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From Bench to Bedside: Advances in the Synthesis of Dibenzosuberane Derivatives and Enhanced Bioactivity

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KEYWORDS

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ABSTRACT:

Dibenzosuberane and dibenzosuberenone scaffolds are widely recognized as important structural frameworks in modern medicinal chemistry and in the synthesis of diverse organic compounds. This review summarizes recent synthetic strategies used to prepare dibenzosuberane and dibenzosuberenone derivatives and discusses their significant biological activities, including potent antidepressant, anticonvulsant, antiproliferative and other pharmacological properties. This study provides a precise overview of suberane and suberenone pharmaceuticals and their wider industrial applications.

1. Introduction

The tricyclic fused rings[1,2] system such as dibenzosuberane, dibenzosuberone, and dibenzosuberenone provide a useful framework for a variety of mechanistic, synthetic, theoretical, and medicinal applications [3–5] **Figure 1**.

These compounds have two aromatic rings and one cycloheptane, cycloheptone, or cycloheptenone ring[6]. They are used a lot as building blocks to make high-quality chemicals and as components of pharamacore[7,8]. This core skeleton exists in the structure of drugs marketed as antidepressants. This class of molecules has attracted noticeable attention from both the synthetic and biological communities due to their interesting chemical structures and potential biological activities[9,10]. They can be used as reactants or reaction intermediates in a number of chemical processes to yield fused bioactive heterocycle derivatives due to their high reactivity and abundance of active carbonyl groups **Figure 2**. The natural products with the dibenzocycloheptyl ring system are known to exhibit a vast range of potent biological activities[11,12] such as antitumor, antimicrobial, anticancer, antidepressants[13], anti-convulsants, anti-inflammatory, antipyretic, CNS stimulant, and anti-HIV agents.

The TCAs (tricyclic antidepressants[14] are a group of medications that have attained extreme popularity. As an illustration, drugs in this class, including amitriptyline[15], imipramine[16], and noxiptiline[17], **Figure 3,** are still used as first-line treatments for depressive disorders. A number of DBS-based analogues have also been created and evaluated for a variety of uses, and synthetic and medicinal chemists are still interested in the moiety. No reports of dibenzosuberane, dibenzosuberone, or dibenzosuberenone occurring naturally are available to our knowledge. There are, however, a few natural products that have the

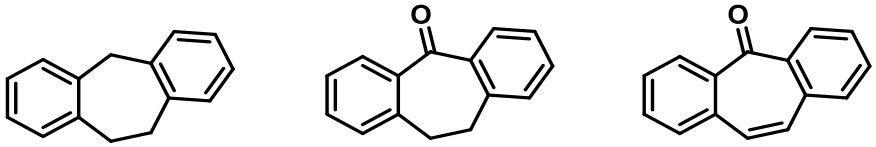

Figure 1: Structures of dibenzosuberane, dibenzosuberone, and dibenzosuberenone.

