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Green Chemistry and Synthesis of Anticancer Molecules: A Review

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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. This review paper 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

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.

Table:1. Green synthesis of anti-cancer molecules

Method use	Reaction condition	Class of compounds synthesized	Cancer cell lines	Refs.
Eco-friendly	Mixture of methyl ketone, aldehyde, active methylene cyanoacetamide, malononitrile,	Novel cyanopyridin	Human liver	[1]

one-pot synthesis	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	e derivatives	HepG2, colon HCT-116, breast MCF-7 cancer	
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	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	Human A549 lung adenocarcinoma epithelial, MCF-7 breast adenocarcinoma, HepG2	[3]

			hepatocellular liver carcinoma, DU145 prostate cancer	
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	Human HT-29 colon cancer and MDA-MB breast cancer and MRP1 inhibitory activity using the insect cell membrane	[4]
Cellulose-supported copper nanoparticlecatalyzed 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 ClaisenSchmidt condensation to yield chalcones	Chalcone-linked 1,2,3-triazoles	Human MCF-7, MIA-Pa-Ca2,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	Human A549 lung adenocarcinoma, MCF-7 breast carcinom	[6]

			a cell line, HCT-116 colon cancer, PC-3 prostate cancer	
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	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	HeLa cervical cancer ,3T3 mouse fibroblast cancer	[8]
Simple, eco-friendly and efficient method	In the presence of NaOH in ethanol, Claisen-Schmidt condensation was used to synthesize α,β-unsaturated carbonyl-based compounds between specific ketones and appropriate aryl aldehydes.	α,β-unsaturated carbonyl-based compounds	PC12 cancer	[9]
Synthesis by using green solvents	In EtOAc 2,3-Dihydrophthalazine-1,4-dione, 5,5-dimethyl clohexane-1,3-dione, aldehyde and calix p-sulfonic acid[4]arene have been dissolved. The mixture was irradiated at 130 ° C for 10 minutes in an MW reactor. This cooled the reaction to room temperature and then added heat. The mixture was put to shape the material in a freezer at 20 ° C	Phthalazine-triones: Calix[4]arene	Human tumor U251 glioma, MCF7 breast NCIADR / RES multiple drug-resistant ovarian, 786-0 renal,	[10]

			NCIH460 lung, non-small cells, prostate PC-3, ovarian OVCAR-03, colon HT-29 and leukemia cancer K562	
One-pot reaction	For 30 minutes, the 2-thioxoimidazolidin-4-one and sodium ethoxide mixture in EtOH was refluxed. CS2 was introduced after cooling and the reaction mixture was stirred for 1 h at room temperature. The solid material was recrystallized from EtOH after solution evaporation to achieve a compound yield of 70–75 percent	Novel 2-thioxoimidazolidin-4-one and benzothiazole thiolate salts	MCF-7 breast carcinoma cancer	[11]
One-pot ultrasoundpromoted synthesis	One-pot synthesis of 5-amino-2-(4-chlorophenyl)- 7-replaced phenyl-8,8a-dihydro-7H-3,4) thiadiazolo(3,2-α)pyrimidine-6-carbonitrile derivatives from three component reactions of 5-(4-chlorophenyl)-1,3,4-thiadiazol-2 amine, aromatic aldehydes and malonitrile in the presence of NaOH under reflux and ultrasonic irradiation	5-amino-2-(4-chlorophenyl)- 7-substituted phenyl-8,8adihydro-7H-(1,3,4)thiadiazolo (3,2-α)pyrimidine-6-carbonitrile derivatives	MCF-7, K562, HeLa and PC-3 cancer	[12]

This chemistry includes a range of modern techniques for synthesizing bioactive compounds, such as microwave-assisted synthesis, solvent-free synthesis aided by solid phase, organocatalyst reaction, multi-component one-pot reactions, and sonochemical synthesis, using ionic liquid techniques. Pharmaceutical companies also develop chemicals in order to reduce and mitigate environmental hazards. Cancer is a disease caused by uncontrolled

growth of the body's cells. There are many developments in treating cancer, but the most common cause of human death remains. There is a significant increase in the number of cancer patients worldwide, particularly in developed countries. In 2014, global spending on cancer medicines increased by 10.3% to $100 billion, according to the global oncology trend report (2015).

