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Chemotherapeutic Importance of Oxepines

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Abstract

Recently oxepine derivatives, especially the benzoxepine have been found to occupy an incredibly important position in medicinal and pharmaceutical industries. Various synthetic routes have been developed for the synthesis and functionalization of this class of compound. From his review, it is shown evidently that compounds containing oxepine framework have excellent biological activities and should be desirable in designing novel biological agents. This review x-rays the chemotherapeutic applications of oxepines and further highlight their privileged place in the design of pharmacological agents.

Keywords: ***anticancer, antimicrobial, heterocycles, oxepines, seven-membered ring, synthesis***

Introduction

In recent years, the chemistry of seven-membered heterocyclic ring systems has been conquered by the chemistry of oxygen heterocycles. The seven-membered oxygen heterocycles (oxepine, I) system is a pharmaceutically important structural unit of some natural products such as tournefolic acid B (II) [1] bauhiniastatin 1 (III) [2] which has found wide application in the design and discovery of novel bioactive molecules and drugs. Consequently, compounds with the oxepine ring have been recurrently found to exhibit potent biological activities such as anti-breast cancer [3], anti-implantation agent [4], anti-HIV [5], non-steroidal estrogen [6], antifungal [7], anxiolytic [8], cyclooxygenase inhibitory [9], and aminopeptidase N (APN) inhibitory activities [10], and others. Due to the importance of oxepine core as a pharmacophore, wide synthetic efforts have been made to the design and synthesis of oxepine-containing heterocycles [11-15]. This review reports various dedicated researches on the synthesis and medicinal properties of seven-membered oxepines in order to project the chemotherapeutic potentials of this class of compound.

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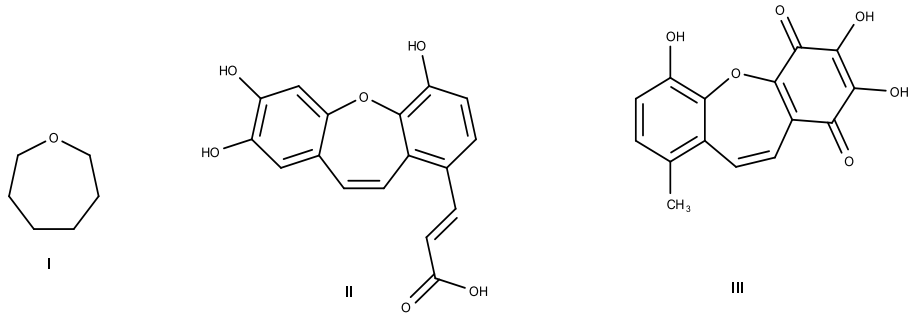
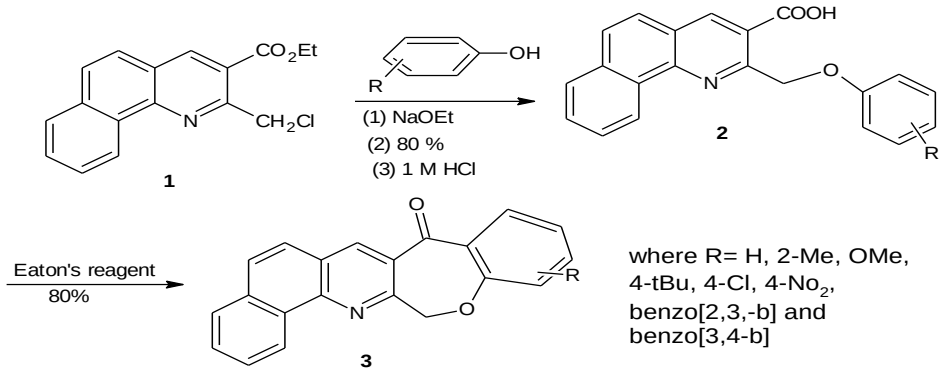


