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A Review on Different Synthetic Route and the Medicinal Aplications of 2-(3-(Dimethylamino)Propyl) Isoindoline-1,3-Dione Derivatives

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Abstract

2-(3-(Dimethylamino)Propyl)Isoindoline-1,3-Dione (DAPID) derivatives have been obtained by the reaction of the phthalic acid anhydride derivatives with N, N dimethyl propyl amine derivatives. The yield of DAPID type derivative was 60% by classical way which was carried out in our laboratory. But when this reaction was carried out by modern way i.e. microwave enhance method, then the yield was 85% to 91% with short time. 3-(1,3-dioxoisoindolin-2-yl)-N,N-dimethylpropan-1-ammonium perchlorate (DIDAP) derivatives have been obtained by the reaction of 2-(3-(Dimethylamino)Propyl)Isoindoline-1,3-Dione (DAPID) derivatives with salt. The DIDAP compound was synthesized in a different route followed by able to show it's excellent anticancer activity against hepatomas Hep G2 Cell line.

Keywords: DAPID • DIDAP • Biocidal activity

Introduction

At the present time, the most serious public health problems in the world are cancerous disease [1-3]. Cancer is a big clinical challenge to human beings causing demolition from high malady and mortality rates. Among various types of tissue originated cancers, liver cancer is one of the damning and invective cancers in children younger than 5 years of age worldwide but also the fifth record common cancer in males and the seventh record common cancer in females, and is the third significance cause of cancer-related death worldwide [4-8]. In spite of advances in liver cancer treatment, it is one of the most tough cancers to treat. For patients first stage Hepatocellular Carcinoma (HCC), surgery, local destructive therapies, and liver replacement take remedial potential. However, repetition of HCC is a major problem after remedial treatment, reaching an incidence of more than 70% at 5 yr. Even in first stage patients, small HCC (<3 cm) receiving surgery, the 5 yr survival rate is not satisfactory (47% to 53%). Typically, HCC is mostly diagnosed at a primary stage, and many patients with primary stage are not eligible for the remedial therapies. Furthermore, customary systemic chemotherapy shows low working efficiency and samll survival benefits [9]. The approval of a multikinase vanquisher, sorafenib, has shown some progressive benefit in patients with primary HCC and conserved liver function, highlighting a promising molecular targeted strategy for primary HCC. Solution of liver cancer is now multidisciplinary, and multi model treatment options are chosen generally on an individualized basis according to the complex interplay of tumor stage and the extent of underlying liver disease, as well as the patient's overall general health. There are various recommendations for the managing of liver cancers across the specialties and geographic areas such as major management of liver cancer guidelines from the United States National Comprehensive Cancer Network (NCCN), Europe (European Association for the Study of the Liver-European Organization for Research and Treatment of Cancer (EASLEORTC)), and Asia (consensus statement from the Asian Oncology Summit 2009 (AOS)) [10].

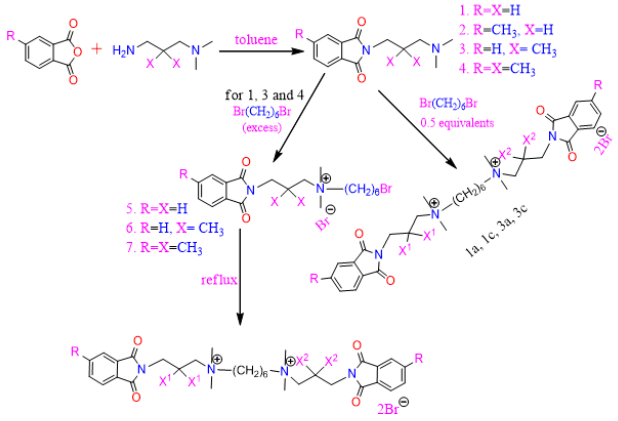

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Figure 1. Synthesis pathway of the compounds.

