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Anticancer Activities of 1,3-Diaryltriazene Based Compounds: An Overview

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Abstract

The present article discusses the anticancer and antitumor properties of aliphatic and aromatic triazene compounds and their derivatives. The triazene molecule is an essential tool in organic synthesis, acting as the starting material or the reactive intermediate in various organic transformations. In addition, it possesses interesting biological properties. The most explored biological application of the triazene moiety is its cytotoxic effect. The present review highlights the antineoplastic activities of the triazene molecule *in vitro* and *in vivo,* as well as its different derivatives and complexes.

Keywords: *Anticancer Properties;1,3-Diaryltriazene; Metal Complexes*

Introduction

The 1,3-diaryltriazene ligands are azo compounds characterized by a diazoamino group (N=N–NH) consisting of three consecutive nitrogen centers (Kölmel, Jung & Braese, 2013). The synthesis of the first triazene ligand can be traced back to 1859, when the ligand 1,3-bisphenyltriazene was described in connection with diazonium salt preparation (Griess, 1859). The ligands are isoelectronic with amidinates, although the central nitrogen imparts greater acidity to the N-H protons in triazenes. Triazenes and its derivatives consist of a versatile and diverse group of compounds and have received considerable attention in the research arena due to its varied coordination modes (Garzon *et al*., 2015). The ligand usually functions as a bidentate, monoanionic N, N-chelating ligand through dissociation of the acidic N–H proton. It coordinates with the metal center, forming a four-membered chelate ring (Guha Roy*,* Butcher *&* Bhattacharya, 2008). The 1,3-diaryltriazenide anion is a 'short-bite' ligand, having the capacity to act as a bidentate chelating ligand, as stated earlier, along with being a monodentate and a bridging ligand (Nimitsiriwat *et al*., 2007). The ligands are important in natural product preparations, combinatorial chemistry, and biological applications (Canakci *et al*., 2019). The biomedical applications include antibacterial (Abd Halim *et al*., 2023; Cappoen *et al*., 2014) and antifungal properties (Ombaka*,* Muguna *&* Gichumbi, 2012), efficient carbonic anhydrase inhibition (Işık *et al*., 2020; Supuran, 2017), and prolific use in the evolution of numerous anticancer compounds.

The discovery of the antitumor properties of cisplatin heralded a new era of synthetic chemistry in the field of metal-dependent anticancer drugs (Rosenberg, Van Camp & Krigas, 1965). However, cis-platin and other platinum-based drugs possess a lot of undesired effects *viz*., high toxicity and the development of strong resistance to drugs (Heffeter *et al*., 2008). As a result, there is a need to explore newer chemotherapeutic agents. Keeping this in mind, 1,3-diaryltriazenes were selected as the preferred ligand to complex with suitable metals because of its demonstrated ability as antitumor agents. The present review consists of a brief discussion of the anticancer properties of free 1,3-diaryltriazenes and its derivatives, along with some of its complexes.

Discussion

Triazenes as Alkylating agents

Dacarbazine 5-(3,3-dimethyl-1-triazenyl)-imidazole-4-carboxamide (DTIC) (2) is a triazene that is used in the treatment of cancer (Meer *et al*., 1986). It has been sanctioned by the Food and Drug Administration (FDA) for medical use. The synthesis of dacarbazine is presented in Figure 1.

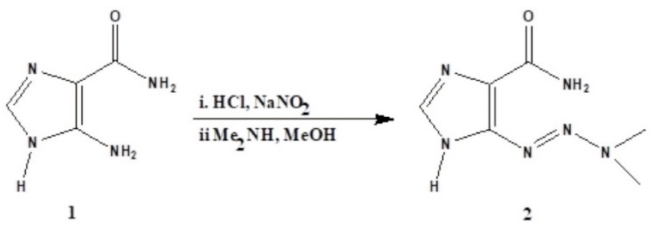


Figure 1: Synthesis of Dacarbazine

On being activated by the hemeprotein enzyme *viz.*, cytochrome P450, dacarbazine undergoes proteolytic decomposition under *in vivo* conditions. This decomposition results in the formation of methyldiazonium ion, which is extremely reactive and effective in the alkylation of DNA (Meer *et al*., 1986). The N^7 position of the guanine base serves as the most common site of DNA alkylation. However, methylguanine adducts formed at the DNA O^6 position are mainly responsible for cytotoxicity and genetic mutation because they can disturb the base pairing, generating an incorrect base pair and causing cell death. Dacarbazine has been one of the most long-established drugs used to treat Hodgkin disease and melanoma (Ogura *et al*., 2010). However, it causes severe side effects in the form of skin toxicity, bone marrow suppression, cardiac and hepatic toxicity, and nausea.

