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Anticancer Perspectives of *Tryptanthrin* Derivatives: An Update From 2017-21

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Abstract

Cancer is one of the most life threatening diseases throughout the globe and also a leading cause of mortality. Despite huge advancements in the health sector, still it is considered as dreadful and dangerous health ailment. According to WHO report, more than 10 million people have died due to cancer in 2020. Drugs from natural origin has been focused to explore anticancer potentials in the past few years and several active constituents and their derivatives has been discovered as promising clinical candidates. *Tryptanthrin* is one such naturally occurring alkaloid with cytotoxic ability. It exerts anticancer activity mainly by binding to the different type of kinases. There are several reports available describing synthetic procedures for *tryptanthrin* and its derivatives. In the present compilation we have summerised lates synthetic strategies (past five years) for *tryptanthrin* derivatives along with important aspects of Structural-Activity Relationship (SAR). Although many investigations have been done on *tryptanthrin*, still no promising therapeutic candidate has been introduced to the market.

Keywords: Cancer; *Tryptanthrin*; Cytotoxic; Kinases; Synthetic

Introduction

Tryptanthrin is a naturally occurring alkaloid that is obtained from fungi named Candida lipolytica. These fungi mainly flourished in L-tryptophan [1]. *Tryptanthrin* is chemically known as indolo [2,1-b] quinazoline-6,12-dione. In this compound, a quinazoline ring is connected to an indole ring and contains a carbonyl group at the 6th and 12th position [2]. *Tryptanthrin* is also obtained from plants named Isatis [3], Calanthe [4], Wrightia [5], and Strobilanthus [6]. This naturally occurring compound is yellow in nature. Some alkaloids like candidine and phaitanthrins were obtained from natural sources which have a similar core [7]. These compounds are used as antitumor [8,9], antimalarial, anti-inflammatory [10-12]and as antimicrobial agents [2]. The effectiveness of *tryptanthrin* as an anti-tuberculosis and anti-tumour medication is now being investigated in preclinical studies [5]. *Tryptanthrin* has received a lot of interest as an anticancer drug in recent years, although its biology in cancer cells is still unknown [8,13]. Many compounds have been found in nature containing indolo [2,1-b] quinazoline moiety (Figure 1-3). Trypthanthrin is synthesized through many reactions such as, by thermolysis of isatin [14], Cu-catalyzed oxidation of indole [15], Dakin oxidation of indole-3-carbaldehydes [16]. *Tryptanthrin* is also synthesized by radical oxidative cyclization from quinazolin-4(3H)- one [17]. Synthetic strategies and SAR of *tryptanthrin* derivatives Yang et al, synthesized a series of N-benzyl/aryl-substituted *tryptanthrin* derivatives which were assessed on different cell lines such as HeLa, HEK293, U87 MG. They also assessed their inhibitory efficacy on IDO1, TDO and IDO2. Among these, IDO1 and TDO have high inhibitory than IDO2. These three enzymes have different therapeutic roles. IDO1 is an enzyme-containing heme in different organs such as the lungs, small intestine and placenta. The enzyme TDO was present in high concentration in the liver and plays important role in neurogenesis. Among all synthesized compounds, compound 1 was found to be most potent. They synthesized methylisatoic anhydride by using 5-methylisatin which follows Baeyer-Villiger oxidation in which 3-chloroperbenzoic acid acts as an oxygen donor. NBS was used as a brominating agent which synthesizes compounds in presence of potassium iodide as a catalyst. They synthesized another series of compounds by using Pd (OAc)2 as a catalyst which followed the same procedure. The Ki value of compound 1 was found to be 2.64μM, 6.32μM and 0.31μM against IDO1, ODO2 and TDO, respectively. The inhibitory activity of compound 1 was found to be 0.02μM, 18.66μM and 0.09μM against IDO1, ODO2 and TDO, respectively.