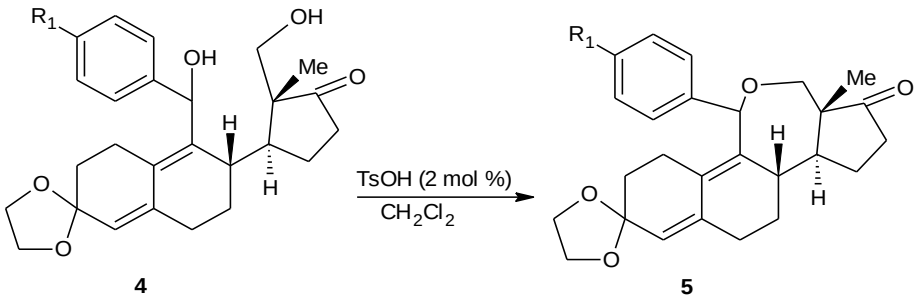
Synthetic approach

Synthesis of benzo[h]areno[6,7]oxepino[3,4-b]quinoline-8(14H)-ones (3) have been accomplished with a good yield [16] using ethyl 2-(chloromethyl)benzo[h]quinoline-3-carboxylate (1) in generating the arylmethyl moiety (2) through Williamson reaction with substituted phenol in the presence of NaOEt/EtOH which finally gave compound 3with the help of an Eaton's reagent at over 80 % yield (scheme 1).



Scheme1: **Synthesis of benzo[h]areno[6,7]oxepino[3,4-b]quinoline-8(14H)-ones**

In the synthesis of a novel pseudo-steroid, containing a fused oxepine ring system which gave an excellent yield, p-TsOH, was used as a catalyst for cyclodehydration preparation of the oxepine ring system and over 92% yield of the product was obtained [17, 18](scheme 2).



Scheme 2: **Cyclodehydration reaction of oxepine ring system**

Synthesis of bauhinoxepineJ have been carried out through decarbonylative radical cyclization onto a quinone unit of 6 to give the oxepine ring 7 [18]. In other word, an excellent yield (86%) of thioalkenyloxepines (9) through radical cyclisation of 1-ethenyl-2-(prop-2yn-1-yl)benzene(8) have also been reported [12] (scheme 3a-b).

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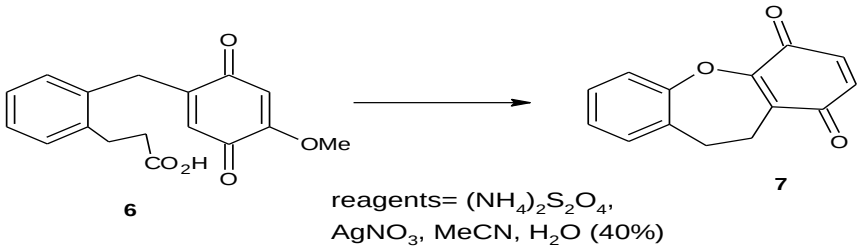
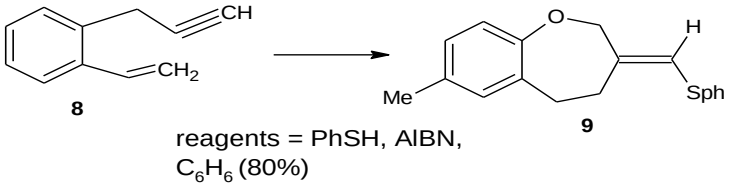
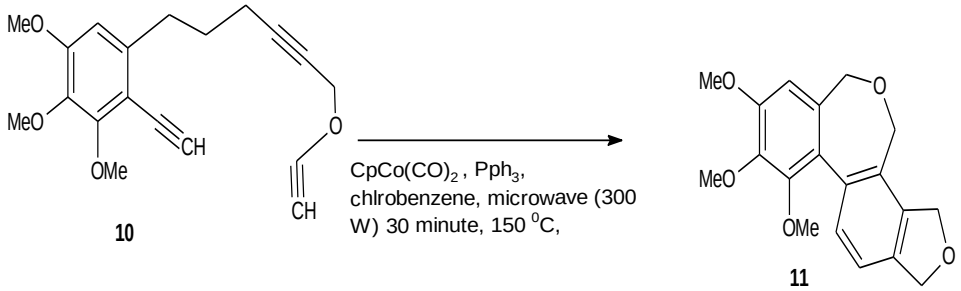


