

Research Article

Synthesis and Molecular Docking of Some Grossgemin Amino Derivatives as Tubulin Inhibitors Targeting Colchicine Binding Site

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Six amino derivatives of grossgemin (2–7) were synthesized according to the reported essential pharmacophoric features of colchicine binding site inhibitors (CBSIs). The derivatives 4–6 were obtained for the first time. The pharmacophoric features of 2–7 as CBSIs were studied to be almost identical. Furthermore, the 3D-flexible alignment of compound 5 as a representative example with colchicine showed a very good overlapping. In agreement, compounds 2–7 docked into CBS with binding modes very similar to that of colchicine and exhibited binding free energies of –24.57, –25.05, –32.16, –29.34, –26.38, and –26.86 (kcal/mol), respectively. The binding free energies of 4–7 were better than that of colchicine (–26.13 kcal/mol) with a noticeable superiority to compound 4.

1. Introduction

Natural products are an untapped reservoir of biologically active compounds starting from the dawn of history and till the present [1, 2]. The biological values of natural products are undeniable either obtained from plants [3, 4], marines [5, 6], or microbes [7–10]. The biological activities are owned to the secondary metabolites which could be classified according to their chemical structures to be saponins [11, 12], flavonoids [13, 14], pyrones [15], alkaloids [16, 17], steroids [18], and sesquiterpenes [19–21].

Grossgemin (1) is a sesquiterpene lactone of guanine structure and a characteristic component of *Chartolepis intermedia* Boiss. which grows in Central and Northern Kazakhstan [22]. Grossgemin (Figure 1) was previously isolated from the aerial parts of several herbal plants and

exhibited a wide spectrum of biological activities [23, 24]. Various biologically active analogs of grossgemin have been synthesized before possessing cytotoxic [25–27] and antimicrobial [26] activities.

Furthermore, seven out of nine sesquiterpene lactones that have been isolated from *Camchaya calcarea*, having chemical structures similar to that of grossgemin, showed potent antimycobacterial and moderate antiplasmodial activity. Interestingly, three of them exhibited strong cytotoxicity against small-cell lung cancer cell lines (NCI-H187) [28].

Tubulin is the protein dimer that is the principal component of microtubule filaments. The microtubule filaments play an essential role in the mitotic nuclear division of eukaryotic cells [29]. Tubulin inhibition is one of the main targets in the field of medicinal chemistry to design and

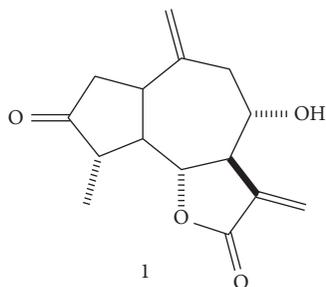


FIGURE 1: Chemical structure of grossgemin.

synthesize pharmacologically active drugs either as antimicrobial or anticancer drugs [30].

Colchicine binds to tubulin via the colchicine binding site that is located between the α and β tubulin subunits [31]. Figure 2 explains the seven pharmacophoric features shared by all tubulin inhibitors that act as colchicine binding site inhibitors (CBSIs). These features are one hydrogen bond donor (D1), three hydrogen bond acceptors (A1, A2, and A3), two hydrophobic centers (H1 and H2), and one planar group (R1) [32, 33]. Consequently, any molecule will have these seven pharmacophoric features or most of them will be considered as a CBSI.

It is important to mention that the pharmacophoric features of CBSIs can be presented through two planes. Features A1, D1, H1, and R1 lie in the first plane A and features A2, A3, and H2 lie in the second plane B. Relative to each other, planes A and B have a tilt of 45° [33, 34] (Figure 3).

2. Results

2.1. Synthesis of Grossgemin Analogs. To obtain new and biologically active derivatives of grossgemin, the reactions with morpholine, piperidine, and dibenzyl-, dibutyl-, diisopropyl-, and dipropylamines were undertaken under conditions similar to those described before (Figure 4) [35].

The derivatives 2, 3, and 7 were previously synthesized [35, 36] while derivatives 4–6 were obtained for the first time; the structures of synthesized compounds were established using ^1H , ^{13}C NMR spectroscopy and two-dimensional spectroscopy DEPT, COSY, HSQC, and HMBC.

2.2. Pharmacophoric Features and Structure Alignment. Compounds 2–7 were synthesized according to the reported essential pharmacophoric features of CBSIs. Figure 5 shows that compounds 2 and 5 as examples have six out of the seven pharmacophoric features of the CBSI: hydrogen bond donor (D1), two hydrogen bond acceptors (A1 and A2), two hydrophobic centers (H1 and H2), and one planar group (R1).

2.3. Flexible Alignment. 3D-flexible alignment of representative compound 5 with colchicine is presented in Figure 6. In the figure, it is possible to observe that, in general, the

structure of compound 5 has a very good overlap with the reference molecule (colchicine).

2.4. Molecular Docking. The synthesized compounds were docked against the colchicine binding site of tubulin heterodimers using MOE2014 software to determine the binding free energy and binding mode. The *in silico* molecular docking studies give a clear idea about the binding mode and the affinity between the docked candidates and the prospective protein target. The better biological effect is expected by the most similar binding mode to that of the reference ligand (colchicine) and the lower binding free energy [37].

