5 Hz, 2H, CH_2), 3.27 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.45 (m, 1H, CH), 3.57 (dd, *J* = 1.8, 8.9 Hz, 1H, CH), 3.62–3.87 (m, 2H, CH_2), 3.99 (td, *J* = 3.9, 6.6 Hz, 4H, $2CH_2$), 4.31 (d, *J* = 9.9 Hz, 1H, CH), 4.84 (br, 2H, NH_2), 5.19 (s, 1H, CH), 5.83–5.92 (m, 2H, 2CH), 6.37 (br, 1H, NH), 6.58 (t, *J* = 11.6 Hz, 1H, CH), 6.72–6.75 (m, 2H, 2ArH), 6.85 (d, *J* = 8.67 Hz, 1H, ArH), 6.95 (d, *J* = 11.7 Hz, 1H, CH), 7.26 (s, 1H, CH), 9.17 (br, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.3, 12.6, 12.7, 13.8, 19.2, 22.9, 28.5, 31.3, 32.3, 34.4, 35.1, 35.5, 47.1, 56.7, 57.1, 69.1, 72.6, 81.2, 81.5, 81.7, 108.6, 108.7, 114.3, 114.4, 120.9, 126.5, 126.9, 129.7, 132.7, 133.8, 135.0, 135.8, 141.3, 144.8, 148.4, 149.5, 156.0, 168.4, 180.6, 183.7; HMS calculated for $C_{44}H_{63}N_3O_{10}$ $(M+Na)^+$ 816.4406, found 816.4402.

The water solubility of DGH was carried out by comparison with GDM as previously described (Taechowisan *et al*., 2020).

MTT assay for cell viability

Two normal cell lines [African green monkey kidney cells (Vero); Rhesus monkey kidney cells (LLC-MK2)] and three cancer cell lines [human breast carcinoma cells (MDA-MB-231]; human hepatocellular carcinoma cells (HepG2); and human cervical carcinoma cells (HeLa) (from the Korean Cell Line Bank)) were grown in DMEM medium supplemented with 10% in a 37°C, 5% CO_2 humidified incubator. Cytotoxicity assay was *carried out* as described in a previous publication (Taechowisan *et al*., 2020).

Molecular docking analysis

The two-dimensional structures of geldanamycin and DGH were drawn and converted to SMILES strings with ChemDraw software (http://cambridgesoft.com) and the SMILES Translator and Structure Generator (https://cactus.nci.nih.gov/translate/), respectively. The energies of these compounds were optimized and converted to #D format, saved as Protein Data Bank (PDB) files using UCSF Chimera v.1.14 (University of California, CA), and further used for molecular docking analysis.

The 3D structure of Hsp90 with the cocrystallized geldanamycin (1YET) was retrieved from the PDB and chosen for molecular docking studies. The 3D structure of 1YET is taken for docking geldanamycin and DGH to obtain the predictions of ligand binding. The water molecules were taken out from its structure using Discovery Studio software (Accelrys Inc.). Docking simulations were undertaken with Hsp90 as the target (1YET) and geldanamycin, 17-DMAG, and DGH as the ligands using AutoDock Vina to predict the ligand-binding sites on Hsp90. Docking analysis was performed as detailed by Taechowisan *et al*. (2021).

Prediction of ADMET by computational analysis

The computational prediction of the compounds was performed using two types of online software SwissADME (http://swissadme.ch) and Pre-ADMET (https://preadmet.bmdrc.kr) to obtain relative results for pharmacokinetic profile (absorption, distribution, metabolism, excretion, and toxicity; ADMET) of the molecules. The ADMET profiles of DGH were analyzed in comparison with geldanamycin.

Statistical analysis

Each result represents the means ± standard deviation of three experiments. SPSS v.16.0 (SPSS Inc., Chicago, IL) software was used for the data analysis. Comparisons between the two groups were analyzed using the two-tailed Dunnett's *t*-tests treated compound 1 as a control group. A p-value < 0.05 was considered to indicate statistical significance.

