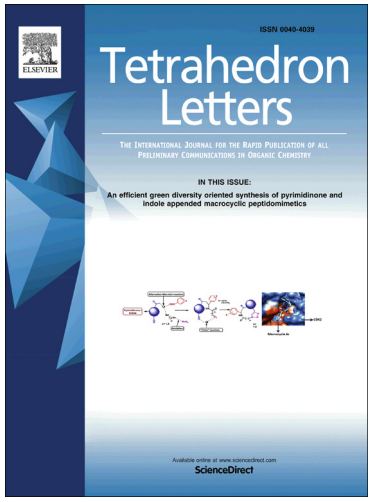

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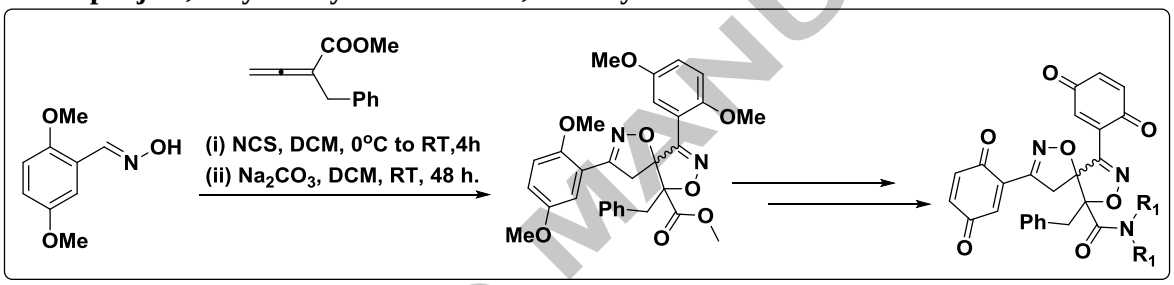
K. Jones. M. Swapnaja[a,b], Satyanarayana Yennam[a*], Murthy Chavali[c]



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Design and Synthesis of Spirobiisoxazoline Dibenzoquinone Derivatives via [3+2] Double 1,3-Dipolar Cycloaddition Reaction

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Abstract: "A series of novel spirobiisoxazoline dibenzoquinone derivatives were synthesized starting from 2,5-dimethoxybenzaldehyde in a six-step synthetic sequence". The key step [3+2] double 1,3-dipolar cycloaddition of oxime chloride with allenoate was performed under mild reaction conditions using sodium carbonate at ambient temperature. This is the first innovative synthesis of Spirobiisoxazoline Dibenzoquinone system where quinone ring is alkylated to isoxazoline moiety.

Spiro compounds are a particular class of naturally occurring substances characterized by highly pronounced biological properties [1-2]. Keeping in view of diverse biological activities associated with spiro heterocyclic compounds, it was thought to construct a novel system by the conjugation of these bioactive rings together in a single molecular framework to see the additive effects towards their biological activities.

Natural and nonnatural isoxazolines and spirocyclic isoxazoline derivatives have emerged as promising drug candidates due to their significant biological activities [3] resulting in an overall antiproliferative effect on a variety of cancer cell lines. The natural product 11-deoxyfistularin-3 [4] contains two spirocyclic isoxazoline moieties and is cytotoxic toward estrogen dependent MCF-7 breast cancer cells (LD50= 17 mg/L). Other closely related spirocyclic isoxazoline natural products such as fistularin-3, [7] psammaplysin A, [5] exhibits cytotoxic activity and aerothionin, homoaerothio-nin [6], Fig. 1 are known for antimicrobial activity. Quinones have attained great interest from a medical and toxicological perspective due to their unique reactivity and high prevalence in the environment. Natural and synthetic quinone derivatives are well known for antitumor activity [9]. Many drugs such as daunorubicin, doxorubicin Fig.2, epirubicin, mitomycin, mitoxantrones, and saintopin, which are used clinically in the therapy of solid cancers [10]. The quinone anticancer compounds undergo enzymatic reduction via one or two electrons to give the corresponding semiquinone radical or hydroquinone. These semiquinone and the superoxide radical anion will generate the hydroxyl radical and which is the cause of DNA strand breaks [11].

In recent years, the strategy employing to design new bioactive hybrid molecules gained more importance due to their improved biological activity compared to the standard drugs. Such dual action compounds, or hybrid compounds, offer the possibility to overcome the current resistance and reduce the appearance of new resistant strains [12]. Based on this hypothesis, previously we have synthesized quinone five membered phenyl/heterocyclic hybrids [13-16].