The docking study of colchicine as a reference compound gave a binding energy value of -26.13 (Table 1). In detail, the trimethoxy phenyl ring occupied the first pocket of the colchicine binding site and could form two hydrophobic interactions with the amino acids Lys254 and Leu248. Furthermore, the side chain of the (acetamide moiety) occupied the second cavity of the colchicine binding site. The central ring formed two hydrophobic interactions with Ala250 and Leu255. Furthermore, the methoxytropone moiety occupied the third pocket of the receptor forming one hydrogen bond with Lys352 (Figure 7).

Compound 3 showed a binding mode like that of colchicine, with an affinity value of -25.05 kcal/mol (Table 1). The seven-membered ring ((R)-3-methylenecycloheptan-1-ol) occupied the first cavity of the colchicine binding site forming one hydrogen bond with Lys254. The 3-(piperidin-1-ylmethyl) dihydrofuran-2 (3H)-one moiety occupied the second cavity of the colchicine binding site, forming five hydrophobic interactions with Ala354, Cys241, Ile378, Val318, and Ala316. Additionally, it formed one hydrogen bond with Cys241. Furthermore, the 2-methylcyclopentan-1-one moiety occupied the third pocket of the colchicine binding site, forming two hydrogen bonds with Val181 and Lys352. Also, it formed three hydrophobic interactions with Ala180 and Lys352 (Figure 8).

Compound 4 as affinity value of -32.16 kcal/mol. The (1S, 6R)-6-hydroxy-1-methyl-4-methyleneoctahydroazulen-2 (1H)-one moiety occupied the first pocket of the colchicine binding site forming three hydrogen bonds with Asn101, Asn258, and Gln11. Also, it formed a hydrophobic interaction with Ala180. The first phenyl ring and dihydrofuran-2 (3H)-one moiety occupied the second cavity of the colchicine binding site. The phenyl ring formed three hydrophobic interactions with Cys241, Lue255, and Ala250. The dihydrofuran-2 (3H)-one moiety formed a hydrogen bond with Ala250. The second phenyl moiety occupied the third cavity of the colchicine binding site forming two hydrophobic interactions with Lys352 and Val315 (Figure 9).

The binding mode of compound 5 was combined with a binding energy of -29.34 kcal/mol. The (1S, 6R)-6-hydroxy-1-methyl-4-methyleneoctahydroazulen-2 (1H)-one moiety occupied the first cavity of the colchicine binding site, forming two hydrophobic interactions with Lys254 and Ala180. Additionally, one butyl moiety and dihydrofuran-2 (3H)-one moiety occupied the second cavity of the

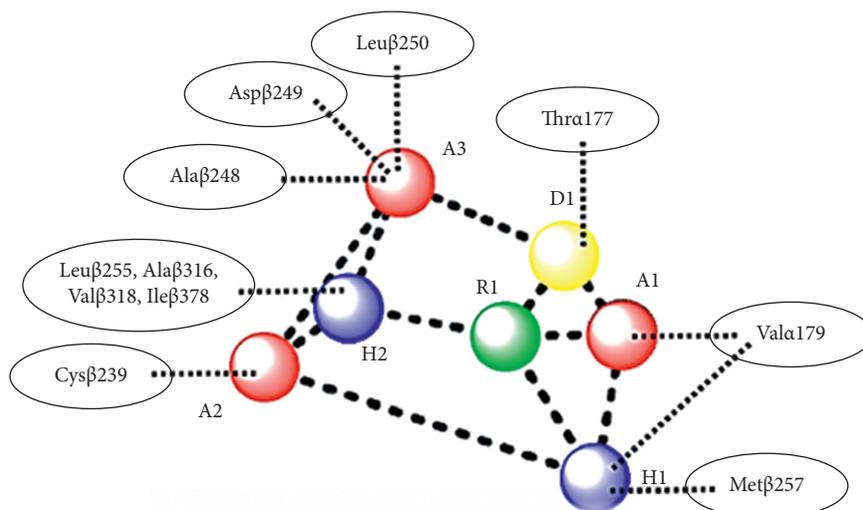


FIGURE 2: The seven essential pharmacophoric features of CBSIs (based on Ref. [32, 33]).

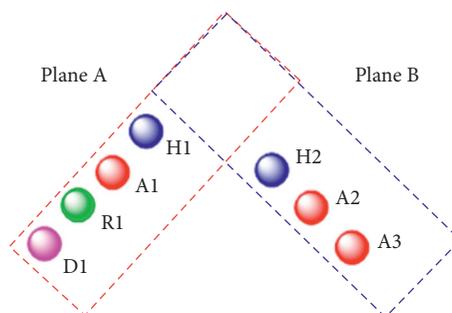


FIGURE 3: The pharmacophoric model of CBSIs with two planes: plane A (red) consists of points A1, D1, H1 and R1; plane B (blue) consists of points A2, A3, and H2 (based on Ref. [33, 34]).