Though most popular marketable anticancer drugs are essentially heterocyclic organic compounds and natural products, but recently metal complexes are going to much attention in anticancer research [11]. Cis-platin discovery was breaktrough in 1965 by Rosenberg et al. . This discovery has been showed a new branched of metal based anticancer drug in current anticancer drug discovery. This was successfully moved to the clinical support of many second generation platinum drugs such as oxalopatin, nedaplatin, carboplatin and other metal complexes for treatment of a diversity of cancers in several countries [12]. However the role of metal complexes in oncology was significantly good but they have been found to be associated with severe toxicity issues. So the rational experimental work on ligand design and synthesis of metal complex for targeting of particular protein part is active research area in bio-organometallic and medicinal chemistry. The synthesis of coordination compound with rationally designed architectures of ligand structures have distinct power to transfer cytotoxic metals to the specific enzymes, proteins or cell organelles and then the toxicity of metal complex is reduced [13-19]. The novel frameworks with O, N and S hetero donar ligands are going to much responsiveness in experimental anticancer drug design. Among the various metal coordination compounds, the transition metal complexes with Schiff base type ligands have shown a great potential anticancer activity such as pthalimide and indoline derivative ligand have attracted medicinal chemists due to their easy availability, fast optimization as well as presence of biologically active hetero nucleus which is showing biological and pharmaceutical activities. These model studies have proved to be useful in understanding the role of metal ions in specified coordination geometries signifying the course and nature of reactions in a particular system [20-25].

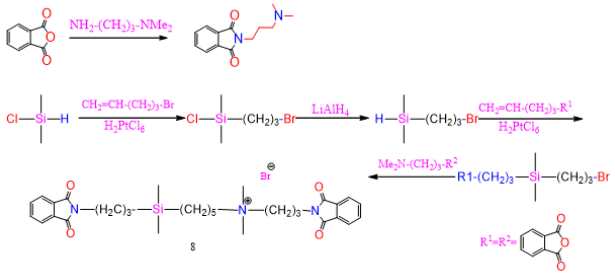

Figure 2. Synthesis pathway of the 8 compound.

In the midst, thalidomide is a multi-target drug that affects several cellular processes, including peptidase inhibition, (Cyclooxygenase) COX inhibition, glucosidase inhibition and androgen receptor antagonism. Research studies on the structure activity relationship (SAR) of the metabolites and correspondents of thalidomide have revealed that the phthalimide ring system is an essential pharmacophoric fragment. Phthalimide (isoindoline1,3-dione) has usually been employed in the design of potential antitumour, immunomodulatory, antiangiogenic, anti-microbial and anti-inflammatory drug candidates [26]. Further, heterocyclic hits are of considerable utility in synthetic medicines or pesticides and biochemical effects. Heterocycles containing pyrazole, imidazo[1,2-b]-pyrazole, pyrazolopyrimidine, pyrazolo-triazine scaffolds exhibit versatile biological properties such as anti-inflammatory, antifungal, antioxidant, antitumor and immunosuppressive agents. Hence, molecular hybridization strategy via introduction of different pharmacophoric fragments might improve the biological activity of phthalimide derivatives [27].

Synthesis

Different synthesis procedure of 2-(3-(dimethylamino) isoindoline-1,3–dione (DAPID) derivatives

The organic chemists synthesized of 2-(3-(dimethylamino)propyl)isoindoline-1,3–dione (DAPID) derivatives by different procedure [28-30].3-(N, N-dimethylamino)-propylphthalimide and the corresponding methylphthalimides 1 and 2 were obtained by conversion of two molecules of the phthalic acid anhydride derivatives with N, N dimethyl propyl amine derivatives. To achieve the phthalimides 3 and 4, phthalic acid anhydride and methylphthalic acid anhydride, respectively, were refluxed in the presence of 1,3-diamino-N, N-2,2-tetramethylpropane in toluene using a water separator (Figure 1). The compound 16 was prepared by Abdel-Hafez et.al. according to Figure 4. At first, Phthalic anhydride (0.5 g), 1.1 eq. of the appropriate amine were added to a 50 mL round-bottomed flask equipped with a reflux condenser. Then, the mixture was heated to gentle boiling at 150~250 ~ for between 5-15 min. After the reaction, the reaction mixture was cooled and then benzene (30 mL) was added before solidification to form a slurry mixture. Finally, the precipitate was filtered, washed twice with water, and the crude material was crystallized from light petrol ether 60-80°C [31-36].