Scheme 3a



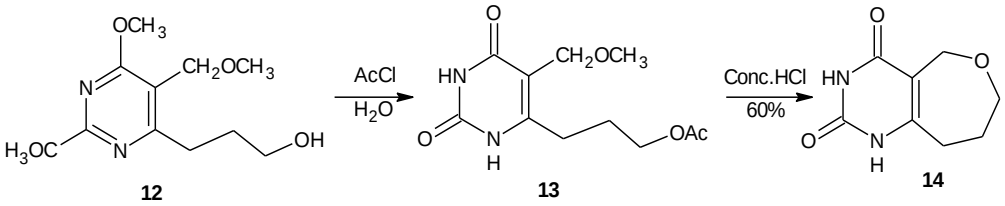
Scheme 3b

Majumdar et al. [19] reported a [2+2+2] cycloaddition approach (alkyne cyclotrimerization) used to prepare series of 6 oxallocolchicinoids which gave an excellent yield (>90%, scheme 4).



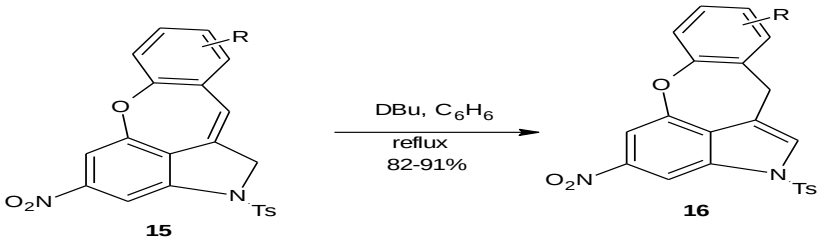
Scheme 4: **A[2+2+2] cycloaddition approach for synthesis of oxepine ring system**

A new bicyclic oxepinopyrimidine(14)has been described [20]. It involves acetylation of alcohol 12 to produce the acetate derivative (13) which then cyclised to the oxepine derivatives on treatment with concentrated hydrochloric acid (scheme 5).



Scheme 5**: Synthesis of new bicyclic oxepinopyrimidine**

Through Knoevenagel condensation followed by intramolecular nucleophilic displacement of an aromatic nitro group, fused indolo-benzoxepines(16) was synthesized in a good yield (78%) after base catalysed rearrangement of the alkene was achieved [21] (scheme 6).



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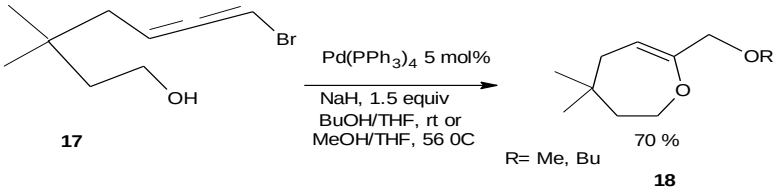
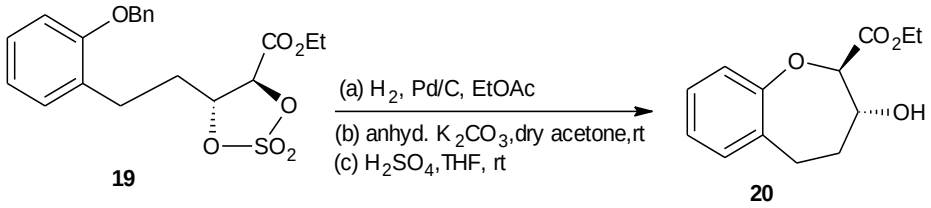
Scheme 6: **Synthesis of oxepine derivative**

Ohno et al. developed a highly Regio- and stereoselective synthesis of oxepine derivatives through cyclization of bromoallenes (17) attached with a hydroxy group by a four-carbon atom tether in the presence of a palladium (0) catalyst and alcohol [22]. In this reaction, the bromoallenes acted as an allyldication equivalent, and the intramolecular nucleophilic attack took place completely at the central carbon atom of the allene derivative (scheme 7).