Among which compound 1 was active against the HeLa cell line which showed an IC_{50} value of 0.02μM. In mice bearing LLC tumour, the volume of the tumour was decreased to 56.2% with 1 instead of 1-L-MT which have the capability of reducing only 33.6%. Thus,

compound 1 has a higher inhibitory potential than 1-L-MT. The inhibitory potential of compound 1 was also seen on H22 bearing tumour mice. The results showed that compound 1 decreased the tumour by 47.3% and 15.8% by 1-L-MT [18]. Synthetic strategies and SAR of *tryptanthrin* derivativesYang et al, synthesized a series of N-benzyl/aryl-substituted *tryptanthrin* derivatives which were assessed on different cell lines such as HeLa, HEK293, U87 MG. They also assessed their inhibitory efficacy on IDO1, TDO and IDO2. Among these, IDO1 and TDO have high inhibitory than IDO2. These three enzymes have different therapeutic roles. IDO1 is an enzyme-containing heme in different organs such as the lungs, small intestine and placenta. The enzyme TDO was present in high concentration in the liver and plays important role in neurogenesis. Among all synthesized compounds, compound 1 was found to be most potent. They synthesized methylisatoic anhydride by using 5-methylisatin which follows Baeyer-Villiger oxidation in which 3-chloroperbenzoic acid acts as an oxygen donor. NBS was used as a brominating agent which synthesizes compounds in presence of potassium iodide as a catalyst. They synthesized another series of compounds by using Pd (OAc)2 as a catalyst which followed the same procedure. The Ki value of compound 1 was found to be 2.64μM, 6.32μM and 0.31μM against IDO1, ODO2 and TDO, respectively. The inhibitory activity of compound 1 was found to be 0.02μM, 18.66μM and 0.09μM against IDO1, ODO2 and TDO, respectively. Among which compound 1 was active against the HeLa cell line which showed an IC_{50} value of 0.02μM. In mice bearing LLC tumour, the volume of the tumour was decreased to 56.2% with 1 instead of 1-L-MT which have the capability of reducing only 33.6%. Thus, compound 1 has a higher inhibitory potential than 1-L-MT. The inhibitory potential of compound 1 was also seen on H22 bearing tumour mice. The results showed that compound 1 decreased the tumour by 47.3% and 15.8% by 1-L-MT [18,19] synthesized newer *tryptanthrin* derivatives as promising anticancer agents. These *tryptanthrin* derivatives were prepared by using isatoic anhydride and indoline-2,3-dione as a reactant. Total 12 derivatives were prepared, among which compounds with Bromo (compound 3) and nitro substituent were found to be most potent. The IC_{50} value of these compounds was found to be 2.0μM and 1.4μM, respectively. SAR studies showed that if the EW group such as bromine, fluorine and iodine was introduced at the 8th position, the anticancer activity of the compound increased (Figure 4). Moreover, if the bromine group was introduced at the C-2 position, the anticancer activity decreased. The anticancer activity was assessed against the Hep3B cell line. Doxorubicin was taken as a reference drug. The cell viability was determined by performing an MTT assay. The flow cytometric analysis was also carried out by taking etoposide as a positive control. Results showed that when the cells were treated with compound 3 (5 μmol/L), the number of cells increased from 11.9% to $_{50}$.8% in the G2/M phase. So, it was found that compound 3 was active only on the S phase. As similar, the concentration of cells reduced in the G2/M phase while treated with nitro derivatives. Again, flow cytometric analysis was performed by taking staurosporine as +ve control instead of etoposide. Results showed that the number of cells showed significantly reduced in S and G2/M phase. Overall cytotoxicity results showed that compound 3 was effective at S and G2/M phase and cause cessation of the cell cycle [20]. Guda and co-workers designed and synthesized a series of substituted hydrazono indolo [2,1-b] quinazoline-6,12-dione compounds which showed anticancer and antimicrobial activities. They synthesized a total of 22 compounds among which compound 4 was found to be most potent as an anticancer agent. The anticancer activity was evaluated against four cancer cell lines MCF-6. A549. HeLa and HEK-293. But compound 4 showed anticancer activity against only three cell lines MCF-7, A549, HeLa which have IC_{50} of 07.14± 1.285 μM, 09.18± 0.968 μM and 10.57 ± 0.581 μM respectively which was compared with IC_{50} value of cisplatin i.e. 4.28± 0.355 μM, 5.14± 0.421 μM, 3.88± 0.354 μM. But this compound was inactive against the HEK-293 cell line. Compound 4 was synthesized by reacting isatoin anhydride and hydrazine intermediate with toluene and THF as solvent. The crystal structure of compound 4 showed that the bond length of carbon-17 and oxygen-2 was 1.236 Å and 1.243 Å.

