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BIOLOGICAL POTENTIAL OF AN ELIXIR MOLECULE- ARYL TRIAZENE: AN UPDATED REVIEW

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ABSTRACT

The introduction of different nitrogen moieties in the chemical structure increases the application of many synthetic drugs for different ailments now a days. This provides medicinal chemistry researcher to synthesis newer compounds containing nitrogen atom. Compounds containing triazene chain are toxic to cells and are generally used as alkylating agents in anticancer treatment. In this review article, biological potency of aryl triazene was studied by using different triazene derivatives. Antibacterial studies were performed by the use of different strains of bacteria like *Enterococcus faecalis, Bacillus cereus*, etc. and anti-tubercular was done by using *Mycobacterium tuberculosis* ($H_{37}R_V$ stain) and *Mycobacterium lufu.* The anti-inflammatory activity was studied by inducing adjuvant arthritis (AA) by subplantar injections on a group of white mongrel rats. *In vitro* antileukemic studies are performed against K562 (human chronic myelogenous leukaemia) cell line and RAJI (human Burkitt lymphoma) cell lines at 10µM of test compounds. Halogen substituted molecules are more potent than other substituted derivatives especially in antibacterial and antileukemic studies. Increasing the length of triazene chain normally decreases the activity in the homologous series. Methyl substituted compounds are showing better activity than other alkyl substituted derivatives. This article highlights the different biological activities of Aryl Triazenes.

KEYWORDS

N-Arylcarbamate triazene**,** 4-(3, 3-Dimethyltriazeno)-N-acylbenzenesulfamide, 3-methyl-4-(3, 3-dimethyl triazeno)-5-(substituted benzamido) pyrazole, Antibacterial activity, Anti-tubercular activity, Anti-inflammatory activity and Antitumor activity.

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INTRODUCTION

Triazene which is considered as one of the important versatile nitrogenous compound synthesised mainly from diazonium salts by diazotization reaction[1] of primary amines and are not found in nature. They are also called as triazanylene, is an unsaturated inorganic compound with 3 nitrogen atoms and having a double bond in between two nitrogen atoms. It is the second

simplest member of the azene class of hydro-nitrogen compounds. Being an electron rich group, it is able to adsorb metallic[2] and organic cations[3]. Triazene group can be easily converted to lactams[4], triazoles, dibenzopyranones and coumarins and they are showing wide variety of activities.

Aryl triazenes are those compounds in which this triazene chain is bonded to an aryl ring. Some of those aryl triazenes are widely used as anticancer agents[5]. They mainly work by alkylating guanine at the O-6 and N-7 position and thus considered as alkylating agent in cancer therapy. Examples are dacarbazine[6] and temozolomide[7]. Dacarbazine, 5-(3,3-dimethyl-1-triazenyl) imidazole-4-carboxamide (DTIC), have been used as one of the important anticancer drug which is used to treat malignant melanoma and Hodgkin tumours resistant to the MOPP therapy[8]. The mechanism of action of these compounds includes the methylation of guanine at O-6 position results in the formation of highly reactive species, Methyl diazonium ion[9]. The antitumor effect of these drugs are based on the formation of an adduct (DNA O^6-methyl guanine adduct) that will generate base pairs which will mismatches with cytosine and thymine. These adduct results in the cell death of tumour origin and it will provoke somatic point mutations if the cell survives which is represented by C: G→T: A transition in DNA helix. Triazene drugs are showing excellent pharmacokinetic properties and less toxicity[10]. Because of this potent activity shown by the triazene drugs results in the research and development of various aryl and heteroaryl triazeno derivatives[11]. Aryl ring may be benzene, pyrazole, imidazole, thiazole, oxazole, isoxazole, etc.

In this current study, different aryl triazenes are synthesising and determining their various biological activities according to the change in their molecular structure using different heterocyclic aromatic rings. The synthesis of novel aryl triazene derivatives remains the main focus of current medicinal research.

