Chapter 4

# Green Chemistry and Synthesis of Anticancer Molecules

Shagufta Perveen and Areej Mohammad Al-Taweel

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.70419

**Abstract**

Green chemistry is a modern area of chemistry merged with chemical engineering methods. It highlighted the synthesis of molecules in a manner of using environment-friendly chemical reagents with low waste material for enhancing environmental performance which reduce the formation of hazard substances. Modern researches are trying to reduce the risk of human kind health and the environment of our world by doing magnificent work in the field of green chemistry. In the pharmaceutical field, green chemistry works very well with the formation of many drugs and it utilizes non-hazards, reproducible and environment-friendly solvents with low time and money costs by using catalyst, microwave, ultrasonic, solid phase and solvent-free synthesis. Until now, scientist has synthesized many anticancer molecules by using these modern green chemistry techniques. These compounds showed significant anticancer activities against many human cancer cell lines. In this chapter, we will cover different views and the recently published literature to summarize the role of green chemistry in the synthesis of anticancer compounds.

**Keywords:** green synthetic approaches, anticancer activity, synthesis of active molecules, cancer cell lines

## 1. Introduction

Green chemistry is a modern way for the synthesis of organic compounds and designed different drugs under facile protocols, efficient conditions, environmentally benign and high yielding method of molecules with advantages over traditional organic synthetic methods. It usually reduces waste by-products, costs and develops environmentally friendly procedures.

| Method use | Reaction condition | Class of compounds synthesized | Cancer cell lines | Refs. |
|---|---|---|---|---|
| Eco-friendly one-pot synthesis | Mixture of methyl ketone, aldehyde, active methylene cyanoacetamide, malononitrile, ethylcyanoacetate and 2 mL of glycol/ammonium acetate was added to the reaction vessel and placed into MW reactor then allowed to react under MW irradiation at 200–400 W power and 120°C for 6–8 min. The compound was collected by filtration and recrystallized from ethanol/DMF to give pure amino-cyanopyridine and oxo-cyanopyridine derivatives | Novel cyanopyridine derivatives (**1**) | Human liver HepG2, colon HCT-116, breast MCF-7 cancer | [1] |
| Microwave-assisted synthesis | A mixture consisting of methyl salicylate and sodium was heated to 110°C. When the reaction with sodium was completed after 5–10 min, mixture was irradiated for 30 min at 160–200°C using a 200 W MW source. Chromatographic separation of crude mixture on silica gel column gave the pure products | Salicyloyloxy and 2-methoxybenzoyloxy androstane and stigmastane derivatives (**2**) | Human breast adenocarcinoma ER+, MCF-7, estrogen receptor negative breast adenocarcinoma ER+, MDA-MB-231, prostate cancer PC-3 and normal fetal lung fibroblasts MRC-5 cancer | [2] |
| One-pot synthesis | Reaction of 2-chloro-3-chloromethyl-quinoline with terminal alkyne in the presence of KI, NaN3 and precatalyst copper(II)sulfate in combination with Na-ascorbate was examined in water at room temperature | Quinoline, triazole and dihydroquinoline (**3**) | Human A549 lung adenocarcinoma epithelial, MCF-7 breast adenocarcinoma, HepG2 hepatocellular liver carcinoma, DU145 prostate cancer | [3] |
| Microwave-assisted synthesis | Ethyl/methyl acetoacetate and an aldehyde were taken into a beaker and dissolved in minimum quantity of dimethylformamide. To this solution, ammonium acetate was added. Reaction mixture was subjected to microwave irradiation at 480 W for 2–6 min, with a pulse rate of 60 s each in a microwave oven. After completion of the reaction on TLC, the resultant product was filtered, washed with chill water and recrystallized | 4-alkyl/aryl-3,5-bis(carboethoxy/carbomethoxy)-1,4-dihydro-2,6-imethylpyridines (**4**) | Human HT-29 colon cancer and MDA-MB breast cancer and MRP1 inhibitory activity using the insect cell membrane | [4] |

| Method use | Reaction condition | Class of compounds synthesized | Cancer cell lines | Refs. |
|---|---|---|---|---|
| Cellulose-supported copper nanoparticle-catalyzed click reaction in water | 4-hydroxybenzaldehyde treated with propargyl bromide in the presence of K2CO3 in dry acetone under reflux to yield 4-*O*-propargylated benzaldehyde. In the next step, 4-*O*-propargylated benzaldehyde was reacted with substituted acetophenones via base-catalyzed Claisen-Schmidt condensation to yield chalcones | Chalcone-linked 1,2,3-triazoles (**5**) | Human MCF-7, MIA-Pa-Ca-2,A549, HepG2 cancer | [5] |
| Copper-mediated synthesis | Functionalized pyrazolopyridine derivatives via copper-promoted cyclization of pyridyl acetates and benzonitriles in DMSO under argon atmosphere, converted to corresponding pyrazolo[1, 5-a]pyridines from commercially available aromatic nitriles and various pyridyl acetates | Novel pyrazolo, pyridine derivatives (**6**) | Human A549 lung adenocarcinoma, MCF-7 breast carcinoma cell line, HCT-116 colon cancer, PC-3 prostate cancer | [6] |
| Microwave conditions | Quinolone derivatives were synthesized by reacting 2,3-dihydro-8-nitro-4-quinolones with aromatic aldehydes by pyrrolidine base-catalyzed condensation reaction and were treated with hydrazine derivatives under MW condition, which afforded pyrazolo quinoline derivatives in high yields | Pyrazolo[4,3-c] quinoline (5a-i, 7a-b) and pyrano[3,2-c] quinoline derivatives (**7**) | Human MCF-7 breast and A549 lung cancer | [7] |
| Facile protocol, efficient and environmentally benign | Synthetic route to barbituric acid derivatives substituted at C5-position. Addition of barbituric acid analogous into nitrostyrene, in water mediated by diethylamine as base gave the target 5-monoalkylbarbiturates in excellent yield | Pyrimidine-2,4,6-trione derivatives (**8**) | HeLa cervical cancer and 3T3 mouse fibroblast cancer | [8] |
| Simple, eco-friendly and efficient method | To synthesize $\alpha,\beta$-unsaturated carbonyl-based compounds, Claisen-Schmidt condensation was used between different ketones and suitable aryl aldehydes in the presence of NaOH in ethanol | $\alpha,\beta$-unsaturated carbonyl-based compounds (**9**) | PC12 cancer | [9] |

| Method use | Reaction condition | Class of compounds synthesized | Cancer cell lines | Refs. |
|---|---|---|---|---|
| Synthesis by using green solvents | 2,3-Dihydrophthalazine-1,4-dione, 5,5-dimethyl clohexane-1,3-dione, aldehyde and p-sulfonic acid calix[4]arene were dissolved in EtOAc. The mixture was irradiated in a MW reactor for 10 min at 130°C. The reaction was cooled to room temperature and then water was added. The mixture was placed in a freezer at 20°C to form the product | Phthalazine-triones: Calix[4]arene (**10**) | Human tumor U251 glioma, MCF7 breast NCIADR/ RES multiple drug-resistant ovarian, 786-0 renal, NCI-H460 lung, non-small cells, PC-3 prostate, OVCAR-03 ovarian, HT-29 colon and K562 leukemia cancer | [10] |
| One-pot reaction | Mixture of 2-thioxoimidazolidin-4-one and sodium ethoxide in EtOH was refluxed for 30 min. After cooling, CS2 was added and the reaction mixture was stirred at room temperature for 1 h. After evaporation of solution, the solid product was recrystallized from EtOH to give compound in 70–75% yield | Novel 2-thioxoimidazolidin-4-one and benzothiazole thiolate salts (**11**) | MCF-7 breast carcinoma cancer | [11] |
| One-pot ultrasound-promoted synthesis | One-pot synthesis of 5-amino-2-(4-chlorophenyl)-7-substituted phenyl-8,8a-dihydro-7H-3,4) thiadiazolo(3,2-$\alpha$)pyrimidine-6-carbonitrile derivatives from three component reactions of 5-(4-chlorophenyl)-1,3,4-thiadiazol-2 amine, aromatic aldehydes and malononitrile in the presence of NaOH under reflux and ultrasonic irradiation | 5-amino-2-(4-chlorophenyl)-7-substituted phenyl-8,8a-dihydro-7H-(1,3,4)thiadiazolo (3,2-$\alpha$)pyrimidine-6-carbonitrile derivatives (**12**) | MCF-7, K562, HeLa and PC-3 cancer | [12] |
| Microwave-assisted synthesis | Microwave irradiation of mixture of aldehyde and 1,2-phenylenediamine at 80°C, 150 W for 5 min using Na2S2O5 for oxidation, the product 1H-benzo[d] imidazol-2-yl)-6,7,8-trimethoxynaphthalen-1-ol was isolated in excellent 95% yield | 2-quinolizinylbenzimidazole and 2-naphthalylbenzimidazole derivatives (**13**) | Human breast MCF-7 cancer | [13] |
| Laccase-catalyzed green synthesis | These reactions were carried out using catechol, 2,3-dihydro-2-thioxopyrimidin-4(1H)-ones and enzyme laccase, phosphate buffer pH 6 and EtOH with nice yields 95% | Novel pyrimidobenzothiazoles and catechol thioethers (**14**) | Human HepG2 cancer | [14] |
| Microwave-assisted Hantzsch type condensation reactions | A solution of $\alpha$-halocarbonyl derivative in dry acetone was added to the solution of benzylidene hydrazine carboseleno amide derivative in DMF. The reaction mixture was stirred at room temperature for 1 day and then neutralized with NaHCO3. The precipitate was filtered and then recrystallized from EtOH | Aryl-hydrazinyl-1,3-selenazole andaroyl-hydrazonyl-1,3-selenazoles (**15**) | Human leukemia cell lines CCRF-CEM and HL60 and carcinoma cell lines MDA-MB231, HCT116 and U87MG | [15] |