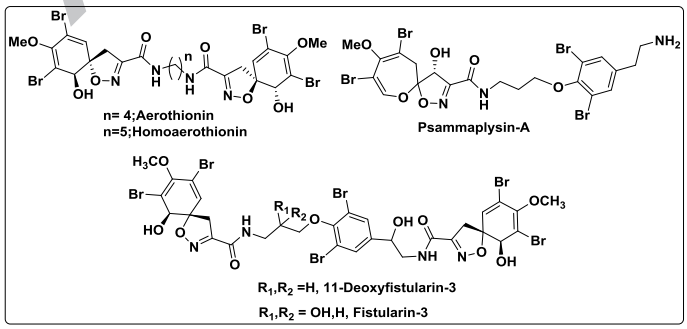


Fig. 1. Spiroisoxazoline Natural Products

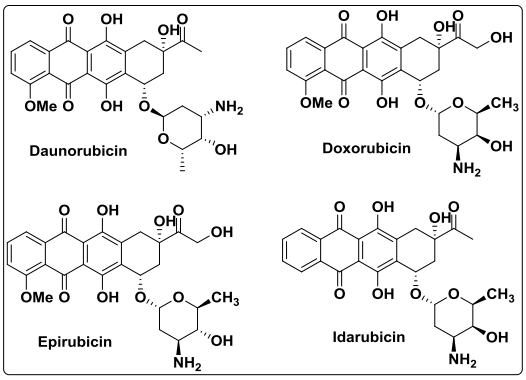


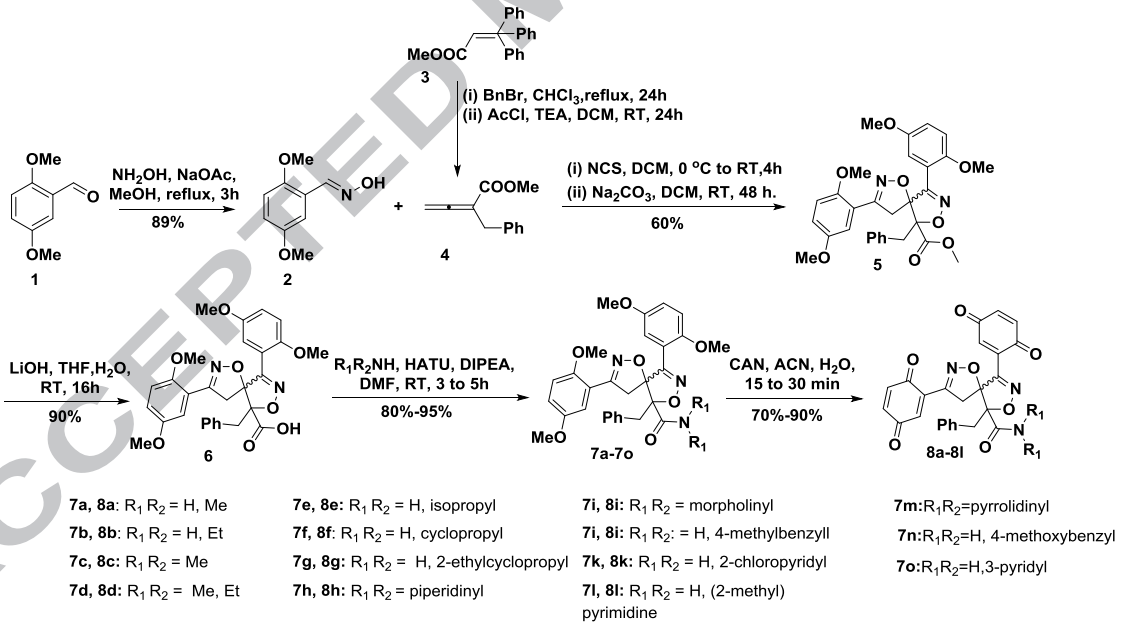
Fig. 2. Known Quinone Drugs

In this rationale, we are encouraged to discover rarely addressed new class of spirobiisoxazoline derivatives by double 1,3-dipolar cycloaddition reaction and the conjugates of these new molecules with biologically active quinones. Herein we have designed and synthesized spirobiisoxazoline dibenzoquinone derivatives as new hybrid molecules to identify more potent biologically active compounds.

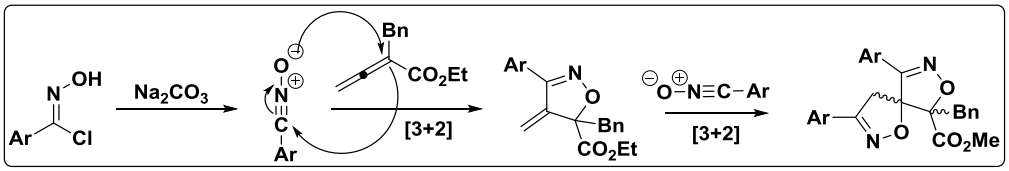
Several cycloaddition reactions were reported to approach isoxazoline and spiroisoxazoline skeleton over the years. [17] The strategy based on the cycloaddition of nitrile oxide, has been revealed to be very feasible and trustworthy by many research groups. [18] Whereas, in the above reports, limited reaction partners (alkenes) were reacted with nitrile oxides to construct the isoxazoline frameworks [19] and very few reports were addressed the formation of spirocyclic biisoxazolines *via* intramolecular double 1,3-dipolar cycloaddition of dienes. [20]. Therefore, evolving further approaches is still highly desirable.

