Synthesis of Anticancer Polyaromatic Compounds

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Contributor: Bimal Banik

Bimal Krishna Banik

Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Deanship of Research, Prince Mohammad Bin Fahd University, Al Khobar 31952, KSA; Email: bimalbanik10@gmail.com (mailto:bimalbanik10@gmail.com); bbanik@pmu.edu.sa (mailto:bbanik@pmu.edu.sa)

Synthesis of several polycyclic aromatic compounds is described. Some of these agents have demonstrated selective anticancer activities in vitro and in animal model. Preliminary mechanistic investigations about the cause of bioactivity are also performed.

Keywords: Polyaromatic compounds ; anticancer ; chrysene ; dibenzofluorene

Introduction

Synthesis and biological evaluation of polyaromatic compounds as anticancer agents is an interesting research topic. It is know that some polyaromatic compounds have mutagenic activities. But, mutagenic activations depend on many causes. Suitably substituted polyaromatic compounds exert selective anticancer activities mitigating mutagenic effects.

Results and Discussions

To functionalized aromatic system, electrophilic reaction is widely used. Nitration of aromatic hydrocarbon is a good method for introducing a nitro group in the aromatic system. Nitration of aromatic hydrocarbons by bismuth nitrate impregnated with solid support was performed [1]. These nitro aromatic compounds were reduced to aromatic amines by samarium and indium metal [2]. The aromatic amine was subsequently coupled with a side chain to afford the diamide. Aromatic amide on reduction afforded corresponding amine. Using primary and secondary amino compounds, a diverse polycyclic aromatic compounds was prepared [3]. The amide that has N-methyl piperazine side chain was more potent than that of piperidine side chain against a few cancer cell lines. A 4-carbon chain containing compound was better in activity compared to a 3 or 5-carbon chain containing amides. Structure-activity study indicated that nature and length of the appended chain was crucial in the biological activity of the amides [4]. In contrast, the amines were more active than the amides regardless of the terminal units present in the system.

The amides were then converted to bromo, nitro, phenol, ether and keto derivatives by several chemical manipulations [5].

In previous investigations, a series of mono substituted chrysene derivatives were synthesized and some of them demonstrated specific antitumor activity [4][5]. These studies suggested possible interactions at the tumour cell membrane as an alternate target for anticancer activity. The basic terminal sites had interaction with negative component of the phospho lipid bilayer in the cell membrane. The terminal polar group helped to bind the molecule to the cell surface and the amino group present in the molecule was good enough for this binding and therefore, to enhance the *in vitro* cytotoxicity.

In vitro cytoxicity of these substituted chrysenes was conducted against numerous cancer cell lines. Electron withdrawing groups (bromo, nitro and acetyl) were found to decrease the activity against all cancer cell lines. But, electron donating methoxy group at 12-position increased the activity compared to the 12-unsubstituted compound.

These results suggested that a polar and basic group at the terminal side chain may maintain or improve the activities of the derivatives. On this basis, derivatives that have polar hydroxyl and amino groups at the terminal site of these compounds were prepared. These were evaluated against numerous cancer cell lines in vitro. It was notable to observe better activity of the compounds that have alcohol and amino groups at the terminal site of these derivatives [5].

Disubstitued Chrysenes

Synthesis of numerous 6, 12-disubstitued chrysenes was performed. In addition, these molecules were also tested against numerous human and animal tumor cell lines. Specifically, three disubstituted derivatives were prepared through a sequence of reactions Synthesis of symmetrical amide (same terminal heterocyclic rings on the aliphatic side chain) was prepared from 6-aminochrysene.

6-Aminochrysnene on standard acetylation reaction produced 6-acetamidochrysene. 6-Acetamidochrysene on nitration with concentrated nitric acid produced the 12-nitro derivative. Bismuth nitrate-impregnated with clay also produced the same nitro compound. The nitro amide on reduction and hydrolysis reaction afforded the 6, 12-diaminochrysene. Since we prepared a number of derivatives with 6-aminochrysene, availability of the new 6, 12-diamino compound of chrysene is helpful for huge possibilities. A coupling reaction with the side chain afforded the amide which was then reduced to produce the amine. The amine was converted to the hydrochloride salt. It was important that coupling reaction with the acid hindered no problems with 6, 12-diamnochrysene and proceeded smoothly.

