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Enaminones as building blocks in drug development: Recent advances in their chemistry, synthesis, and biological properties

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ABSTRACT

The enaminone scaffold is a versatile building block used in organic synthesis. The amine – alkene – carbonyl conjugated system, having both nucleophilic and electrophilic characteristics, allows for a highly reactive center, that can serve as a pharmacophore for molecules in drug development. Analogs with this moiety have an array of pharmacological responses such as antiviral, anti-inflammatory, antitumor, anticancer and anticonvulsant activities. Herein, this review provides insight of current synthetic methodologies that employ enaminones as intermediates and their preparations. Structure activity relationship studies of various enaminone analogs will be examined in this review as well.

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1. Introduction

Enaminones are enamines of β-dicarbonyl compounds and their usefulness in medicinal chemistry as building blocks for novel drug candidates has been vastly studied over the years [1,2]. Enaminones are known as vinylogous amides (Fig. 1) and consists of a conjugated system of an amino group linked through a carbon – carbon double bond to a carbonyl group. The vinylogous amide exhibits a

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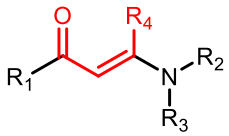


Fig. 1. General structure of the enaminone system.

typical "push-pull" system where the carbonyl group pulls electron density to itself from the amino group [3,4]. This makes enaminones very reactive in addition to being able to form intramolecular hydrogen bonds and different tautomeric components such as the enaminone scaffold (O═C−C═C−NH) or as an iminoenol (HO−C═C−C═N) [5]. Enaminones typically contain the delocalized nucleophilicity of enamines with the delocalized electrophilicity of enones, their versatility as synthetic intermediates provide an excellent scaffold for organic synthesis [3]. The electron rich carbon centers of the enaminone system provides the stability needed during organic synthesis as a result of their electrophilic nature. In addition to the electrophilicity of the carbonyl group, the amino group supplies the nucleophilicity needed to participate in nucleophilic substitution reactions [6,7]. Through electrophilic and nucleophilic substitution reactions, enaminones are effective as building blocks in the organic synthesis of acyclic, aromatic, and heterocyclic compounds, such as indoles, tetrahydropyridine, tetrahydropyrimidine, carbazoles, quinolines, acridines or phenanthridines [8]. The enaminone containing analogs have been shown to provide efficacy in a large variety of drug classes including antibiotics [8], anti-inflammatory [9], antitubercular [10], antinociceptive [1], anticonvulsants [11], antitumor [12], antifungal [13], and antidepressant [14] agents.

Enaminones are typically derived from synthetic origins and do not occur naturally [4–7,10–19]. They have been used extensively in organic synthesis as precursors for other naturally occurring compounds [20]. For this reason, there are several different methods of synthesizing enaminones, some examples of which include the condensation of 1,3-dicarbonyl compounds with amines [7], amination of 5-trifluromethyl diketone [15], enaminone synthesis from the gold's reagent [19], and silver-catalyzed propargyl alcohols and amines [7] among other methods that have been studied in recent years. Although these new methods provide numerous ways for synthesizing enaminones, there are limitations such as, expensive and unavailable reagents, low product yield, extreme reaction conditions, and long reaction times [7]. This has encouraged new basis for enaminone synthesis that avoid these shortcomings.

Enaminones can be classified as acyclic or cyclic. Cyclic and acyclic enaminones have shown to be very useful intermediates in the synthesis of drug therapies or as natural products displaying biological activity [1,16,21–29]. For example, enaminones are utilized as an intermediate in the synthesis of 2–261 (2-chloro-α-[[4 (chlorophenyl)amino]methylene]-N-[(1S)-1-methylpropyl]-β-oxobenzenepropanamide), a potential anticonvulsant drug (Fig. 2)

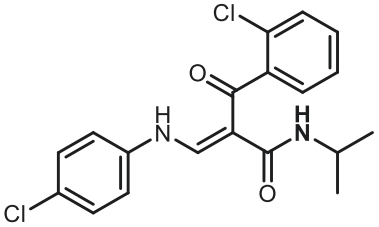


Fig. 2. Enaminone 2-261.