BIOLOGICAL POTENTIAL OF ARYL TRIAZENE DERIVATIVES

Antibacterial property

Vanessia O Dominguis and co-workers were synthesised different benzene triazene derivatives by using scheme 1[12] and the schematic representation was given in Figure No.1. The synthesised derivatives A-C are given as Figure No.5, Figure No.6 and Figure No.7 and they were having antibacterial property. They were showing good activity against both gram-positive and gram-negative bacteria. Among the three synthesised compounds, derivative A was the most active triazene which inhibits some of the bacterial strains like *Enterococcus faecalis* ATCC 29212, *Aeromonas hidrophyla* and *Klebsiella oxytoca* and having an MIC value of 128µg mL^{-1} and for *Bacillus cereus* the MIC value was 32 µg mL^{-1}. Derivative B was also inhibiting some of the strains like *Streptococcus agalactiae* with an MIC value of 64 µg mL^{-1}. Derivative C was not having good activity when compared with A and B.

Antitubercular activity

A. V. Velikorodov and co-workers were synthesised different triazene derivatives of N-arylcarbamates by using scheme 2[13] and the schematic representation was given in Figure No.2. The Antitubercular activity of synthesised derivatives was studied using standard species of *Mycobacterium tuberculosis* ($H_{37}R_V$ stain) and *Mycobacterium lufu*. The minimum inhibiting concentrations (MIC) as well as minimum bactericidal concentrations (MBC) were determined. The synthesised derivatives are given as Figure No.8 and Figure No.9. Also Acute toxicity (LD_{50}) was determined using white mongrel mice weighing 20-25g and the results were statistically processed and were given in the Table No.1.

N-arylcarbamate triazene derivatives D-H were showing great antimycobacterial activity against M.tuberculosis and M.lufu. And the activity shown by these derivatives were comparable to standard drugs like Dapsone and Isoniazid.

Anti-inflammatory activity

M. Kazhemekaite and co-workers synthesised different 4-(3, 3-Dimethyl triazeno)-N-acylbenzenesulfamide derivatives by using synthesising scheme 3[14] and the schematic representation was given in Figure No.3. The synthesised derivatives are given as Figure No.10, Figure No.11 and Figure No.12 and the derivatives I-K were having anti-inflammatory property. The anti-inflammatory activity of synthesised derivatives was studied by inducing adjuvant arthritis (AA) by subplantar injections on a group of white mongrel rats. Acetyl salicylic acid was used as standard drug. The results were summarised in the Table No.2.

Study indicates that triazeno derivatives contains aliphatic acid residue in the sulfamide group shows greater anti-inflammatory activity. The derivatives I, J and K on the 17th day of experiment shows an efficacy greater than that of standard drug Acetyl salicylic acid which is only -38.5.

Antitumor activity

Giuseppe Daidone *et al,* synthesised various 3-methyl-4-(3, 3-dimethyl triazeno)-5-(substituted benzamido) pyrazole derivatives by using scheme 4[15] and the schematic representation was given as Figure No.4. The synthesised derivatives are given as Figure No.13, Figure No.14 and Figure No.15 and the derivatives L-N were having anti tumour property.

The synthesised derivatives were evaluated against K562 (human chronic myelogenous leukaemia) cell line and RAJI (human Burkitt lymphoma) cell lines at 10µM of test compounds. The standard drug used for the evaluation was Methotrexate. The results were summarised in Table No.3.

The derivative L and M bearing chlorine atom were showing activity higher than that of reference drug Methotrexate. Derivative M (3, 4 dichloro derivative) was the most active one against both K562 and RAJI cell lines, with IC50 value 6µM. Derivative N also showing the activity but it was less than that of L and M. Derivatives bearing one and two chlorine atoms exhibits higher antitumor property than the others.