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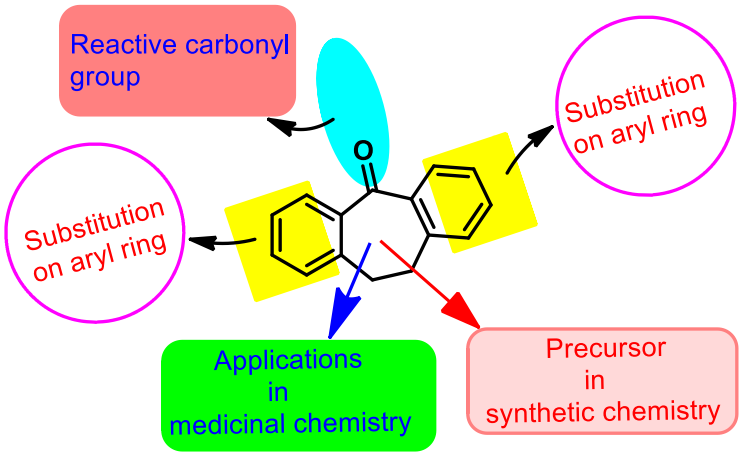
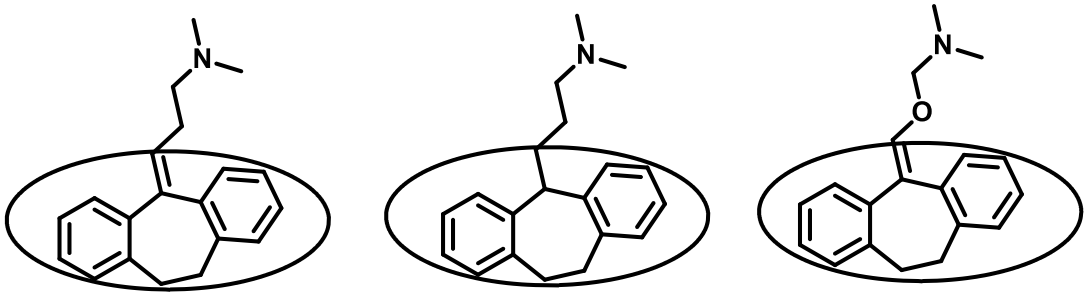


Figure 2 Probable reactive sites of dibenzosuberone moiety.



Amitriptyline **I** **Imipramine** **II** **Noxiptiline** **III**

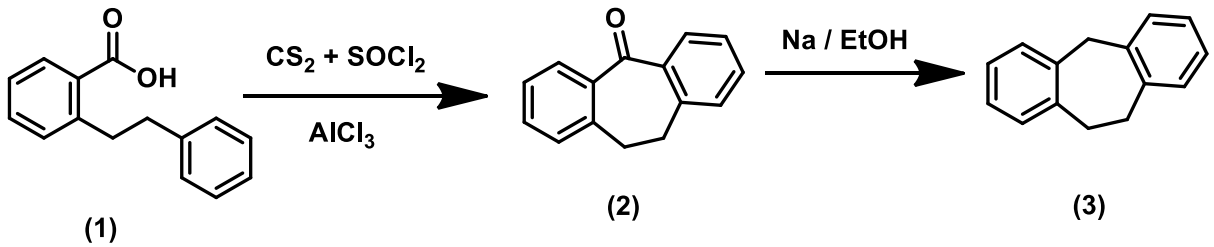
Figure 3 Structures of commercially available drug containing dibenzosuberane moiety (I-III).

dibenzocycloheptyl ring system in their structures. Some of the naturally occurring products, such as vaticanol C, hopeaphenol, and diptoindonesin, were isolated from tree bark.

Recent Development in the Synthesis of Dibenzosuberone

1. Triebs et al. first reported[18] the synthesis of dibenzosuberone and dibenzouberane by Friedal-Craft's acylation by the cyclization of 2-phenethylbenzoic acid (**1**) to form compound (**2**), further reduction of (**2**) in the presence of Na/ethanol resulting in the synthesis of dibenzosuberane (**3**) **Scheme 1**.

2. Kiyama[19] introduced a method for synthesising substituted dibenzosuberone (**7**). In this reaction, 2-(p-tolyl) acetonitrile (**4**) and 3-hydroxyisobenzofuran-1(3H)-one (**5**) reacts in the presence of sodium methoxide to form an intermediate (**6**). The reduction of the intermediate followed by the Friedal-Crafts reaction results in the formation of compound (**7**) **Scheme 2**.