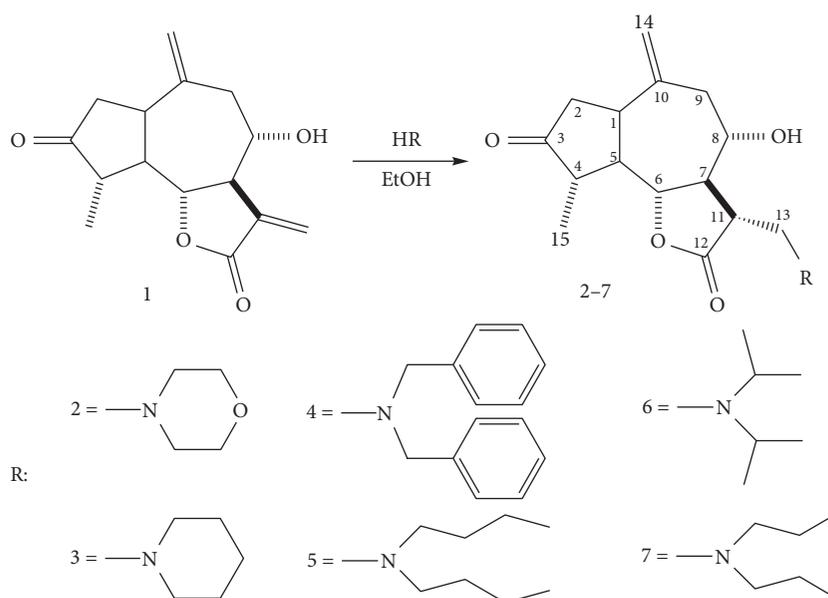


FIGURE 4: Scheme for the synthesis of grossgeminin derivatives.

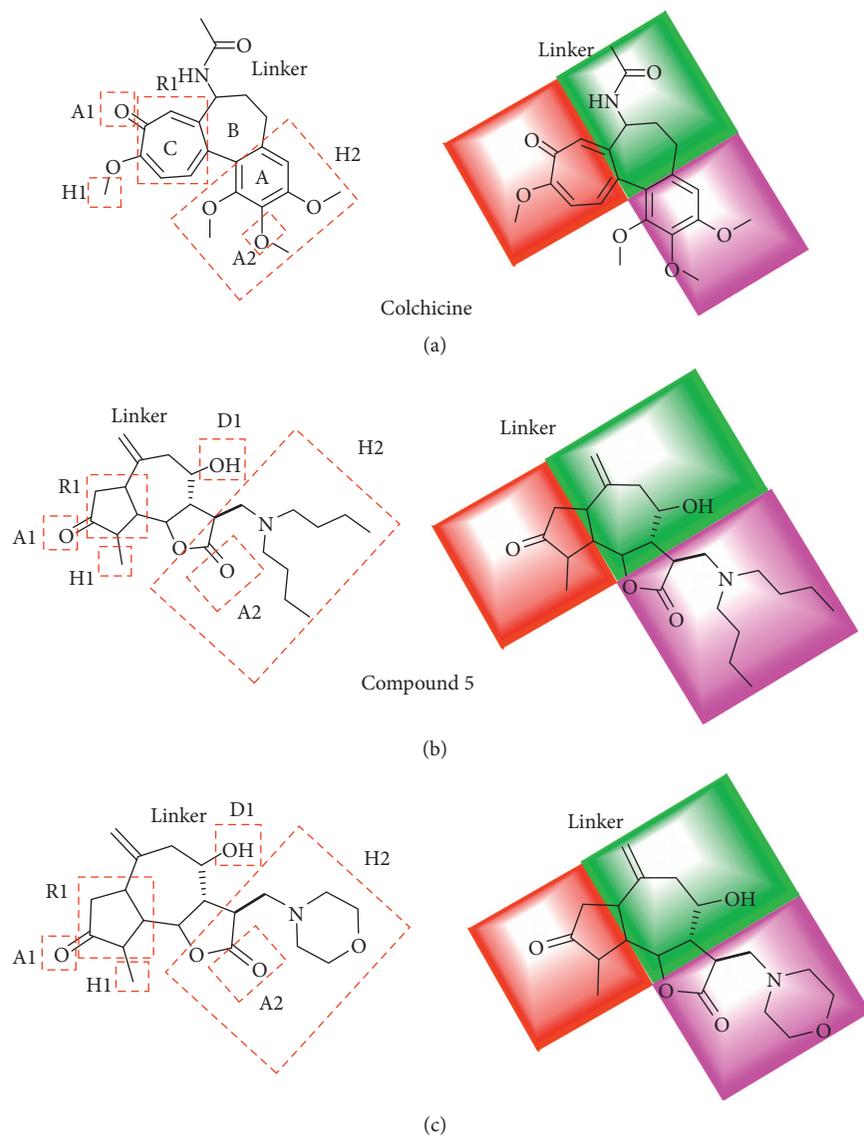


FIGURE 5: Essential pharmacophoric features of colchicine, compounds 2 and 5 as CBSIs.