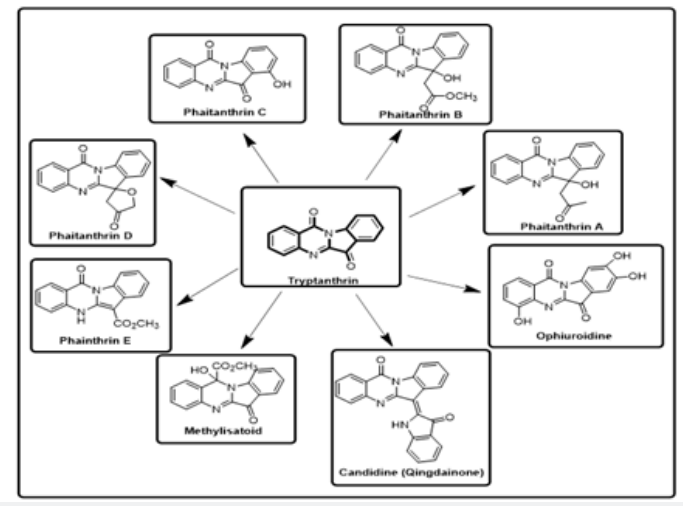

Figure 1: Tryptanthrin derivatives obtained from natural resources.

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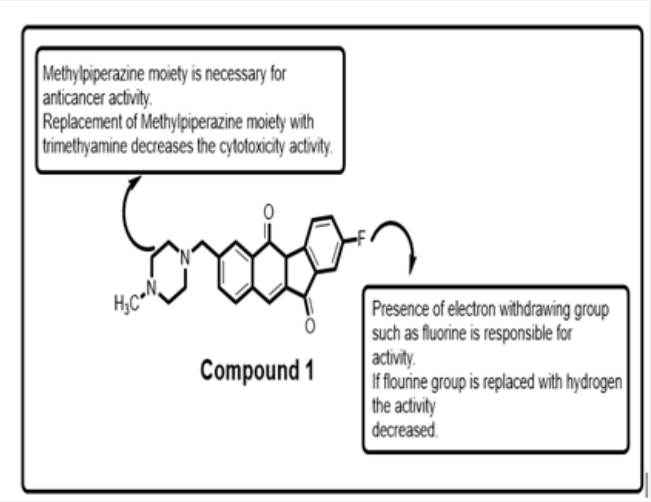

Figure 2: SAR of N-benzyl/aryl-substituted tryptanthrin derivatives.

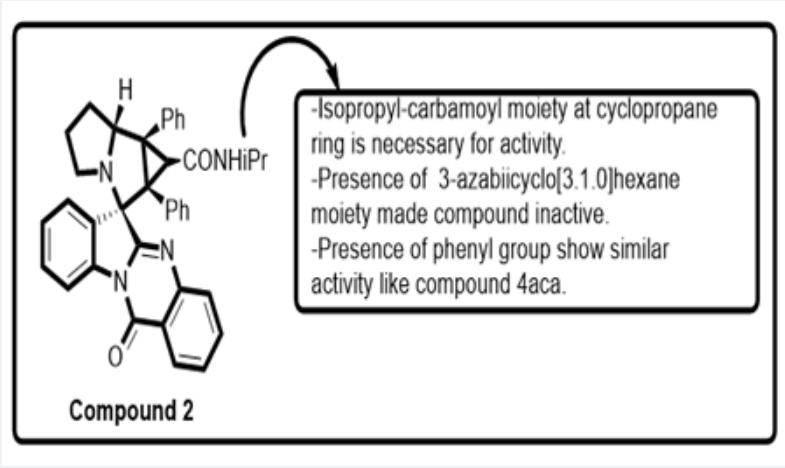

Figure 3: SAR of spiro-fused indolo[2,1-b] quinazoline.

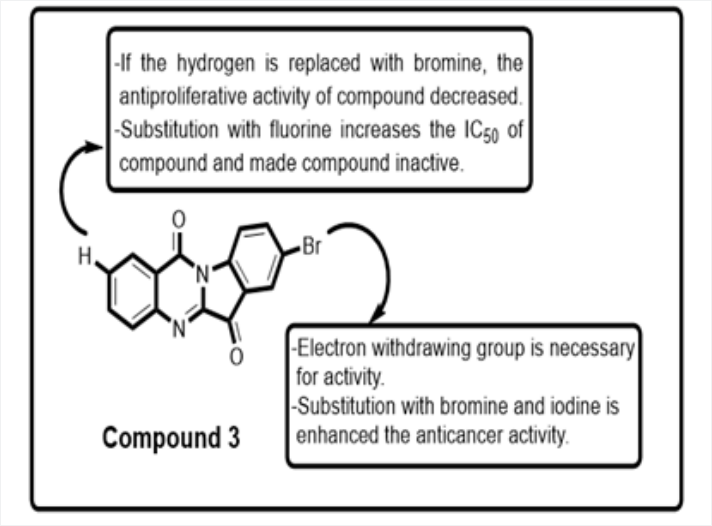

Figure 4: SAR of most potent tryptanthrin derivative.