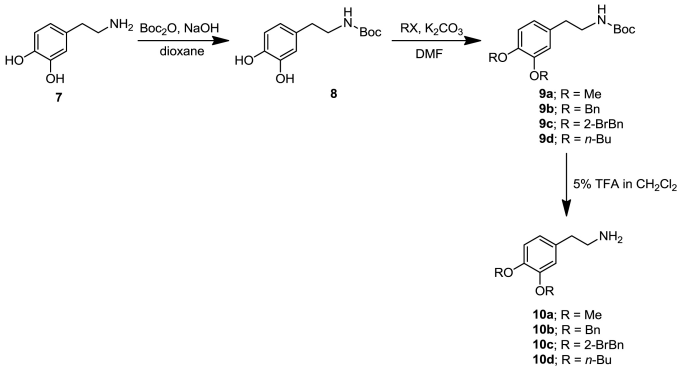
RESULTS

In the present work, a series of DGH were synthesized via nucleophilic substitution of GDM (**1**) as described in Methods section (Schemes 1 and 2).

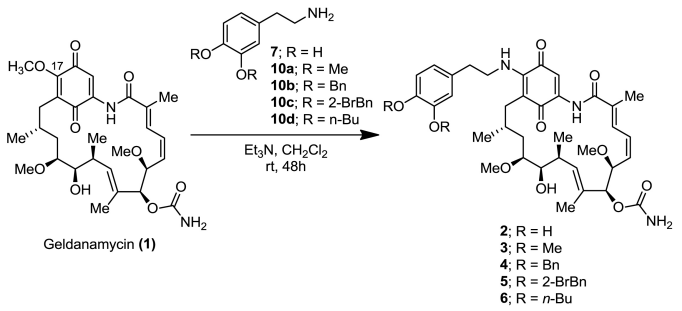
The solubility in water of compound **1** was found to be 0.152 mM (Table 1). In contrast, the solubility of DGH in water was between 0.386 mM and 5.464 mM, approximately 2.53–35.94 times better than that of GDM. These data suggest that the conjugation of a dopamine moiety to GDM at the C17-position greatly enhanced their solubility in water.

GDM and DGH were also assessed for cytotoxicity activity against two normal cell lines (Vero and LLC-MK2 cells) and three cancer cell lines (MDA-MB-231, HepG2, and HeLa) using the MTT assay. All DGH showed weak cytotoxicity activity toward Vero and LLC-MK2 cells with IC_{50} values in the range of

104.52–496.31 µg/ml (Table 2). The results show that DGH has low toxicity to normal cells compared with GDM and doxorubicin. All DGH showed less cytotoxicity activity toward HeLa cells than geldanamycin. Compounds **2**, **3**, and **6** were also active against MDA-MB231 cells with IC_{50} values of 41.88, 52.12, and 70.93 µg/ml, respectively. Amongst these compounds, only compound **6** was activity against HeLa cells with IC_{50} values of 89.38 µg/ml. Compounds **4** and **5** were not active on cytotoxicity against both normal cells and cancer cells. In addition, the therapeutic index of DGH is greater than those of GDM, informing that DGH has safety as the concentration required to cause toxicity. It suggested that some of them (compounds **2**, **3**, and **6**) were toxic to some cancer cells. Therefore, they could be the *potential drug* candidate against some cancers.



Scheme 1. Syntheses of dopamine derivatives **10a**–**10d**.



Scheme 2. Syntheses of 17-demethoxygeldanamycin derivatives **2**–**6**.

Hsp90; PBD ID: 1YET was selected for molecular docking studies. Comparative docking of 1YET with 17-DMAG, GDM, and DGH was carried out to provide evidence in support of their inhibitory effects on Hsp90 interactions. The results of docking studies (as shown in Table 3) revealed that 17-DMAG participated in interactions through five hydrogen bonds with Ser52, Asp54, Lys58, Asp93, and Phe138 to the N-terminal ATP-binding pocket of Hsp90, with a binding energy of −136.55 kcal/mol. Geldanamycin bridged four hydrogen bonds with Ser52, Lys58, Asp93, and Phe138 to the N-terminal ATP-binding pocket of Hsp90, with a binding energy of −133.06 kcal/mol. Compound **2** formed six hydrogen bonds with Glu47, Asn106 (three positions), Gly137, and Phe138 to the N-terminal ATP-binding pocket, with a binding energy of −101.06 kcal/mol. Compound **3** formed three hydrogen bonds with Lys58, Gly137, and Phe138 to the N-terminal ATP-binding pocket, with a binding energy of −98.54 kcal/mol. Compound **4** formed two hydrogen bonds with Gln212 and Ile218 to the N-terminal part of Hsp90 (outside active site), with a binding energy of −108.12 kcal/mol. Compound **5** did not form a hydrogen bond to any part of the Hsp90 molecule.