[18]. An example of an enaminone derivative acting as a natural product can be seen in the production of non-symmetrical enamine products used as non-cytotoxic antibiotics which is discussed later in this review [8]. Based on the versatility of the enaminone system as a useful scaffold, a vast amount of research is being conducted to investigate their clinical usefulness. This review article provides a recent comprehensive review of research utilizing the enaminone system in different drug classes, structure activity relationships (SAR) studies, and for current research. Our lab has been actively involved in contributing to enaminone research for the past 10 years, focusing on potential anti-convulsant agents with using the enaminone system as our pharmacophore [11,16].

2. Medicinal chemistry of enaminones

a. Synthesis of Enaminones

The reactivity of the enaminone system can be attributed to a combination of the nucleophilicity of enamines and the electrophilicity of enones. This unique combination creates a conjugated "push-pull" system, where the amine substituent pulls the electron density, and the carbonyl substituent pushes the electron density towards itself.

An article reported by Michael et al. describes enaminones as building blocks for natural product synthesis. The authors illustrate the reactivity of the enaminone system, that contains several nucleophilic and electrophilic sites within the enaminone molecule. With this conjugated system, the nitrogen and the carbon of the enaminone moiety can both act as nucleophiles. Upon delocalization of electrons, the nucleophilic character of the N and C, can be extended to the carbonyl group of this system via conjugation (Fig. 3).

The enaminone system encompasses enone properties as well and may act as acceptors to undergo a 1,2 or a 1,4 addition (**Fig. 3**). In this report, the authors outline a synthetic approach of taking advantage of the enaminone system's reactivity via incorporation of the enaminone scaffold into systems that already contain electrophilic or nucleophilic sites, thereby acting as corresponding reaction partners. It was suggested this synthetic strategy can serve as a synthetic handle, that can undergo annulation to gain access to common alkaloid motifs such as quinolizidines, indolizidines and perhydroindoles. A literature example of this methodology being implemented is the report of Michael and coworkers, synthesis of tricyclic analogs of quinolone antibacterial agents [30]. To synthesize the cyclic enaminone derivatives, an intramolecular cyclization was executed under acidic conditions with polyphosphoric acid and cyclic enaminone intermediates **1a-i**, at 100 °C for 1–1.5 h. The

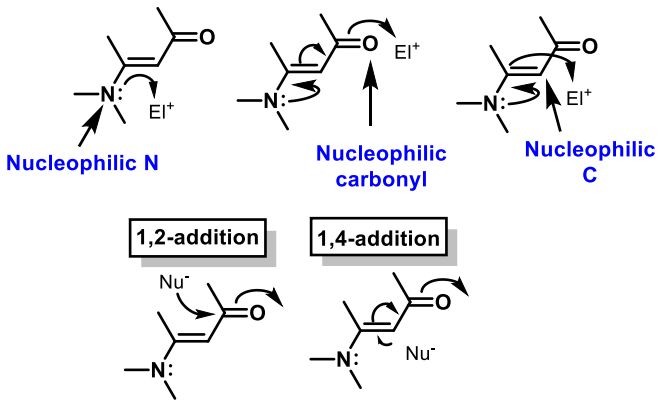
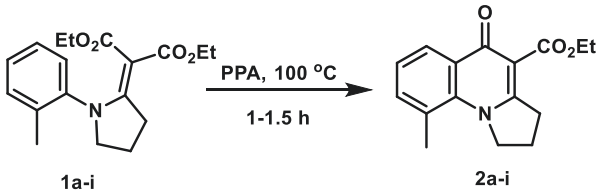
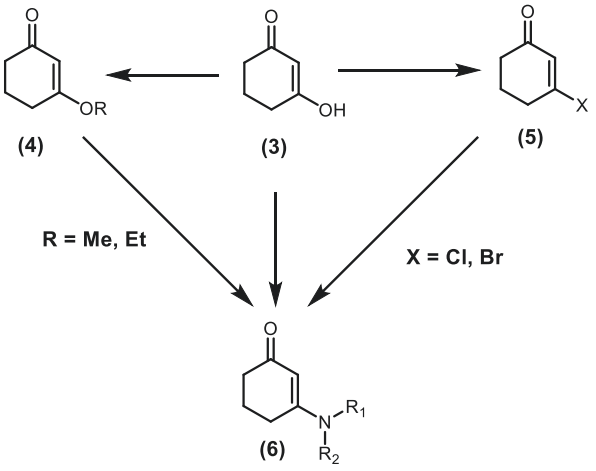


Fig. 3. Reactive sites of the enaminone system.