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Compound 4 showed interactions which were (C-H*O, C–H*π and C*N). The antibacterial activity was also evaluated which showed that compound 4 was found to be most potent against two gram-positive bacteria such as S, aureus and B. subtilis, two gram-negative bacteria E. coli and K. pneumonia. SAR studies showed that indole and quinazoline cores were necessary for the cytotoxic activity (Figure 5). Substituted *tryptanthrin* showed the highest cytotoxicity than unsubstituted *tryptanthrin*. If electron-donating groups such as methyl and methoxy were added in C2 and C8 positions, the cytotoxicity activity of the compounds decreased. Replacement of hydrogen with bromine at the C8 position, the anticancer activity of compound 4 was increased. Molecular docking studies of synthesized compounds have been performed. The 3D structure of the Indoleamine 2, 3-dioxygenase enzyme was taken as a target from the protein data bank with PDB ID: 2d0U. Results showed that compound 4 has the highest binding energy -11.25Kcal/mol. Results showed that compound 4 showed H-bonding with His346 and hydrophobic with di-ketone with Phe163, Ile217 and Ile349 with π–π stacking [21], designed and synthesized a series of 8-substituted-6-hydrazonoindolo [2, 1-b] quinazolin-12(6H)-one compound that showed antioxidant and anticancer activities. They synthesized a total of 18 compounds among which compound 5 was found to be most potent against four cancer cell lines MCF-7, A549, HeLa and HEK293 which have IC_{50} of 9.42 ± 1.239 μM, 7.19 ± 0.991 μM, 9.42 ± 1.594 μM and 64.12±1.482 μM, respectively as compared to cisplatin. Results showed that compounds with pyridine moiety also showed better anticancer activity with IC_{50} of 11.60, 9.42 and 6.01 and 7.18 against four cancer cell lines, respectively. All the compounds were synthesized through Suzuki coupling. The cytotoxicity activity was evaluated through an MTT assay using tetrazolium dye. SAR studies explained that anticancer activity was dependent upon the moiety present on the core moiety (Figure 6). If the position of C2 and C8 were changed with the electron-withdrawing group, the potency of the compound increased. If the 4-pyridyl and 4-carboxyphenyl group was introduced at C8, the anticancer activity of compounds increased. Substituted *tryptanthrin* showed the highest cytotoxicity than unsubstituted *tryptanthrin*. Substituted scaffold only showed higher activity with MCF-7. A549 and HeLa cell lines, but there was no significant effect on the HEK293 cell line. The antioxidant activity was also evaluated by DPPH assay. Results showed that compounds 5 were found to be active with IC_{50} of 5.02 μM. Ascorbic acid was taken as a reference drug which has an IC_{50} of 3.48 μM. Docking studies were performed on three receptors IDO1, EGFR and HER2. Among these, receptor IDO1 was found to be the most suitable target. Here compound 5 showed H-bonding with His346 and nitrogen of *tryptanthrin* moiety which have a bond distance of 3.0734 Å [22], described a new strategy for the synthesis of 7- ((2-(dimethylamino) ethyl) amino) indolo[2,1-b] quinazoline-6,12-dione derivatives as potent antiproliferative agents.