Table 1. The solubility of geldanamycin (**1**) and synthetic compounds (**2** to **6**).

Compounds	MW	Water solubility (mg /ml)	Water solubility (mM)	Relative solubility
1	560	0.085 ± 0.004	0.152 ± 0.002	1.00
2	681	3.333 ± 1.154	4.894 ± 1.695[f]	32.19
3	709	0.666 ± 0.577	0.940 ± 0.814[d]	6.18
4	862	0.333 ± 0.577	0.386 ± 0.669[e]	2.53
5	1019	1.333 ± 0.577	1.308 ± 0.566[e]	8.60
6	793	4.333 ± 0.577	5.464 ± 0.728[f]	35.94

[a]The results of measurements (mean ± SD).
[b, c, d,e,f]Significant differences ($p < 0.05$).

Table 2. Cytotoxicity activity (IC_{50}) of geldanamycin (**1**) and synthetic compounds (**2** to **6**).

Compounds	IC_{50} (µg/ml)					Therapeutic index		
	Vero	LLC-MK2	MDA-MB-231	HeLa	HepG2	MDA-MB-231	HeLa	HepG2
1	54.25	45.61	68.98	16.00	677.49	0.78	0.49	0.08
2	104.52[a]	397.84[b]	41.88[c]	115.98[d]	150.64[e]	2.49	0.90	0.69
3	181.00[a]	429.17[b]	52.12[c]	185.63[d]	160.88[e]	3.47	0.97	1.12
4	376.70[a]	496.31[b]	271.84[c]	316.30[d]	637.76	1.38	1.19	0.59
5	364.31[a]	458.95[b]	263.07[c]	269.95[d]	649.40	1.38	1.35	0.56
6	369.44[a]	221.19[b]	70.93	89.38[d]	175.66[e]	5.20	4.13	2.10
Doxorubicin	99.48[a]	98.92[b]	<6.25[c]	1.95[d]	92.16[e]	>15.92	51.02	1.08

[a, b, c, d, e]Significant differences from the compound **1** ($p < 0.05$).

Table 3. Geldanamycin (**1**) and its derivatives (**2** to **6**) to inhibit Hsp90 protein based on the molecular docking simulation.

Compounds	$\Delta G_{binding}$ (kcal /mol)	Number of hydrogen bond	Docking site
17-DMAG[a]	−136.55	5	In active site
1	−133.06	4	In active site
2	−101.06	6	Partly bound in active site
3	−98.54	3	Partly bound in active site
4	−108.12	2	Outside active site
5[b]	—	—	Did not bind to the active site
6	−97.03	3	Partly bound in active site

[a]17-DMAG; 17-dimethylamino ethylamino-17-demethoxygeldanamycin.

[b]Compound **5** is not docked in Hsp90 molecule; its docking score is zero.

Compound **6** formed three hydrogen bonds with Glu47, Lys112, and Gly137 to the N-terminal ATP-binding pocket of Hsp90, with a binding energy of −97.03 kcal/mol. Figure 1 displays the 2D interactions of the compounds and Hsp90 obtained from molecular docking using LIGPLOT. As can be seen, 17-DMAG formed the highest number of hydrogen bonds (Fig. 1a). To display the docking results, compound **4** participated in interactions outside the active site of the N-terminal part of Hsp90 and compound **5** did not form a hydrogen bond to any part of the Hsp90 molecule; they were carried out using the BIOVIA Discovery Studio as shown in Figure 2e and f, respectively. Figure 3 shows the hydrogen bond acceptor and hydrogen bond donors and how the ligand is set inside the cavity. The green patches present denote the hydrogen bond acceptor and the pink patches represent the