It is worthwhile to note at this point that numerous reports were published prior to the synthesis of dacarbazine, putting forward evidence of the strong antineoplastic activity of 1-phenyl-3,3-dimethyltriazene (3, Figure 2). This resulted in the use of aryl groups

other than those obtained from aniline to produce dimethylaryl triazenes for anticancer study, eventually culminating in the synthesis and use of dacarbazine (Kimball & Haley, 2002).

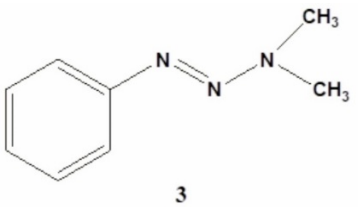


Figure 2: Structure of 1-phenyl-3,3-dimethyltriazene (*Kimball & Haley, 2002*)

Another triazene based antineoplastic compound is diminazene aceturate (Berenil) (4, Figure 3). It forms facile complexes by binding smoothly into the minor groove of AT-rich domains of DNA. Berenil indicates a weak anticancer property against L1210 leukaemia cells (Cimbora-Zovko *et al*., 2011).

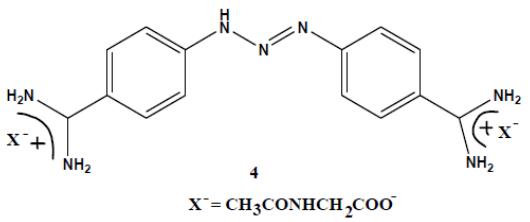


Figure 3: Structure of Berenil

A list of the most prominent molecules exhibiting antineoplastic effects among those discussed in this article is presented in Table 1. The table expresses the cell lines against which the molecules display anticancer activity along with their efficiency in terms of IC_{50} or GI_{50} values. It reveals that the 1,3-diaryltriazene molecules manifest antineoplastic characteristics against a variety of cell lines with satisfactory efficiency.

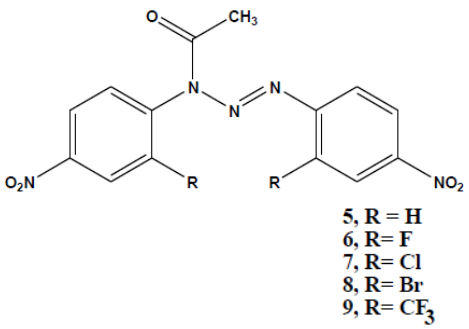
Table 1: *A List of the Most Prominent Molecules Exhibiting Antineoplastic Effects*

Name of the molecules	Working cell lines	Efficiency
3-acetyl-1,3-bis(2-chloro-4-nitrophenyl)-1-triazene	HeLa	IC_{50} :0.63±0.05 μM
1-(4-nitrophenyl)-3-(3-hydroxyphenyl) triazene	HT29, PC3, HepG2 HL60, HeLa, MCF7, Jurkat, K562	IC_{50} :1.51-8.87 μM
1-(4-nitrophenyl)-3-(2-hydroxyphenyl) triazene	HT29, PC3, HepG2 HL60, HeLa, MCF7, Jurkat, K562	IC_{50} :1.13-4.20 μM
1, 3-bis (2-cyanophenyl) triazene	HT29, PC3, HepG2 HL60, HeLa, MCF7, Jurkat, K562	IC_{50} :1.04-2.39 μM

1,3-bis(2-ethoxyphenyl) triazene	HT29, PC3, HepG2 HL60, HeLa, MCF7, Jurkat, K562	IC_{50} :0.67-3.33 μM
Ethyl 2-(3,3-dibuthyl-1-triazenyl)-1H-pyrido[2,3-c] pyrrolo-3-carboxylate	Jurkat, K562	GI_{50} :2.2-5.5 μM
Ethyl 2-(3,3-dibenzyl1-triazenyl)-1H-pyrido[2,3-c] pyrrolo-3-carboxylate	Jurkat, K562	GI_{50} :2.5-8.2 μM
1-(4-(3-(benzo[d]thiazol-2-yl) triaz-2-en-1-yl)phenyl)ethan-1-one	MCF7, HCT116	IC_{50} :10-50 μM
1-(2-chloroethyl)-3-methyl-3-carbethoxytriazene	H125, U251, MCF7, OVCAR4, MALME-3M, LOX	IC_{50} :2.5-25 μM
1-(2-chloroethyl)-3-methy-3-(methylcarbamoyl)triazene	H125, U251, MCF7, OVCAR4, MALME-3M, LOX	IC_{50} :10-30 μM
4-(3-(4-chlorophenyl) triaz-1-en-1-yl)-(pyrimidin-2-yl) benzenesulfonamide	BHK21	IC_{50} :0.03 μg/mL
Ag(I) and Cu(II) complexes of 1,3-diaryltriazene-substituted sulfonamide	MDA-MB231, DLD1, ECC1, HeLa, PC3, HT29, DU145	IC_{50} :2.1-28.2 μM
1,3-diaryltriazenido(*p*-cymene) ruthenium(II) complexes	HeLa	IC_{50} :0.103 ± 0.006 μM

