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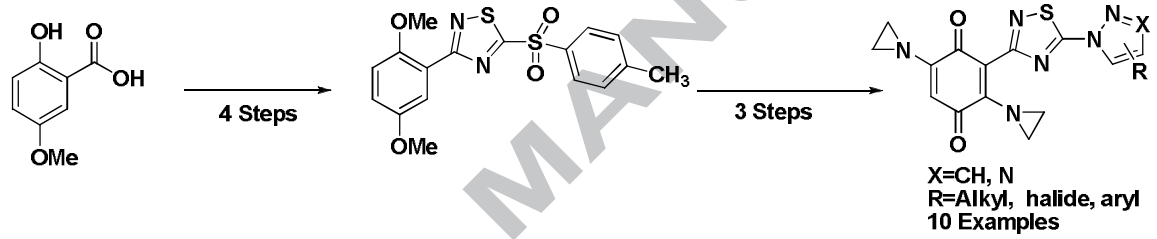

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Design and Synthesis of Diaziridinyl Quinone Thiadiazole Hybrids via Nitrile Sulfide Cycloaddition Reaction as a Key Step

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Abstract: A series of novel diaziridinyl quinone thiadiazole hybrids (**9a**-**9j**) were synthesized starting from 2-hydroxy-5-methoxybenzoic acid **1** in a 7 steps synthetic sequence. The key step in the scheme involves the nitrile sulfide cycloaddition reaction of oxathiazolone **4** with *p*-tosylcyanide to obtain 1,2,4-thiadiazole derivative **5**. We have demonstrated that *p*-tosyl group of thiadiazole **5** can be displaced with various nitrogen heterocycles to generate unknown 3,5-disubstituted thiadiazole derivatives.

The quinone containing compounds have been widely used for their antitumor and anticancer activities. But the problems associated with these compounds such as toxicity and drug resistance has stimulated an increasing demand for the discovery of new and novel anti-tumor agents.[1] In the last few decades, a significant progress has been made towards the screening of quinone containing compounds for antitumor activity[2]. Mitomycin C,