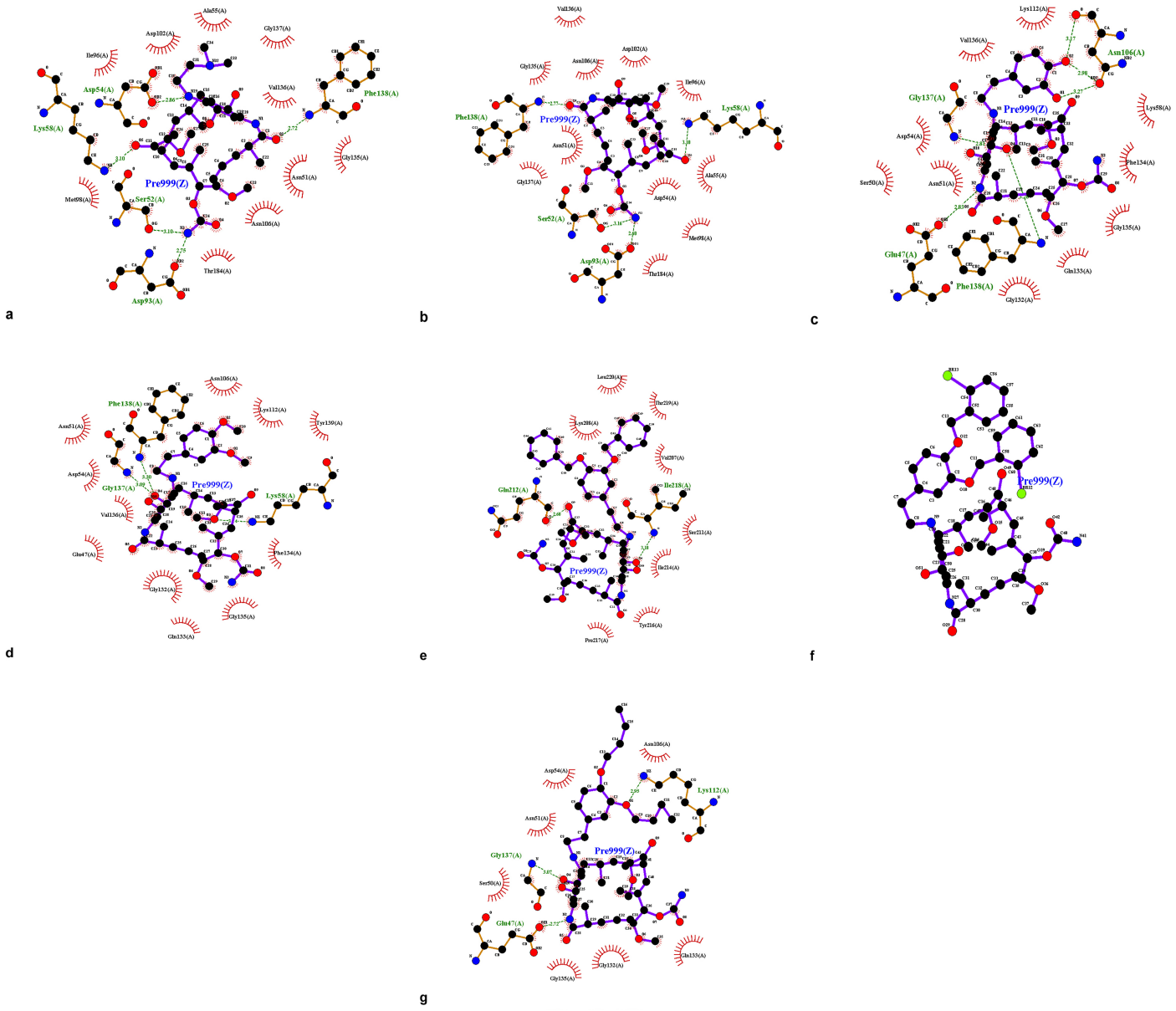


Figure 1. LIGPLOT diagram showing hydrogen-bonding interactions (the green dashed lines) and hydrophobic contacts (the red crescents with the bristles) for the ligand: 17-DMAG (**a)** and compounds **1** to **6** (b to g) with Hsp90 molecule, respectively.