Acyl substitution in Triazenes

Diminazene aceturate, or Berenil, has two amidinium functionalities that are strong electron-withdrawing groups. Taking this fact into account, Cimbora-Zovko *et al.* (2011) studied a series of triazene compounds having electron withdrawing groups in both the benzene rings of 1,3-diphenyltriazene. Various triazene derivatives bearing fluoro, trifluoromethyl, chloro, bromo and nitro substitutions were synthesized. Cimbora-Zovko *et al.* (2011) reported the compounds to be active against HeLa cells. They further stated that the presence of an acetyl group, resulted in increased cytotoxicity. This was probably since acytylated triazenes can selectively transfer an acetyl group to various amino moieties in different solutions *viz*., aqueous, and alcoholic solutions. The compounds that demonstrated substantial antitumor activities against HeLa cells are represented in Figure 4.



5, R = H
6, R= F
7, R= Cl
8, R= Br
9, R= CF_3

Figure 4: Acetyl substituted 1,3-diaryltriazenes

Farina *et al.* (1982) discussed the cytotoxic property of 1-(4-acetylphenyl)-3.3-dimethyltriazene (10) against isolated mouse hepatocytes *in vitro* and mouse TLXS lymphoma *in vivo*. They put forward the mechanism that the dimethyltriazenes undergo oxidative N-demethylation, forming monomethyltriazenes, which is the active cytotoxic moiety (Figure 5). It is intriguing to note that Farina *et al.* (1982) demonstrated *in vivo* anticancer activity of acetyl substituted triazenes. In addition, since the mechanism and the active species have been clearly understood, it can be stated that acyl substitution in triazenes has adequate potential as antineoplastic agents.

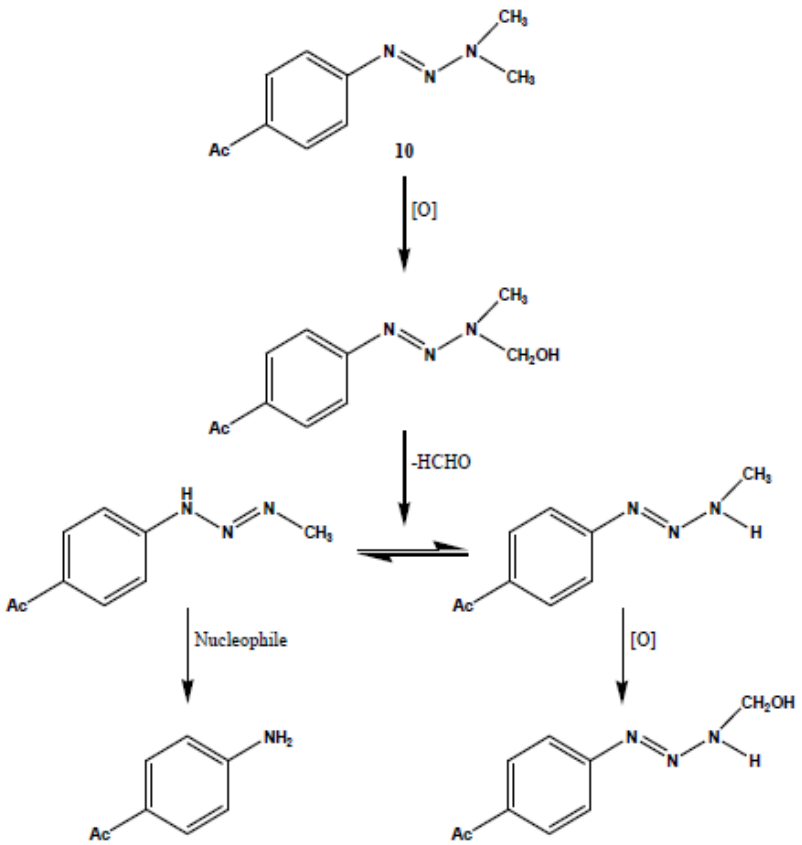


Figure 5 : Oxidative N-demethylation of dimethyltriazene (*Farina et al., 1982*)