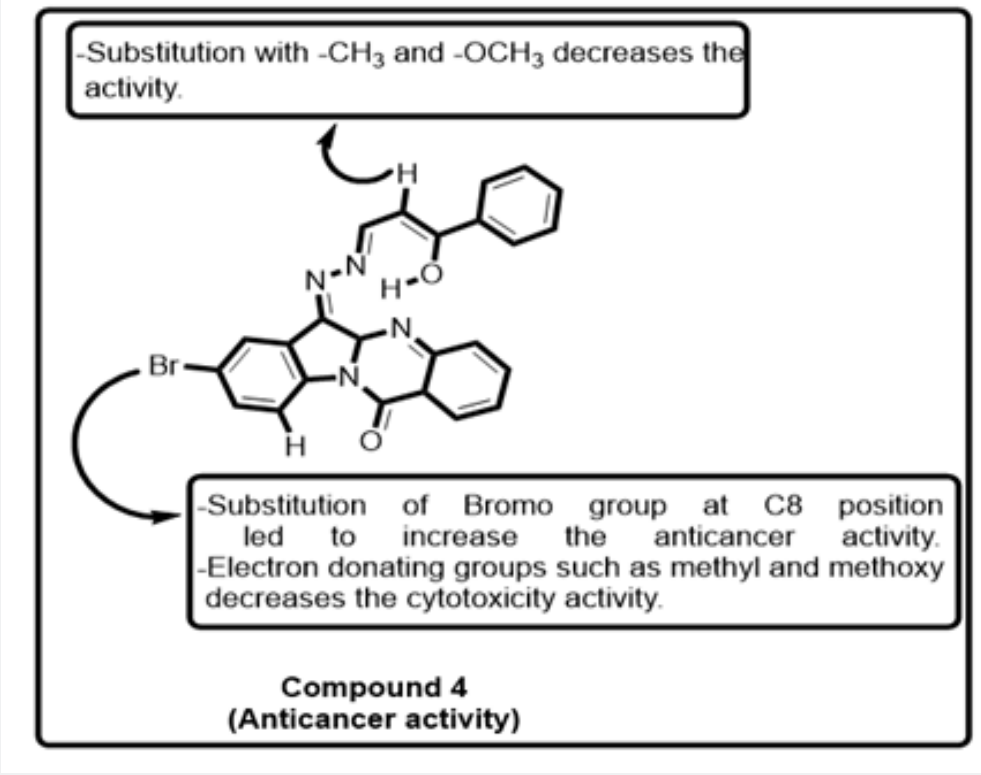

Figure 5: SAR of most potent substituted hydrazono indolo[2,1-b] quinazoline-6,12-dione compound.

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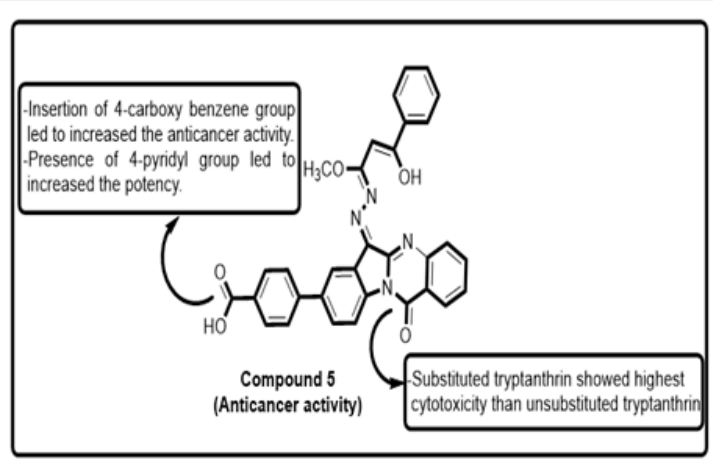

Figure 6: SAR of most potent 8-substituted-6-hydrazonoindolo [2, 1-b] quinazolin-12(6H)-one derivative.

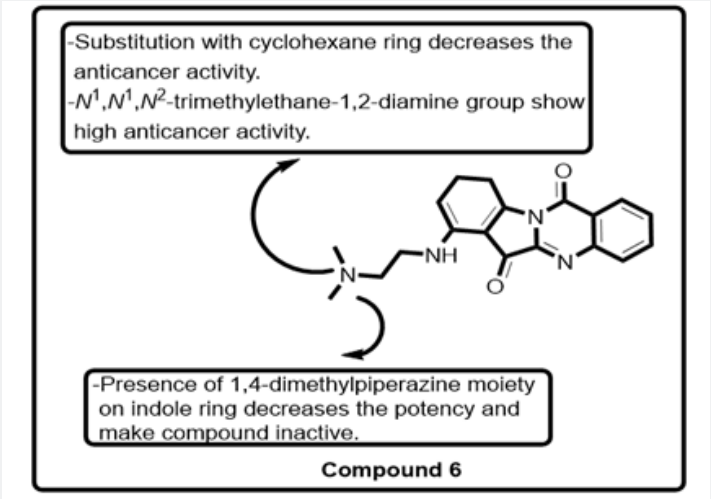

Figure 7: 7- SAR of most potent ((2-(dimethylamino)ethyl)amino)indolo[2,1-b]quinazoline-6,12-dione derivatives.