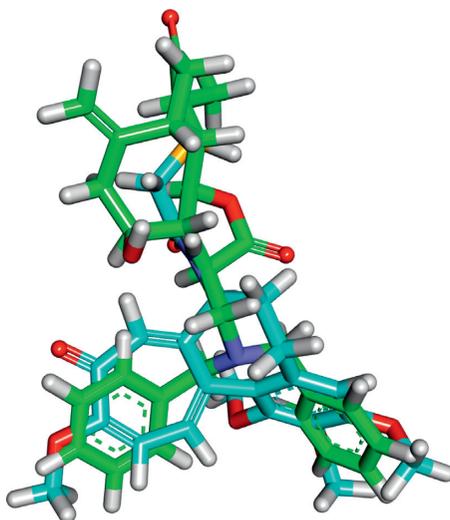


FIGURE 6: Flexible alignment of compound 5 (carbon atoms in green) with the colchicine (carbon atoms in turquoise).

TABLE 1: The docking scores of the synthesized compounds, colchicine, and colchicine against tubulin receptor.

| Comp. | Binding free energy (kcal/mol) | Comp. | Binding free energy (kcal/mol) |
|-------|--------------------------------|------------|--------------------------------|
| 1 | -18.00 | 5 | -29.34 |
| 2 | -24.57 | 6 | -26.38 |
| 3 | -25.05 | 7 | -26.86 |
| 4 | -32.16 | Colchicine | -26.13 |

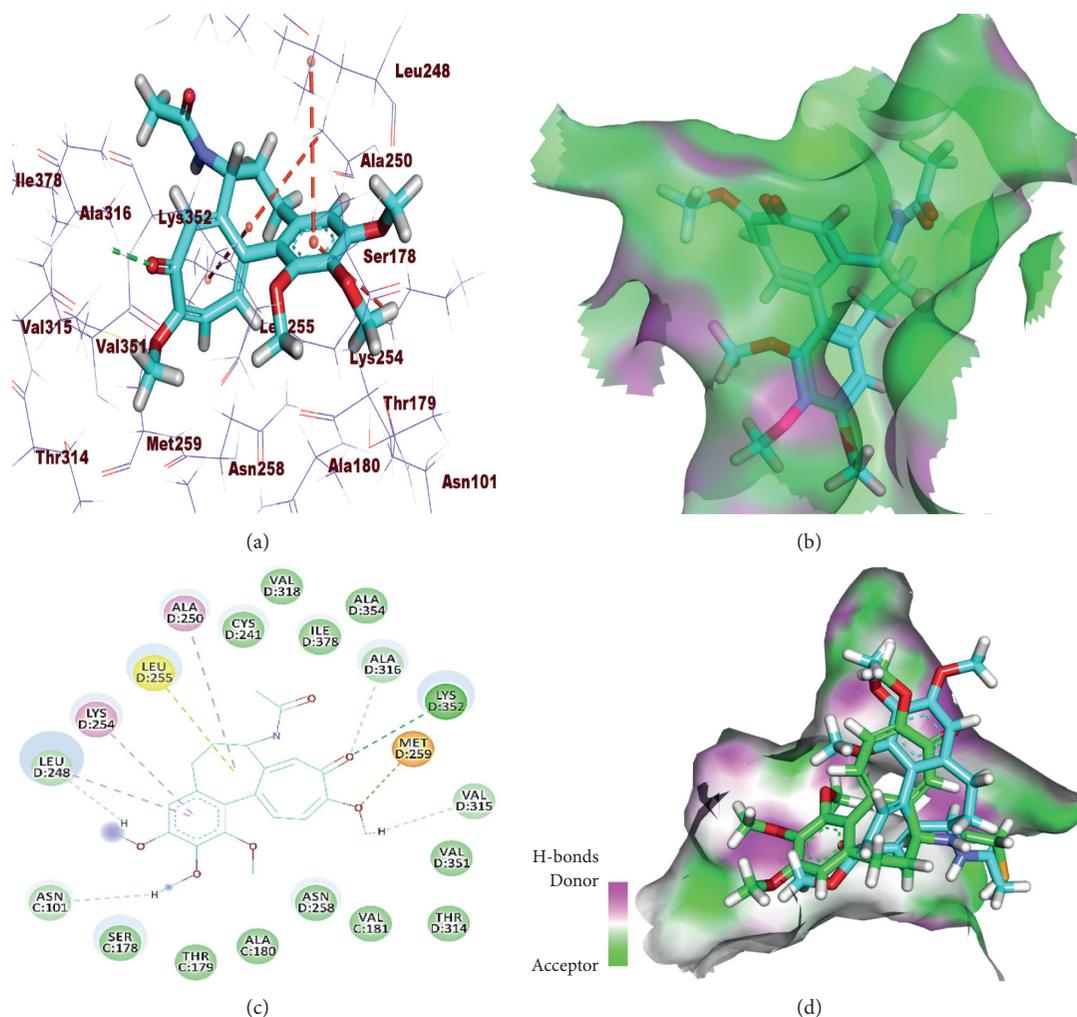


FIGURE 7: (a) 3D structure of colchicine, docked into the colchicine binding site. (b) Mapping surface showing colchicine, occupying the active pocket of colchicine binding site. (c) 2D structure of colchicine, docked into the colchicine binding site. (d) 3D alignment of colchicine (carbon atoms in turquoise) with the DAMA-colchicine (carbon atoms in green).

colchicine binding site, forming two hydrophobic interactions with Cys241 and Ala316. Also, it formed a hydrogen bond with Leu255. Furthermore, the other butyl moiety occupied the third pocket of the colchicine binding site forming two hydrophobic interactions with Val181 and Met259 (Figure 10).