Many cycloaddition reactions of allenoates described the formation of only carbon-carbon double bond.[21] Zecchiet al. reported the minor formation of spirobiisoxazoline from the cycloaddition between nitrile oxide and substituted allene. [22] Guoet al. have reported an efficient double 1,3-dipolar cycloaddition of allenoates with nitril-imines for the construction of spirobidihydropyrazoles. [23] Recently Xinye Shang et al. addressed the double 1,3-dipolar cycloaddition involved DABCO combined with Et_3N, 2-substituted buta-2,3-dienoates reacted with oxime chlorides to afford spirobiisoxazolines.[24]

Herein we are interested to develop a mild, simple "thermal free" methodology to synthesize spirobiisoxazolines by inorganic base (Na_2CO_3) mediated double "1, 3 dipolar" cycloaddition reaction at room temperature for easy workup and isolation in very good yield. Further, a literature survey reveals no report on the synthesis of spirobiisoxazoline with dibenzoquione novel nucleus yet so far. As part of our ongoing program to develop efficient compounds and robust methods for the preparation of biologically relevant molecules from readily available building blocks, which are novel yet resemble known biological activity by virtue of the presence of some critical structural features, we have developed a facile, simple and mild methodology for the synthesis of novel spiro biisoxazoline dibenzoquinone derivatives.



Scheme1. Synthesis of Spirobiisoxazoline Dibenzoquinone Derivatives (8a-8m).



Scheme 2. Plausible mechanism of double 1,3 Dipolar cycloaddition reaction

For the synthesis of spirobiisoxazoline dibenzoquinone compounds **8a-8l**, (**Scheme 1**) commercially available 2,5-dimethoxybenzaldehyde (**1**) was reacted hydroxylamine hydrochloride in MeOH at reflux afforded oxime **2** (89%). Oxime **2** was treated with NCS in DCM afforded oxime chloride which on further treatment with allenoate **4** resulted dimethoxy spirobiisoxazoline **5**. Therefore, a reactive intermediate nitrile oxide could be easily generated in situ from oxime chloride in the presence of Na_2CO_3 in DCM and the nitrile oxide was expected to react with allenoate to furnish the desired dimethoxy spirobiisoxazoline **5 (Scheme 2)** as diastereomeric mixture (9:1, 60 %) by [3+2] by double 1,3-dipolar cycloaddition. In this investigation, the reaction of oxime chloride precursor with allenoate **4** was chosen as the model reaction with the use of Na_2CO_3 as the base in dichloromethane at RT for 48 h to give the corresponding product spirobiiosxazoline **5** in 60% yield (Table 1, entry 5). Further investigation was carried out to optimise reaction condition by taking the combination of different solvents such as ACN, DCM, $CHCl_3$ and THF with different bases like Na_2CO_3, K_2CO_3, Cs_2CO_3 and NaOH. The results clearly indicated that the reaction media played an important role in the process (entries 1–16). An enhancement of the yield was achieved when the reaction was carried out in DCM with Na_2CO_3 (60%) at RT for 48h. After that, the reaction with K_2CO_3 in CHCl3 gave good yield (52%), the yields with remaining systems were not desirable. The reaction with NaOH as base is poor yielding. The base catalyzed hydrolysis of compound **5** gave the key intermediate carboxylic acid derivative **6** (90%), which was subjected to amide coupling with various aliphatic, aromatic, acyclic and cyclic, primary/ secondary amines. Acid amine coupling was carried out by using HATU as coupling reagent, which afforded corresponding mide derivatives (**7a-7o**) in 80-95% yield,. These amide derivatives (**7a-7o**) upon oxidation with ceric ammonium nitrate in ACN/Water at 0 ^oC resulted in spirobiisoxazoline dibenzoquinone derivatives **(8a-8l)** as yellow solids with very good yield (70-90%) **(Fig.3)**. However, quinones (**8m**, **8n and 8o**) obtained with some of the amides **m** (pyrrolidine) **n** (4-methoxybenzyl), **o** (3-pyridyl) were found to be unstable even at 0 ^oC and thus we were unsuccessful in isolating these compounds. The synthesized stable compounds **(8a-8l)** were well characterized by "IR, ^1H NMR, ^{13}C NMR & HRMS specromerty".