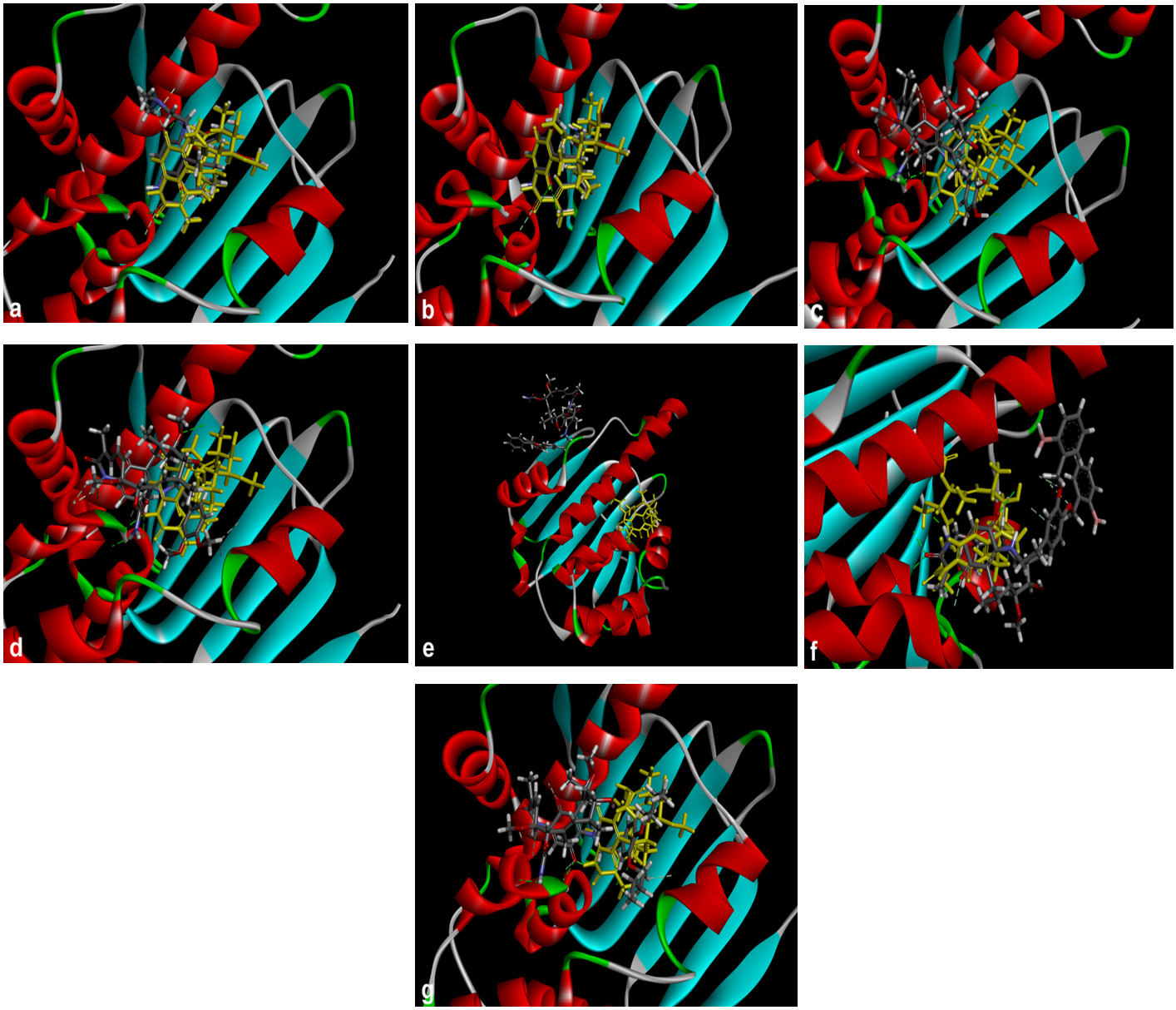


Figure 2. Crystal structure superimposed on Hsp90 (1YET) docked 17-DMAG (a) and compounds **1** to **6** (b to g) with Hsp90 molecule, respectively. Compound **5** was not docked in Hsp90 molecule (f). The brown molecule was represented by geldanamycin.

hydrogen bond donor and they show how the ligand is present inside the cavity. As can be seen, compound **5** did not participate in the hydrogen bond acceptor or donor to any part of the Hsp90 molecule (Fig. 3f).