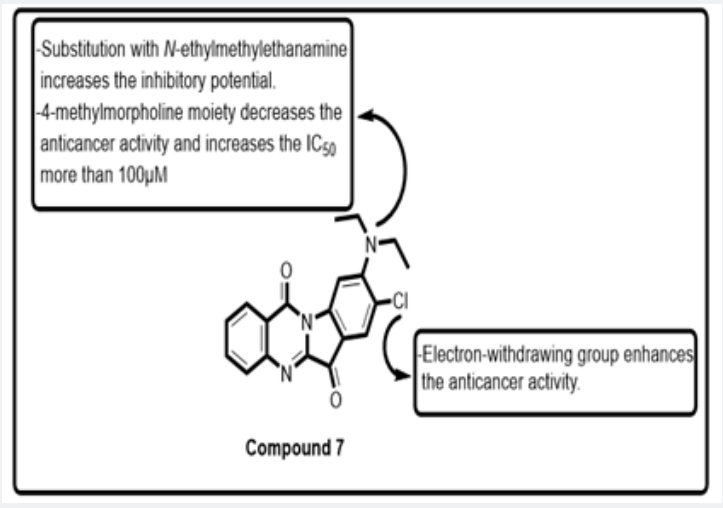

Figure 8: SAR of most potent compound.

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They synthesized 10 compounds, among them compound 6 was found to be most potent. The IC_{50} value of compound 6 was found to be 26.6 ± 4.7 µM. These all compounds were screened as topoisomerase inhibitors. The antiproliferative activity of all the synthesized derivatives was evaluated on cell lines like jurket, CCRF-CEM, CEM/C2 HL-60 (Leukemia cancer cell lines), HT-29, Dld-1 (Colon cancer cell lines), MCF-7 (Breast cancer cell line). They found that anticancer activity was 2.5-fold greater than reference drug etoposide which have an IC_{50} of 68.3 ± 5.4 µM. The IC_{50} of compound 5 was 8.26 while the cells were treated with CCRF-CEM cell line for 72h. results showed that the IC_{50} of compound 6 was 5 fold greater than *tryptanthrin* which have an IC_{50} of 44.36 µM for 72h. The cytotoxic potential of compound 5 was also seen. Results showed that the GI_{50} of compound 5 (1.36 µM) was greater than *tryptanthrin* (14.47 µM) after 72h treatment., SAR studies revealed that the presence of N, N-dimethyl alkylamine substituent was necessary for anticancer activity (Figure 7). The mechanism of action revealed that the particular compound inhibited the G2 phase and cause cell arrest. Compound 6 mainly broke the DNA strand by inhibiting topoIIα. ADMET properties of compound 6 were also recorded which explained that compound 6 has high GI absorption and followed Lipinsky rule of five. By considering all results, they found that compound 6 acts as a hit compound to design new topoisomerase inhibitors [23,24]. Hou and co-workers reported the synthesis of *tryptanthrin* derivatives as potent anticancer agents. They synthesized 15 compounds, among them, compound 7 was found to be most potent. The anticancer activity was assessed on three cancer cell lines- A549, HCT116 and MDA-MB-231. IC_{50} value of compound 7 was found to be 1.48 µM, 1.29 µM and 1.78 µM among three cell lines- A549, HCT116 and MDA-MB-231, respectively. Gefitinib was taken as a reference drug having IC_{50} value of 5.44 µM, 6.46 µM and 45.31 µM. Here, 8- fluoro *tryptanthrin* was taken as starting material which reacts with secondary amines in presence of DMSO and CsCO3 by heating at 100ºC. Then different derivatives were designed by making different substitutions on R and R1. SAR studies showed that electron-withdrawing group on indole moiety was necessary for anticancer activity. Substitution with fluorine gave rise to high inhibitory potential. If the cyclic amide group was introduced, the compound become inactive and gave rise to IC_{50} value (More than 100 µM). *Tryptanthrin* has logP value of 1.73 (Figure 8). Results showed that most of the compounds showed lower values. The results of the cytometric assay showed that compound 7 mainly causes the cell arrest at the S phase which gave rise to cell death in A549 [24]. Zheng and co-workers designed and synthesized a series of *tryptanthrin* derivatives by using secondary amines. The anticancer activity of synthesized compounds was evaluated on three cancer cell lines- A549, HCT116 and MDA-MB-231. Total 36 derivatives were designed, among them compound 8 was found to be most potent. The IC_{50} value of compound 8 was 1.2 µM, 2.01 µM and 0.8 µM among three cancer cell lines- A549, HCT116 and MDA-MB-231, respectively. Gefitinib was taken as a reference which has IC_{50} of 5.44 µM, 6.46 µM and 45.31 µM. Cell proliferative assay was carried out using MTT assay. Most of the synthesized compounds showed IC_{50} more than 100 µM which made compounds inactive. SAR studies showed that electronegative groups were responsible for activity (Figure 9-11). Substitution of fluorine at C-8 of *tryptanthrin* enhanced the activity. If the chlorine group was added the activity of the compound slightly decreased. 7-N-diethylamine group on C-8 of *tryptanthrin* moiety was responsible for activity. If 7-N-diethylamine group was replaced with 7-(Piperidine-1-yl) the compound became inactive (IC_{50} >100 µM). The presence of cyclic amide group made the compound inactive [25].