A simple method was also identified for this purpose. For example, it was found that chrysene with nitric acid treatment produced 6, 12-dinitrochrysene as single compound. The dinitro compound was reduced by hydrazine hydrate/palladium carbon to obtain 6, 12-diaminochrysene. The 6, 12-diaminochrysene was then coupled with the acid side chain in the presence of isobutyl chloroformate to produce the amide. The 6, 12-disubstituted asymmetrical chrysene amide and amine was also prepared. These molecules had different terminal heterocyclic rings. However, no asymmetric carbon center was involved.

In vitro experiments were performed using these compounds. The amide with a terminal piperidine group of chrysene was inactive against all cancer cell lines. However, a similar molecule with a terminal piperazine group demonstrated limited activity against 4 out of 7 cancer cell lines. The amino derivatives of chrysene with a terminal piperidine and pierazine group demonstrated modest activity against three/seven and was active against four/seven cancer cell lines. The changes of activity were seen for all related amino molecules in this series regardless of the nature of the terminal group.

The *in vitro* cytotoxicity data of 6, 12-disubstituted amides demonstrated crucial variations between symmetrical and asymmetrical structures. Interestingly, the symmetrical *bis* diamide molecules with terminal piperidine system and with terminal piperazine group were all inactive against the tested cancer cell lines. But, the bis diamide that had non-symmetrical piperidine/N-methylpiperazine terminal ring demonstrated some activity against three/seven cancer cell lines. It was seen that conversion of the amide to amino molecules was helpful to increase the anticancer activity of the resulting compounds irrespective of the linker and the nature of the terminal groups. Probably, the basic properties of the amino compounds were responsible for their effects.

Because of the excellent *in vitro* activity, a bis diamino compound was tested *in vivo* against human ovarian cancer line, SKOV-3. An administration of this compound was helpful in reducing the tumor number per tumor bearing mouse by 35% and the tumor volume was also reduced by 47%. Importantly, the salt of this amino compound also showed activity *in vivo* against the human ovarian cancer cell line SKOV-3. This was also tested against colon cancer [6].

The monoamine with piperidine caused extensive cytotoxicity while the amide was far less active against human leukemic Jurkat T cells *in vitro.* The reduced activity of the diamide was also proved in a less degree of apoptotic change, one of the important mechanisms of cell death. No effects were demonstrated in a normal, non-transformed line of human YT cells. The activation of caspase-3 during apoptosis was estimated. The results showed that the amino compounds demonstrated superior caspase-3 activity with respect to amides. Jurkat cells incubated with various monoamines with chrysene system were more TUNEL-positive than the amides with a similar group [7].

Samarium-induced reductive dimerization of methyl cinnamate was developed for the preparation of 2, 8-diamino chrysene. The use of samarium in the preparation molecules was demonstrated by our group [8]. For example, samarium was used for the dimerization of imines and carbonyl molecules. Using this reagent, methyl cinnamate and ethyl cinnamate did not dimerize. This reaction produced 3-phenylpropionate due to the reduction of the alkene group. Samarium metal in the presence of aluminum foil or aluminum chloride produced dimeric compound. A cyclization was performed using sulfuric acid to afford the tetracyclic compound. Nitration and reduction-aromatization were then performed to obtain the 2, 8-diamino chrysene. The anticancer activity of the 2, 8-disubstituted compounds were superior to those obtained from 6, 12-disubstitued compounds. We also developed indium-chemistry in this work [8].

Dibenzofluorenes

Following the chemistry as described above, diamide and diamino dibenzofluorenes were prepared. Several reactions were involved in this process including ring formation, nitration, reduction, coupling and oxidation.

The antitumor cytotoxicity of the dibezofluorenes was compared to cisplatin and adriamycin. The didenzofluorene with methylpiperazine side chain was more active than the piperdine analogues. The compounds derived from dibenzofluorene system were more active than chrysene series. All amino compounds were equally active. Interestingly, the *in vitro* activity of the methyl and methoxy derivatives had followed similar results like the 13-unsubstituted dibenzofluorenes [9].

The results of these tests indicate the significance of altering structures in terms of antitumor activities. Some compounds were more active than cisplatin in many of these cancer cell lines.