Hydroxy substitution in Triazenes

Adibi *et al.* (2013) reported that the hydroxy substituted 1,3-diaryltriazenes (Figure 6) displayed cytotoxic activity against cancer cell lines *viz*., HT29, PC3, HepG2 HL60, HeLa, MCF7,

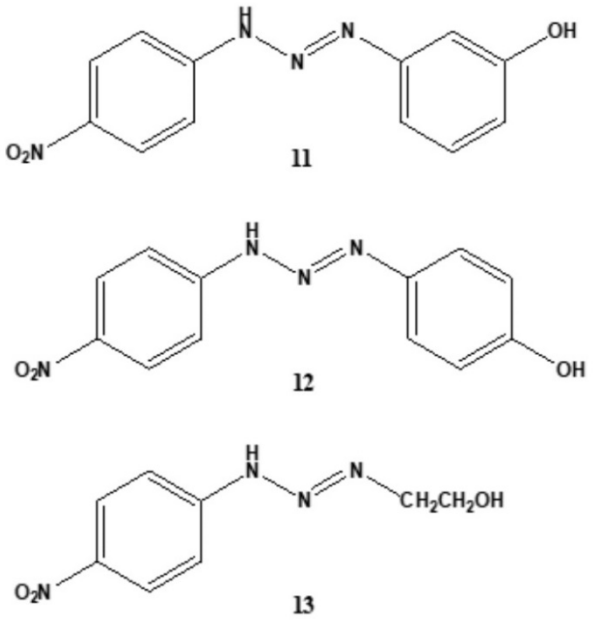


Figure 6: Hydroxy substituted 1,3-diaryltriazenes

Jurkat and K562 and a normal cell line *viz*., HUVEC (Adibi *et al*., 2013). In addition, they also prepared compounds 14,15,16 (Figure 7). 1,3-bis(2-ethoxyphenyl) triazene had IC_{50} value in the range of 0.56-3.33 μM on cancer cell lines and 12.61 μM on non-cancerous cell line. The vast difference between toxic dosage on cancer and normal cell line is a notable factor as this may cause less toxic chemotherapeutic side effects under physiological conditions. However, 1-(4-nitrophenyl)-3-(2-hydroxyethyl) triazene demonstrated weaker impact on cancer cell lines than the other compounds having IC_{50} value in the range 3-15 μM. Adibi *et al.* (2013) concluded that the absence of aromatic ring reduced the selectivity and effectiveness of the triazenes.

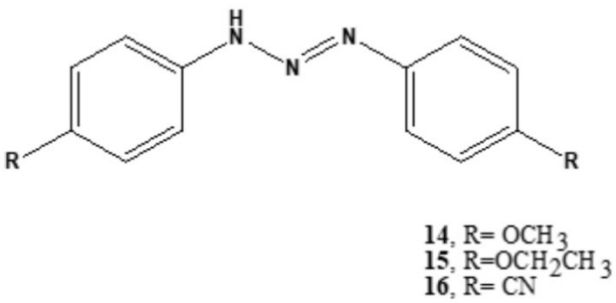


Figure 7: Methoxy, Ethoxy and Cyano substituted 1,3-diaryltriazenes

Heteroaryl Triazeno derivatives

The anticancer activity displayed by dacarbazine led to the development of several heteroaryl triazeno derivatives (El-Moghazy Aly *et al*., 2007). Among the various substituted triazenes synthesized, the azole derivatives were of utmost significance. Triazenotriazoles, pyrazoles, and imidazoles indicated antitumor activities against several types of tumors. The heterocyclic moiety probably controlled the antineoplastic activity such that the efficiency increased with the increase in nucleophilic characteristic of the heterocyclic ring (Diana *et al*., 2011). Based on this idea, Diana *et al.* (2011) discussed the antineoplastic activity of some pyrrole and indole substituted triazenes (Figure 8).