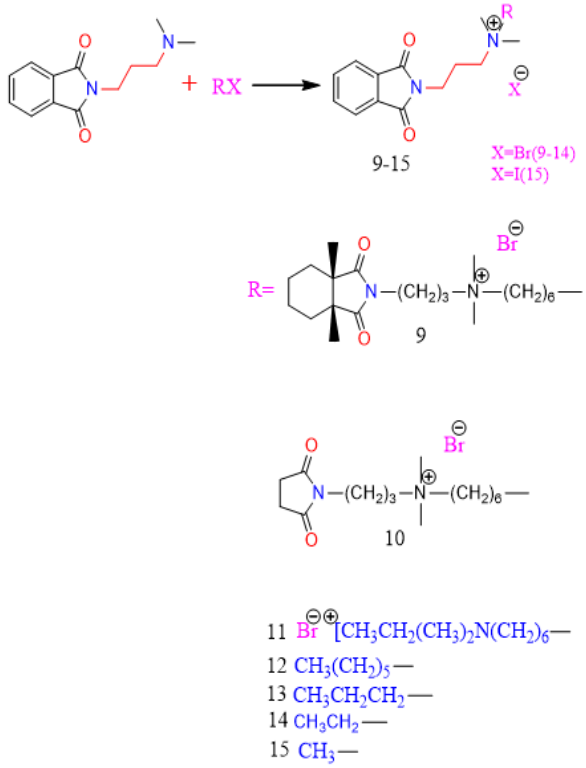

Figure 3. Synthesis pathway of phthalimides derivatives molecules.

The compound 16 also was prepared by Teresa Borowiak et.al. according to Figure 5 but this process was different. At first, N, N-

Dimethyl-3-phthalimidopropylamine was obtained by the reaction of a commercially available N, N-dimethylpropyl-1,3-diamine with phthalic anhydride in acetic acid (Figure 5) [37]. Then, the reaction mixture was heated under reflux for 4 h. The product was purified by method given by B. Brycki et.al. The formation of the imide 16 was published as both a thermal and a microwave-enhanced method (Figure 8). The reaction time was shortened (from hours to minutes) and the yield was improved with microwaves from 85% to 91%. Recently we synthesized compound 16 by classical way with 60% yield [38-41]. At first, 5 ml toluene solution of isobenzofuran-1,3-dione (1.0 mmol, 0.148 g) was added in the stirring 5 ml toluene solution of N1, N1-dimethylpropane-1,3-diamine (1.1 mmol, 0.112 g) followed by P-Toluenesulfonic Acid (PTSA) (50 mg/g) and the reaction was stirred at reflux for 6 h. The formation of the product was examined by running TLC. The reaction mixture was cooled to room temperature and solvent was removed to get the crude [42-45]. The crude was diluted with DCM (Dichloromethane) and washed with water followed by $NaHCO_3$ solution (to remove PTSA and acid product). The solvents were dried over anhydrous sodium sulfate, filtered and solvents were removed to get the crude. The crude was purified by silica gel column chromatography using DCM to 5% MeOH in DCM (Figure 11).

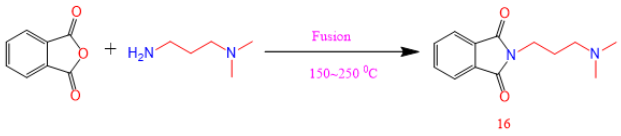

Figure 4. Synthesis pathway of phthalimides derivative molecule 16.

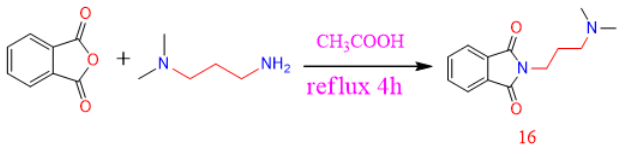

Figure 5. Synthesis different pathway of phthalimide derivative molecule 16.

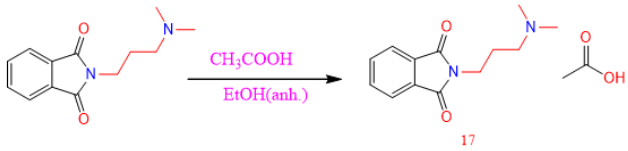

Figure 6. Synthesis pathway of phthalimide derivative molecule 17.

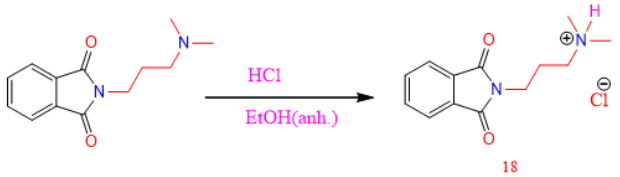

Figure 7. Synthesis pathway of phthalimide derivative molecule 18.