(1) (2) (3)

Scheme 1 Synthesis of dibenzosuberone and dibenzouberane by Friedal-Craft's reaction

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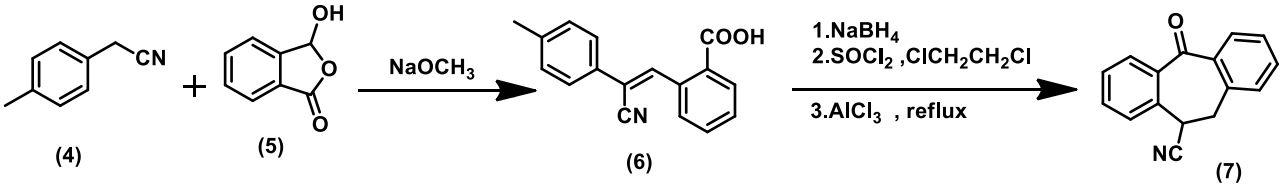


Scheme 2. Synthesis of substituted dibenzosuberone

3. Solveigh et al. reported[20] the synthesis of disubstituted dibenzosuberone (**11**) by Wittig coupling reaction between 2-formyl-5-methoxybenzoic acid (**8**) and 1-chloro-3-(chloromethyl) benzene (**9**) to give compound (**10**), which on catalytic hydrogenation in the presence of platinum oxide followed by Friedal-Craft reaction gives dibenzosuberone analogue (**11**) **Scheme 3**.

Biological importance of dibenzosuberenone

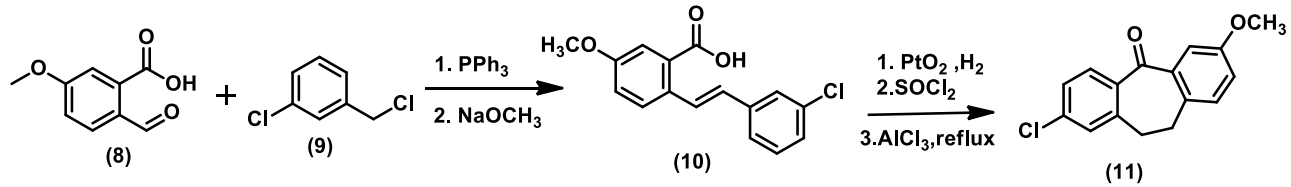
1. Anti-proliferative activity

Lingaiah Nagarapu[21] *et. al.* identified a new class of compound belonging to the significant class of physiologically active benzosuberones **(12)** with a 2,4-thiazolidenone moiety has been produced as a promising anticancer drug **(15a–j)**. The Knoevenagel condensation of compounds **2** with thiazolidenone derivatives in the presence of sodium acetate and glacial acetic acid produced these compounds in significantly greater amounts. These molecules' in vitro cytotoxicity has been investigated using HEK293, a normal cell line, and numerous cancer cell lines from humans, including A549, HeLa, MDA-MB-231, and MCF-7. Compound 6g shown strong cytotoxicity against the human breast adenocarcinoma cell line (MCF-7, IC50 value of 1.91 µM), while compound 6a demonstrated remarkable cytotoxicity with an IC50 value ranging from 2.98 to 13.34 µM against all tested cancer cell lines, comprising HeLa, A549, MCF-7, and MDA-MB-231 **Scheme 4**.

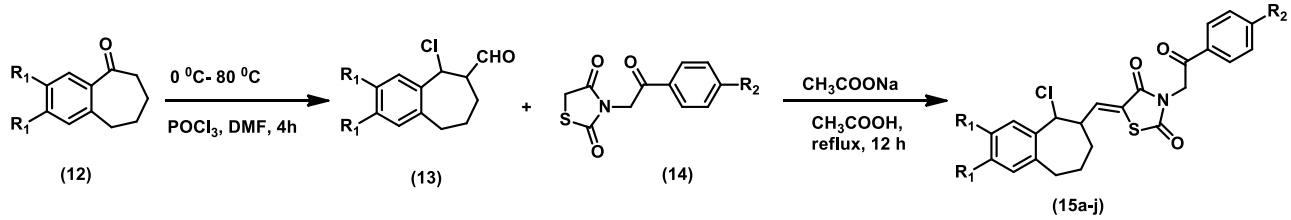
Lalita S. Kumar[22] *et. al.* described the synthesis of two classes of 1H-1,2,3-triazole[23,24] anchored dibenzosuberane attachments were created in order to investigate novel and powerful compounds with anticancer activity. Applying a convergent and linear method. The MTT assay was used to test the in vitro antiproliferative ability of the newly synthesised compounds ive ability against the HepG2 cell lines in order to investigate their molecular interaction with the 5EQG protein. The triazole anchored with an ortho-chloro-substituted aromatic ring (5g) was the most efficient combination towards HepG2 cell lines, according to IC50 values (IC50: 99.64 µg/mL). Similar cytotoxic activity, contrary to HepG2 cell lines, was shown by each of the additional compounds in the series. Molecular docking studies provided evidence for the findings **Scheme 5**.