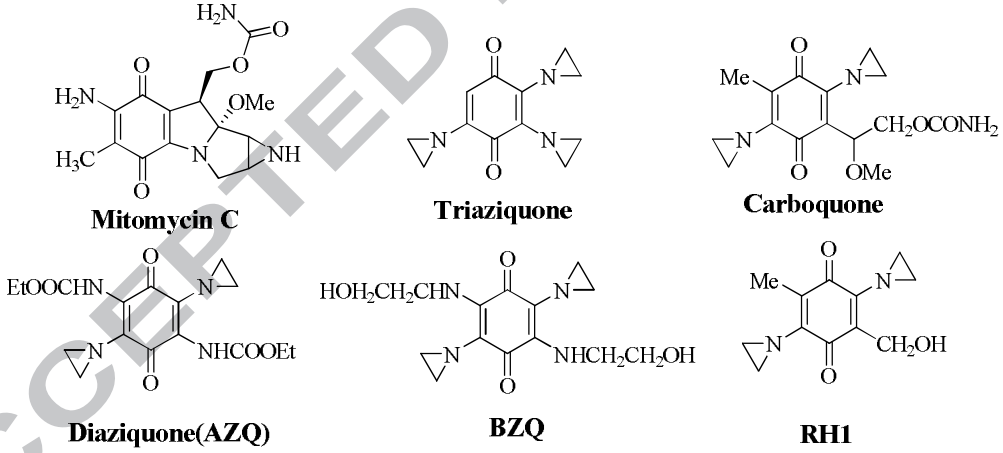

Fig 1: Structure of the drugs conatining aziridinyl quinone moiety

Triaziquone, Carboquone, Diaziquone (AZQ), 2,5-bis(2'-hydroxyethylamino)-3,6-diaziridinyl-1,4-benzoquinone (BZQ) and 2,5-diaziridinyl-3-(hydroxymethyl)-6-methyl-1,4-benzoquinone (RH-1) (**Figure 1**) are the best known drugs containing aziridinyl quinones from the clinical perspective. Essentially, these drugs has three potential active constituent's viz. quinone, an unusual aziridine, and a C-10 carbamate groups[3]. Several studies have shown that all three constituents are essential and play a functional role in the cytotoxic action of these quinones. Reduction oxidation reactions of the quinone group may lead to the formation of oxygen free radicals which can induce DNA damage[4], and this has been observed with Mitomycin C[5] and Diaziquone (AZQ)[6]. Several aziridinyl

Key words: Nitrile sulfide, Cycloaddition, Quinone, Thiadiazole, Diaziridine quinone

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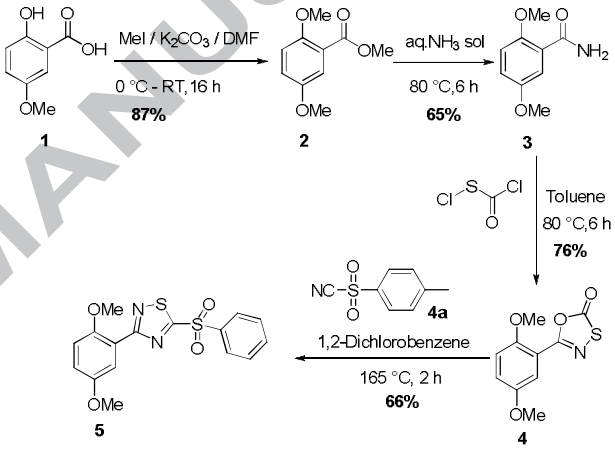
benzoquinone drugs have undergone clinical trials as potential antitumor drugs. These bioreductive compounds are designed to kill cells preferentially within the hypoxia tumor microenvironment[7]. The strain and reactivity of the aziridine ring possessed molecules has interesting biological activity and the efforts in this area has been summarised[8]. Most of the interest in biological activity of aziridine has focused on those chemically modified DNA.

Thiadiazoles represent an important class of heterocyclic compounds that exhibit different types of biological activity.[9] In the past decade, a number of potent compounds based on thiadiazoles have been discovered.[10] Indeed, compounds containing a 1,2,4-thiadiazole fragment have anti-inflammatory,[11,12] antihypertensive,[13] antibacterial,[14,15] and anticonvulsant properties.[16,17] Furthermore, it has been confirmed that many thiadiazole-related compounds are potential drugs in the treatment of disorders of the central nervous system such as Alzheimer's disease due to the antioxidant properties, influence on muscarinic acetylcholine receptors,[18] and inhibition of acetylcholinesterase activity.[19] Compounds containing a 1,2,4- thiadiazole fragment also display high inhibitory activity against glycogen synthase kinase-3β and, therefore, can be used for treatment of neuropathology, disordered motor function, chronic inflammatory process, cancer, and diabetes of type-II.[20] Recently, 2,5-disubstituted-1,2,4-thiadiazole derivatives are shown to be selective S1P1 agonists.[21]

Our approach to develop new chemotherapeutic agents involves the conjugation of two biologically active compounds viz. diaziridinylquinone and thiadiazole to prepare a single hybrid molecule. Based on this hypothesis, we previously synthesized quinone isoxazole (**QI**) hybrid molecules in this laboratory[22]. There are few quinone natural product hybrid molecules has been reported in literature.[23-32] But there are no reports of diaziridinyl quinone five membered heterocyclic hybrids, as per the literature search. The promising biological results of diaziridinylquinone[33-39] and thiadiazole derivatives motivated us to synthesize new diaziridinylquinone heterocyclic hybrids. We herein, report the synthesis of novel diaziridinylquinone thiadiazole (**DAQT**) derivatives as new hybrid molecules to identify more potent biologically active compounds.