Green Synthesis of Various Anticancer Molecules

Green chemistry is one of the valuable concepts for developing new, more effective, solvent-free methods that are less toxic, environmentally friendly and cost-effective for the synthesis of different anticancer molecules. There are many advances in environmentally friendly approaches to the synthesis of biologically active molecules.

2.1. Green Chemistry and Synthesis of Anticancer Molecules

One-pot synthesis of 3-cyano-pyridine derivatives Novel series of 3-cyano-pyridine type derivatives have been synthesized and their cytotoxic activity has been assessed against many human cancer cell lines MCF-7,HCT-116 and HepG-2. Most of the compounds exhibited good-to-moderate activity against cell lines HepG2 and HCT-116, while few compounds were identified (Figure 1). [(1)]

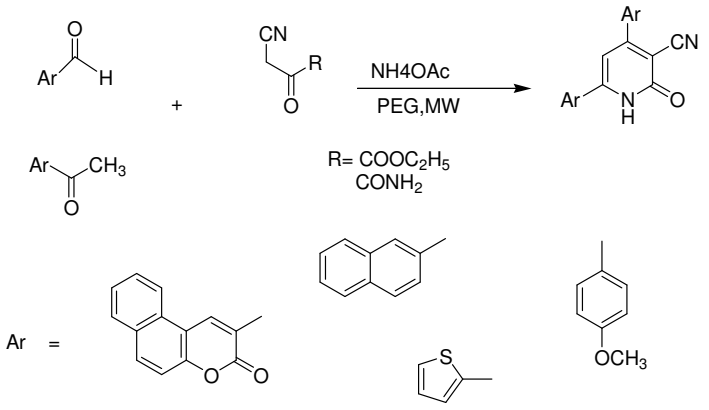

Figure-1. 3-Cyano pyridine derivatives

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[2].

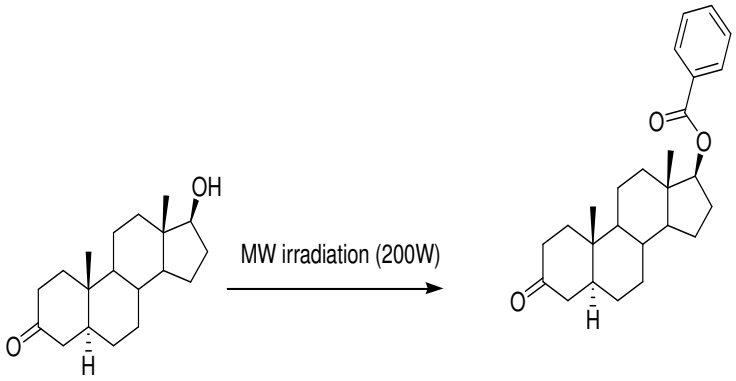

Figure-2. Synthesis of stigmastane derivatives

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.[3]

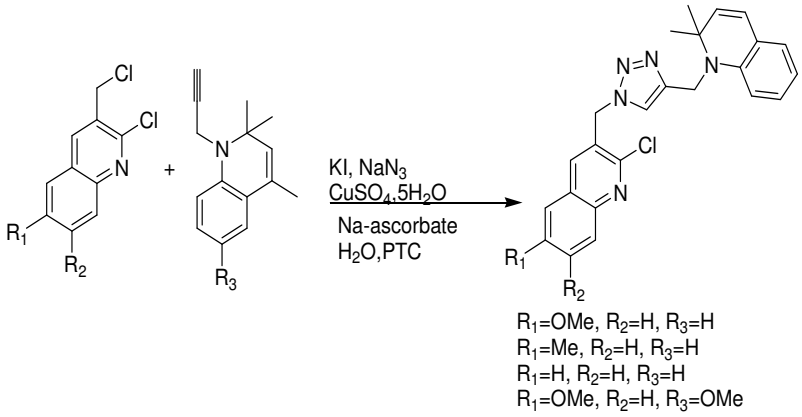

Figure-3. Synthesis of polyazaheterocycles

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.[4]