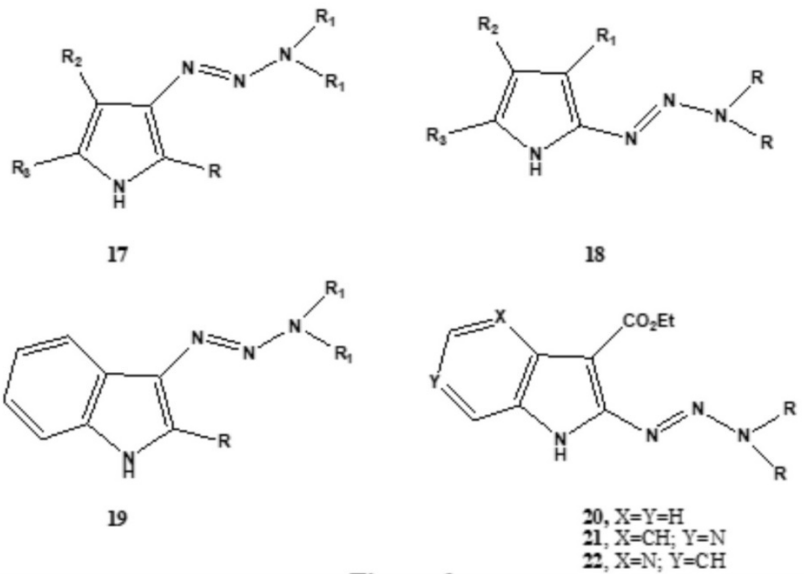
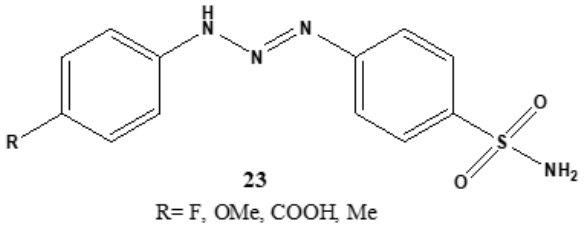


Figure 8: Pyrrole and indole substituted triazenes *(Diana et al., 2011)*

The first heterocyclic triazene synthesized (17) displayed antitumor property against Friend erythroleukemia cells (FLC) with IC_{50} value between 1.1- 3.1 μM. The indole derivative (19) proved to be 20-40 times more active than the triazenopyrrole compounds against multidrug-resistant cells and erythroleukemia with IC_{50} values between 0.10-0.14 μM and 0.053-0.080 μM, respectively. Another pyrrole derivative (18) showed cytotoxicity against leukaemia and lymphoma with an IC_{50} value of 3.9-21 μM. The last compound synthesized was a group of benzofused triazene (20, 21, 22) which expressed antineoplastic activity against Jurkat and K562 cell lines with GI_{50} values between 2.2-12.6 μM.

Alamri *et al*. (2021) worked with three benzothiazole based triazene molecules and found them to be cytotoxic against MCF7 and HCT116 cell lines with IC_{50} values around

40-47 μM and 10-20 μM for MCF7 and HCT116 cell lines respectively. A representative structure is given as Figure 9 (23).



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R= F, OMe, COOH, Me

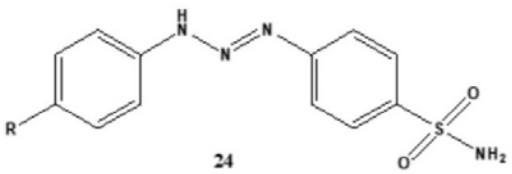
Figure 9: Benzothiazole based triazene *(Alamri et al., 2021)*

Aliphatic Triazenes

Much less is known about the anti-tumor properties of aliphatic triazenes. Smith, Scudiero and Michejda (1990) probed into the antitumor properties of aliphatic triazenes, as these molecules could form alkyldiazonium ions without enzymatic activation (Smith, Scudiero and Michejda, 1990). In this backdrop, they explored the antineoplastic activities of many aliphatic triazenes. They reported that 1,3-diethyltriazene was a potent carcinogen in rats. They synthesized 1,3-dialkyl-3-acyltriazenes and 1-(2-chloroethyl)-3-methyl-3-acyltriazenes which proved to be cytotoxic against several human cancer cell lines *in vitro*. Another compound *viz.*, 1-(2-chloroethyl)-3-methyl-3-carbethoxytriazene (CMC), was most active against leukaemia cells while 1-(2-chloroethyl)-3-methy-3-(methylcarbamoyl)triazene (CMM) was primarily cytotoxic against leukaemia, melanoma, and mammary carcinoma. Rouzer *et al.* (1996) also worked with CMM along with 1-(2-chloroethyl)-3- benzyl-3-(methylcarbamoyl)triazene (CBzM). Both compounds possessed antineoplastic activity *in vivo*, against specific tumor xenografts embedded in nude mice.

