2 Research Objectives

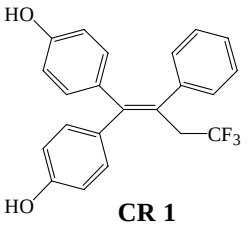
Despite the success of hormone therapy in preventing and treating breast cancer and the increasing understanding on hormone action, man has still many clinic problems and theoretic questions about them to solve and answer. For example, prolonged treatment with the most widely used antiestrogen tamoxifen may develop tamoxifen resistance [Katzenellenbogen, 9] and increases the risk for endometrial cancer [Cosman, 7; Mitlak, 82]. One of the best ways is to develop new hormonal anticancer agents. Stilbene derivatives and their dihydro-derivatives, 1,2-diarylethanes, are of great potential.

2.1 Stilbene Derivatives and Their Alkane Analogues

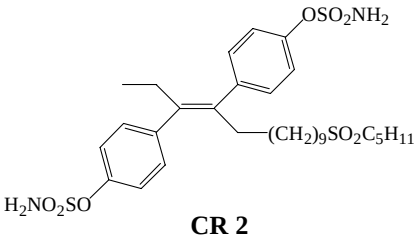
Tamoxifen and diethylstilbestrol are known as examples of stilbene derivatives used (or once used) as anticancer agents for hormone therapy and as standard compounds for hormone studying. Many of their analogues also have been synthesized and investigated as antitumor agents used for the treatment of breast cancer [Macgregor, 15]. Some stilbene derivatives without basic side chain, e.g. **CR 1** (see Scheme 4), have been tested in breast cancer cell line and showed high antiestrogenic activities [Lubczyk, 83 and 84]. Several sulfamoyloxy-substituted stilbenes, e. g. **CR 2**, could inhibit the growth of human breast cancer cells by a combination of antiestrogen action and enzyme inhibition [Walter, 85]. Some commercially available stilbene derivatives also exhibited significant estrogenic activities on breast cancer cell line [Sanoh, 86]. In particular, resveratrol (**CR 3**), which is a phytoestrogen found in grapes and present in red wine, has been regarded as a potential anticancer agent functioning also in chemoprevention and inhibition of breast cancer because of its multiple pharmacological effects and its safety [Le Corre, 87; Ulrich, 88; Levenson, 89; Roberti, 90]. A number of its analogues have been synthesized and biologically evaluated [Roberti, 90; Lion, 91]. As examples of halogen-subustituted stilbenes, a series of 2,6-dichloro-4-hydroxy-substituted stilbene derivatives, e. g. **CR 4**, were prepared and tested to be estrogens in the uterus weight test. Their corresponding dihydro-derivatives 1,2-diarylethanes, e. g. **CR 5**, possessed significant estrogenic activities and were active as biological response modifiers in animals bearing hormone-sensitive breast cancer [Schertl, 92].

In addition, 1,2-diaryl-1,2-diazidoethane **CR6** functioned as an estrogen *in vivo* [Gust, 93]. Introducing 1,2-diarylethanes into a platinum complex produced the new potential anticancer

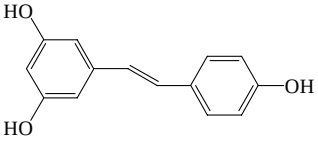
platinum complexes **CR 7** and **CR 8**. [Gust, 94 and 95]. Based on the above-mentioned results, a project for development of new potential anticancer agents is designed.



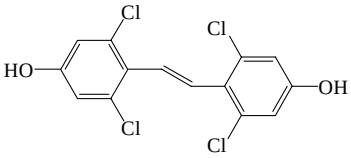
CR 1



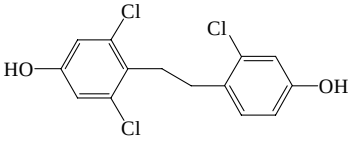
CR 2



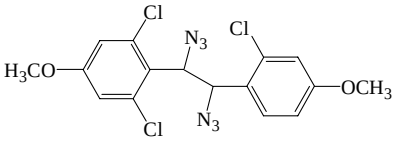
CR 3 (Resveratrol)



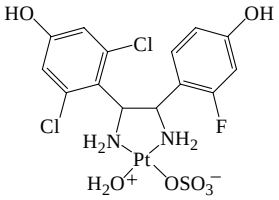
CR 4



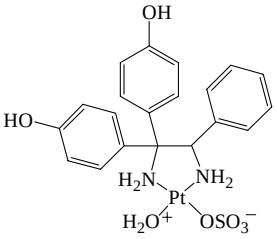
CR 5



CR 6



CR 7



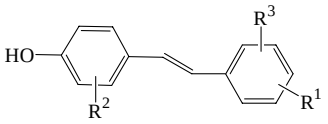
CR 8

Scheme 4

2.2 Research Objectives

This project mainly deals with syntheses and biological evaluation of novel stilbene derivatives and 1,2-diaryl-1,2-diazidoethanes, which are expected to be potential anticancer agents functioning above all in prevention and treatment of breast cancer. Research objectives include:

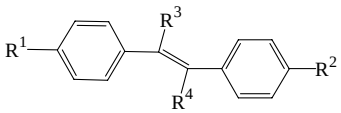
1) Syntheses of novel stilbene derivatives, which bear a hydroxy group in 4-position on one phenyl ring and a methoxy or another hydroxy group in the other phenyl ring and comprise at least one group of F and Cl in 2 or 6 (2' or 6')-position by each stilbene depicted in scheme 5;



R^1 = OCH_3, OH; R^2, R^3 = H, F, Cl (or double substituent Cl_2).

Scheme 5

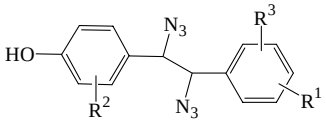
2) Syntheses of novel tetrasubstituted stilbene derivatives or compounds containing a stilbene structure as depicted in scheme 6, wherein at least one of R^1 and R^2 is a methoxy or hydroxy group, while R^3 and R^4 are alkyl, aryl groups or both together form a ring structure;



R^1, R^2 = H, OCH_3, OH; R^3, R^4 = alkyl, aryl, or R^3 and R^4 form a ring.

Scheme 6

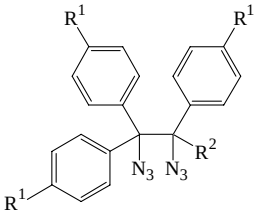
3) Syntheses of novel 1,2-diaryl-1,2-diazidoethanes depicted in scheme 7, wherein R^1 is a methoxy or hydroxy group, while R^2 and R^3 are selected from the group of H, F, Cl, and double substituent Cl_2;



R^1 = OCH_3, OH; R^2, R^3 = H, F, Cl (or double substituent Cl_2).

Scheme 7

4) Syntheses of tetrasubstituted 1,2-diazidoethanes depicted in scheme 8, wherein R^1 is a methoxy group and R^2 is a methyl or ethyl group;



R^1 = OCH_3; R^2 =CH_3, C_2H_5.

Scheme 8

5) Pharmacological evaluation of all target compounds for estrogenic or antiestrogenic effect in a luciferase assay using MCF-7-2a cells.