| Method use | Reaction condition | Class of compounds synthesized | Cancer cell lines | Refs. |
|---|---|---|---|---|
| Catalyst-free, green approach | Mixture of 2-(1H-pyrrol-1-yl) aniline and isatin in EtOH was refluxed at 80°C for 6 h. The progress of reaction was monitored by TLC. On the completion, it cooled to room temperature and then precipitated product was filtered, washed with EtOH and dried by rotavapor to afford pure compound | Pyrrolospirooxindole derivatives (**16**) | Human prostate cancer DU-145 | [16] |
| Simple and convenient one-pot four-component synthesis | Benzaldehyde was reacted with morpholine and 2,4-dinitrophenyl hydrazine in the presence of a chiral pyrrolidine-based catalyst in EtOH. In the next step, compounds were reacted with cinnamaldehyde in the presence of chiral catalyst in toluene at room temperature for 5 h. Compounds were obtained in excellent yields (88–96%) | Morpholine-pyrazolidine derivatives (**17**) | HepG2 liver, HeLa cervical and MCF-7 breast cancer | [17] |
| Novel one-pot cyclocondensation | A mixture of three components, thiosemicarbazide, 5-acyl thiazoles and phenacyl chlorides, was dissolved in freshly prepared non-volatile organic solvent, DIPEAc and the solution was stirred at room temperature for 30 min. Then, the products were isolated with excellent yields, 82–96% | New bithiazolyl hydrazones (**18**) | MCF-7, HCT116 and THP-1 cancers | [18] |
| One-pot synthesis | Series of *N*-(aminosulfonyl)-4-podophyllotoxin carbamates were synthesized with amines and *N*-(chlorosulfonyl)-4-podophyllotoxin carbamate dry CH2Cl2 via Burgess-type intermediate, which generated in situ by reaction of PPT and chlorosulfonyl isocyanate CSI in the presence of pyridine | N-(aminosulfonyl)-4-podophyllotoxin carbamates (**19**) | Human tumor HeLa, A-549, HCT-8 and HepG2, human fetal lung fibroblast WI-38 cancer cells | [19] |
| One-pot solvent-free synthesis | Tryptamine, 2-hydroxy-4,6-dimethylpyrimidine and appropriate thiazole-4-carboxylate were homogenized and then heated at 100–105°C for 5–6 h. The reaction mixture was concentrated and the crude product so obtained was crystallized from EtOH | Bacillamide analogues (**20**) | Human colorectal tumor HCT-116, breast adenocarcinoma MDA-MB-231 and immune system JURKAT cancer | [20] |
| Microwave-assisted synthesis | Amine and ferulic acid were mixed together in 1:1 ratio for mono-amide and 2:1 molar ratio for bisamide. The reaction mixture was irradiated in microwave at 180–450 Watt for 3–7 min. The reaction progress was monitored by TLC. Products were obtained and purified by crystallization | Ferulic acid amide derivatives (**21**) | Human breast MDA-MB-231 and MCF-7, cervical HeLa, lung A549 and liver HepG2 | [21] |


http://dx.doi.org/10.5772/intechopen.70419

| Method use | Reaction condition | Class of compounds synthesized | Cancer cell lines | Refs. |
|---|---|---|---|---|
| Catalyst under solvent-free conditions | The aromatic aldehyde, 2-hydroxy-1,4-naphthoquinone and 2-naphthol grinded in a mortar for 5 min. Then, InCl3 was added and the reaction mixture was grinded 15 min again then placed in a sealed tube and kept in an oven at 120°C for 3 h. The resulting crude was purified by chromatography | Dibenzo anthracenes (**22**) | HEL human erythroleukemia and MCF7 breast cancer | [22] |

**Table 1.** Anticancer molecules by green synthesis.

This chemistry surrounds a series of modern techniques for synthesizing bioactive compounds, such as microwave-assisted synthesis, solid phase supported solvent-free synthesis, reaction with organocatalyst, one-pot multicomponent reactions and sonochemical synthesis, using ionic liquids techniques. Pharmaceutical companies are also improving chemicals to reduce environmental hazards and to minimize ecological risks.

Cancer is a disease generated by uncontrolled cell growth in the body. There are many progresses for cancer treatment but it remains mostly common cause of human death. The number of cancer patients is increasing significantly worldwide, especially in developed countries. According to the global oncology trend report (2015), global spending on cancer medications rose 10.3% in 2014 to $100 billion from $ 75 billion in 2009. Therefore, there is a quick and urgent need of systematic approach to the development of new chemotherapeutic agents with superior efficacy, lower toxicity as well as better selectivity. The methods used in green chemistry organic synthesis of molecules are playing wide role for designing the anticancer drugs. In this chapter, we discuss the most recent literature on green synthesis of different molecules and their anticancer potential on different human cancer cell lines (**Table 1**).

## 2. Green synthesis of different anticancer molecules

Green chemistry is one of the valuable concepts for the development of new, more effective, solvent-free less toxic, environmentally friendly and cost-efficient methods for the synthesis of different anticancer molecules. There are many developments for the environmentally friendly approaches for the synthesis of biologically active molecules such as microwave-assisted synthesis, one-pot synthesis, solvent-free synthesis, enzyme-catalyzed synthesis, solid phase synthesis, ultrasound promoted and catalyst-free synthesis. Herein, we are discussing some recently published cytotoxic molecules, which have been synthesized by different green synthesis approaches (**Figure 1**).

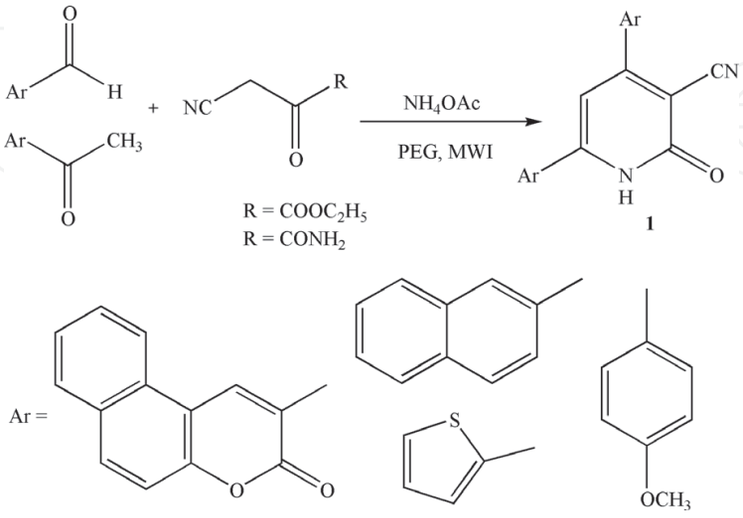



**Figure 1.** 3-cyano pyridine derivatives.

### 2.1. One-pot synthesis of 3-cyano pyridine derivatives

Novel series of 3-cyano pyridine type derivatives were synthesized and their cytotoxic activity was evaluated against many human MCF-7, HCT-116 and HepG-2 cancer cell lines. Most of the compounds showed good-to-moderate activity against HepG2 and HCT-116 cell lines, whereas only few compounds showed significant cytotoxic activity against MCF-7 breast cancer cell line (**Figure 1**) [1].

### 2.2. Microwave-assisted solvent-free synthesis of stigmastane derivatives

The microwave-assisted synthesis in most cases was more successful regarding to the reaction time and the yields of product. These reactions are more environmentally friendly too, compared to the conventional synthetic methods. In this research, a convenient simple microwave-assisted solvent-free synthesis of 2-methoxybenzoyloxy androstane, salicyloyloxy stigmastane derivatives from methyl salicylate and appropriate steroidal precursors has done. 2-Methoxybenzoyl ester exhibited significant cytotoxic activity against MDA-MB-231 cells. Most of the compounds strongly inhibited growth of PC-3 cells, whereas salicyloyloxy stigmastane derivative showed the best inhibition potency (**Figure 2**) [2].

### 2.3. One-pot synthesis of polyazaheterocycles in water

Synthesis of these polyazaheterocycles was carried out by green synthetic strategy that involved one-pot azidation and CuAAC under mild conditions in water. Many compounds were synthesized and evaluated for their cytotoxic effects against four human cancer cell lines, including A549 (lung), MCF-7 (breast), HepG2 (hepatocellular) and DU145 (prostate). Some of the compounds showed strong activities against A549 cancer cells (**Figure 3**) [3].