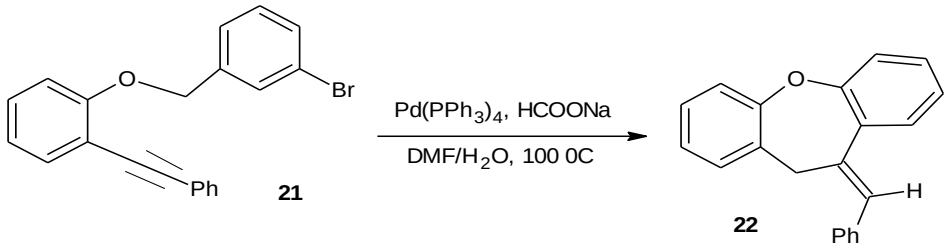
Scheme 7: **Regio and stereoselective synthesis of oxepine derivative.**

Das et al. reported synthesis of functionalized 1-benzoxepine (19) through 7-endo-tet carbo-cyclisation of a cyclic sulphate to afford good yield of compound 20 (97%, scheme 8) [23].



Scheme 8: **Synthesis of functionalized 1-benzoxepine through a 7-endo-tet carbocyclization of cyclic sulphate.**

An effective and straightforward method for the construction of potentially bioactive di-benzoxepine framework through palladium-mediated reductive Mizoroki-Heck cyclization have been greatly established [19]. In the method, they used palladium catalyzed reductive Mizoroki-Heck coupling of 1-((3-bromobenzyl) oxy)-2- (phenylethynyl)-benzene (21) to afford dibenzo[b,e]oxepine (22) and a combination of Pd(PPh3)4 and HCOONa in aqueous DMF was also used for the transformation. In other word, the cyclization product is gotten regio-selectively and the procedure is said to be equally active for both aliphatic and aromatic alkyne containing substrates (scheme 9).



Scheme 9: **Palladium catalyzed reductive Mizoroki-Heck coupling**

Arnold et al. carried out a two-step synthesis of a dihydrodibenz[b,f]oxepine derivative by Heck arylation reaction followed by intramolecular O-arylation (scheme 10) [24].

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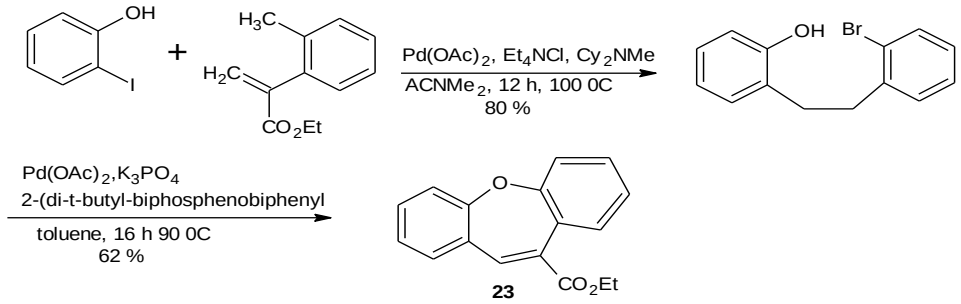
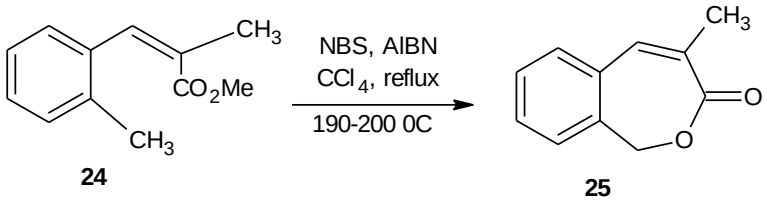


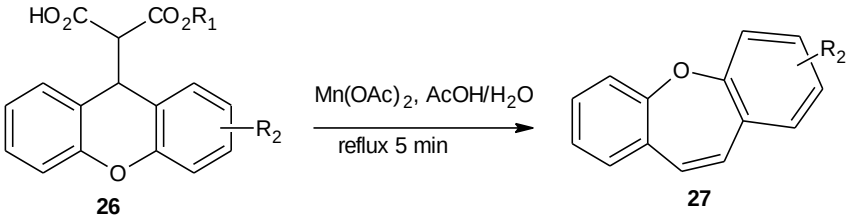
Scheme 10: **synthesis of a dihydrodibenz[b,f]oxepine derivative**

Glukhov and Kirillov reported a synthesis of benzoxepine through cyclization reaction. Dialkyl-2-(2-methylbenzylidine) malonate was cyclized using NBS, ALBN CCl4 under reflux for 190-200 oC to benzoxepine-3-one-4-carboxylates in a good yield (86%, scheme 11) [25].