3. Experimental

3.1. General Procedure for the Preparation of Amino Derivatives of Grossgemin 2–7. A sample of grossgemin 1 was

dissolved with 3 ml of ethyl alcohol at 20°C and the amine was added in a ratio of 1 : 1.2 to 1 with intensive stirring. After the end of the reaction (15–60 min, TLC control in the hexane-ethyl acetate system (1 : 1.5), manifestation, by spraying 1% vanillin solution in H₂SO₄ and a saturated solution of KMnO₄), the mixture was washed 1 : 1 with the CHCl₃ : H₂O (x3) system and the organic part was separated in a dividing funnel. The resulting solution was dried with Na₂SO₄ and filtered and then distilled on a rotary evaporator. Purification was carried out by CC, depending on the purity of the product. The yield of derivatives 2–7 is from 37.74 to 90.53%.

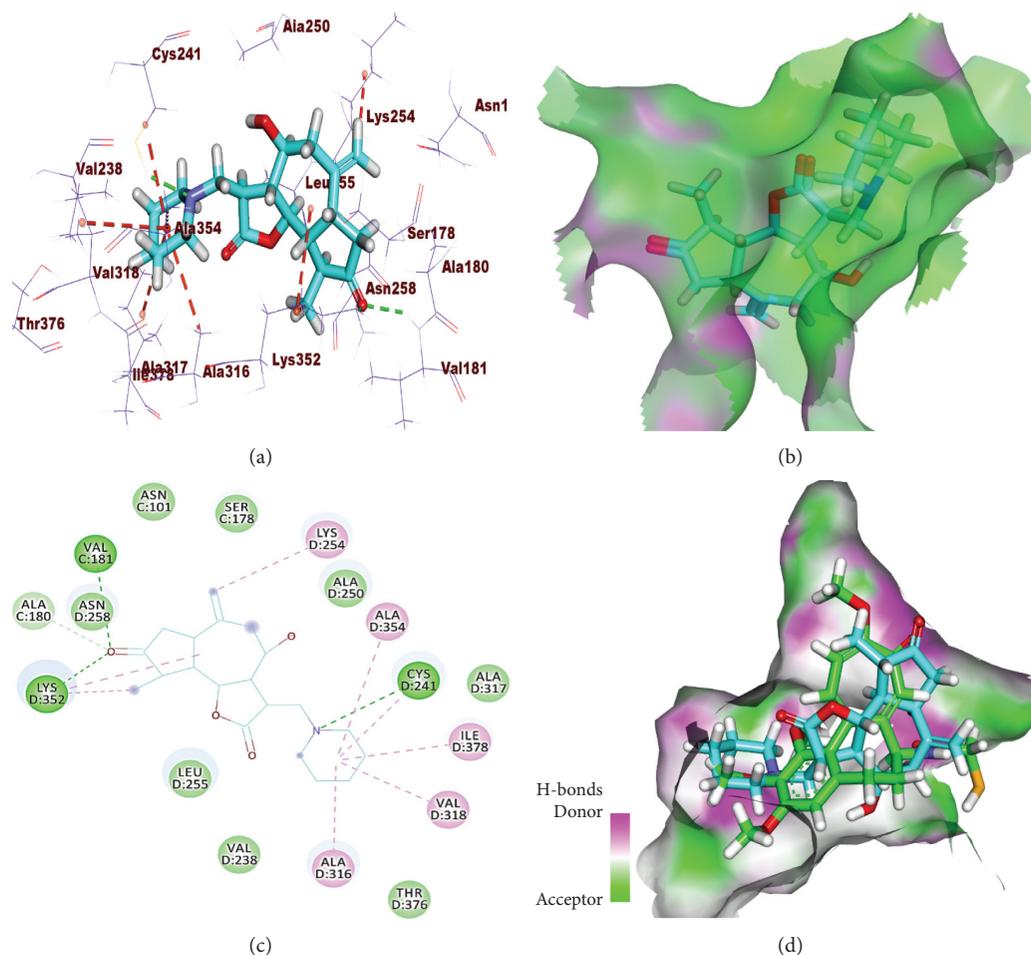


FIGURE 8: (a) 3D structure of compound 3, docked into the colchicine binding site. (b) Mapping surface showing compound 3, occupying the active pocket of colchicine binding site. (c) 2D structure of compound 3, docked into the colchicine binding site. (d) 3D alignment of compound 3 (carbon atoms in turquoise) with the DAMA-colchicine (carbon atoms in green).

3.1.1. *13-Dibenzylamino-3-keto-1,5,7 α ,4,6,8 β (H)-8(α)-hydroxyguai-10(14)-en-12,6-olide 4*. A colorless oily substance with the composition of $C_{29}H_{32}NO_4$. R_f 0.71. Yield 49 mg (90.53%).