Table No.1: LD50 and Anti-tubercular properties of Triazene derivatives of N-Arylcarbamates

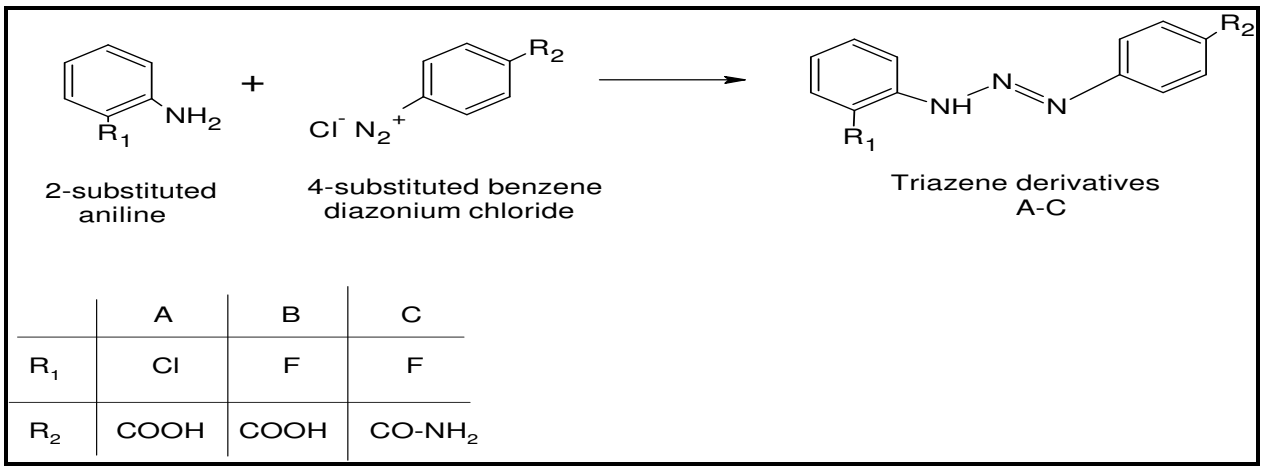
S.No	DERIVATIVES	LD_{50} mg/kg	TEST MICROBIAL STRAINS			
			Mycobacterium tuberculosis		*Mycobacterium lufu*	
			MIC µg/ml	MBC µg/ml	MIC µg/ml	MBC µg/ml
1	D	1005	3.2±0.55	8.0±2.45	3.6±0.45	6.4±1.09
2	E	1000	3.4±0.61	8.4±2.13	3.9±0.54	6.7±2.04
3	F	987	3.3±0.58	8.5±2.34	3.8±0.61	6.8±2.13
4	G	935	4.5±1.17	9.1±1.04	4.2±2.32	7.3±2.20
5	H	842	5.1±2.13	9.7±1.41	4.3±2.17	8.0±1.94
6	Dapsone		28.8±10.43	89.6±17.53	3.2±0.55	4.4±1.10
7	Isoniazid		2.4±0.45	7.2±0.89	8.8±2.19	11.2±2.19

Table No.2: Anti-inflammatory and acute toxicity of triazene derivatives

S.No	DERIVATIVES	LD_{50} mg/kg	Therapeutic Dose,mg/kg (p.o)	Increment of joint tumefaction against control (%)		
				3rd day	11th day	17th day
1	I	1400	140	-8.9	-26.7	-47.2 p<0.06
2	J	1400	140	-22.3	-46.7 p<0.05	-67.2 p<0.001
3	K	1400	140	-	-29.6	-69.9 p<0.001
4	Acetylsalicylic Acid	1300	140	-22.5 p<0.02	-47.2 p<0.01	-38.5 p<0.05

Table No.3: Percentage growth inhibition of triazene derivatives on K562 and RAJI cell lines

S.No	DERIVATIVES	K562	RAJI
1	L	93.1±6.8	89.2±10.3
2	M	97.8±2.1	99.4±1.2
3	N	90.8±8.3	63.3±6.4
4	Methotrexate	86.7±3.2	75.1±3.5