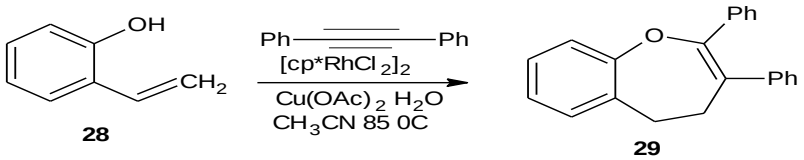
Scheme 11: **synthesis of benzoxepine through cyclization reaction**

Through oxidative 1,2 radical ring expansion, Cong et al. prepared a di-benzoxepines and a good yield of about 81% of compound 27 was obtained (scheme 12) [26].



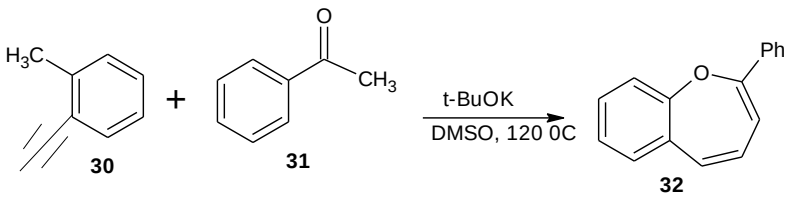
Scheme 12: **Synthesis of a di-benzoxepines through an oxidative 1,2 radical ring expansion**

Seoane et al. synthesized benzoxepine derivative (29) from O-vinylphenol (28)and diphenylacetylene through a formal [5 + 2] cycloaddition in the presence of catalytic amounts of [Cp*RhCl2]2 and Cu(OAc)2 with a good yield (89%, scheme 13) [27].



Scheme 13: **Synthesis of benzoxepine derivative**

Ouyang et al. synthesized 2-phenylbenzo[b]oxepine (32) through base-promoted formal [4+3] annulation of 2-fluorophenylacetylene (30) with acetophenone (31). The reaction was carried out using t-BuOK as a base in DMSO (scheme 14) [28].



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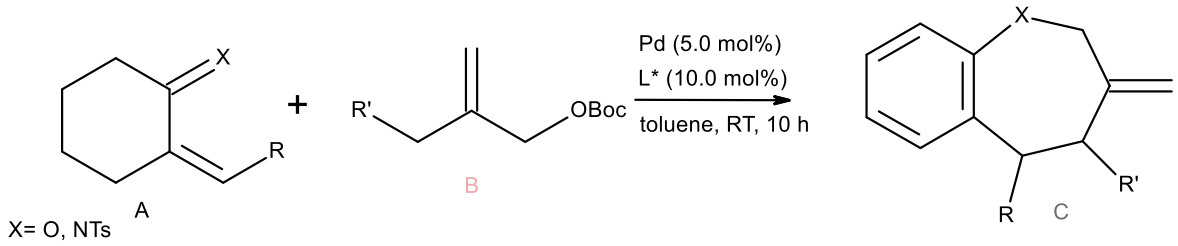
Scheme 14: **Synthesis of benzoxepine derivative through[4+3] annulation**

Trost and Zuo reported the palladium catalysed [4+3] cycloaddition in the highly regio-, diastereo- and enantioselective synthesis of tetrahydroazepines and benzo[b]oxepines (C)[29]. They developed a novel palladium(0) catalysed asymmetric [4+3] annulation for the building of seven-membered heterocyclic compounds while suppressing the potential [3+2] side pathway through fine tuning of the reaction conditions. The products were obtained in excellent yields of up to 98% (scheme 15).