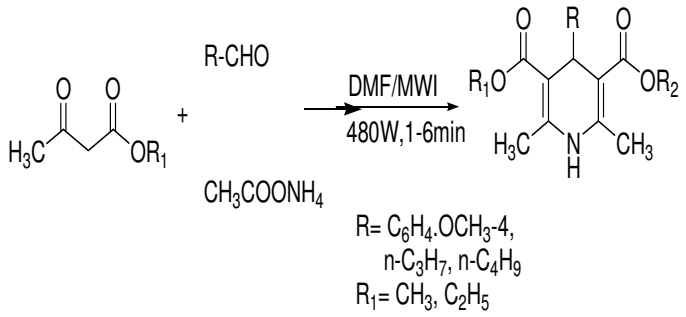

Figure-4. Synthesis of carboethoxy/carbomethoxy derivatives

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. [5]

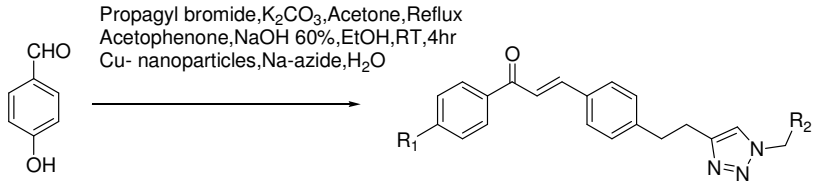

Figure-5. Synthesis of chalcone derivatives

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. [6]

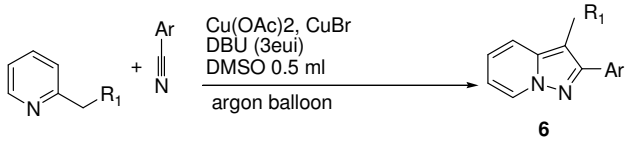

Figure-6. Synthesis of pyridine derivatives.

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. (7)

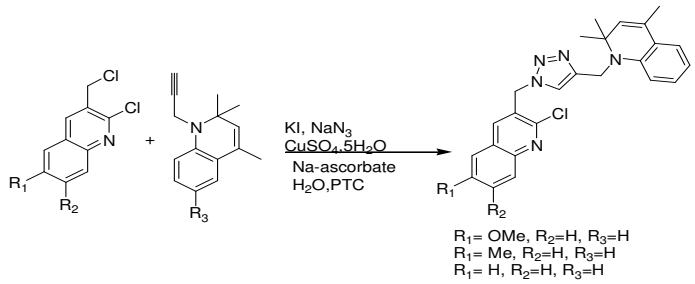

Figure-7. Synthesis of quinoline analogues.

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. (8)

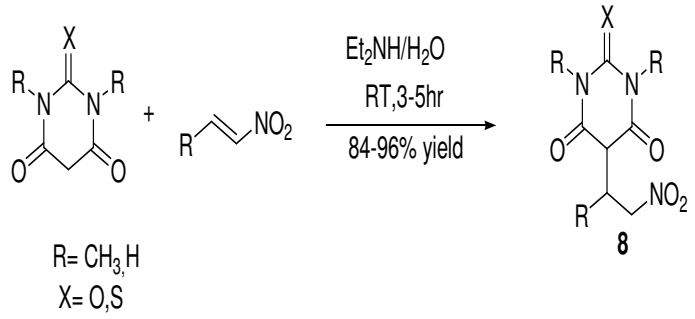

Figure-8. Synthesis of quinoline cycloheximide.