	A	B	C
R_1	Cl	F	F
R_2	COOH	COOH	$CO\text{-}NH_2$

Figure No.1: Synthesis of triazene derivative A-C

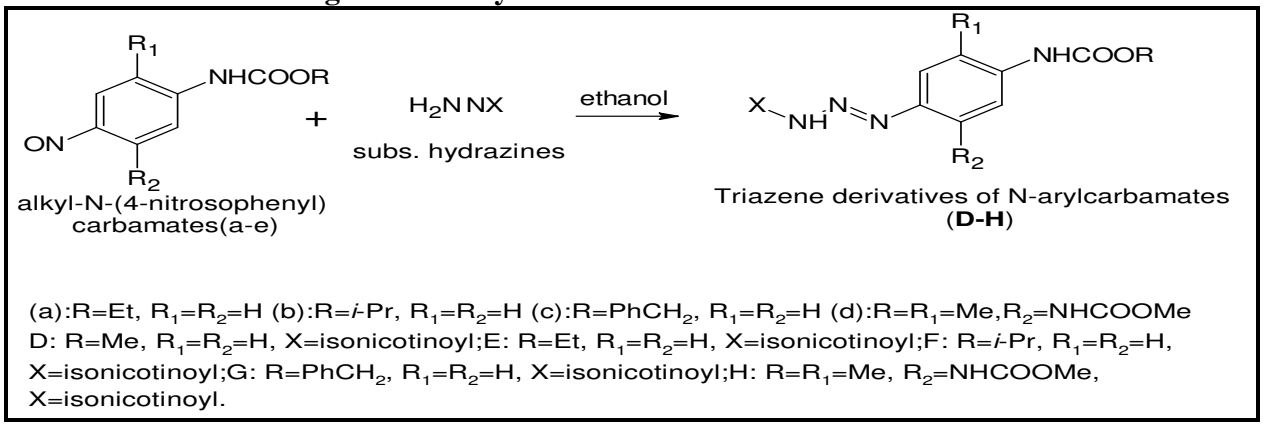
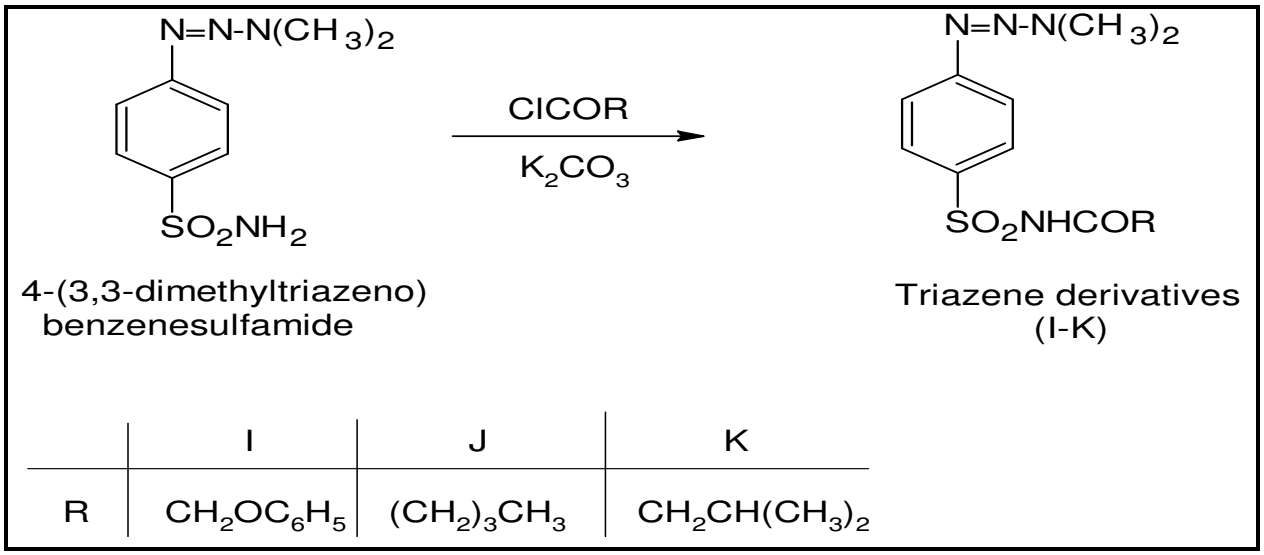
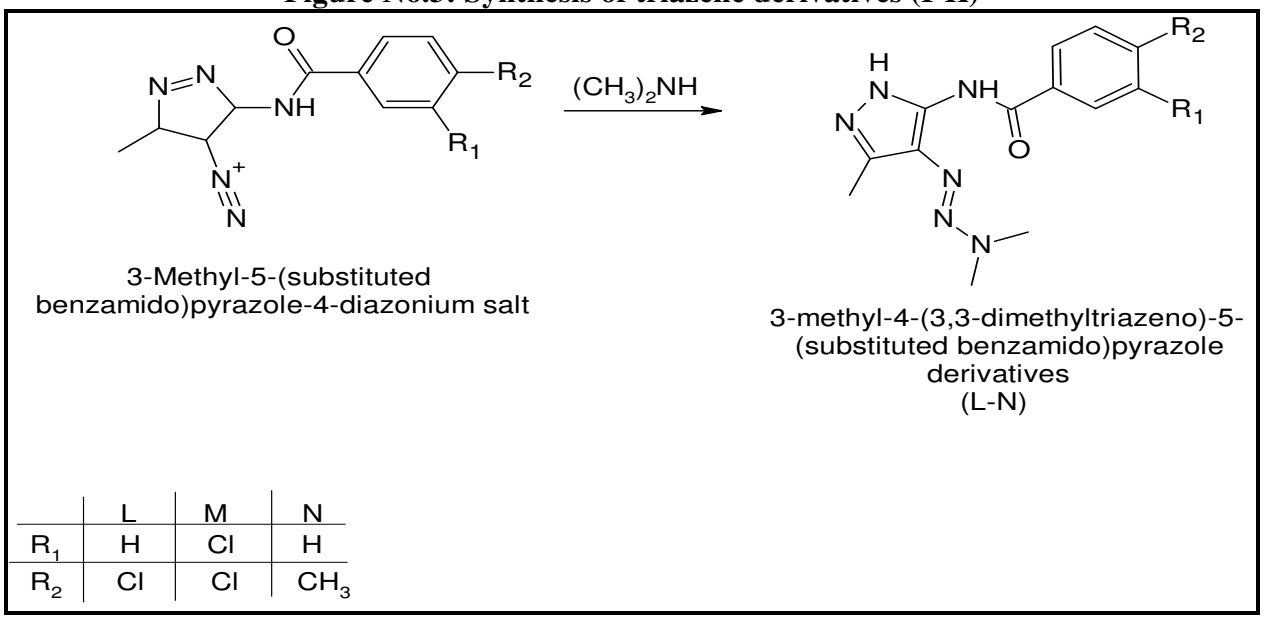