2. Anti-Hepatitis C Virus (HCV) activity

Thoraya A. Farghaly[25] *et. al.* reported that 2-dimethylamino-methylenebenozosuberone **(22)** is produced when



Scheme 3 Synthesis of disubstituted dibenzosuberone



Scheme 4 Synthesis of potent anti-proliferative compounds.

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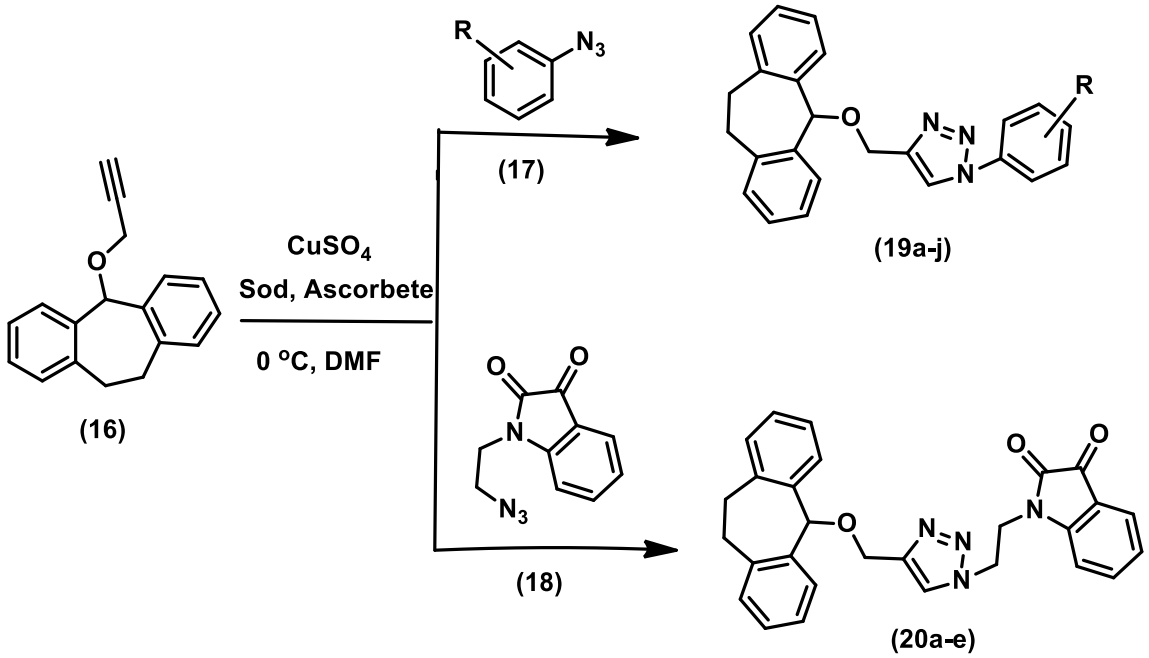

Scheme 5 Triazole derivative synthesis of dibenzosuberane.