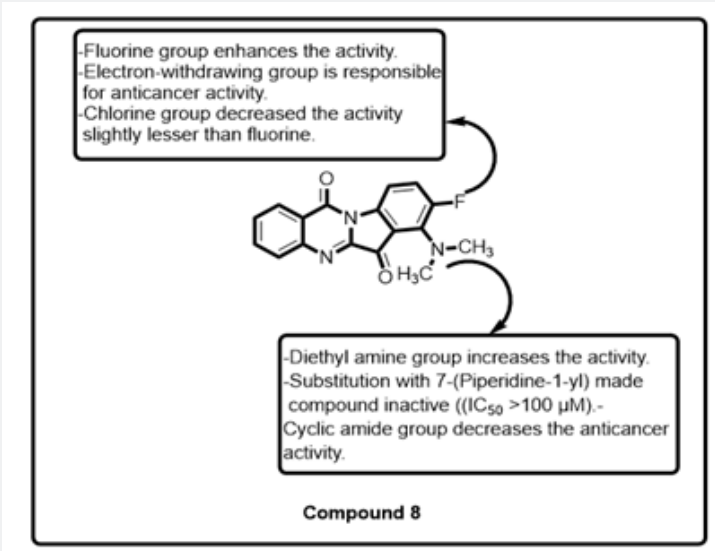

Figure 9: SAR of most potent compound 8.

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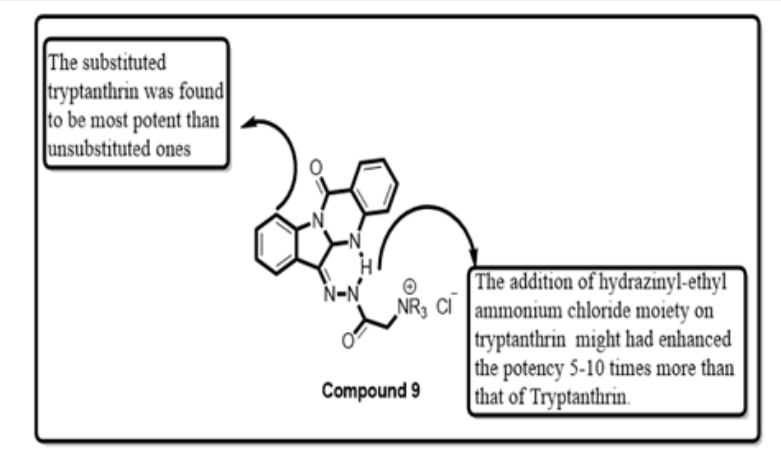

Figure 10: SAR of tryptanthrin analogue (compound 9).