Figure No.2: Synthesis of triazene derivatives of N-arylcarbamates (D-H)



	I	J	K
R	$CH_2OC_6H_5$	$(CH_2)_3CH_3$	$CH_2CH(CH_3)_2$

Figure No.3: Synthesis of triazene derivatives (I-K)



	L	M	N
R_1	H	Cl	H
R_2	Cl	Cl	CH_3

Figure No.4: Synthesis of 3-methyl-4-(3, 3-dimethyltriazeno)-5-(substituted benzamido) pyrazole derivatives (L-N)

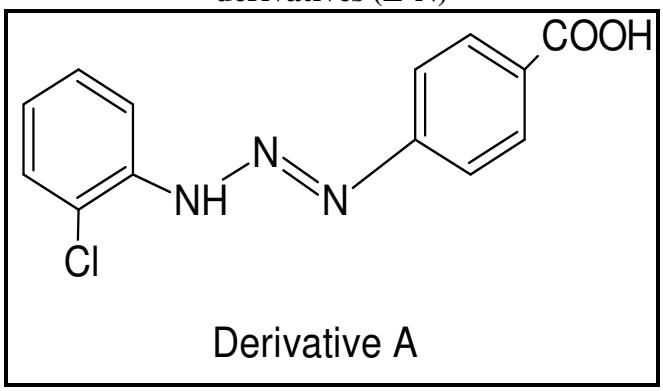


Figure No.5: Structure of derivative A

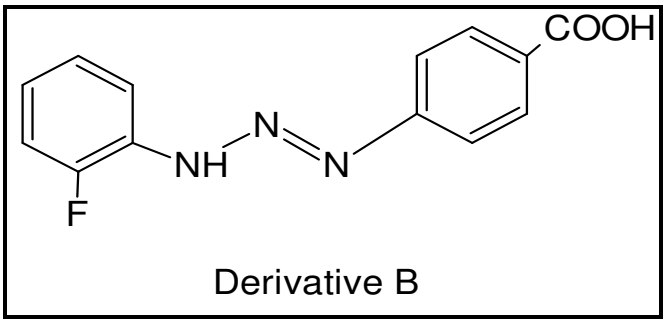


Figure No.6: Structure of derivative B

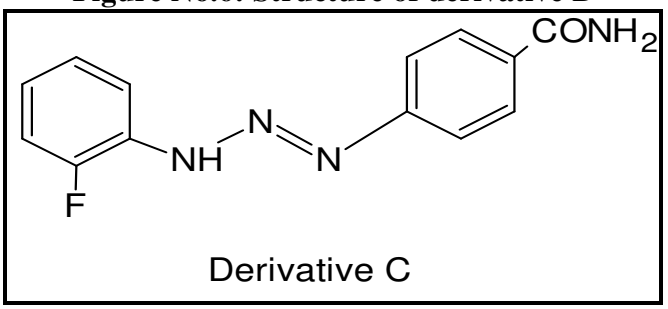


Figure No.7: Structure of derivative C

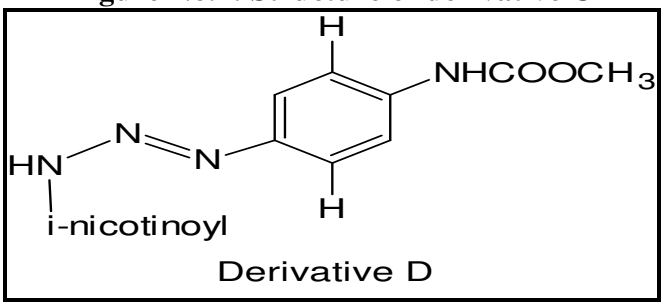


Figure No.8: Structure of derivative D

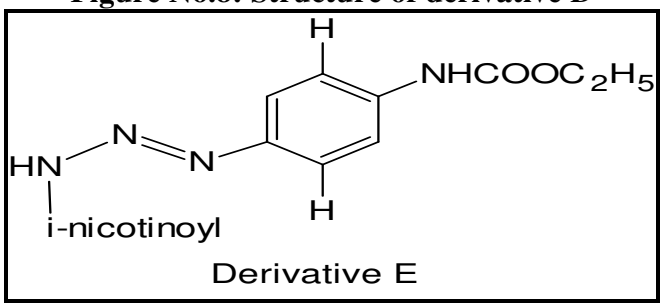


Figure No.9: Structure of derivative E

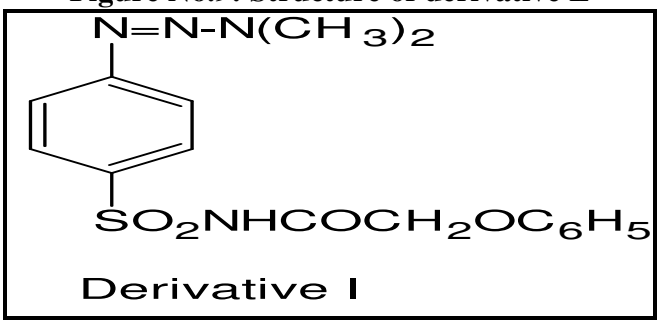


Figure No.10: Structure of derivative I

Figure No.11: Structure of derivative J

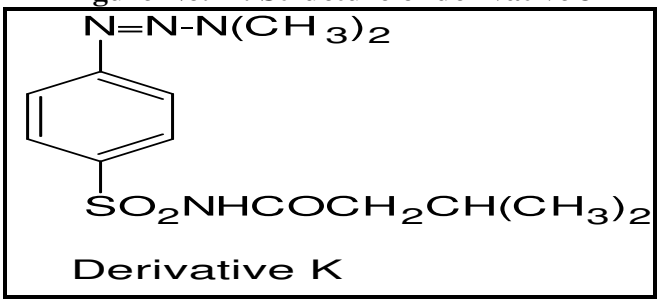


Figure No.12: Structure of derivative K

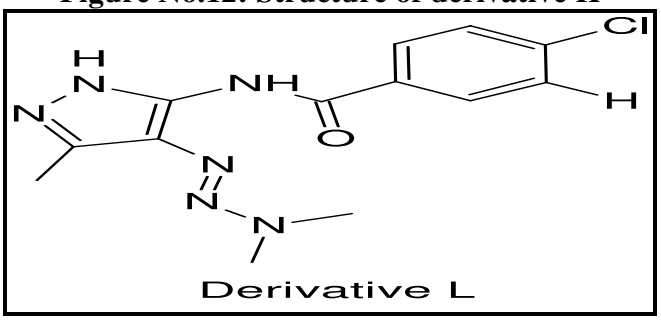


Figure No.13: Structure of derivative L

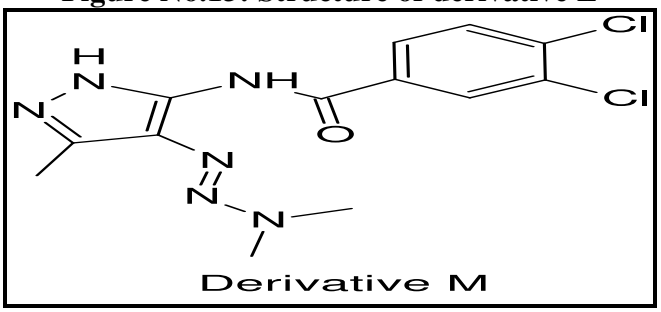


Figure No.14: Structure of derivative M