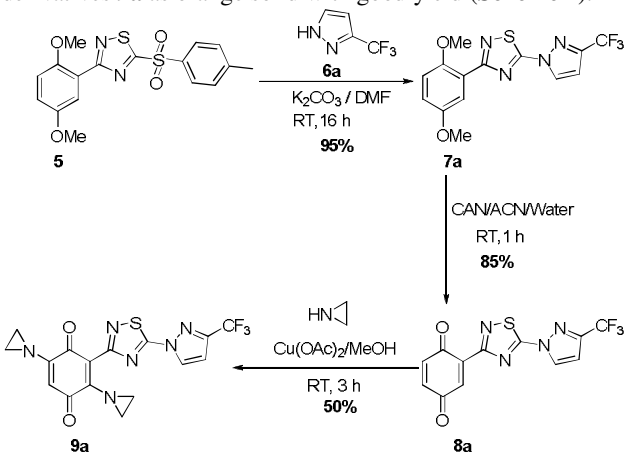
The synthesis starts with the commercially available 2-hydroxy-5-methoxybenzoic acid **1** (**Scheme 1**) which was converted to methyl 2,5-dimethoxybenzoate **2** using MeI/K_2CO_3/DMF condition. Compound **2** was treated with aqueous ammonia in sealed tube at 80 °C for 6 h to obtain 2,5-dimethoxybenzamide **3** in very good yields. The compound **3** was characterized by ^{1}H NMR and MS data. The compound **3** on reaction with chlorocarbonyl sulfenyl chloride in toluene at 80 °C for 6 h gave 2,5-dimethoxy substituted 1,3,4-oxathiazol-2-one **4**. The compound **4** was characterized by ^{1}H NMR and MS data. M+1 peak at 240 in the MS spectra along with ^{1}H NMR data indicate the product formation. We did not observe any isomer formation in the reaction. The key step nitrile sulfide cycloaddition reaction[40] of 1,3,4-oxathiazol-2-one **4** with *p*-toluenesulfonylcyanide was performed in 1,2-dichlorobenzene at 165 °C for 2 h to obtain *p*-tosyl substituted thiadiazole derivative **5**. The nitrile sulfides generated in situ by thermal decomposition of 1,3,4-oxathiazol-2-one **4** reacted with dipolarphile tosyl cyanide in a 1,3-dipolar cyclization reaction to provide the thiadiazole intermediate containing a labile 5-tosyl substituents. No side product was observed during the cycloaddition reaction as determined by LC-MS analysis. The compound **5** was characterized by spectroscopic analysis. ^{1}H NMR shows peak at 2.4 δ corresponds to methyl proton and two singlets at 3.8 δ correspond two methoxy groups. MS analysis shows M+1 peak at 377 which confirmed the formation of compound **5**.



Scheme 1: Synthesis of tosyl substituted thiadiazole derivative

After obtaining the key intermediate **5**, we want to explore the displacement reaction with various nitrogen nucleophiles. Thus, treatment of compound **5** with pyrazole **6a** in presence of K_2CO_3/DMF at room temperature gave the 5-pyrazolyl-3-phenyl thiadiazole derivative **7a** in good yield (**Scheme 2**). The compound **7a** on oxidation using cerium ammonium nitrate in acetonitrile/water (1:1) at room temperature for 1 h gave quinone thiadiazole hybrid derivatives **8a** in very good yield. The compound **8a** was characterized by ^{1}H NMR, ^{13}C NMR, and HRMS data. The characteristic quinone proton at 6.9 δ in ^{1}H NMR spectrum confirms the oxidation of compound **7a** to generate compound **8a**. IR spectrum of the compound **8a** shows the carbonyl peaks at 1655 cm^{-1}. The two carbonyl peaks at 187.3 and 183.8 δ in ^{13}C NMR spectrum validate the benzoquinone moiety. All the benzoquinones are characteristic yellowish solid. Finally the aziridine moiety was introduced into the quinone ring system by reaction of compound **8a** with freshly prepared aziridine[41] in the presence of $Cu(OAc)_2$ in MeOH at room temperature to

afford novel diaziridinyl benzoquinone thiadiazole derivatives **9a** as orange solid with good yield (**Scheme 2**).