Synthesis procedure of different type of 3-(1,3-dioxoisoindolin-2-yl)-N, N-dimethylpropan-1-ammonium perchlorate (DIDAP) derivatives

The organic chemists also synthesized of different type of 3-(1,3-dioxoisoindolin-2-yl)-N,N-Dimethylpropan-1-Ammonium Perchlorate (DIDAP) derivatives by the reaction of 2-(3-(Dimethylamino)Propyl)Isoindoline-1,3-Dione (DAPID) derivatives with salt. Phthalimide derivatives 1a and 3a were obtained by conversion of two molecules of the phthalimide derivatives with dibromohexane. Conversion of two molecules of 3 and 4, respectively, with dibromohexane gave the symmetrical compounds 1c and 3c. To obtain the nonsymmetrical compounds, the phthalimides 1, 3, and 4 first have to be alkylated by using an excess of dibromohexane without any reaction solvent to achieve 5, 6, and 7, respectively [46-48]. Alkylation of 3 with 5, 2 with 6, 1 with 7, and 2 with 7 by refluxing in acetonitrile gave 1b, 2a, 2b, 2c, and 3b, respectively (Figure 1). The above compounds were prepared by Alexandra Raasch et.al. Seraina Duda-Johner et.al, Compound 8 was prepared in four-step syntheses according to Figure 2 mechanism. The synthesis of the phthalimides derivatives characterized by an unilateral succinimide 10 was already reported by Bender et al. The synthesis of an unilateral trans substituted cyclohexanedicarbonic acid imide compound 9 was performed in analogy to Staudt et al. by alkylation of N,N-dimethylaminopropylphthalimide with dibromohexane and connecting the monobromo compound with the corresponding dimethylaminopropyl cyclohexanedicarbonic acid imide [49].

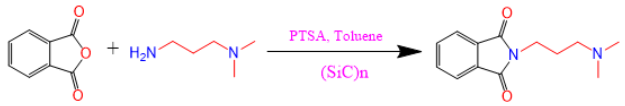

Figure 8. Synthesis different pathway of phthalimide derivative molecule 16.

Compound 11 missing the second imide moiety was obtained by alkylation of dimethylaminopropylphthalimide with the corresponding amino-substituted bromohexane which was achieved be refluxing dibromohexane and N-ethyldimethylamine in ethanol for 20 h. The monoquaternary compounds 12-15 can be easily obtained by alkylation of dimethyl amino propyl phthalimide with the corresponding iodo- or bromoalkane (Figure 3). The multistep synthesis of the 15 starting from pipecolic acid has been recently reported by Holzgrabe, U et.al. The Teresa Borowiak et.al. Prepared N, N-Dimethyl-3-phthalimidopropylamine acetate (Figure 6) by reaction of equimolar amounts of N, N-dimethyl-3-phthalimidopropylamine and acetic acid in anhydrous ethanol [50].

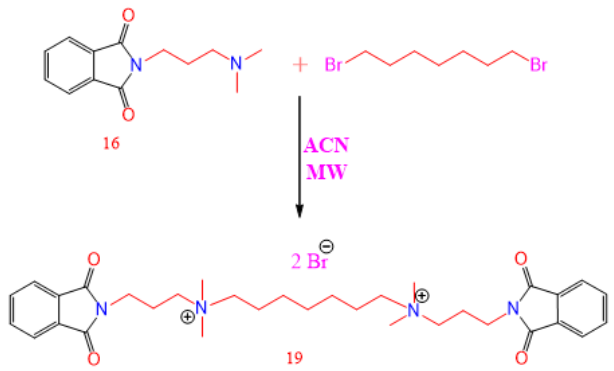

Figure 9. Synthesis pathway of phthalimide derivative molecule 19.

The product was purified by crystallization from hexane. Yield 65%, mp 40-41°C. The Teresa Borowiak et.al also prepared N, N-Dimethyl-3-phthalimidopropylamonium hydrochloride (Figure 7) was obtained by reaction of N, N-dimethyl-3-phthalimidopropylamine with equimolar amount of hydrochloric acid in anhydrous ethanol. The product was crystallized from anhydrous ethanol. Yield 65%, mp 203-205°C [51]. Phthalimide derivative 19 was synthesized in the classical way (time 2 h, yield 80%) and but in a microwave oven (time 30 min, yield 91%). N, N-dimethyl(carboethoxymethyl)-3-phthalimidopropylammonium chloride dihydrate (20) was prepared by reaction of equimolar amounts of N, N-dimethyl-3-phthalimidopropylamine and ethyl chloroacetate acid in anhydrous ethanol. The product was purified by crystallization from ethanol. N, N-dimethyl(carboxymethyl)-3-phthalimidopropylammonium hydrochloride was prepared by reaction equimolar amounts of N, N-dimethyl-3-phthalimidopropylamine and chloroacetic acid in anhydrous ethanol. The product was purified by crystallization from ethanol [52]. Recently we synthesized 3-(1,3-Dioxoisoindolin-2-yl)-N,N-Dimethylpropan-1-Ammonium Perchlorate (DIDAP). At first methanolic solution (2 ml) of sodium perchlorate (0.5 mmol, 0.061 g) was added in a stirred methanolic solution (2 ml) of ligand 16 (0.5 mmol, 0.116 g) and the reaction was stirring for 30 min. Then 5 ml of acetonitrile solution was added and the reaction was stirring for another one hour. The reaction mixture was kept few days for crystallization purpose. After 15 days a colorless needle shaped crystal was obtained. Yield: 80% [53].