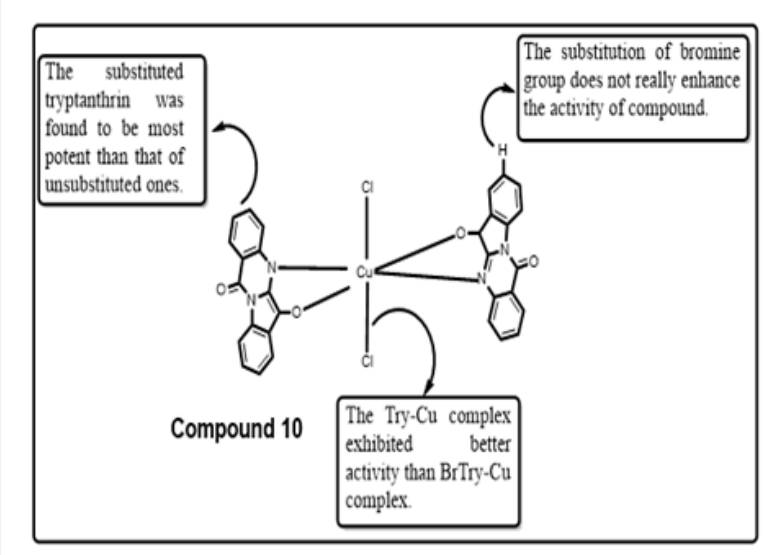

Figure 11: SAR of copper complexes of tryptanthrin.

Popov and co-workers designed and synthesized a novel compound named Mostotrin [9], which was found to have more solubility in water than that of the mother compound *Tryptanthrin* (TR). They elucidated the structure of the compound using NMR and mass spectrometry, and the structure is further confirmed by X-ray crystallographic technique. Furthermore, they performed in-vitro cytotoxicity examination against tumour cells and the in-vivo activities were performed and evaluated on anti-cancer effects, toxicity and anti-inflammatory actions. The compound 9 showed five to ten times higher anticancer activity against HCT-116, MCF-7 and K-562 cancer cell lines but was found to be less toxic than TR with LD_{50} of 375mg/kg while TR had LD_{50} of 75mg/kg. The anti-proliferative activity of the compound and *tryptanthrin* were evaluated in comparison to the reference drug (doxorubin) against various tumour cell lines named HCT-116, MCF-7, B16-F0, K-562 and MDA-MB-231. The IC_{50} of the compound 9 was found to be 5.0, 11.0, $>_{50}$, 1.0 and 46.0 μM and IC_{50} value of TR was found to be $>_{50}$, $>_{50}$, 48.3, 42.4, 21.2 μM with comparison to reference (doxorubicin) with IC_{50} of 0.11, 0.61, 0.55, 0.10, 0.52 μM for HCT-116, MCF-7, B16-F0, K-562 and MDA-MB-231, respectively. Later on, SAR studies were performed and revealed that the substituted *tryptanthrin* was found to be most potent than unsubstituted ones. The addition of hydrazinyl-ethyl ammonium moiety on *tryptanthrin* chloride might have enhanced the potency 5-10 times more than that of *Tryptanthrin* [26], designed and synthesized a novel series of copper complexes of *tryptanthrin* derivatives with various substitutions that inhibit telomerase activity and also enhance mitochondria-promoted apoptosis and arrest the S-phase of the cell cycle in BEL-7402. They designed the copper complexes of *tryptanthrin* (compound 10), Bromo *tryptanthrin*,

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$[CU^{II}(Try)_2Cl_2]$ (Try-Cu), and $[Cu^{II}(BrTry)_2Cl_2]$ (BrTry-Cu). The in-vitro antitumor activity of Try-Cu and BrTry-Cu compounds were tested against human carcinoma cell lines such as BEL-07402, T-24, MGC80-3, and HepG2, and one normal human hepatic cell line which is HL-02. Among the synthesized compounds, the compound Try-Cu was found to be most potent and exhibited good anticancer activity against the four selected cell lines with IC_{50} of 4.02 to 9.03 μM but low activity against human liver cell line HL-7702. Later on, SAR studies were performed and revealed that the substituted tryptanthrin was found to be most potent than unsubstituted ones. The substitution of the bromine group does not enhance the activity of the compound. The *tryptanthrin* with copper complex exerted the highest activity [27].

Conclusion

It is evidenced by several reports that *tryptanthrin* and its derivatives have excellent potential to combat cancer. These work by binding to kinases and inhibiting the phosphorylation step. *Tryptanthrin* derivatives have shown promising results against breast, lungs, cervical and blood cancer. Various synthetic procedures include Dakin oxidation, thermolysis of isatin, metal-catalyzed oxidation of indole and radical oxidative cyclization from quinazolin-4(3H)-one. Beyond all the reported studies, still, further clinical investigations are required to discover a suitable therapeutic agent against cancer.

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