Scheme-2: Synthesis of diaziridinylbenzoquinone thiadiazole derivatives

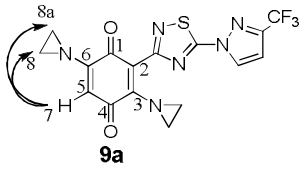
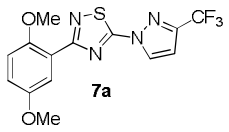
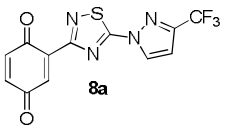
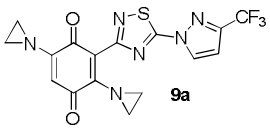
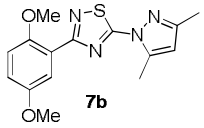
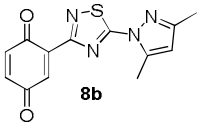
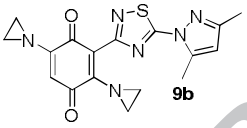
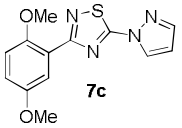
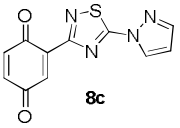
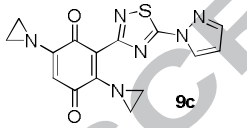
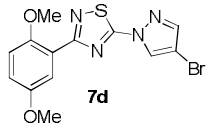
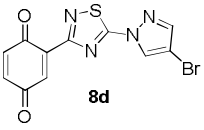
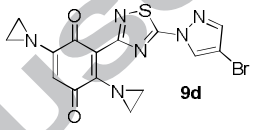
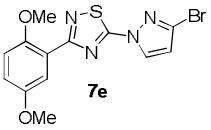
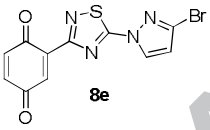
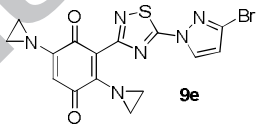
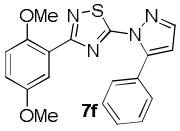
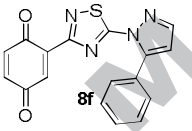
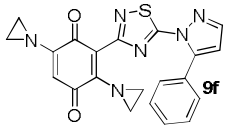
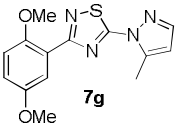
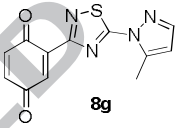
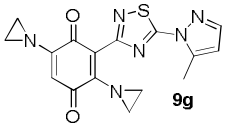
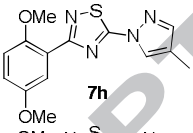
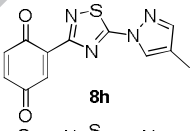
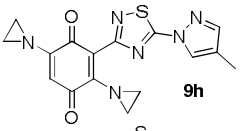
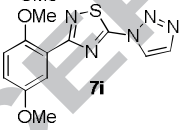
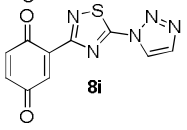
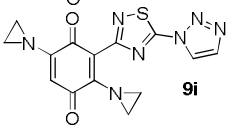
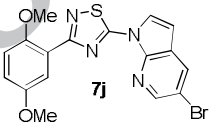
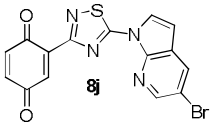
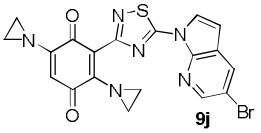