1H NMR (500 MHz, $CDCl_3$, δ , ppm, J/Hz): 2.20 (1H, m, H-1), 2.07 (1H, m, H-2a), 2.88 (1H, m, H-2b), 1.81 (1H, q, J = 9.8, H-4), 2.02 (1H, m, H-5), 3.83 (1H, m, H-6), 2.53 (1H, t, J = 9, H-7), 3.49 (1H, td, J = 5.7; 9.5, H-8), 2.45 (2H, d, J = 6.9, H-9), 2.88 (1H, d, H-11), 2.70 (1H, t, J = 13.3, H-13a), 3.04 (1H, dd, J = 2.3; 13.5, H-13b), 4.69, 5.03 (each 1H, s, H-14a, 14b), 1.15 (3H, d, J = 7.1, H-15), 3.43 (2H at C-16, 17, d, J = 12.9, H-16a, 17a), 3.89 (2H at C-16, 17, d, J = 12.9, H-16b, 17b), 7.35 (10H at C-20-29, m, H-20-29).

^{13}C NMR (125.76 MHz, $CDCl_3$, δ , ppm): 47.16 (CH, C-1), 47.70 (CH, C-2), 175.08 (C, C-3), 54.98 (CH, C-4), 51.06 (CH, C-5), 83.05 (CH, C-6), 44.76 (CH, C-7), 73.76 (CH, C-8), 43.33 (CH_2 , C-9), 52.79 (C, C-10), 39.53 (CH, C-11), 144.32 (C, C-12), 55.44 (CH_2 , C-13), 114.39 (CH_2 , C-14), 14.47 (CH_3 , C-15), 59.61 (CH_2 , C-16), 59.61 (CH_2 , C-17), 136.10 (C, C-18), 136.10 (C, C-19), 130.13 (CH, C-20), 130.13 (CH, C-21), 128.68 (CH, C-22), 128.68 (CH, C-23),

127.97 (CH, C-24), 127.97 (CH, C-25), 128.68 (CH, C-26), 128.68 (CH, C-27), 130.13 (CH, C-28), 130.13 (CH, C-29).

3.1.2. *13-Dibutylamino-3-keto-1,5,7 α ,4,6,8 β (H)-8(α)-hydroxyguai-10(14)-en-12,6-olide 5*. A colorless oily substance with the composition of $C_{23}H_{36}NO_4$. R_f 0.66. Yield 28 mg (37.74%).

1H NMR (500 MHz, $CDCl_3$, δ , ppm, J/Hz): 3.11 (1H, td, J = 5.1; 7.9, H-1), 2.50 (2H, t, J = 7.8, H-2), 2.31 (1H, m, H-4), 2.66 (1H, m, H-5), 4.01 (1H, t, J = 9.5, H-6), 2.25 (1H, m, H-7), 3.58 (1H, td, J = 5.7; 9.4, H-8), 1.23 (2H, d, J = 7, H-9), 2.25 (1H, m, H-11), 2.58 (1H, m, H-13a), 3.04 (1H, dd, J = 9.5; 13.2, H-13b), 4.74, 5.05 (each 1H, s, H-14a, 14b), 1.21 (3H, d, J = 7, H-15), 2.87 (2H at C-16, 17, dd, J = 5.5; 12.8, H-16a, 17a), 2.15 (2H at C-16, 17, t, J = 9.6, H-16b, 17b), 1.47 (4H at C-18, 19, m, H-18-19), 1.29 (4H at C-20, 21, sq, J = 7.2, H-20-21), 0.91 (4H at C-22, 23, t, J = 7.3, H-22-23).

^{13}C NMR (125.76 MHz, $CDCl_3$, δ , ppm): 39.76 (CH, C-1), 43.22 (CH, C-2), 175.28 (C, C-3), 47.24 (CH, C-4), 45.77 (CH, C-5), 82.74 (CH, C-6), 51.03 (CH, C-7), 73.68