Complexes of 1,3-diayltriazenes

A series of silver (I) and copper (II) complexes of 1,3-diaryltriazene-substituted sulfonamide (24, Figure 10) derivatives were investigated by Canakci *et al.* (2019).



24

R= F, OMe, COOH, Me

Figure 10: 1,3-diaryltriazene-substituted sulfonamide *(Canakci et al., 2019)*

The anticancer activity of the free ligands and their Ag (I) and Cu (II) complexes was explored against the reported cancer cell lines *viz*., MDA-MB231, DLD1, ECC1, HeLa, PC3, HT29 and DU145 and non-cancerous cell lines *viz*., PNT1A, HEK293 and ARPE19. A vast majority of the complexes exhibited enhanced antitumor activity compared to their corresponding free ligands. The potency of some of the metal complexes was comparable to that of 5-Fluorouracil (5-FU), which is a widely used drug with IC_{50} value of 19.15 μM. The -COOH substituted triazene complexes presented cytotoxic activity much greater than the other complexes. This is probably due to the electron withdrawing (-I and -R) effects of the carboxylic acid group. In this context, it is relevant to mention that Aydin *et al*. (2023) synthesized a series of sulfadiazine derivatives of 1,3-diaryltriazine compounds that manifested *in vitro* antineoplastic activity against BHK21 cell line, exhibiting IC_{50} values between 0.03-0.18 μg/mL (25, Figure 11).

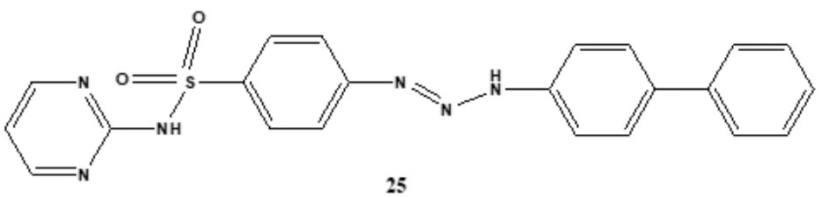


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Figure 11: Sulfadiazine derivative of triazine

Another metal that has been receiving constant attention among researchers because of its antitumor properties is ruthenium. This is mainly because the ruthenium complexes are less toxic and can mimic iron under certain physiological conditions (Vajs *et al*., 2015). The rapidly dividing cancer cells have significant affinity for iron. Thus, ruthenium, which belongs to the same group as iron in the periodic table, accumulates more in tumor cells than in normal cells. Till date, two ruthenium complexes *viz*., KP1019 {(IndH)[*trans*-$RuCl_4(Ind)_2$], Ind = indazole} and NAMI-A {(ImH)[*trans*-$RuCl_4$(dmso-S)(Im)], Im = imidazole} have reached human clinical trials (Alessio & Messori, 2019). This prompted the researchers to synthesize ruthenium complexes of 1,3-diaryltriazenes as it has been a well-established concept that a synergistic effect can occur from the unification of two pharmacophores into one compound. Vajs *et al*. (2015) synthesized ruthenium complexes of a series of substituted 1,3-diaryltriazenes using $[RuCl_2(\eta^6$-p-cymene$)]_2$ as the starting material. They introduced electron withdrawing groups *viz*., -F, -Cl, -Br, -CN and $-CF_3$ in the 1,3-diphenyltriazene backbone. The cytotoxic property of the complexes was probed using human cervical carcinoma HeLa cells. All the complexes revealed prominent antitumor property with IC_{50} below 6 μM. The ruthenium complex having chloro and trifluromethyl disubstituted triazene ligand was found to show highest cytotoxicity with IC_{50} of 0.103 ± 0.006 μM at the end of 72 h incubation period.

Overall, the anticancer property of the complexes was found to be much enhanced than that of the corresponding free ligands confirming the phenomenon of synergistic effect.

Conclusion

The overview traces the journey of 1,3-diaryltriazene as a potential antineoplastic agent. It is interesting to note that many of the triazene based molecules have shown considerable promise as anticancer agents *in vivo*. It is also worthwhile to mention that the triazene molecules with electron withdrawing groups displayed a greater cytotoxic effect. Despite its importance, few researches have been found in the literature on the antitumor property of these molecules. Consequently, there is much scope for the expansion of research focused on the cytotoxic properties of molecules with the triazene scaffold.

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