### 2.4. Microwave irradiated one-pot synthesis of carboethoxy/carbomethoxy derivatives

Fourteen carboethoxy/carbomethoxy derivatives have been synthesized by conventional and microwave irradiation method from a one-pot three-component reaction mixture, consisting of, alkyl acetoacetate, aldehyde and ammonium acetate. The synthesized products have been evaluated for their cytotoxic activity against MDA-MB (breast) and HT-29 (colon) human cancer cell lines. Few compounds exhibit some degree of cytotoxicity and it was low when compared with standard (**Figure 4**) [4].

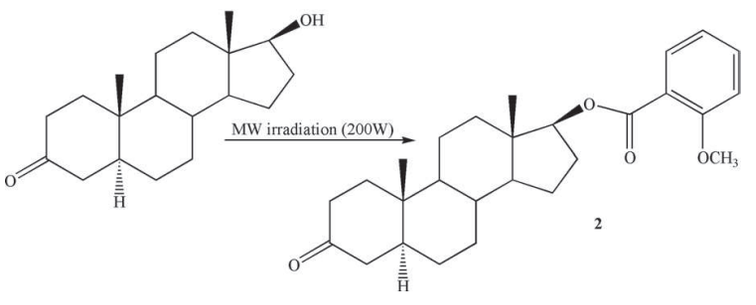



**Figure 2.** Synthesis of stigmastane derivatives.

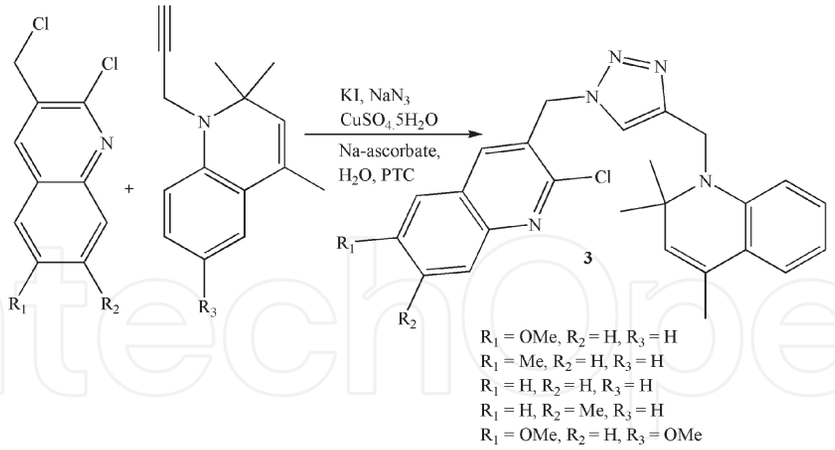



**Figure 3.** Synthesis of polyazaheterocycles.

### 2.5. Cellulose-supported copper nanoparticle-catalyzed synthesis of chalcone derivatives

Chalcone-linked 1,2,3-triazole derivatives were synthesized in water by cellulose-supported copper nanoparticle-catalyzed click reaction. All the products were subjected to MTT cytotoxicity assay against four human cancer cell lines A549, MCF-7, HepG2 and MIA-Pa-Ca-2 for testing their anticancer potential. Few compounds were found to be most active against all cancer cell lines and showed better activity when compared to reference drug (**Figure 5**) [5].

### 2.6. Copper-mediated synthesis of pyrazolo pyridine derivatives

Some novel pyrazolo pyridine type compounds were synthesized by facile procedures and showed significant cytotoxic potential on different human cancer cell lines. They revealed various cancer cell lines (HCT-116, A549, MCF-7, PC-3) determined by SRB assay (**Figure 6**) [6].

### 2.7. Microwave-assisted synthesis of quinoline analogues

A new class of pyrazolo[4,3-c]quinoline and pyrano[3,2-c]quinoline analogues was synthesized in good yields by microwave conditions. For enhancing the yield of products, multicomponent one-pot synthesis has been developed. The cytotoxicity of these compounds was also evaluated against MCF-7 and A549 cancer cell lines. Most of the compounds displayed moderate-to-good anticancer activity against these cell lines (**Figure 7**) [7].

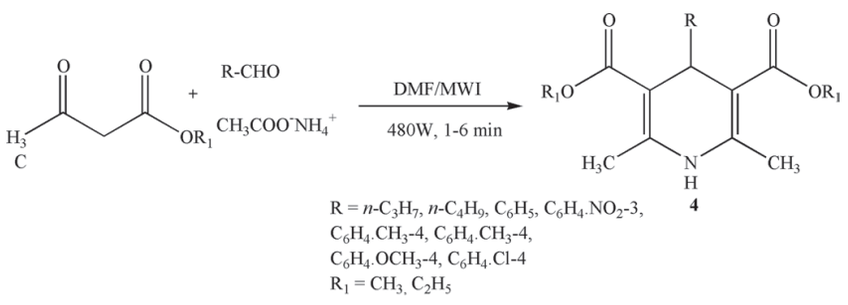



**Figure 4.** Synthesis of carboethoxy/carbomethoxy derivatives.

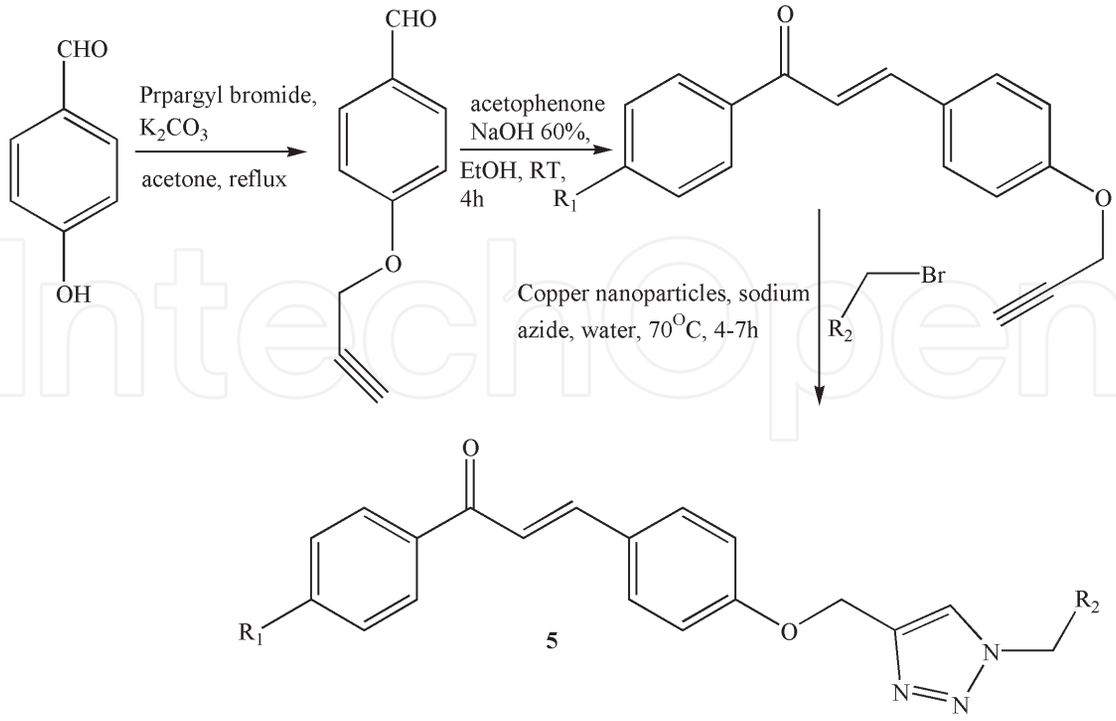



**Figure 5.** Synthesis of chalcone derivatives.

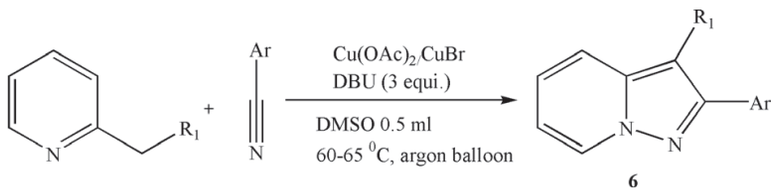



**Figure 6.** Synthesis of pyridine derivatives.

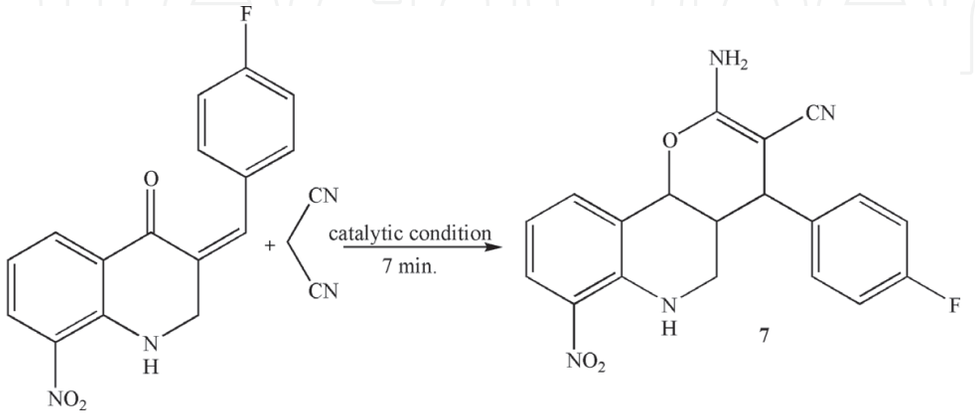



**Figure 7.** Synthesis of quinoline analogues.

### 2.8. Facile protocol, efficient and environmentally benign synthesis of cycloheximide

In this research, they describe a facile and efficient protocol and environmentally benign for the synthesis of C5-substituted barbiturate acid in water. The synthesized compounds tested for different assay and provided promising results against a-glucosidase inhibitor. The cytotoxic activity of compound against 3T3 cell resulted that compounds showed significant to weak activity against the standard cycloheximide (**Figure 8**) [8].