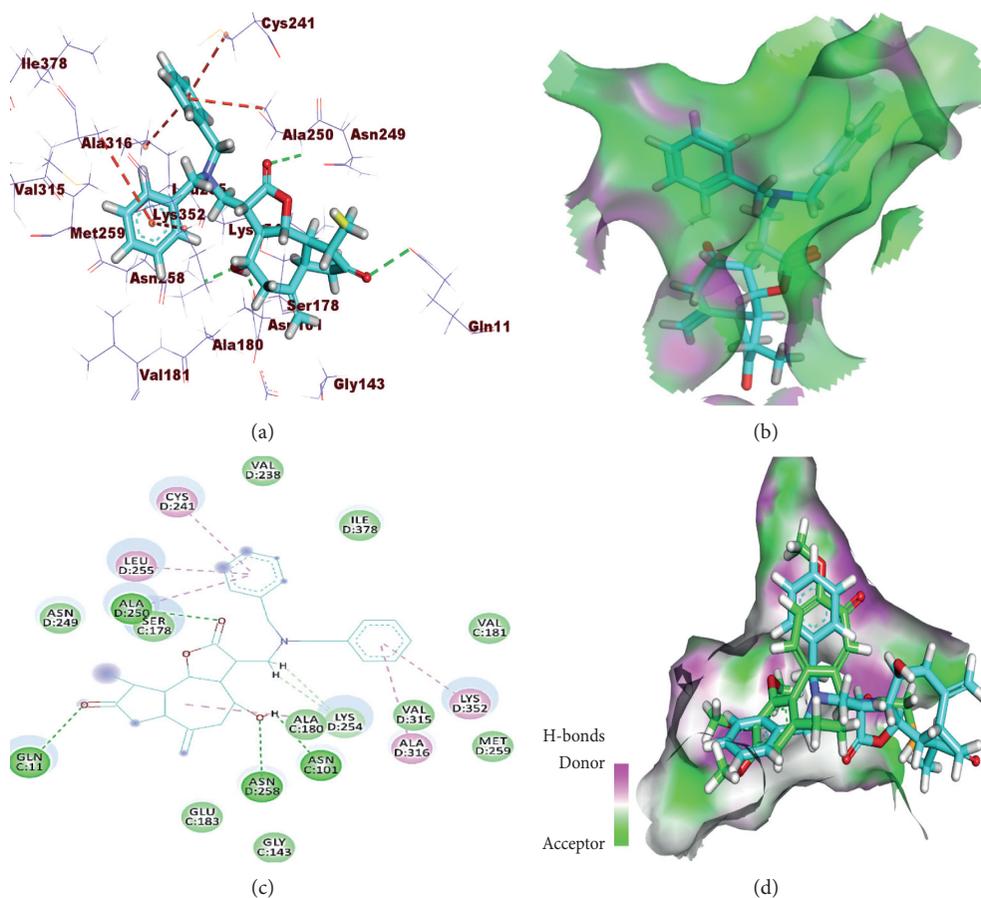


FIGURE 9: (a) 3D structure of compound 4, docked into the colchicine binding site. (b) Mapping surface showing compound 4, occupying the active pocket of colchicine binding site. (c) 2D structure of compound 4, docked into the colchicine binding site. (d) 3D alignment of compound 4 (carbon atoms in turquoise) with the DAMA-colchicine (carbon atoms in green).

(CH, C-8), 29.69 (CH₂, C-9), 53.60 (C, C-10), 56.34 (CH, C-11), 144.38 (C, C-12), 55.87 (CH₂, C-13), 114.42 (CH₂, C-14), 14.73 (CH₃, C-15), 47.53 (CH₂, C-16), 47.53 (CH₂, C-17), 27.94 (CH₂, C-18), 27.94 (CH₂, C-19), 20.69 (CH₂, C-20), 20.69 (CH₂, C-21), 13.93 (CH₃, C-22), 13.93 (CH₃, C-23).

3.1.3. 13-Di-isopropylamino-3-keto-1,5,7 α ,4, 6,8 β (H)-8(α)-hydroxy-guai-10(14)-en-12,6-olide 6. A colorless crystalline substance with the composition of C₂₁H₃₂NO₄. R_f0.53. Yield 47.8 mg (69.3%). M.p. 93.0-93.6°C.

NMR ¹H (500 MHz, CDCl₃, δ , ppm, J/Hz): 3.12 (1H, td, J = 4; 8, H-1), 2.51 (2H, m, H-2), 2.29 (1H, m, H-4), 2.23 (1H, m, H-5), 4.00 (1H, m, H-6), 2.47 (1H, m, H-7), 2.81 (1H, m, H-8), 3.51 (1H, t, J = 9.1, H-9a), 4.00 (1H, m, H-9b), 3.65 (1H, td, J = 5.8; 9.5, H-11), 2.20 and 2.84 (2H, m, H-13), 4.76, 5.06 (each 1H, s, H-14a, 14b), 1.21 (3H, d, J = 6.8, H-15), 3.44 (2H at C-16, 17, s, H-16, 17), 1.23 (12H at C-18-21, d, J = 8.1, H-18-21).

NMR [¹³C (125.76 MHz, CDCl₃, δ , ppm): 39.78 (CH, C-1), 43.25 (CH, C-2), 174.03 (C, C-3), 47.21 (CH, C-4), 51.13 (CH, C-5), 82.93 (CH, C-6), 53.49 (CH, C-7), 47.48 (CH, C-8), 71.93 (CH₂, C-9), 29.68 (C, C-10), 74.14 (CH, C-11), 143.90 (C, C-12), 47.04 (CH₂, C-13), 114.90 (CH₂,

C-14), 14.65 (CH₃, C-15), 59.27 (CH, C-16), 59.27 (CH, C-17), 14.65 (CH₃, C-18), 14.65 (CH₃, C-19), 14.65 (CH₃, C-20), 14.65 (CH₃, C-21).