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. (9)

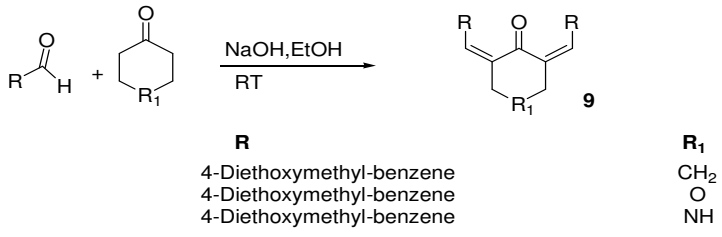

Figure-9. Synthesis of α,β-unsaturated carbonyl-based compounds

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]

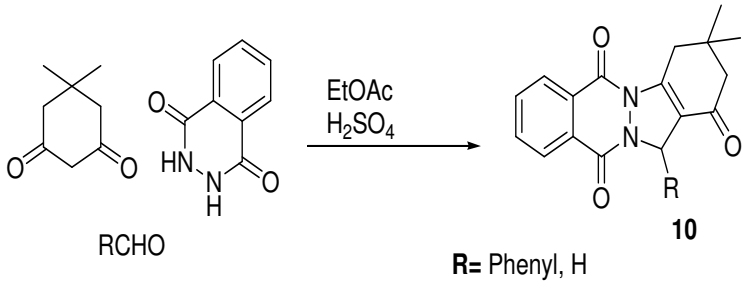

Figure-10. Synthesis of phthalazine-trione derivatives

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. Compound cytotoxic activity was measured against breast cell MCF-7 and high-to-moderate anticancer activity was shown (Figure 11).[11]

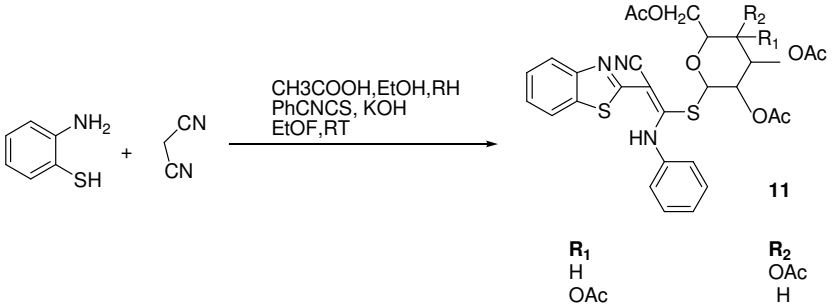

Figure-11. Synthesis of thioxoimidazolidin and benzothiazole derivatives.

2.12. Green synthesis of pyrimidine-6-carbonitrile derivatives

This is a natural synthetic solution for phenyl-8,8a-dihydro-7H-(1,3,4)thiadiazolo(3,2-α) pyrimidine-6-carbonitrile-substituted antitumor 5-amino-2-(4-chlorophenyl)-7. This protocol can be applied to a wide range of substrates. The benefits are eco-friendly catalyst use, reduced time, quick system work-up, fast insulation and high material yield.

One compound was found to have the highest GI50 value for PC-3, HeLa, K562 and MCF-7 cancer cell lines. [12]

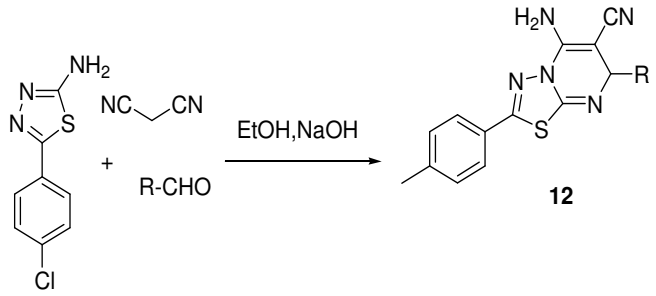

Figure-12. Synthesis of pyrimidine-6-carbonitrile derivatives.

CONCLUSION

The data from this review could be very helpful in identifying the recently published anticancer molecules approaches synthesized through various approaches to green chemistry.

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