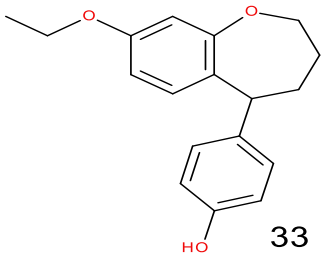
Scheme 15: **palladium catalysed 4+3 cycloaddition**

Chemotherapeutic potentials of Oxepines

Oxepine which represent a ubiquitous class of oxygen containing heterocycles have found application not only in bioactive natural products but also in pharmaceuticals. In other words, several compounds bearing oxepine derivatives, most especially the benzoxepine skeleton have been recurrently reported by researchers as a new prospective drug. According to Belen'kii, dibenzo[b,f]oxepine have showed potential as remedies for hyperuricemia and/or gout, it also modulate the activity of L-isoaspartyl(D-aspartyl) O-methyltransferase and/or glyceraldehyde-3-phosphate dehydrogenase which enables the prevention, treatment or alleviation of type 1 and/or type II diabetes, autoimmune response and neurodegenerative diseases [30]. Aside from these activities, other pharmaceutical application of oxepine are shown below.

Nonsteroidal Estrogen Activity

Sarkhel et al. synthesized mono and bisbenzo[b]oxepines and evaluated them for nonsteroidal estrogen activity [6]. In silico docking studies were carried out to understand their activities. Among the synthesized compounds, 4-((8-methoxy2,3,4,5-tetrahydrobenzo[b]oxepin-5-yl)methyl)phenol (33) and 8,8'-dimethoxy-2,2',3,3',4,4',5,5'-octahydro5,5'-dibenzo[b]oxepine (34)showed the best activity.



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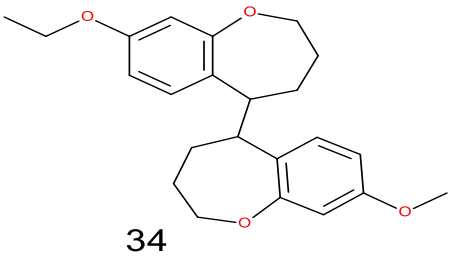

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Anticancer Activity

Series of substituted dibenzo[b,f]oxepines have been reported by Ansari et al. as a new class of anti-breast cancer agents [3]. All the prototype molecules exhibited potential antiproliferative activity against ER positive and ER negative breast cancer cell lines.

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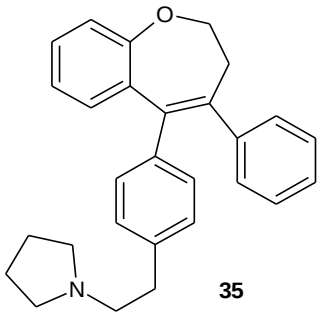
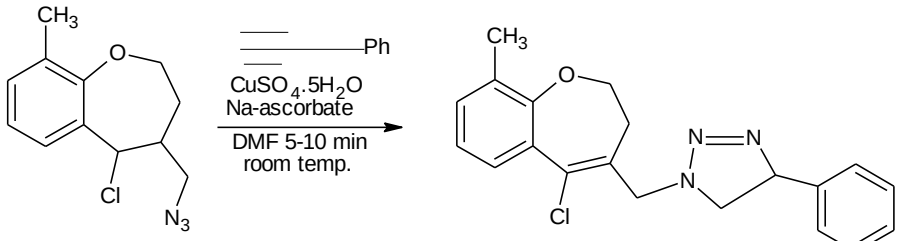


35

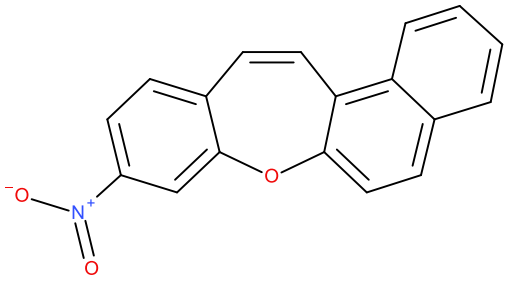
Of all the compound tested, 1-(4-(4-phenyl-2,3-dihydrobenzo[b]oxepin-5-yl) phenethyl)pyrrolidine (35) exhibited potent invitro anti-proliferative activity at 1.33 µM and 5 µM when tested against MCF-7 and MDA-MB-231 cell lines.