Scheme 1. *Michael* et al. *synthesis of tricyclic quinolone enaminones.*



Scheme 2. *Dixon and Greenhill synthesis of cylic enaminones* [20].

desired enaminone derivatives **2a-i** were produced in moderate to good yields (46–69%).

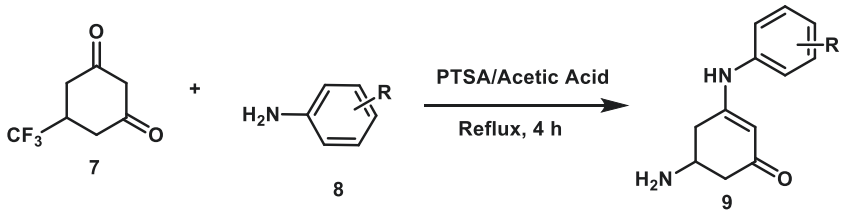
Standard synthetic methodology employed for the synthesis of enaminones involves a reaction of either a primary, secondary amine or ammonia and 1,3-diketone or 3-keto ester. This synthetic route presents challenges and often yields small quantities of product or no product at all. This is due to the nature of the amines used in the reaction having low nucleophilicity and are more resistant to reactivity [31]. The reaction conditions necessary to perform synthesis via this method are difficult to achieve, often requiring a Dean-Stark apparatus and a refluxing aromatic solvent [7]. For this reason, synthetic chemists have developed strategies to overcome the problematic syntheses of enaminones (see Scheme 1).

A study conducted by synthetic chemists Dixon and Greenhill showed that conversion of the diketone into a vinylogous ester or a vinylogous acid halide produced faster rates of hydrolysis as shown in Scheme 2 [31]. Synthetic efforts of chemists Dixon and Greenhill would establish the blueprint for the synthesis of cyclic enaminones.

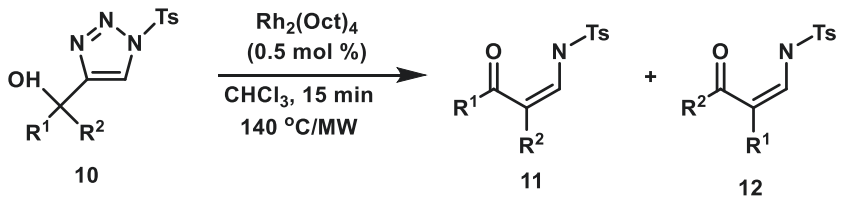
An example of this synthetic method being utilized can be seen in the work of Apraku and Okoro (Scheme 3), in which 5-trifluromethyl diketone was reacted with a corresponding benzylamine derivative to produce enaminone products with efficacy in epilepsy models *in vivo* [15].

Miura and co-workers employed a rhodium-catalyzed denitrogenative rearrangement of 1-(N-tosyl-1,2,3-triazol-4-yl)-ethanol **10** [32]. Initially, the 1-(N-tosyl-1,2,3-triazol-4-yl)-ethanol was prepared from but-3-yn-2-ol and tosyl azide. Upon the addition of a catalytic amount of $Rh_2(Oct)_4$, **10** would undergo a rearrangement to yield the Z-isomer of the enaminone analog **11**. Previous research efforts of Miura and colleagues, showed that an α-imino rhodium (II) carbenoid is electrophilic enough to warrant a nucleophilic addition of water, thus illustrating the electron-deficient nature of the carbenoid carbon, Scheme 4.