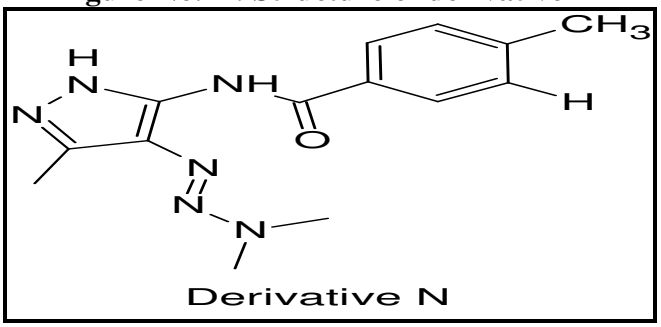


Figure No.15: Structure of derivative N

CONCLUSION

Although aryl triazenes were reported for its anti-cancer activity like darbazine, it was found that various other aryl triazenes were also showing different activities like anti-bacterial, anti-inflammatory, anti-tubercular, etc. Apart from this, some of the derivatives were showing very much potency against leukemic cell lines more than that of established drugs like Methotrexate. Halogen substituted molecules were showing varieties of activities and they were more potent than other substituted triazene derivatives especially in antibacterial and antileukemic studies. Increasing the length of triazene chain normally decreases the activity in the homologous series. Methyl substituted compounds were showing better activity than other alkyl substituted derivatives. So aryl triazenes was one of the magical moiety possessing many activities that can be marketed for the treatment of so many ailments in future.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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