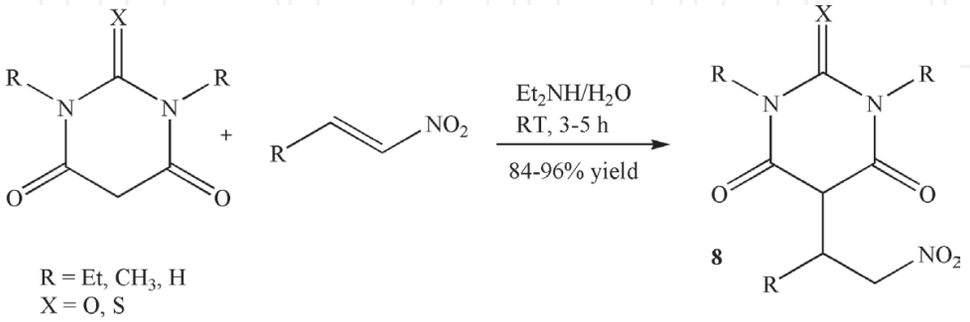
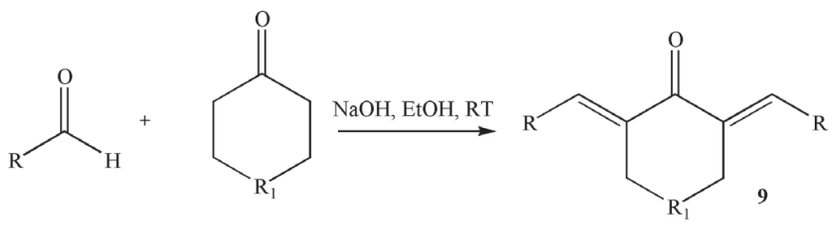



**Figure 8.** Synthesis of quinoline cycloheximide.

### 2.9. Simple, eco-friendly and efficient synthesis of α,β-unsaturated carbonyl compounds

A novel series of carbonyl compounds was synthesized by environment-friendly, simple and efficient method. Compounds were tested for cytotoxicity. All strong antioxidant compounds showed strong protective effect against PC12 cell line (**Figure 9**) [9].




| R | $R_1$ |
|---|---|
| 4-Diethoxymethyl-benzene | $CH_2$ |
| 4-Diethoxymethyl-benzene | O |
| 4-Diethoxymethyl-benzene | NH |
| 4-Diethoxymethyl-benzene | $NCH_3$ |
| 4-Diethoxymethyl-benzene | $NCH_2$-benzene |
| Phenyl-2-$NO_2$-4-diethylamine | $CH_2$ |
| Phenyl-2-$NO_2$-4-diethylamine | O |
| Phenyl-2-$NO_2$-4-diethylamine | NH |
| Phenyl-2-$NO_2$-4-diethylamine | $NCH_3$ |
| Phenyl-2-$NO_2$-4-diethylamine | $NCH_2$-benzene |
| Phenyl-4-pyrrolidine | $CH_2$ |
| Phenyl-4-pyrrolidine | O |
| Phenyl-4-pyrrolidine | NH |
| Phenyl-4-pyrrolidine | $NCH_3$ |
| Phenyl-4-pyrrolidine | $NCH_2$-benzene |

**Figure 9.** Synthesis of α,β-unsaturated carbonyl-based compounds.

## 2.10. Green methodology synthesis of 2H-indazolo[2,1-b]phthalazine-trione derivatives

An efficient green method was used for the synthesis of 2H-indazolo[2,1-b]phthalazine-trione derivatives. Many compounds were obtained in good yields within 10 min. Among all tested cell lines, K562 leukemia cell line was most sensitive (**Figure 10**) [10].

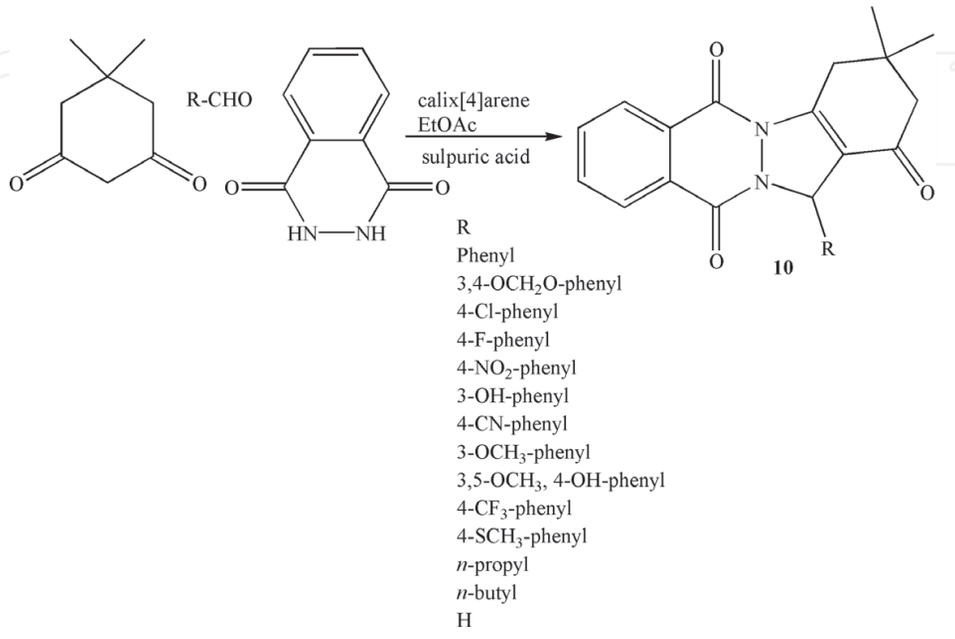



**Figure 10.** Synthesis of phthalazine-trione derivatives.

## 2.11. Green synthesis of thioxoimidazolidin and benzothiazole derivatives

A series of 2-thioxoimidazolidin-4-one and benzothiazole thioglycosides were synthesized by one-pot reaction. The cytotoxic activity of compound was evaluated against MCF-7 breast cell and it showed high-to-moderate anticancer activities (**Figure 11**) [11].

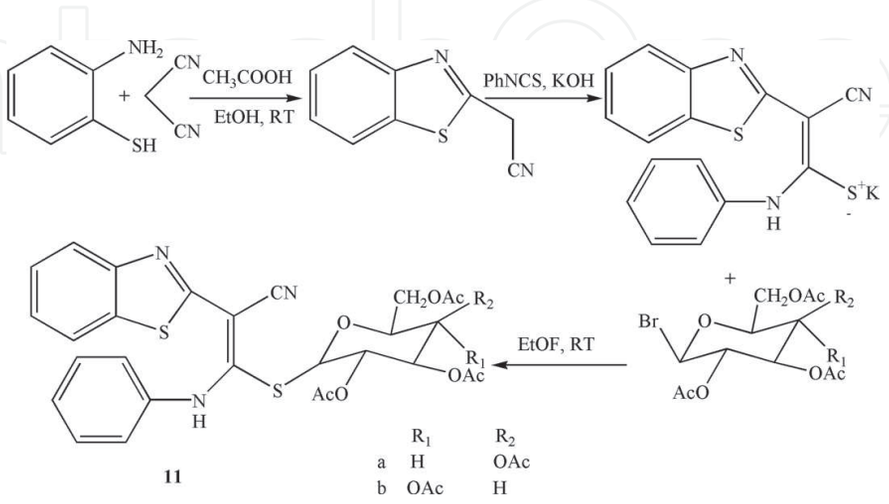



**Figure 11.** Synthesis of thioxoimidazolidin and benzothiazole derivatives.

## 2.12. Green synthesis of pyrimidine-6-carbonitrile derivatives

This is a green synthetic approach for the formation of antitumor active 5-amino-2-(4-chlorophenyl)-7-substituted phenyl-8,8a-dihydro-7H-(1,3,4)thiadiazolo(3,2-$\alpha$) pyrimidine-6-carbonitrile. This protocol is extendable to a wide variety of many substrates. The advantages are the use of eco-friendly catalyst, reduced time, simple work-up process, ease of isolation and high yield of product. One compound was found to have the highest GI50 value for PC-3, HeLa, K562 and MCF-7 cancer cell lines (**Figure 12**) [12].