The predicted ADMET profiles of GDM and DGH are presented in Table 4. The compounds have *high polarity* (hydrophilic); the TPSA values are greater than 140. Compounds **1**, **2**, **3**, and **6** have ideal lipophilicity (average of Log $P_{o/w} \leq 5$). This result suggested that these compounds have good absorption and permeation. The predicted values of Caco2-cell permeability are ≥ 0.90; therefore, these compounds have high Caco2-cell permeability and are the ease of absorption. These compounds have good intestinal absorption, because the predicted values of human intestinal absorption are greater than 30%. These compounds are predicted to have high skin permeability (the log Kp < -2.5). The compounds are predicted to be substrates of P-glycoprotein; they may be excreted from cells by P-glycoprotein. However, compounds **1**, **2**, and **3** are also predicted not to be a P-glycoprotein inhibitor. The compounds **1**, **2**, **3**, and **4** are predicted to moderately cross the blood-brain barrier ($-1 <$ logBB < 0.3), but compounds **5** and **6** easily crossed (logBB > 0.3). These compounds are substrates for CYP3A4, but not substrates for CYP2D6. They are also predicted to be CYP3A4 inhibitor. Therefore, they may be metabolized in the liver. They also suggest that these compounds have not mutagenic activity by AMES test, but they may inhibit the hERG channel and may cause cardiotoxicity. The predicted results indicate that the ADMET properties of DGH are similar to those of GDM. However, they were a cytochrome substrate and inhibitor and hERG inhibitor, which may cause hepatotoxicity and cardiotoxicity, respectively. This should be taken with precautions.