benzosuberone **(21)** combines with dimethylformamide–dimethylacetal (DMF–DMA). This compound then reacts with heterocyclic amines to produce new heterocyclic ring systems. Additionally, the equivalent benzo is produced when enaminone (**23)** combines with the hydrate of hydrazine and hydroxylamine hydrochloride. Pyrazole (**25)**, cyclohepta [1,2–c], and benzo[2,1–d]isoxazole cyclohepta (**26)**. Furthermore, they demonstrated benzo[6,7]-cyclohepta[1,2–b]pyridines were synthesised when enaminone 2 reacted with active methylene compounds. Additionally, through assessing their capacity to safeguard against ONOO-induced tyrosine nitration, ten synthesised compounds' capacity to react with the physiologically significant reactive nitrogen species, peroxynitrite, was indirectly examined. The 1,1-diphenyl-2-picrylhydrazyl (DPPH) investigation was also used to investigate the antioxidant capabilities of these 10 compounds **Scheme 6**.

3. Anti-viral activity

M.A Murray[26] *et. al.* reported that by preventing the cytopathic reaction in organisms infected with HRV14 or HRV16, a number of combinations of dibenzofuran and dibenzosuberol have been shown to inhibit rhinovirus replication in vitro. Treatment with these substances effectively decreased the quantity and magnitude of viral plaque in a dose-dependent manner, hence influencing viral spread. With IC50 values of 25 μM in cytopathy tests, 2-hydroxy-3-dibenzofuran carboxylic acid demonstrated equivalent efficacy against HRV16 and HRV14. Similarly, at concentrations greater than 30 μM, dibenzosuberenone successfully inhibited the synthesis of HRV16 proteins, RNA from viral infections, and infectious virus particles. Time-of-addition investigations demonstrate that for chemicals to be effective antivirals, they must be given either prior to or during the viral procedure of adsorption. Dibenzosuberenone is ineffective as an immediate inactivating agent, but it can stop virus particles from adhering to cells and stopping subsequent stages of the reproduction cycle. These substances probably influence receptor connections necessary for adherence and subsequent cell entry by interacting with viral capsid proteins **Table 1.**

4. Anti-inflammatory Activity

According to Solveigh C. Koeberle[27] et al. a number of were also produced. They were all less active than their respective phenylamino derivatives (17a versus 11b, 17c versus 16f, and 17d versus 16i). We believe that the disappearance of the hydrogen bond is responsible for this dropin activity. According to the crystalline structure of Skepinone-like (2) (13), Asp169, which is situated in an antagonistic pocket of the enzyme, may create a (mediated by water) hydrogen bond with the phenylamino

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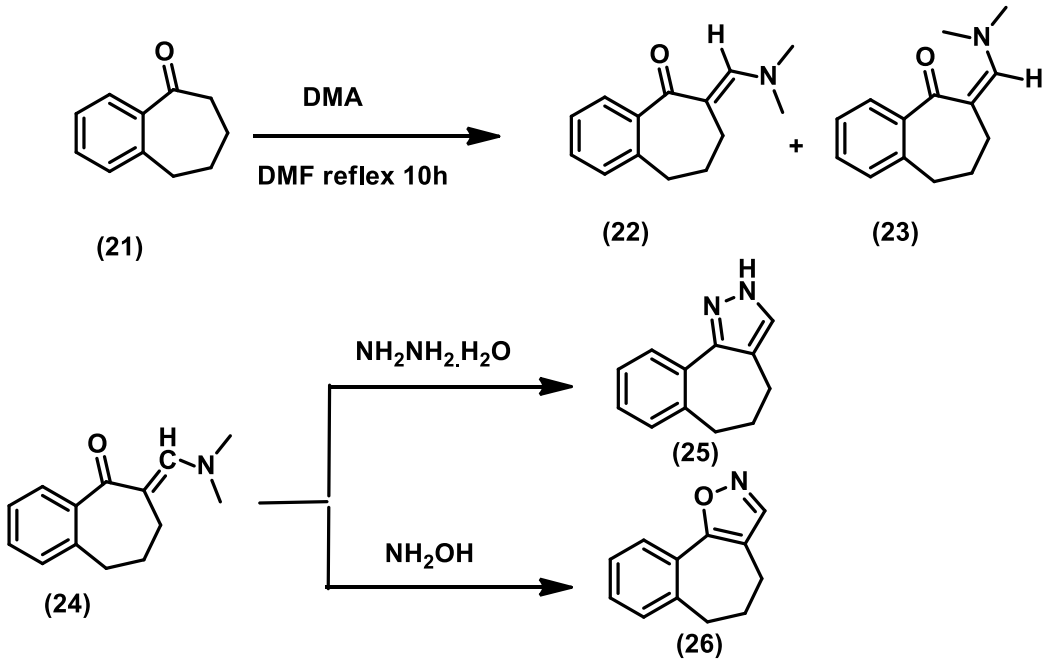
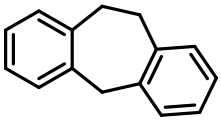
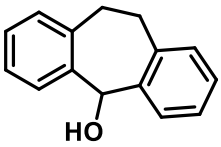
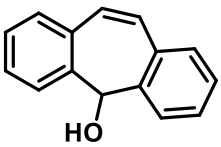
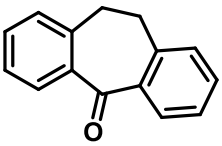