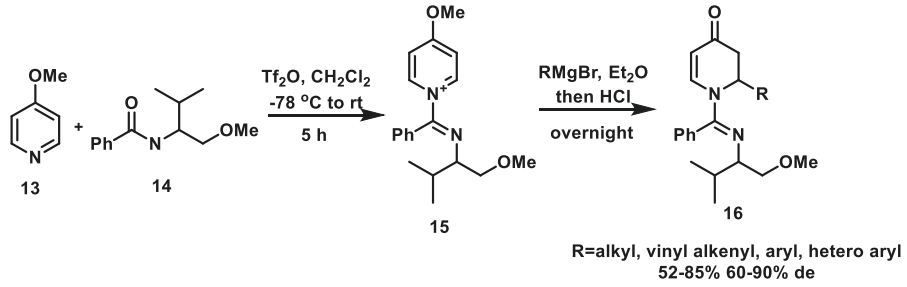
With this knowledge in hand, Miura et al. hypothesized a 1,2-hydride or 1,2-alkyl shift for the current study described. The authors proposed from the electron pushing effect of the hydroxyl group of an α-imino rhodium (II) carbenoid derived from 1-(N-tosyl-1,2,3-triazol-4-yl)-ethanol, induces an intramolecular 1,2-hydride or 1,2-alkyl shift to the neighboring electron-deficient carbenoid carbon. The synthetic route to generate the desired product involved the conversion of 1-(N-tosyl-1,2,3-triazol-4-yl) ethanol **10** into enaminone (Z)-4-(tosylamino)-but-3-en-2-one **11 and 12**, via a denitrogenative rearrangement reaction carried out in chloroform at 140 °C for 15 min under microwave irradiation conditions, utilizing a catalytic amount of $Rh_2(Oct)_4$ (0.5 mol%, Oct = octanoate). The authors concluded that a 1,2-hydride shift predominated over the 1,2-alkyl shift. Further investigation of various alkyl substituents (**R**^{1} and **R**^{2}) and their effect on the 1,2-migration revealed that aromatic functional groups could compete with the 1,2-hydride migration, as a phenyl-substituted substrate afforded a mixture of **11** and **12** with a percent yield of



Scheme 3. *Apraku* et al. *synthesis of the benzylamine enaminones* [15].



Scheme 4. *Miura* et al. *rhodium-catalyzed synthesis of acyclicenaminones.*



Scheme 5. Charette et al. e*nantioselective synthesis of cyclic enaminones*.

58% and 25% respectively. Regarding primary and secondary alkyl functional groups, the primary alkyl group took precedence over the secondary alkyl groups in the 1,2-migration. From these results, a 1,2-migration order was established based on the predominant products generated from the reaction. The order of 1,2-migration was: hydride > phenyl > primary alkyl > secondary alkyl, with secondary alkyls being the least preferred for the 1,2-migration.

2.1. Cyclic enaminones

Cyclic enaminones are organic molecules in which the enaminone scaffold is embedded into the skeleton of the molecule [33]. Two distinct forms of the cyclic enaminone system exists: the bicyclic and endocyclic enaminones As shown in Fig. 4.

In the bicyclic form, the enaminone can be either cis or trans isomers (see Scheme 5). The endocyclic form is represented by a 6-membered ring (a 2,3-dihydro-4-pyridone structure) and its occurrence exists only in the cisoid form. The cyclic enaminone 2,3-dihydro-4-pyridone is an attractive organic intermediate for the synthesis of molecules that contain a heterocyclic piperidine. The piperidine moiety is prevalent in several pharmaceutical drugs such as, Risperdal and Haldol. One common strategy synthetic chemist's employ in the development of cyclic enaminones, is

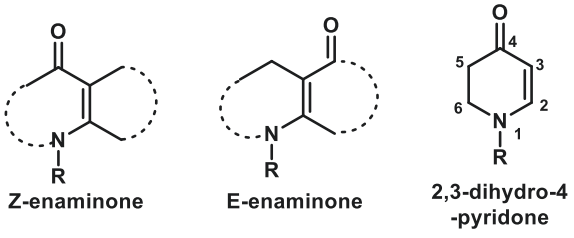


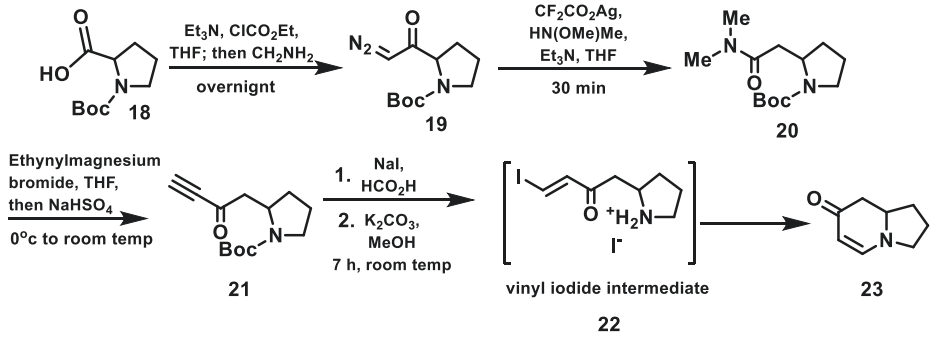
Fig. 4. Bicyclic and endocyclic enaminones.