Kuntala et al. synthesized series of novel benzoxepinetriazole hybrids (36) using a copper catalyzed azide-alkyne cycloaddition (CuAAC) strategy [31]. Anticancer activity of these compounds were tested against two cancer cell lines e.g. colon cancer cell line HCT15 of 80 µg/mL and lung cancer cell line NCI-H226 of 80 µg/mL. Among the synthesized compounds tested, compound 36 showed good activity with GI50 (the concentration required to achieve 50% growth inhibition) value of 52.5 and 41.3 µg/mL against HCT15 and NCI-H226 cells.



36

Garbicz et al. reported some dibenzo[b,f]oxepines derivatives as anticancer compounds. The results of cytotoxic assay and flow cytometry analysis revealed that 9-nitrobenzo[b]naphtha[1,2-f]oxepine as the most active and the molecular modelling showed good interaction with tubulin [32].



9-nitrobenzo[b]naphtha[1,2-f]oxepine

Anti-HIV Agent

Seto et al. synthesized 1-benzoxepine derivatives containing polar substituents (such as phosphonate, phosphine oxide or pyridine N-oxide), an orally active CCR5 (C-C chemokine receptor type 5) antagonists as anti-HIV-1 agents [5]. The compound N-{4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl}-7-(4-methylphenyl)-2,3-dihydro-1-benzoxepine-4-carboxamide (37)showed the most potent CCR5 antagonistic activity (IC50 =7.2 nM) and inhibitory effect (IC50 = 5.4 nM) on the HIV-1 Env-mediated membrane fusion. The compound also had an acceptable pharmacokinetic property in rats.

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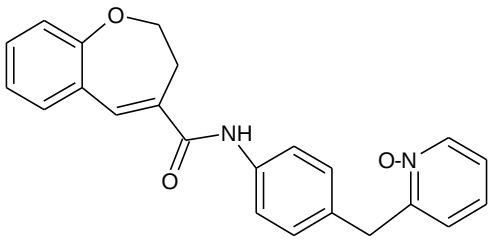

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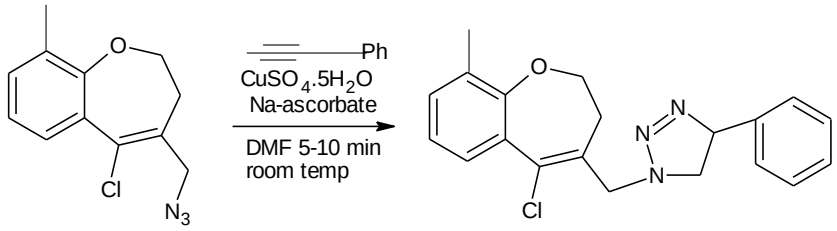
Anti-Bacterial Activity

Kuntala et al. synthesized series of novel benzoxepinetriazole hybrids (38) using CuAAC strategy and tested them for in vitro anti-bacterial activity against Gram +ve, Staphylococcus aureus and Klebsiella species and Gram—ve Pseudomonas aeruginosa and Escherichia coli using Pefloxacin, a quinolone based broad spectrum antibiotic (that is active against both gram positive and gram negative bacteria) as a positive reference at a concentration of 0.04 mg/50 µL [31]. Among the synthesized compounds (38) showed an excellent activity at 100 µg/mLagainst Escherichia coli over the gram +ve strains, signifying special effectiveness of the present class of compounds towards gram (-ve) species.



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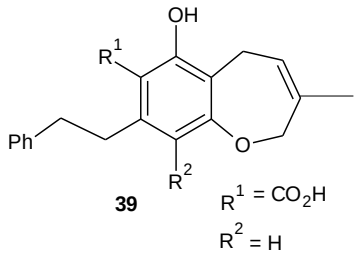
Cyclooxygenase inhibitory actions

Asakawa et al. isolated radulanins H and radulanins E from the liver wort Radula perrottetii and Radula variabilis which was 3-methyl-2,5-dihydro-1-benzoxepine derivatives [33]. Radulanin H (39) was reported to exhibits important cyclooxygenase inhibitory actions.