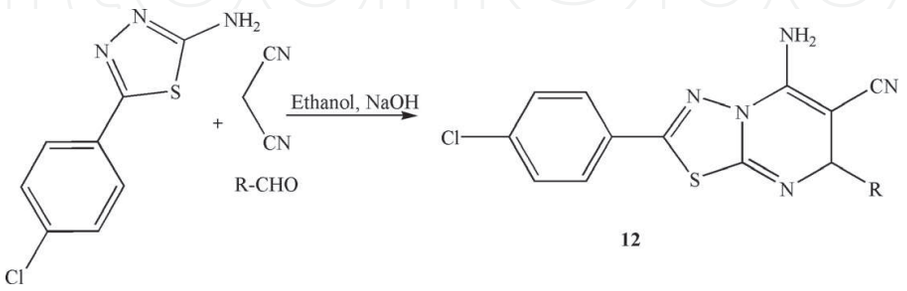



**Figure 12.** Synthesis of pyrimidine-6-carbonitrile derivatives.

## 2.13. Microwave-assisted synthesis of benzimidazole derivatives

Twelve 2-quinolizinylbenzimidazole and 2-naphthalylbenzimidazole type compounds have been synthesized under MW microwave condition. These compounds were tested for cytotoxicity against human breast cancer cell line MCF-7. The results showed that some compounds were found to be as active as standard Tamoxifen (**Figure 13**) [13].

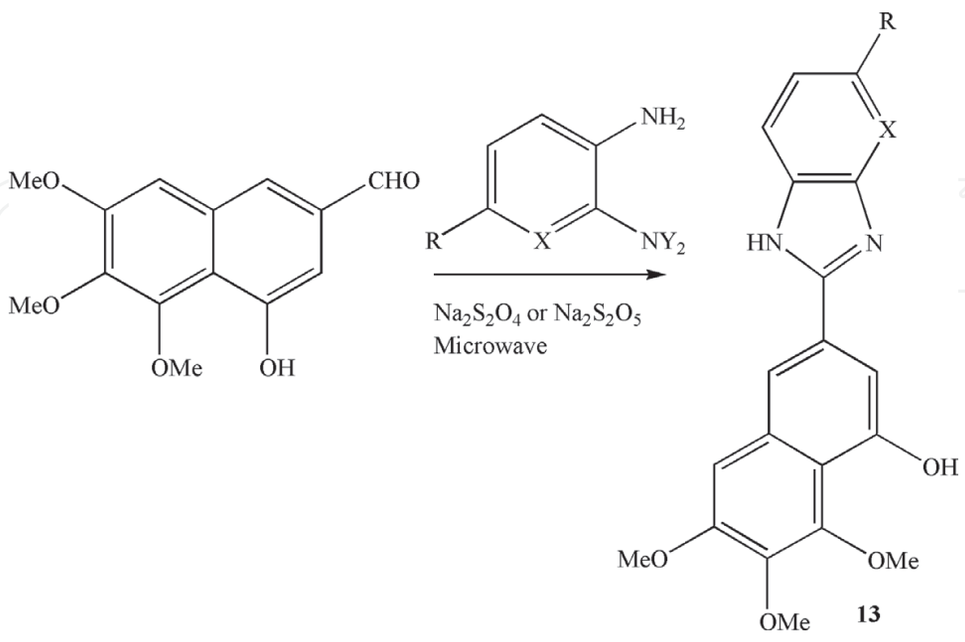



**Figure 13.** Synthesis of pyrimidine-6-carbonitrile derivatives.

### 2.14. Enzyme laccase-catalyzed green synthesis of pyrimidobenzothiazoles

This is a newly developed method for the synthesis of pyrimidobenzothiazoles and catechol thioethers, and it addressed many of the principles of green chemistry. These reactions were catalyzed by laccase enzyme and transformations were completely safe and non-toxic aerial oxygen as the sole oxidant. This reaction delivers the products in an excellent yield. Among all tested compounds, few compounds showed moderate-to-good activity against HepG2 cell line (**Figure 14**) [14].

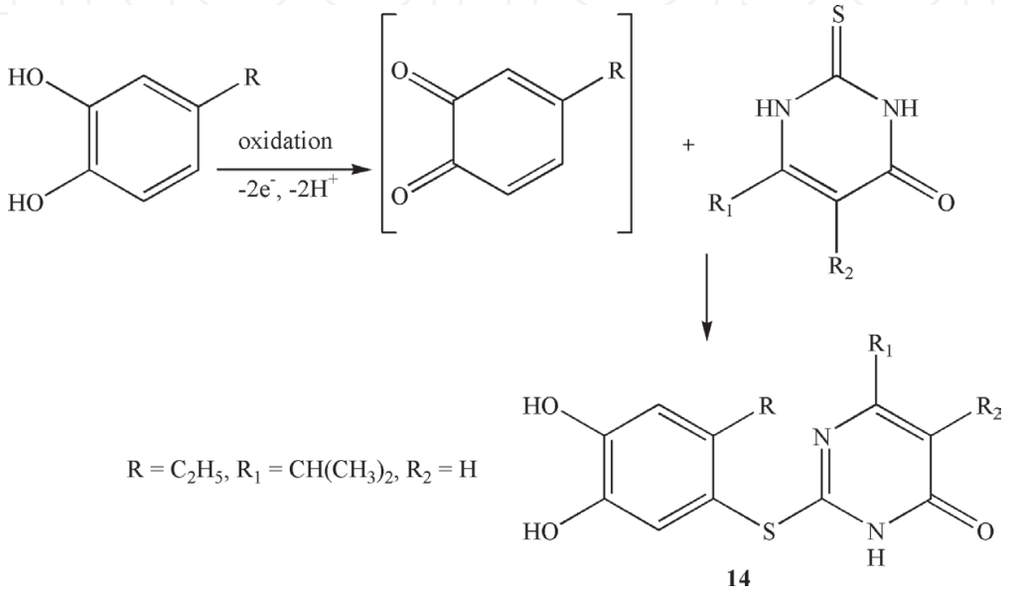



**Figure 14.** Synthesis of pyrimidobenzothiazoles.

### 2.15. Microwave-assisted synthesis of 1,3-selenazole derivatives

Synthesis of new 1,3-selenazole derivatives has been done by MW-assisted Hantzsch condensation reactions. Compound were screened for anti-proliferative effects against leukemia cell lines (HL60 and CCRF-CEM) and carcinoma cell lines (HCT116, MDA-MB231 and U87MG) and it gave moderate cytotoxicity against all tested cell lines (**Figure 15**) [15].

### 2.16. Environment-friendly synthesis of 5′H-spiro[indoline-3,4′-pyrrolo(1,2-a) quinoxalin]-2-ones

A very simple-to-perform, efficient, mild and environment-friendly benign formation of 5′H-spiro[indoline-3,4′-pyrrolo(1,2-a)quinoxalin]-2-ones has been developed without any catalysts. This method includes simplicity of operation, clean reaction, no side products and good yields. Purification of product is very simple, involving a filtration and washing. The synthesized compound with piperonyl substitution on 5-chloroisatin nitrogen showed highest cytotoxicity. Its $IC_{50}$ values are comparable to that of the standard doxorubicin (**Figure 16**) [16].

http://dx.doi.org/10.5772/intechopen.70419

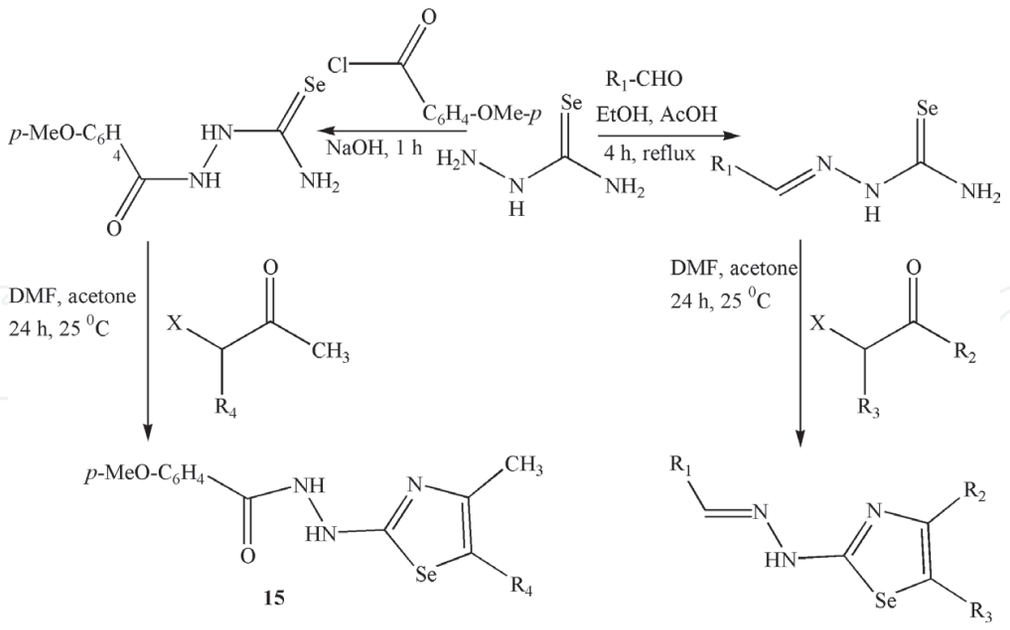



**Figure 15.** Synthesis of 1,3-selenazole derivatives.

## 2.17. One-pot four-component synthesis of morpholine-connected pyrazolidine derivatives

A simple and convenient one-pot four component reaction of morpholine connected with pyrazolidine derivatives was developed using metal-free catalysis. Cytotoxicity was evaluated using HeLa (cervical), HepG2 (liver) and MCF-7 (breast) cancer cell lines, and compounds showed significant cytotoxicity against tested cells (**Figure 17**) [17].