stereoselective reactions utilizing asymmetric methodology. Charette et al. developed a stereoselective synthesis of enantioenriched (enantiopure) cyclic enaminones as shown in Scheme 6 [34]. The reaction proceeded via the nucleophilic addition of Grignard reagents to a chiral salt, derived from 4-methoxy pyridine and triflic anhydride. To develop the cyclic enaminones, Pyridium salt **15** was formed in situ from a mixture of amide **14** and 4-methoxy pyridine **13**. The synthesis was carried out in CH_2Cl_2 for 5 h. After the initial synthesis, the resulting salt undergoes reactivity with an ether solution of a Grignard reagent under acidic conditions to afford cyclic enaminone **16** in good yields and diastereoselectivity (52–85% yield, 60–90% de).

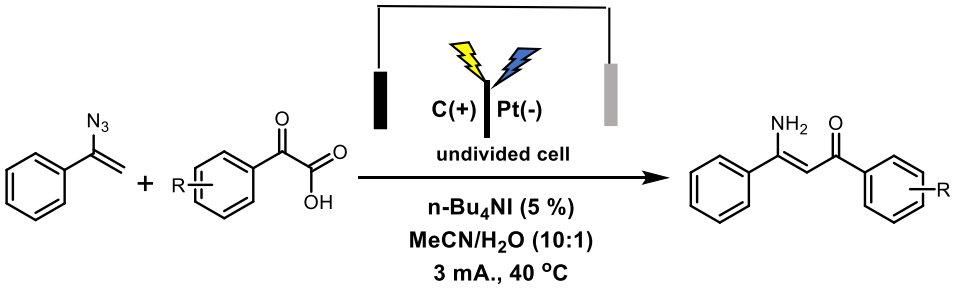
Niphakis and coworkers, reported a total synthesis of natural products (+)-ipalbidine and (+)-antofine [35]. (+)-Ipalbidine contains a wide-range of biological activity, acting as an oxygen-free radical scavenger and as a nonaddictive analgesic. (+)-Antofine exhibits antiproliferative and antiviral activity (Scheme 7). In this study, to generate the cyclic enaminone **22**, initially the authors prepared a diazoketone **19** from Boc-ʟ-proline **18**. Upon the treatment of the diazoketone with a catalytic amount of silver trifluoroacetate (CF_3CO_2Ag) in the presence of N, O-dimethylhydroxylamine would generate Weinreb amide **20**. The addition of ethylmagnesium bromide produced ynone **21**. In the next step, the boc-protecting group was removed under acidic conditions with the use of formic acid. Treatment of the yone with sodium iodide, generated vinyl iodide intermediate **22**, which underwent a 6-endo-trig cyclization. The resulting 6-endo-trig cyclization, afforded the indolizidine intermediate **23** (a bicyclic enaminone) in an excellent yield (96%) as seen in Scheme 6.

2.2. Novel synthetic methodology for the synthesis of enaminones

Novel synthetic methodologies have emerged in the past decades for the synthesis of enaminones. Recent studies have explored new synthetic strategies such as electrochemical organic



Scheme 6. *Niphakis* et al., *synthesis of* the indolizidine *enaminone* intermediate.



Scheme 8. Electrochemical strategy for the synthesis of acyclic diphenyl *enaminones*.

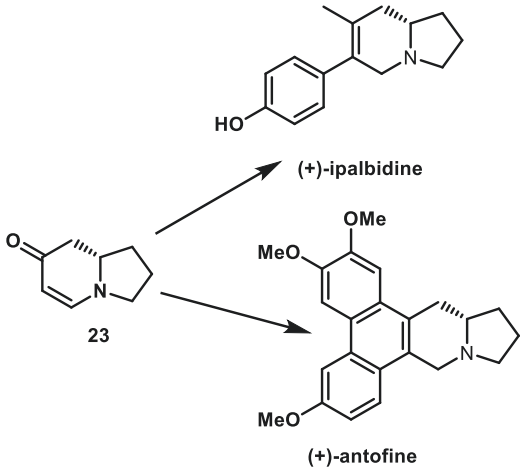
synthesis, the use of microwave irradiation and regio- and stereoselective reactions. Some labs have employed green chemistry, with the incorporation of one pot syntheses and green reagents to reduce the use of harsh reaction conditions and to eliminate hazardous chemical waste. Herein, we have described several reports of novel synthetic methodology employed to develop enaminone derivatives.