39 $R^1 = CO_2H$, $R^2 = H$

Nonsteroidal Anti-Inflammatory Agent

Nagai et al. synthesized series of tricyclic compounds fused with 1-benzoxepine framework as anti-inflammatory agent [34]. Among the synthesized compounds, 2-(8-methyl-11-oxo-10,11-dihydrodibenzo[b,f]oxepin-2-yl)propanoic acid (40) showed a potent anti-inflammatory activity with ED50 mg/kg of 3.38, 0.30, 6.51 and 0.28 mg/kg for CPE (carrageenan paw edema) rats, UV erythema (guinea pigs), PQW (phenyl-quinone writhing) mice and acetic acid writhing (rats) respectively. LD50 mg/kg (rats) 147 and UD50 mg/kg (rats) 13.8mg/kg.

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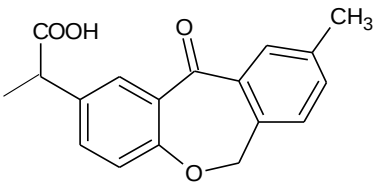

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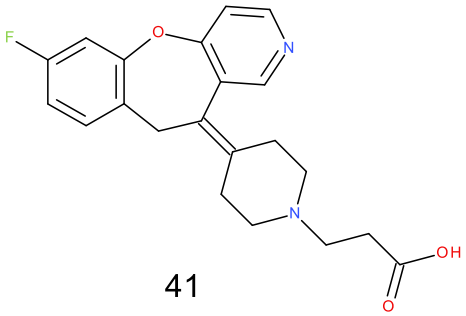
Anti-allergic agent

Benzoxepine derivatives have been discovered as potential anti-allergic agents. Iwasaki et al. reported the synthesis of 3-[4-(8-fluoro-5,11-dihydro[1]benzoxepino[4,3-b]pyridin11-ylidene)piperidino]propanoic acid derivatives (41) as anti-allergic agent with an excellent activity of ED50 (mg/kg)= 0.29 (0.12-0.69) in rat and 0.025 (0.0041-0.15) in mice [35].



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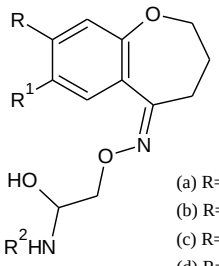
Hypotensive Agent

Substituted oximino-ethers of 3,4-dihydro-1(2H)-benzoxepines were synthesized [4]. The hypotensive activity or ability to lower blood pressure of these compounds was evaluated in anaesthetized cats. Among the synthesized compounds, 42 had the best activity with a fall of Blood pressure (BP) 60(195/) mm kg**.**



(a) R=R^1=H
(b) R=H; R^1=Me
(c) R=H; R^1=OMe
(d) R=R^1=Me

R^2{n-propyl, i-propyl, t-propyl

42

Anti-implantation agent

Andon and Rai synthesized new derivatives of oxepine, 5-substituted 2,3,4,5- tetrahydro-1-benzoxepine as anti-implantation agent [36]. Out of the compounds synthesized, 1-[2-{(7-methoxy-2,3,4,5-tetrahydrobenzo[b]oxepin-5-yl)oxy} ethyl]piperidine (43) displayed good activity of about 67 % in mature female rats at 10 mg/kg dose.

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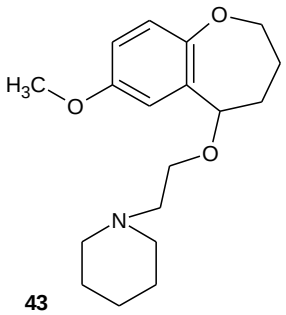

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Conclusion

In recent years oxepine derivatives, especially benzoxepine have gained an incredible importance in medicinal and pharmaceutical industries. From this review, it is shown evidently that compounds containing oxepine framework have good to excellent pharmacological activities and can also be synthesized easily in different ways. As we all know that unavailability of drugs or resistance to the marketed drugs is the main drawbacks for the treatment of many diseases, and seeing the promising pharmaceutical activity of this derivatives, an exploration of this compound may provide some alternative and potential solutions to myriads of problems challenging human wellbeing.

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