Scheme 6 Synthesis of benzo[6,7]cyclohepta[1,2–b]pyridines.

Table 1 Cellular toxicity and antiviral action contrary to HRV14 and HRV16. Drugs were evaluated in 0.1% DMSO at concentrations ranging from 5 to 200 µM. medication concentration that resulted in a 50% reduction in the viral cytopathic impact. Compounds' cytotoxicity to uninfected cells (50% lethal dose).

S. No	Structure	Compound	IC_{50} HRV14	IC_{50} HRV14	LD_{50}
1		Dibenzosuberane	>200	>200	150
2		Dibenzosuberol	50	200	150
3		Dibenzosuberenol	15	50	150
4		Dibenzosuberenone	30	10	>200

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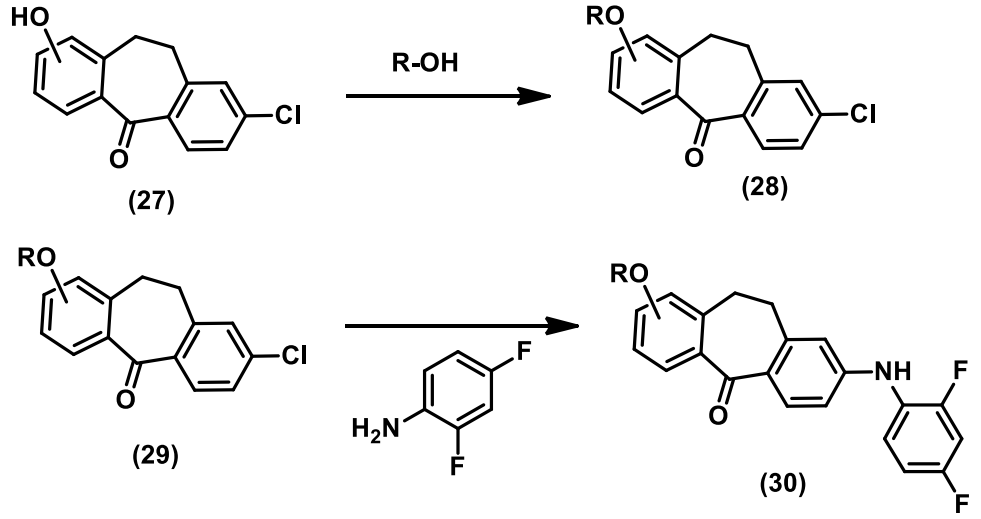
nitrogen. The 2-phenylamino-dibenzosuberones' potency and physicochemical characteristics were enhanced by the addition of hydrophilic moieties at positions 7, 8, and 9. A whole blood experiment evaluating the inhibition of cytokine release yielded extremely strong inhibitors with half of the maximum concentrations of inhibition (IC_{50}) values within the sub nM range **Scheme 7**.