Figure 2:NOEs and HMBC studies of Compound 9a

In order to confirm the positions of aziridine moiety in compound **9a**, NMR studies were conducted (**Fig 2**). The NOESY spectra explain the substitution regioselectivity in compound **9a**. We utilized Heteronuclear Multiple Bond Correlation (HMBC) to obtain proton-carbon long distance couplings over 2 to 3 bonds. HMBC spectroscopy of **9a** where the delay in pulse sequence was optimized for 8 Hz shows both two and three bond coupling cross peaks. Absence of correlation of proton (H7, 6.055 ppm) to the C-2 (114.824 ppm) confirmed the structure of **9a** with aziridine moiety at 3-position and 6-position respectively. NOESY data also supported the structure by showing special correlation of H7 (6.055 ppm) proton with one of the aziridine moiety C8 and C8a.

Once the reaction condition was standardized, various highly substituted nitrogen heterocycles were subjected to displacement reaction to give the compounds **7a-7j** (**Table 1).** We followed the same two step synthetic protocol to obtain diaziridinyl benzoquinone thiadiazole derivatives **9a-9j**. All the compounds **9a-9j** was well characterized by ^{1}H NMR, IR, MS and ^{13}C NMR. The purity of the diaziridinyl benzoquinone thiadiazole derivatives was obtained by HPLC analysis. It is noteworthy to mention here that previously inaccessible triazole, 5-phenyl-pyrazole and azaindole analogues were synthesized in moderate yield (entries 9, 6 and 10). As indicated in **Table 1**, triazole substituted quinone gave the aziridine product in very low yield. Although, 5-pyrazolyl-3-phenyl thiadiazole derivatives having both alkyl as well aryl substituted pyrazole are undergoing the two step reaction protocol smoothly to generate diaziridinyl benzoquinone thiadiazole derivatives, it was observed that aryl substitution gave better yield compared to alkyl group.

Table 1: Synthesis of 2, 5-diaziridinyl-quinone-1,2,4-thiadiazole derivatives

Sl. No	3,5-diaryl-1,2,4-thiadiazole	Yield(%)	Quinone-1,2,4-thiadiazole hybrids	Yield(%)	2,5-Diaziridinyl-quinone-1,2,4-thiadiazole derivatives	Yield(%)
1	 7a	95	 8a	85	 9a	50
2	 7b	64	 8b	96	 9b	38
3	 7c	60	 8c	93	 9c	43
4	 7d	75	 8d	94	 9d	51
5	 7e	74	 8e	94	 9e	34
6	 7f	66	 8f	90	 9f	74
7	 7g	52	 8g	87	 9g	37
8	 7h	87	 8h	82	 9h	46
9	 7i	75	 8i	74	 9i	25
10	 7j	90	 8j	86	 9j	53

Conclusion:

In conclusion, we developed an efficient and simple method to synthesize the diaziridinyl benzoquinone thiadiazole derivatives using nitrile sulfide cycloaddition and oxidation reactions as key steps in good yields. We believe that this methodology will find a wide spread application for synthesis of aziridine quinone and its derivatives. The biological activities of these synthesized compounds for potential antitumor application is undergoing in our group.

Acknowledgements:

Authors are grateful to GVK Biosciences Pvt. Ltd., for the financial support and encouragement. Help from the analytical department for the analytical data is appreciated. We thank Dr. Sudhir Kumar Singh for his invaluable support and motivation.

Supplementary Material

The spectroscopic data (experimental procedure, ^{1}H NMR, ^{13}C NMR, IR and HRMS) associated with this article can be found in the online version

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Highlights

- Synthesis of novel diaziridinyl quinone thiadiazole hybrids.
- 1,2,4-Thiadiazole derivatives by nitrile sulfide cycloaddition reaction.
- Preparation of a large set of 3,5-disubstituted thiadiazole derivatives.