CHAPTER V

CONCLUSION

Geldanamycin was mainly modified at C-17 and/or C-19 to yield fifthteen derivatives including

1. Modification of 17-OCH_3 into other alkoxy derivatives: 17-*O*-ethyl-17-*O*-demetylgeldanamycin (**6**), 17,19-di-*O*-ethyl-17-*O*-demethylgeldanamycin (**7**), 17-*O*-n-propyl-17-*O*-demethylgeldanamycin (**8**), and 17-*O*-benzyl-17-*O*-demethylgeldanamycin (**9**).
2. Modification of 17-OCH_3 into alkylamino derivatives: 17-amino-17-demethoxygeldanamycin (**10**), 17,19-di-methylamino-17-demethoxygeldanamycin (**11**), 17-ethylamino-17-demethoxygeldanamycin (**12**), 17-n-proylamino-17-demethoxy-geldanamycin (**13**), 17,19-di-n-propylamino-17-demethoxygeldanamycin (**14**), 17-allylamino-17-demethoxy-geldanamycin (**15**), 17,19-di-hydroxypropylamino-17-demethoxygeldanamycin (**16**), and 17-benzylamino-17-demethoxygeldanamycin (**17**).
3. Modification at C-19: 19-*O*-methylgeldanamycin (**18**), 19-amino-geldanamycin (**19**), and 19-glutathionylgeldanamycin (**20**).

The other modifications at 11-OH amd conjugated double bonds were also obtained as follows,

1. Modification of 11-OH into other alkoxy derivatives: 11-*O*-methyl-geldanamycin (**21**) and 11-*O*-acetylgeldanamycin (**22**).
2. Reduction of double bond at C-2 to C-5: 2,3,4,5-tetrahydro-geldanamycin (**23**).

All of the eighteen modified analogues as well as three previously isolated ansamycins, geldanamycin (**1**), 17-*O*-demethylgeldanamycin (**2**), and 17-*O*-demethyl-geldanamycin hydroquinone (**5**), including geldanamycin were investigated for biological activities on P19 neuron-like cells and P19 cells. The results revealed that geldanamycin (**1**) and the 17-*O*-alkyl-17-*O*-demethylgeldanamycin analogues, including 17-*O*-ethyl-17-*O*-demethylgeldanamycin (**6**), 17-*O*-n-propyl-17-*O*-demethyl-geldanamycin (**8**), and 17-*O*-benzyl-17-demethoxygeldanamycin (**9**), and 19-*O*-methylgeldanamycin (**18**) possessed the neuritogenic activity on P19 neuron-like cells

when treated at low dose (1 nM) while the rest showed toxicity on P19 neuron-like cells at this concentration.

All of these active compounds were further observed for their neuroprotective property on P19 neuron-like cells, the results presented that they displayed the neuroprotective ability on P19 NLCs at very low dose of 1 nM when co-treated with taxol at 0.65 μM. Therapeutic index between neurotoxicity and neuritogenicity of the active compounds showed that 17-*O*-benzyl-17-*O*-demethylgeldanamycin (**9**), and 19-*O*-methylgeldanamycin (**18**) possessed a wide therapeutic index which was more than 10,000, while geldanamycin (**1**), 17-*O*-ethyl-17-*O*-demethylgeldanamycin (**6**), and 17-*O*-n-propyl-17-*O*-demethylgeldanamycin (**8**) exhibited their therapeutic indices at 2000, 1,600, and 6700, respectively. Therefore, compounds **9** and **18** are promising candidates to be further developed as novel neuroprotective agents. However, other 17-alkoxy derivatives of geldanamycin are essentially further synthesized and evaluated for their neuroprotective ability. The mechanism(s) of action of geldanamycin and its derivatives for neuroprotective ability should be further investigated.

The cytotoxicity assay of the compounds expressed that all of geldanamycin analogues possessed less cytotoxicity on P19 cells than geldanamycin (**1**). However, 17-*O*-ethyl-17-*O*-demethylgeldanamycin (**6**), and 17-*O*-n-propyl-17-*O*-demethyl-geldanamycin (**8**) displayed the cytotoxicity on P19 cells similar to that of geldanamycin. The longer side chain at C-17 position, hydroquinone type, substitutions at C-19 position in the quinone ring, and C-11 position, and reduction of double bond in the ansa ring remarkably reduced cytotoxic activity of geldanamycin.