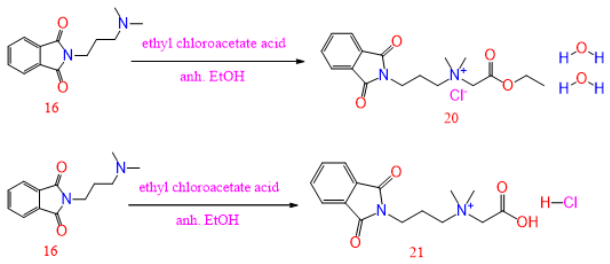

Figure 10. Synthesis pathway of phthalimide derivative molecules 20 and 21.

Application

Now a days, toxicity and resistance play an important role in drug development for the treatment of diseases due to microbes, helminthes and insects. Thus there is still a search for new antimicrobial, anthelmintic and insecticidal agents. N-Mannich bases derived from phthalimide analogous have been extensively used in medicinal chemistry owing to their wide range of biological applications reported in literature. Phthalimide is a colorless solid aromatic imide in which two carbonyl groups bound to an amine functional moiety. It is a very important starting synthone for organic synthetic chemists to prepare diverse biologically active molecules. Numbers of phthalimide derivatives have been synthesized incorporated with interesting biological activities and liquid phase crystalline properties [59], as well as find varied applications in industrial field. Phthalimide and its derivatives have received much attention due to its versatile biological and pharmaceutical activities such as antimicrobial antihypertensive anti-viral, antitumor, anti-inflammatory agents as a inhibitors of HIV-I integrase and serve as ligands to form bioactive metal complexes.

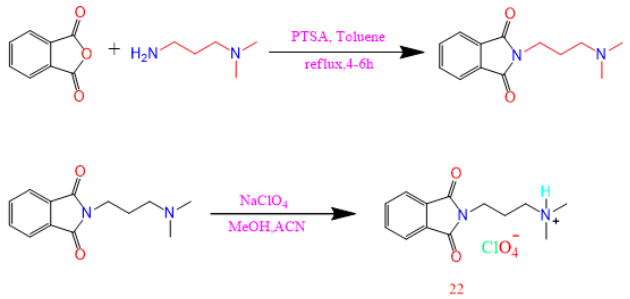

Figure 11. Synthesis different pathway of phthalimide derivative molecule 16 and 22.

Compound 2-(3-(Dimethylamino)Propyl)Isoindoline-1,3-Dione (DAPID) showed higher protective indices (TD50/ED50) than sodium valproate, indicating their maximum anticonvulsant protection is achieved in non-neurotoxic doses. When 2-(3-(Dimethylamino)Propyl)Isoindoline-1,3-Dione (DAPID) react with sodium perchlorate (salt) produced 3-(1,3-Dioxoisoindolin-2-yl)-N,N-Dimethylpropan-1-Ammonium Perchlorate (DIDAP), then the compound DIDAP showed in vitro anticancer activity against human hepatoma cell line Hep-G2 using Sulforhodamine B (SRB) assay.

Conclusion

Synthetic heterocyclic compound continue to be a hot topic in the medicinal chemistry as well as in the bioinorganic field as most popular marketable anticancer drugs are essentially heterocyclic organic compounds and natural products, but recently metal complexes are going to much attention in anticancer research. Earlier DAPID was synthesised in various path by different scientist and anticonvulsant activity was only mentioned while DIDAP was synthesised but they did not find out any anticancer activity. We are, the first team, able to show the anticancer activity of the synthesised DIDAP complex and prepared the said compound in a different route. In this mini review, our main motive is to highlight the different synthetic procedure of phthalimide type heterocycle which act as biological activity.

Declaration of Competing Interest

The authors have no conflicts of interest to declare the content of this article.

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