The introduction of a basic group at the terminal site of these molecules was responsible for the increased activity. The basic unit helped to increase the pKa value so that these molecules are protonated at physiological pH. These type of polyaromatic lipophilic and cationic molecules were expected to bind to anionic components inside cells such as to phosphate groups of nucleic acids (DNA and RNA). These lipophilic compounds were also expected to interact with the lipids in cell membrane. The activity *in vitro* is not proportional to clinical applications in many instances.

Pyrrole-Substitued Polyaromaic Compounds

Synthesis of pyrrole-containing polyaromatic compounds was performed. Iodine-catalyzed and clay-induced reactions were investigated [10]. Although clay worked well, silica gel and alumina failed to react with the substrates to produce the products. The success of montmorillonite-mediated reaction for the synthesis of pyrroles indicated the significance and crucial role of the nature and acidity of the solid support.

Sugar-Containing Polyaromatic Compounds

We developed two important methods for the preparation of sugar-containing polyaromatic compounds *via* glycosylation [11]. Glycosylation of alcohols is an important area of research because of the solubility of the glycosides in water and their medicinal activities of *O*-glycosides.Indium metal-induced method of stereoselective synthesis of b-glycosides by a reaction of alcohol and b-D-bromoglucose was developed. A similar method of b-D-bromoglucoses with other metals produced the glycals.

Reaction of 9-fluorenolwith 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide was performed with indium powder. This method generated a single glycoside stereospecifically. The anomeric carbon stereochemistry of this glycoside was found to be b from NMR analysis of the crude reaction mixture.

A reaction of the dibenzoflurenol with the glycal in the presence of borontrifluoride in anhydrous THF produced two glycosides. The unsaturated glycosides were reacted with acid and the products were obtained in good yield.

Dehydrogenation and Novel Polyaromatic Amines

Reaction of 9,10-dihydrophenanthrene with bismuth nitrate pentahydrate impregnated with clay produced 2,7-dinitro compound in the presence of microwave irradiation. The dinitro product was then used to prepare the diamino derivative under the catalytic hydrogenation reaction over Pd/C in anhydrous ethanol at room temperature. Surprisingly, an aromatic compound corresponding to 2, 7-dinitro-phenanthrene derivative was obtained as the minor product. The formation of a new compound was due to a catalytic oxidative dehydrogenation or aromatization reaction.

Mechanism of Actions

Because of multiple aromatic rings, this area of research was studied on the interaction with the DNA systems. An interaction of these molecules against cell membrane was heavily recognized. This was also exemplified by an experiment with well-known cancer drug, adriamycin. Agarose connected with adriamycin showed significant activity against mouse leukemia L1210. This confirmed serious interaction at the plasma membrane. It was necessary for the linked-adriamycin to enter into the cell nucleus. Adriamycin exerted its activity through the formation of a covalent bond

with the lipid. Thus, the physiological conditions of the cells were altered. The *in vitro* cytotoxicity data of the amino derivatives supported the interaction of these compounds with the cell membrane. The charge density, the nature of the functional groups and lipophilicity and hydrophobicity of a molecule may selectively altered the function of membrane. A variety of reactions, for example, compound's interference with surface receptors, intercalation into the membranes, alteration of ion distribution, and lipid disruption were the most common. The active amino compound that interacts with caspase-3 had also interaction with the membrane of the red blood cells like a membrane stabilizing agent. Possibly this molecule intercalated into the cell membrane by hydrophobic interaction.

Conclusions

We demonstrated various new methods including but not limited to bismuth nitrate-mediated nitration of polyaromatic hydrocarbons, indium-induced reduction of polyaromatic nitro compounds and imines to amino derivatives, samarium-mediated reductive dimerization, one-pot synthesis of dibenzofluorenes, oxidation of activated methylene group to ketone by sodium bismuthate, stereospecific glycoside formation and optical resolution of polyaromatic alcohol with carbohydrates. These methods were used in combination with other available pathways for the preparation of numerous polyaromatic compounds. Structure-activity relationships studies of many of these molecules were conducted against numerous cancer cell lines *in vitro* and useful selectivity was observed. Some of the most active compounds were tested against specific cancer cell lines and a reduction of tumor growth was observed.

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