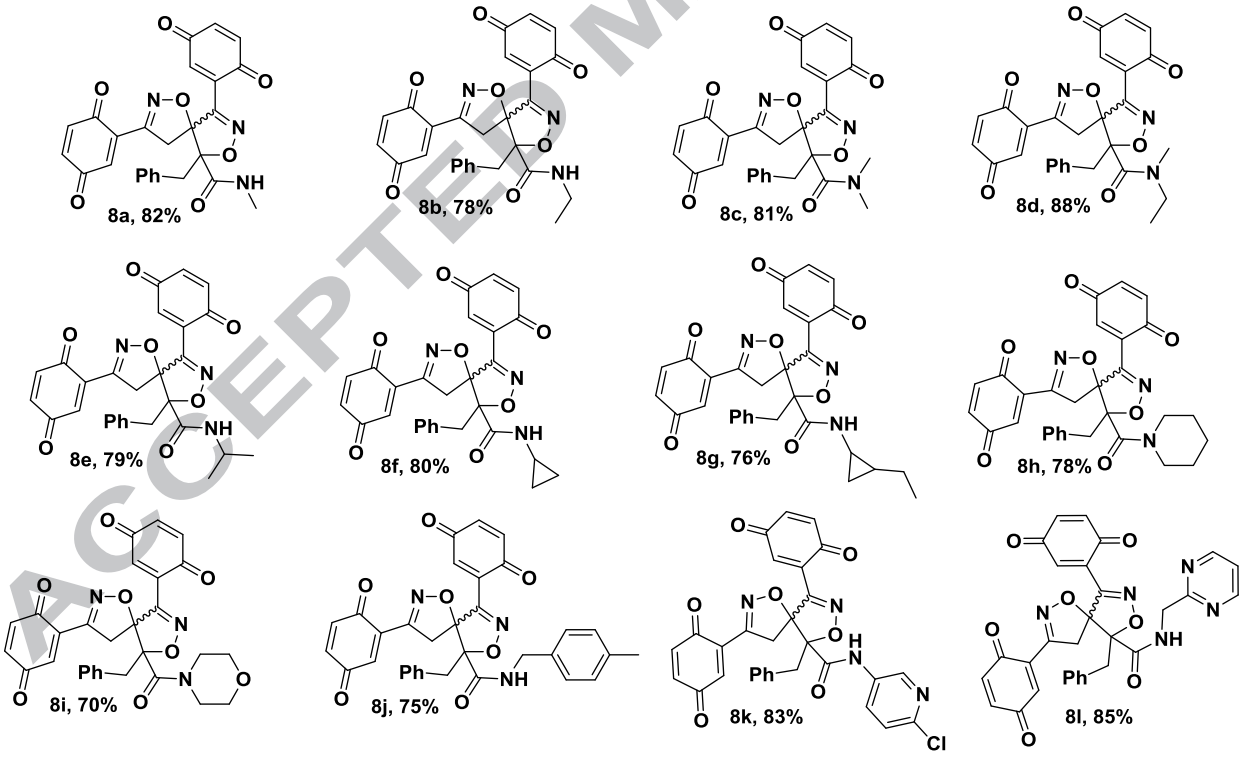


Fig. 3. Spirobiisoxazoline Dibenzoquinone Derivatives **(8a-8l)**

Table 1. Optimization of reaction conditions

Sl.No	Solvent	Conditions	Yield
1	ACN	Na_2CO_3, RT, 64h	32%
2.	ACN	Cs_2CO_3, RT, 48h	22%
3	ACN	K_2CO_3, RT, 48h	32%
4	ACN	NaOH, RT, 48h	10%
5	**DCM**	**Na_2CO_3, RT, 48h**	**60%**
6	DCM	Cs_2CO_3, RT, 48h	25%
7	DCM	K_2CO_3, RT, 48h	48%
8	DCM	NaOH, RT, 48 h	15%
9	$CHCl_3$	Na_2CO_3, RT, 48h	40%
10	$CHCl_3$	Cs_2CO_3, RT, 48 h	28%
11	$CHCl_3$	K_2CO_3, RT, 48h	52%
12	$CHCl_3$	NaOH, RT, 48h	12%
13	THF	Na_2CO_3, RT, 48h	25%
14	THF	Cs_2CO_3, RT, 48h	10%
15	THF	K_2CO_3, RT, 48h	10%
16	THF	NaOH, RT, 48h	traces

In conclusion we synthesized a series of novel spirobioxazoline dibenzoquinone derivatives via [3+2] double 1, 3 dipolar cycloaddition reaction. Hence quinones of spirobiisoxazoline scaffolds are featured in a range of natural and synthetic products with wide-reaching biological activities and useful synthetic intermediates for organic synthesis, spirobiisoxazoline dibenzoquinone based compounds have the ability to become drugs of immense use.

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Research Highlights

- Novel spirobiisoxazoline dibenzoquinone derivatives were synthesized.
- [3+2] Double 1,3-dipolar cycloaddition was performed using allenoate and nitrile oxide.
- The new molecules were successfully separated and characterized.