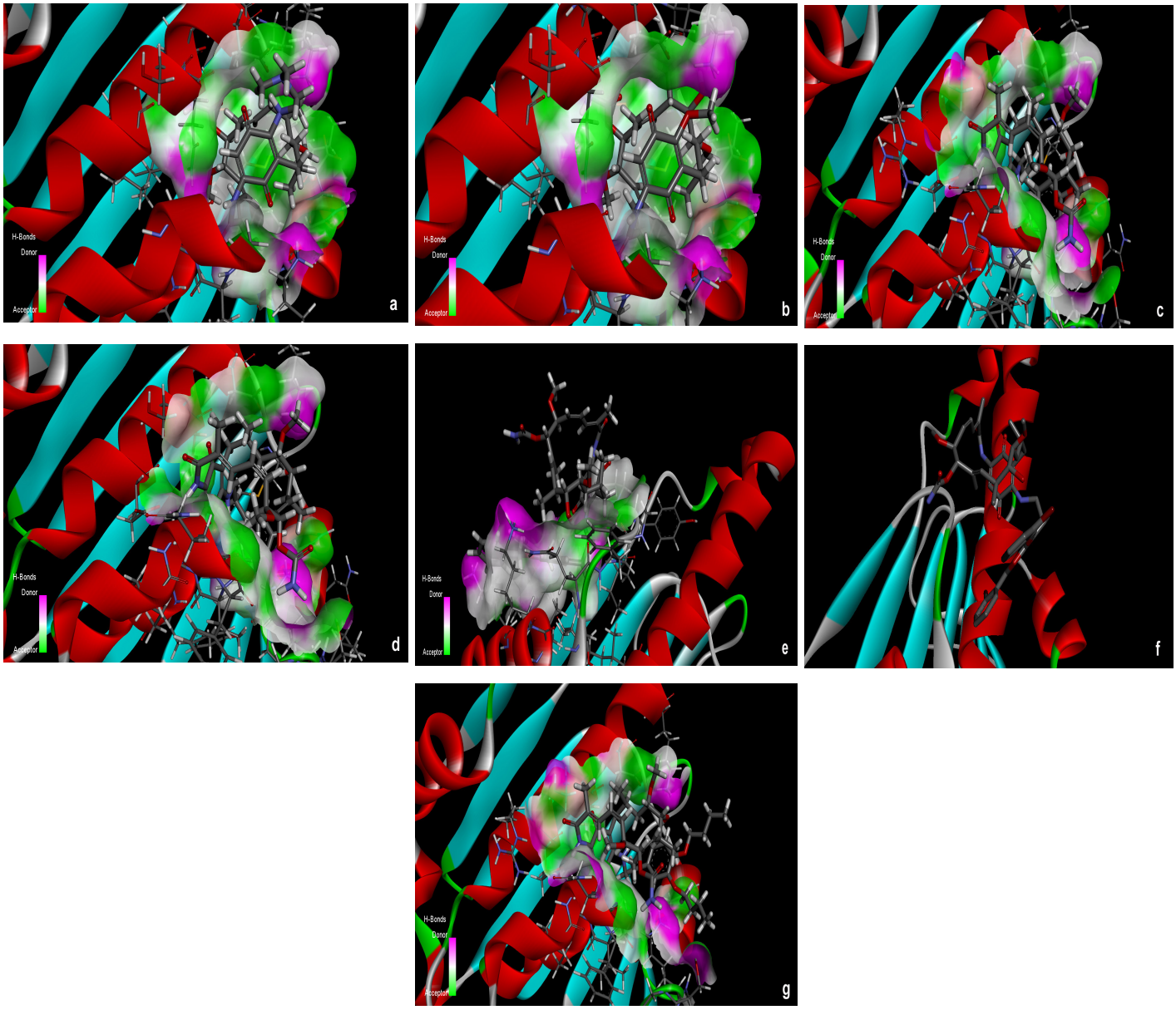


Figure 3. Hydrogen-bonding interactions of 17-DMAG (a), compound **1** (b), compounds **2**, **3,** and **6** (c, d, and g) molecules in the part of the active pocket site, compound **4** molecule at the outside of the active pocket site (e), and compound **5** molecule did not bind to any part of Hsp90 (f), respectively.

DISCUSSION

GDM was the first benzoquinone ansamycin antibiotic generated by *Streptomyces hygroscopicus var. geldanus* which was discovered in 1970 (Johnson *et al*., 2010). Recently, it was also isolated from *S. zerumbet* W14 (Taechowisan *et al*., 2019). It specifically targets and deactivates Hsp90. For the past decade, Hsp90 has been an interesting target molecule for anticancer treatment, because it plays a role in protein functions and cell growth (Chatterjee and Burns, 2017). Although GDM is a potent cell growth inhibitor, however, it suffers from severe hepatotoxicity and insolubility in water (Fukuyo *et al*., 2009; Supko *et al*., 1995). Therefore, the structure modification of this compound to reduce hepatotoxicity and increase water solubility should be carried out. Some of geldanamycin derivatives are in clinical trials, for example, 17-allylamine-17-demethoxygeldanamycin (17-AAG) (Banerji *et al*., 2003; Goetz *et al*., 2005; Heath *et al*., 2008; Ramanathan *et al*., 2005; Solit *et al*., 2008), 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG) (Grem *et al*., 2005), and 17-allylamino-17-demethoxygeldanamycin hydroquinone hydrochloride (Hanson and Vesole, 2009; Sydor *et al*., 2006). However, the toxicity of these compounds was unfavorable, as they caused both cardiac and liver toxicity (Lancet *et al*., 2006; Sequist and Janne, 2007). Meanwhile, novel geldanamycin derivatives have been synthesized which are excellent tools for exploring their biological activities.

In this study, five new geldanamycin derivatives, compounds **2–6**, were synthesized by nucleophilic substitution of GDM (**1**). Position 17 of geldanamycin has been introduced for

Table 4. Predicted ADMET properties of geldanamycin (**1**) and synthetic compounds (**2** to **6**).

Properties[a]	Compounds					
	1	**2**	**3**	**4**	**5**	**6**
TPSA	163.48	206.74	184.74	184.74	184.74	184.74
Consensus Log $P_{o/w}$	1.57	2.01	2.29	5.02	6.31	4.59
Absorption						
Water solubility (log *S*)	−3.25	−5.19	−5.55	−11.38	−12.80	−6.85
Caco2-cell permeability	20.43	19.80	21.61	28.16	24.84	28.27
Human intestinal absorption (% absorbed)	84.62	75.89	91.16	94.20	94.20	92.82
Skin permeability (log Kp cm/s)	−8.31	−8.15	−7.86	−6.67	−6.65	−6.60
P-Glycoprotein substrate	+	+	+	+	+	+
P-Glycoprotein inhibitor	−	−	−	+	+	+
Distribution						
BBB permeability (log BB)	0.0270	0.05	0.04	0.19	1.04	0.39
Metabolism						
CYP2D6 substrate	−	−	−	−	−	−
CYP3A4 substrate	+	+	+	+	+	+
CYP1A2 inhibitor	−	−	−	−	−	−
CYP2C19 inhibitor	−	−	−	−	−	−
CYP2C9 inhibitor	−	−	−	−	−	−
CYP2D6 inhibitor	−	−	−	−	−	−
CYP3A4 inhibitor	+	+	+	+	+	+
Excretion						
Renal OCT2 substrate	−	−	−	−	−	−
Toxicity						
AMES toxicity	−	−	−	−	−	−
hERG inhibitor	+	+	+	±	±	+
Hepatotoxicity	+	+	+	+	+	+
Skin sensitization	−	−	−	−	−	−