3.2. Docking. Crystallographic structure of tubulin [PDB ID: 1SA0, resolution 3.00 Å] was retrieved from Protein Data Bank (<http://www.pdb.org>) and considered as a target for docking simulation. The docking analysis was performed using MOE2014 software to evaluate the free energy and binding modes of the synthesized compounds against tubulin. At first, the crystal structure of the target was prepared by removing water molecules and retaining the two essential chains and the cocrystallized ligand, *N*-deacetyl-*N*-(2-mercaptoacetyl)-colchicine (DAMA-colchicine). Then, the protein structure was protonated, and the hydrogen atoms were hidden. Next, the energy was minimized, and the binding pocket of the protein was defined [34].

The 2D structures of the synthesized compounds and reference ligand (colchicine) were sketched using ChemBioDraw Ultra 14.0 and saved as MDL-SD format. Then, the saved files were opened using MOE and 3D structures were protonated. Next, energy minimization was applied. Before the docking process, validation of the docking protocol was carried out by running the

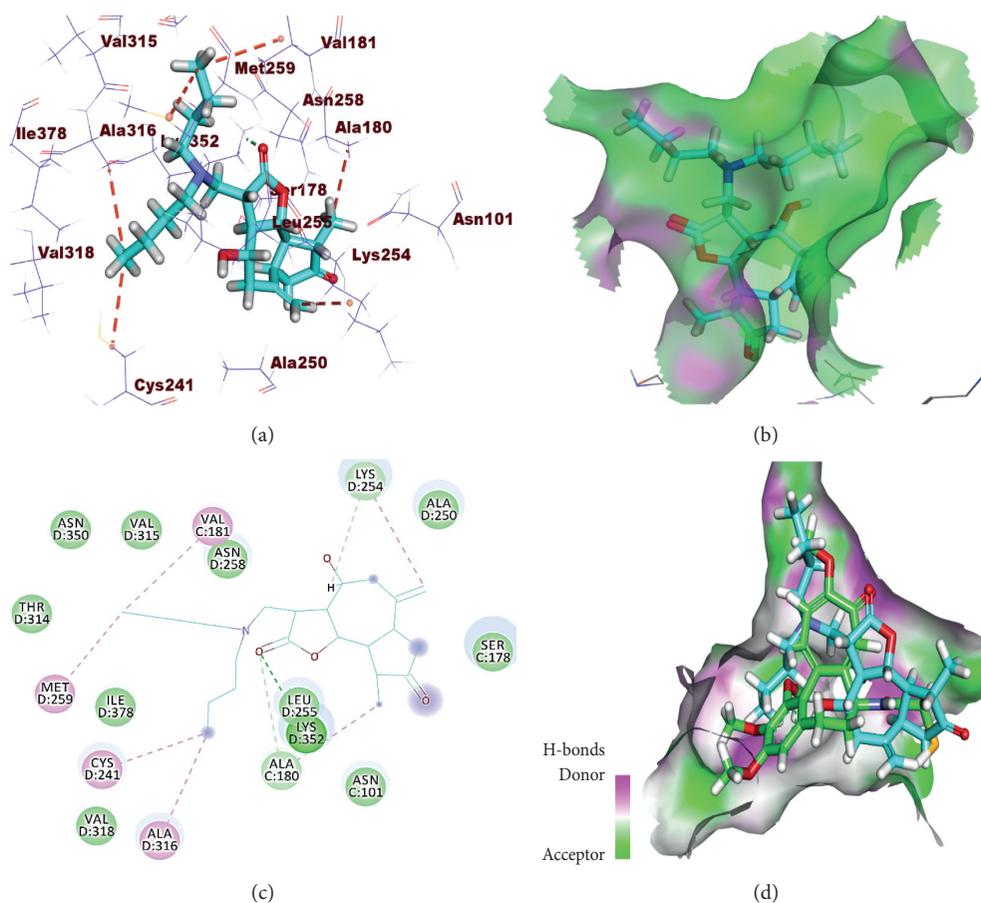


FIGURE 10: (a) 3D structure of compound 5, docked into the colchicine binding site. (b) Mapping surface showing compound 5, occupying the active pocket of colchicine binding site. (c) 2D structure of compound 5, docked into the colchicine binding site. (d) 3D alignment of compound 5 (carbon atoms in turquoise) with the DAMA-colchicine (carbon atoms in green).

simulation only using the cocrystallized ligand (DAMA-colchicine) which showed a low RMSD value. The molecular docking of the synthesized was performed using a default protocol against the target receptor. In each case, 30 docked structures were generated using genetic algorithm searches; ASE was used for scoring and force field (MMFF94) for refinement [38, 39].

4. Conclusion

Six grossgemin amino derivatives (2–7) were synthesized according to be colchicine binding site inhibitors (CBSIs). Six (out of seven) pharmacophoric features as CBSIs were achieved in 2–7. Furthermore, the 3D-flexible alignment of compound 5 as a representative example with colchicine showed a very good overlapping. Consequently, compounds 2–7 were docked into CBS with binding modes very similar to that of colchicine and exhibited very good binding free energies that were better than that of colchicine in compounds 4–7 with a noticeable superiority to compound 4. The obtained compounds (2–7), especially compound 4, could be promising antimicrobial and/or anticancer candidates through being CBSIs.

Data Availability

NMR data of compounds 2–7 are available from the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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