## 2.18. Novel one-pot cyclocondensation

Bithiazolyl hydrazones have been synthesized by one-pot cyclocondensation reaction in freshly prepared ionic liquid at room temperature. Compounds have been evaluated for antitubercular activity and showed potent antitubercular activity (**Figure 18**) [18].

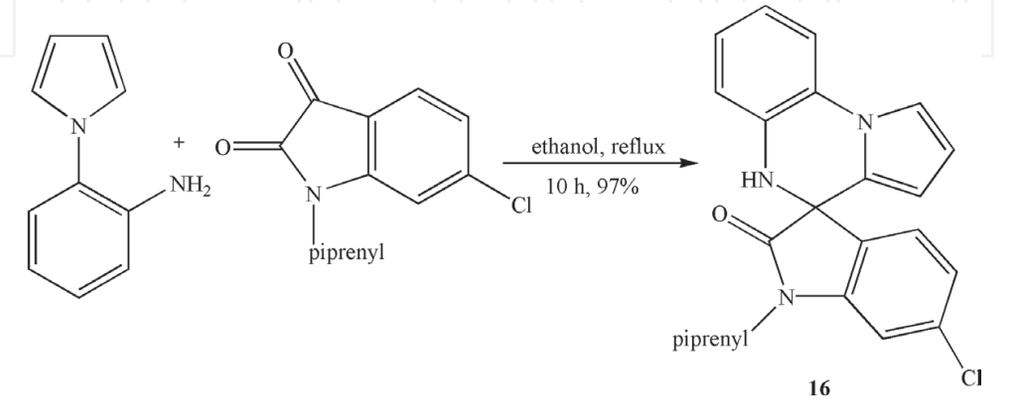



**Figure 16.** Synthesis of spiro[indoline-3,4′-pyrrolo(1,2-a)quinoxalin.

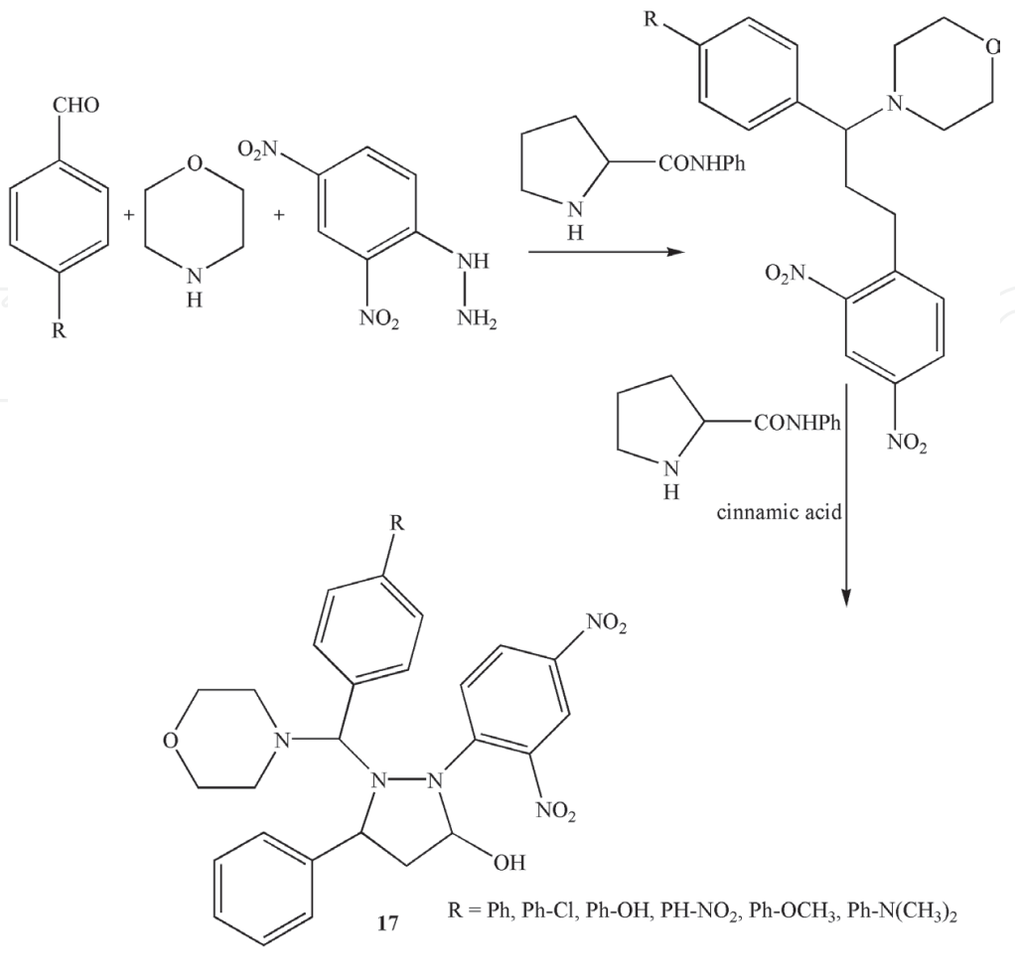



**Figure 17.** Synthesis of morpholine-connected pyrazolidine.

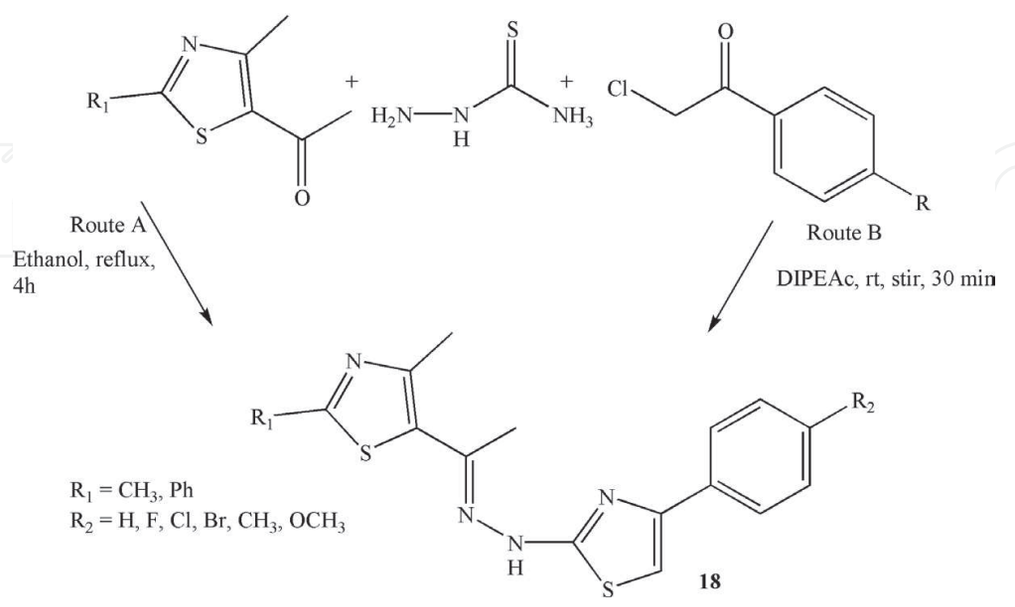



**Figure 18.** Synthesis of bithiazolyl hydrazones.

### 2.19. One-pot synthesis of carbamates

One-pot synthesis of N-(aminosulfonyl)-4-podophyllotoxin carbamates has been done and it showed promising cytotoxic activities. Most effective compound induced HeLa cells cycle arrest in G2/M phase, leading to apoptosis, and activation of cdc2, cyclinB1, p53 and ROS and inhibits polymerization of tubulin and microtubule. These results suggest that these synthesized compounds have strong potential for development as cytotoxic agents (**Figure 19**) [19].

### 2.20. Eco-friendly synthesis of bacillamide

It is an efficient, advanced and eco-friendly route for synthesis of bacillamide analogues through a two-step solvent-free synthesis. Compounds exhibit potent cytotoxic activity against three HCT-116, MDA-MD-231 and JURKATs cancer cell lines and compared with doxorubicin (**Figure 20**) [20].