i. Green Chemistry

Electrochemical organic synthesis has become a tool to synthesize novel compounds via green chemistry. The process of an electrochemical reaction begins with the connection of a power source to a reaction mixture via an electrode (an anode or a cathode). Electrons are transferred from the electrode to the substrate molecule, to produce a reactive intermediate [36]. Given electricity is being utilized to carry out this transformation, a full circuit is required for the reaction to proceed to completion. Therefore, an additional electrode is utilized to combine the reaction with the opposite end of the cell where the additional power source is located. Depending on the type of chemical reaction that occurs, an anodic oxidation is balanced with a reduction reaction in the cathode of the cell, with a transfer of electrons from the substrate to reduce species present within the rection chamber such as, protons and solvent molecules. A cathodic reduction can be balanced in a similar manner with an anodic oxidation. Kong et al. employed the application of electrochemical organic synthesis for the decarboxylative acylation of vinyl azides with α-keto acid, having tertbutylammonium iodide (n-Bu_4NI) serve in a dual role as a redox catalyst and an electrolyte, to afford enaminones shown in Scheme 8 [37].

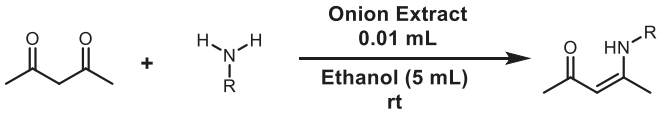
After reaction optimization, the authors developed a substrate scope for the acylation of vinyl azides. Different vinyl azides and α-oxocarboxylic acids bearing electron donating or electron withdrawing groups were investigated. The authors observed that both the azides and α-oxocarboxylic acids with substitution at the ortho, meta and para positions on the aromatic ring produced the enaminone derivatives in good yields. Both electron withdrawing and electron donating groups were tolerated, as they produced similar results (65–80% yield). The authors reported that a 1-napthyl azide derivative would produce the highest yield at 89%.

Prabakaran and colleagues would develop their own green chemistry protocol using onion extract to catalyze the amination of 1,3-dicarbonyl compounds to develop the acyclic enaminones [38]. The synthetic route generated the enamino ester derivatives and β-enaminones in good to excellent yields. Optimization of reaction conditions showed that the reaction proceeded at room temperature in ethanol for 2 h to produce the β-enaminones in excellent yields (97–98% isolated yield) as shown in Scheme 8 [38].

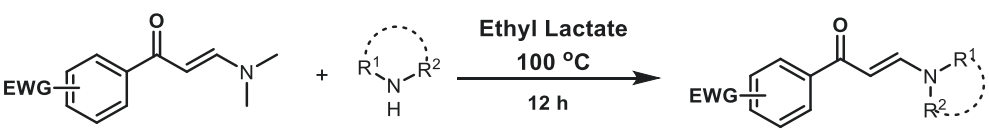


Scheme 7. Niphakis et. al. indolizidine 23 conversion to the indolizidine-derived natural products.

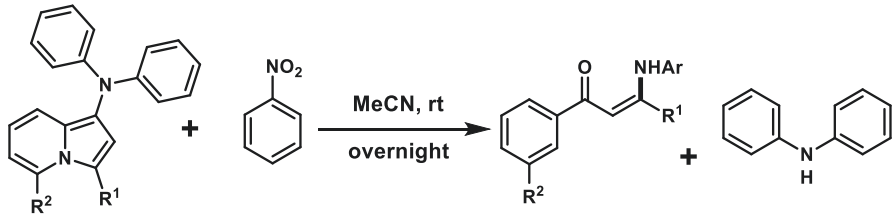
The authors report their proposed mechanism for the onion extract's effectiveness as a catalyst for the synthesis of β-enaminones. According to previous studies conducted, once the onion is sliced, isoalliin is transformed into reactive intermediate 1-propanethial S-oxide, the organic compound responsible for tear production upon cutting onions. Sulfuric acid, hydrogen sulfide and



Scheme 9. General synthesis of acyclic enaminones via onion *extract*.