[a]ADMET, absorption, distribution, metabolism, excretion, and toxicity; AMES, *Salmonella typhimurium* reverse mutation assay; Caco2, Caucasian colon adenocarcinoma cell line; BBB, blood-brain barrier; BB, blood rain; hERG, human ether-a-go-go related gene; Kp, skin permeability constant; OCT2, organic cation transporter 2; TPSA, topological polar surface area.

the synthesis of geldanamycin compounds because its methoxy group is readily displaced by a nucleophile, providing a convenient entry into 17-substituted-17-demethoxygeldanamycin compounds by the S_N2 reaction mechanism (Hamlin *et al*., 2018). By the molecular docking studies, compounds **2**, **3**, and **6** partly bound in the active site of the N-terminal ATP-binding pocket of Hsp90. The binding mode of these compounds with Hsp90 (1YET) using the 3D structure has been predicted to understand the protein-ligand contacts and their interaction. The docking results of these compounds were compared along with 17-DMAG (control compound) in the active site of 1YET. These DGH showed a similar pose as that of 17-DMAG and GDM in the binding pocket. The binding energy of these DGH is in the range of −97.03 to −101.06 kcal/mol, in comparison to 17-DMAG and GDM with a binding energy of −136.55 and −133.06 kcal/mol, respectively. The LIGPLOT showed that DGH formed hydrogen bonding with most similar to that observed in 17-DMAG, and also they showed highly conserved hydrophobic interactions with the same amino acid residues. These interactions occurred on the benzoquinone moiety of geldanamycin molecule. Similar to the findings of previous studies, the molecular docking in the present study has shown that the pocket of Hsp90 is composed of a mixture of polar, charged, and hydrophobic amino acids. These amino acids include Asn51, Asp54, Ala55, Lys58, Asp93, Met98, Asn106, Leu107, Lys112, Gly135, Phe138, and Thr184. Therefore, the bottom of the pocket becomes increasingly hydrophobic; it retains one polar residue and one charged residue at the deepest portion as Thr184 and Asp93, respectively (Abbasi *et al*., 2017; Stebbins *et al*., 1997; Teo *et al*., 2015). The ADMET parameters of the compounds were studied by two types of online software. The correlation of structure and toxicity of these compounds was preliminarily evaluated. These compounds have good absorption and permeation. They are the substrate of P-glycoprotein, so they may be excreted from cells to the body because they also have the potential for cytochrome P450. They are predicted to be metabolized in the liver which may have hepatotoxicity by redox metabolism and glutathione adduct formation (Cysyk *et al*., 2006; Guo *et al*., 2008). Published reports suggest that the benzoquinone moiety in the geldanamycin molecule is responsible for hepatotoxicity (Cysyk *et al*., 2006; Guo *et al*., 2008).

In the present study, the experimental basis was carried out; compounds **2**, **3**, and **6** showed a greater increase in water

solubility and also showed less cytotoxicity than GDM in the normal cell lines and presented greater toxicity to some cancer cell lines. This compound should increase the likelihood of use in future studies. However, compound **4** bound outside the active side and compound **5** did not bind to any part of Hsp90. They were not active on cytotoxicity against both normal cells and cancer cells. The findings confirm that the N-terminal ATP-binding domain is essential for the function of Hsp90 as described previously (Stebbins *et al*. 1997). Doxorubicin is a broad-spectrum chemotherapeutic drug used to treat cancers. In this study, it was used as the positive control. Doxorubicin exhibited greater cytotoxicity against MDA-MB231 and HeLa cells than GDM and DGH. The mechanisms of anticancer activity of doxorubicin were (i) DNA intercalation and topoisomerase-II disruption; (ii) free radical generation and damage to proteins, DNA, and cellular membranes, which were different from geldanamycin and derivatives (Gewirtz, 1999); in addition, the side effect for the use of doxorubicin was cardiotoxicity and doxorubicin resistance was also a problem (Thorn *et al*., 2011; Weiss, 1992). Therefore, the development of Hsp90 inhibitors may become a universal chemotherapeutic of cancers.

CONCLUSION

In summary, novel DGH with anticancer activity, enhanced water solubility, and low toxicity was presented in this study, in comparison with GDM. In particular, compounds **2**, **3**, and **6** showed anticancer activity against some cancer cells; moreover, the study findings revealed, through molecular docking and ADMET analysis, that the development of DGH improved the pharmacokinetic profiles of solubility, cytotoxicity, and anticancer activities. Therefore, Hsp90 could be an anticancer target, and some DGH could be considered as a candidate for anticancer agents.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

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

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