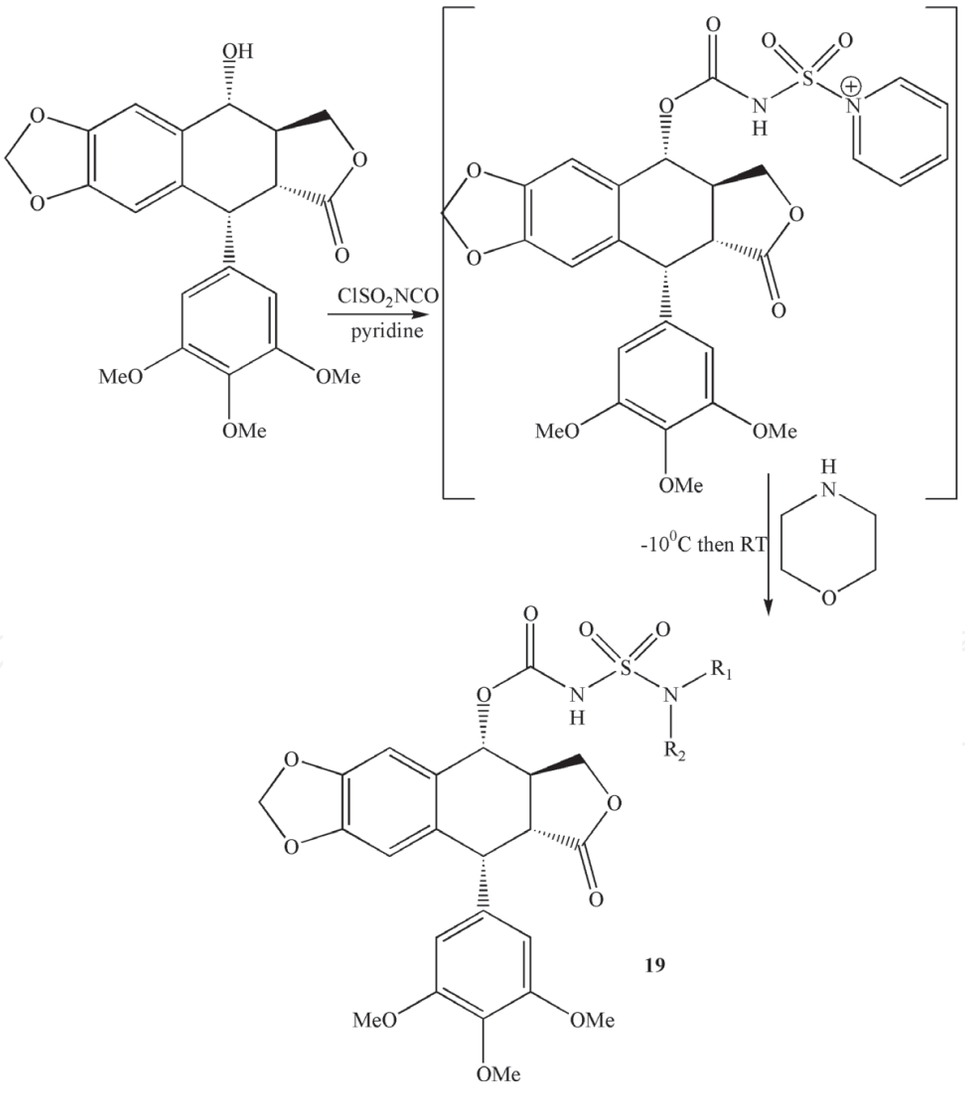



**Figure 19.** Synthesis of N-(aminosulfonyl)-4-podophyllotoxin carbamates.

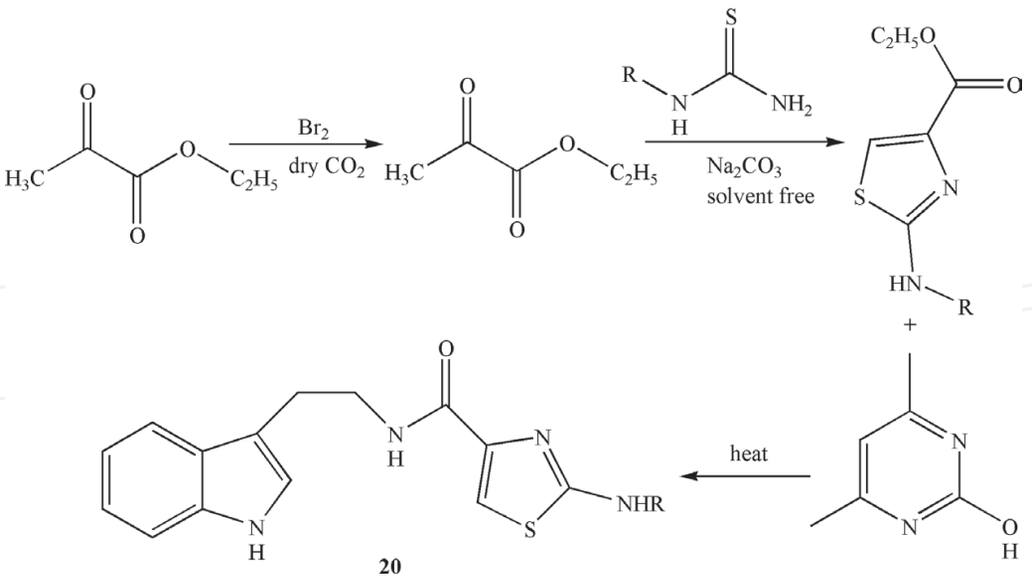
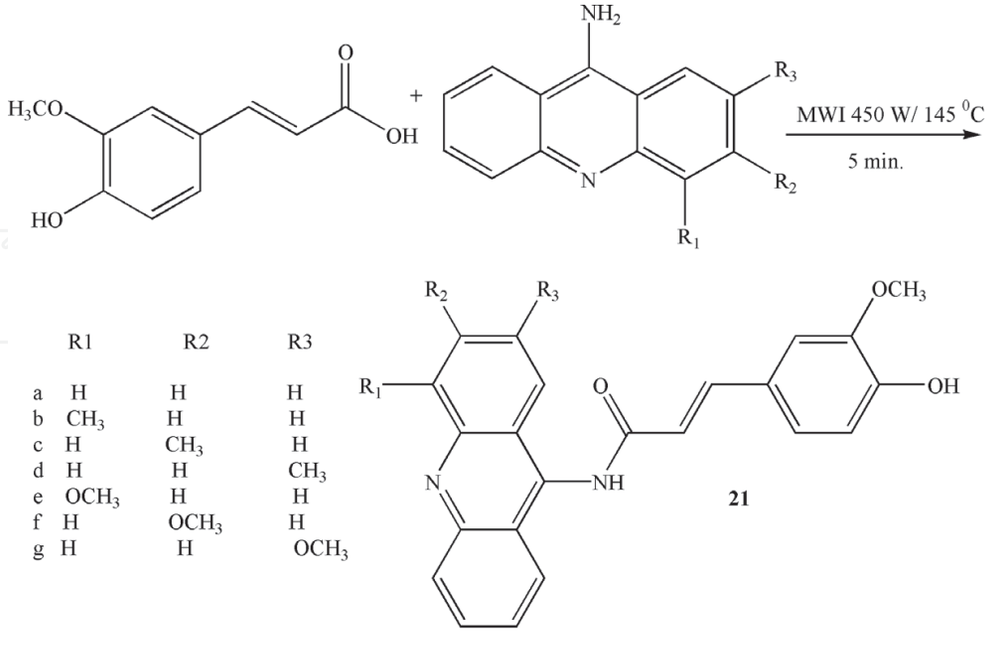



**Figure 20.** Synthesis of bacillamide analogues.

## 2.21. Solvent-free microwave-assisted synthesis of amide derivatives of ferulic acid

In this research work, different amide derivatives of ferulic acid have been synthesized under solvent-free conditions by microwave-assisted reaction. These compounds were found to exhibit noticeable in vitro anticancer activity against breast (MDA-MB-231 and MCF-7), cervical (HeLa), lung (A549) and liver (HepG2) human cancer cell lines (**Figure 21**) [21].




| | R1 | R2 | R3 |
|---|---|---|---|
| a | H | H | H |
| b | $CH_3$ | H | H |
| c | H | $CH_3$ | H |
| d | H | H | $CH_3$ |
| e | $OCH_3$ | H | H |
| f | H | $OCH_3$ | H |
| g | H | H | $OCH_3$ |

**Figure 21.** Synthesis of ferulic acid derivatives.

### 2.22. One-pot synthesis of *o*-quinonic adducts

Dibenzo[a,h]anthracene derivatives were synthesized via a one-pot synthetic protocol with three-component reaction of 2-hydroxy-1,4-naphthoquinone, aromatic aldehydes and 2-naphthol using InCl3 as catalyst under solvent-free condition. These *o*-quinonic adducts showed strong cytotoxicity against MCF-7 and HEL tumoral cell lines (**Figure 22**) [22].

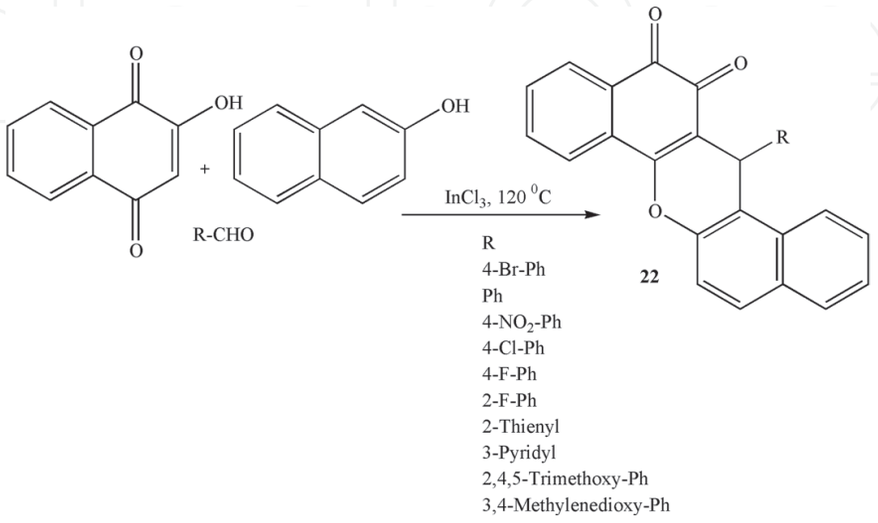



**Figure 22.** Synthesis of *o*-quinonic adducts.

## 3. Conclusion

The data of this chapter could be very helpful to identify the recently published approaches of anticancer molecules synthesized via different green chemistry approaches.