5. Antimicrobial

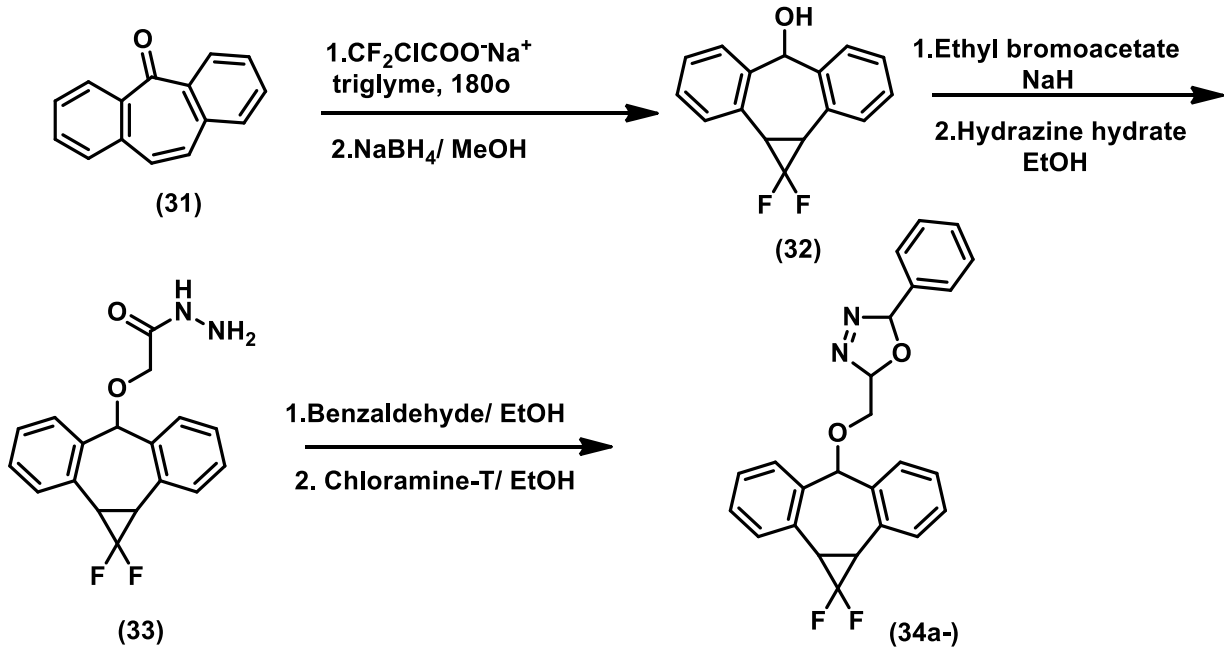
Manjunath Moger[28] et al. reported on a number of 1,3,4-oxadiazole hybrids containing a dibenzosuberane moiety with excellent antibacterial and antifungal activity against gram-positive bacteria, gram-negative bacteria, and the fungi Penicillium marneffei, Trichophyton mentagrophytes, Aspergillus flavus, and Aspergillus fumigatus. All the derivatives showed good activity against fungal and bacterial strains **Scheme 8**.

Conclusion

The basic structure of dibenzosuberenone has garnered significant interest from the synthetic and biological worlds because of its invaluable scaffold of dibenzosub-



Scheme 7 Synthesis of Phenylamino-Substituted 7-Methoxy- and 7-Hydroxy-dibenzosuberones.



Scheme 8 Synthesis of 1,3,4-oxadiazole hybrids containing dibenzosuberane moiety

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erenone. the many initiatives pertaining to the synthesis and uses of dibenzosuberenone. We would take into consideration the review's intended objectives to aid in the organised presentation and comprehending of the research findings established thus far, as well as potentially introduce groundbreaking ideas to the area. We anticipate that this evaluation will be helpful for heterocyclic and pharmaceutical applications in addition to organic synthesis.

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