## Acknowledgements

This book chapter was supported by a grant from the "Research Center of the Female Scientific and Medical Colleges," Deanship of Scientific Research, King Saud University.

## Author details

Shagufta Perveen* and Areej Mohammad Al-Taweel

*Address all correspondence to: shagufta792000@yahoo.com

Department of Pharmacognosy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

## References

[1] Khaled AMA, Ghada HA, Abeer ME. Eco-friendly synthesis of novel cyanopyridine derivatives and their anticancer and PIM-1 kinase inhibitory activities. European Journal of Medicinal Chemistry 2017;**134**:357-365. DOI: 10.1016/j.ejmech.2017.04.024.

[2] Katarina MPG, Evgenija AD, Mihaly S, Janos G, Janos JC. Microwave assisted synthesis and biomedical potency of salicyloyloxy and 2-methoxybenzoyloxy androstane and stigmastane derivatives. Steroids 2015;**94**:31-40. DOI: 10.1016/j.steroids.2014.12.008

[3] Koduru SSP, Edupuganti VVSR. Design of new hybrid template by linking quinoline, triazole and dihydroquinoline pharmacophoric groups: A greener approach to novel polyazaheterocycles as cytotoxic agents. Bioorganic & Medicinal Chemistry Letters 2015;**25**:1057-1063. DOI: 10.1016/j.bmcl.2015.01.012

[4] Srinivas NA, Mahendar P, Sadanandam A, Achaiah G, Malla RV. Synthesis, anticancer and MRP1 inhibitory activities of 4-alkyl/aryl-3,5-bis(carboethoxy/carbomethoxy)-1, 4-dihydro-2, 6-dimethylpyridines. Medicinal Chemistry Research 2013;**22**:147-155. DOI: 10.1007/s00044-012-9994-0

[5] Pinki Y, Kashmiri L, Ashwani K, Santosh KG, Sundeep J. Green synthesis and anticancer potential of chalcone linked-1,2,3-triazoles. European Journal of Medicinal Chemistry 2017;**126**:944-953. DOI: 10.1016/j.ejmech.2016.11.030

[6] Chitrakar R, Arem Q, Darapaneni CM, Shashank KS. Design, synthesis and cytotoxicity studies of novel pyrazolo[1, 5-a] pyridine derivatives. European Journal of Medicinal Chemistry 2017;**126**:277-285. DOI: 10.1016/j.ejmech.2016.11.037

[7] Thangaraj A, Sadasivam M, Subashini G, Selvaraj S, Athar A, Palathurai SM. Biologically active perspective synthesis of heteroannulated 8-nitroquinolines with green chemistry approach. Bioorganic & Medicinal Chemistry Letters 2017;**27**:1538-1546. DOI: 10.1016/j.bmcl.2017.02.042

[8] Assem B, Mohammad SI, Abdullah MA, Hazem AG, Sammer Y, Mahwish A, Nimra NS, Choudhary MI, Ruqaiya K, Zaheer U. Synthesis of pyrimidine-2,4,6-trione derivatives: Anti-oxidant, anti-cancer, a-glucosidase, b-glucuronidase inhibition and their molecular docking studies. Bioorganic Chemistry 2016;**68**:72-79. DOI: 10.1016/j.bioorg.2016.07.009

[9] Syed NAB, Ibrahim J, Vijay HM, Devidas TM, Muhammad S, Hassan MN, Muhammad WA. Synthesis of $\alpha$, $\beta$-unsaturated carbonyl based compounds as acetylcholinesterase and butyrylcholinesterase inhibitors: Characterization, molecular modeling, QSAR studies and effect against amyloid $\beta$-induced cytotoxicity. European Journal of Medicinal Chemistry 2014;**83**:355-365. DOI: 10.1016/j.ejmech.2014.06.034

[10] Yuri FR, Cleiton MS, Daniel LS, Jeferson GS, Ana LTGR, Joao EC, Sergio AF, Angelo F. Phthalazine-triones: Calix[4]arene-assisted synthesis using green solvents and their anticancer activities against human cancer cells, Arabian Journal of Chemistry (2016) in press. DOI: 10.1016/j.arabjc.2016.04.007

[11] Elgemeie GH, Farag AB, Amin KM, El-Badry OM and Hassan GS. Design, synthesis and cytotoxic evaluation of novel heterocyclic thioglycosides. Medicinal Chemistry 2014;**4**:814-820. DOI: 10.4172/2161-0444.1000234

[12] Shailee VT, Julio AS, Vazquez-Tato MP, Aniket PS, Deepak KL, Anna PGN. Ultrasound mediated one-pot, three component synthesis, docking and ADME prediction of novel 5-amino-2-(4-chlorophenyl)-7-substituted phenyl-8,8a-dihydro-7H-(1,3,4)thiadiazolo (3, 2-$\alpha$) pyrimidine-6-carbonitrile derivatives as anticancer agents. Molecules 2016;**21**:894. DOI: 10.3390/molecules21080894

[13] Hue TBB, Quy TKH, Won KO, Duy DV, Yen NTC, Cuc TKT, Em CP, Phuong TT, Loan TT, Hieu VM. Microwave assisted synthesis and cytotoxic activity evaluations of new benzimidazole derivatives. Tetrahedron Letters 2016;**57**:887-891. DOI: 10.1016/j.tetlet.2016.01.042

[14] Abdel-Mohsen HT, Conrad J, Harms K, Nohr D, Beifuss U. Laccase-catalyzed green synthesis and cytotoxic activity of novel pyrimidobenzothiazoles and catechol thioethers. RSC Advances 2017; **7**:17427-17441. DOI: 10.1039/c6ra28102h

[15] Adriana IG, Luiza G, Victor K, Luminita S, Thomas E, Valentin Z. Microwave-assisted synthesis of new selenazole derivatives with antiproliferative activity. Molecules 2013;**18**: 4679-4688. DOI: 10.3390/molecules18044679

[16] Ahmed K, Rasala M, Nayak VL, Korrapati SB, Kumar GB, Anver BS, Jeevak SK, Abdullah A. Discovery of pyrrolospirooxindole derivatives as novel cyclin dependent kinase 4 (CDK4) inhibitors by catalyst-free, green approach. European Journal of Medicinal Chemistry 2016;**108**:476-485. DOI: 10.1016/j.ejmech.2015.11.046

[17] Radhakrishnan SK, Meera M, Salem SA, Aseer M, Akbar I. Synthesis of new morpholine-connected pyrazolidine derivatives and their antimicrobial, antioxidant, and cytotoxic activities. Bioorganic & Medicinal Chemistry Letters 2017;**27**:66-71. DOI: 10.1016/j.bmcl.2016.11.032

[18] Mahendra BB, Sambhaji TD, Amarsinh RD, Laxman UN, Vijay K, Dhiman S, Ramrao AM. New bithiazolyl hydrazones: Novel synthesis, characterization and antitubercular evaluation. Bioorganic & Medicinal Chemistry Letters 2017;**27**:288-294. DOI: 10.1016/j.bmcl.2016.11.056

[19] Xiao-Hui X, Xiao-Wen G, Shi-Liang F, You-Zhen M, Shi-Wu C, Ling H. One-pot synthesis and biological evaluation of N-(aminosulfonyl)-4-podophyllotoxin carbamates as potential anticancer agents. Bioorganic & Medicinal Chemistry Letters 2017;**27**:2890-2894. DOI: 10.1016/j.bmcl.2017.04.082

[20] Sunil K, Ranjana A, Virender K, Rachna S, Bhumi P, Pawan K, Dhirender K. Solvent-free synthesis of bacillamide analogues as novel cytotoxic and anti-inflammatory agents. European Journal of Medicinal Chemistry 2016;**123**:718-726. DOI: 10.1016/j.ejmech.2016.07.033

[21] Naresh K, Sandeep K, Sheenu A, Kumar N, Sham MS, Prasad VB, Partha R, Vikas P. Ferulic acid amide derivatives as anticancer and antioxidant agents: Synthesis, thermal,

biological and computational studies. Medicinal Chemistry Research 2016;**25**:1175-1192. DOI: 10.1007/s00044-016-1562-6

[22] Idaira HF, Angel A, Patricia M, Matias L, Leandro F, Ana E. Indium catalyzed solvent-free multicomponent synthesis of cytotoxic dibenzo[*a,h*]anthracenes from aldehydes, 2-hydroxy-1,4-naphthoquinone, and 2-naphthol. Tetrahedron 2014;**70**:8480-8487. DOI: 10.1016/j.tet.2014.09.076



IntechOpen