Scheme 10. Synthesis of various tertiary enaminones via *transamination*.



Scheme 11. *González-Soria* et al. *substrate selective synthesis of enaminones.*

propanethial are generated once water is added to 1-propanethial S-oxide [22]. The carbonyls of the acetyl acetone are activated by the acids produced from the 1-propanethial S-oxide/water mixture. Upon activation, the amine will act as a nucleophile, which allows for the addition of the amine to one of the carbonyl carbons, to produce β-enaminones in good to excellent yields (up to 95%) [38].

Gao et al. reported a green protocol for the synthesis of N, N-disubstituted enaminones via a transamination reaction [39]. The authors stated the amino group of the enaminone system is involved in the construction of the final product, as an alternative to being eliminated during the reaction [39]. This also gives rise to molecular diversity of the enaminones synthesized (see Scheme 9). The authors investigated the synthesis of tertiary enaminones with diversity in the amino group by functionalizing the substituent. This synthetic strategy was achieved by employing a bio-based green solvent, ethyl lactate as the medium for the transamination as shown in Scheme 10 [39].

Upon optimization of reaction conditions, it was shown that allowing the reaction to proceed at 100 °C in ethyl lactate without the use of a catalyst, would yield the best results (63–87% yield respectively) [39]. The N, N-disubstituted amines utilized in the reaction were generally tolerable of the substituents attached to the aromatic ring neighboring the carbonyl of the enaminone system. However, the authors observed that the electron-withdrawing groups, nitro and cyano, would yield the desired enaminone, but in significantly low yields.

ii. Regioselective Reactions of Enaminones

González-Soria et al., reported a substrate-controlled synthesis of pyrroles and enaminones from indolizines and nitroso compounds [40]. The authors state that the reaction is driven by the nature of the substituents attached to position 3 of the indolizine ring. Being aromatic or aliphatic in nature, will determine if enaminones or pyrroles are afforded from the synthesis. To the author's excitement, the β-enaminones and pyrroles are produced under mild and catalyst free conditions [40]. The model substrates used during the reaction optimization were indolizine and nitrobenzene as shown in Scheme 11. For improved results, the reaction was carried out in acetonitrile to afford the enaminone derivatives in moderate to good yields (40–88%) [40]. A wide range of substituted indolizines were utilized in the reaction. All substituent types were tolerated; electron donating, electron withdrawing and electron neutral. Once the desired β-enaminone was generated, González-Soria and colleagues used the substrate as a synthetic intermediate that would undergo conversion into pyridinyl-containing isoxazole, pyrazoles, and indole compounds. Each heterocyclic derivative generated from the enaminone, was synthesized in moderate to good yields (56%–85%) [40].

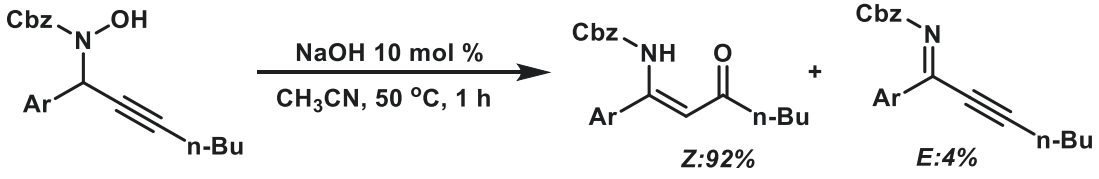
Gayon et al. reported a catalytic isomerization of propargylic hydroxyl amines to (Z)-β-enaminones, for the synthesis of pyrimidines [41]. Initially, the authors investigated strategy aimed to developing trisubstituted isoxazoles. During the study, it was observed that a propargylic hydroxyl amine rearranged to produce a Cbz-protected enaminone as a single Z-diastereomer. Scheme 12.

From this observation, the authors optimized reaction conditions to generate a series of (Z)-β-enaminones. Upon reaction optimization, it was shown that the reaction proceeded efficiently in acetonitrile, utilizing NaOH as the base for the reaction (10 mol %), at 50 °C for 1 h. The reaction generated the (Z)-β-enaminones in an 86% yield. To determine the limitations and scope of the isomerization Gayon and colleagues, investigated substituent effects at the propargylic position. Aryl substituents bearing electron-withdrawing and electron-donating groups at the para or meta position were both tolerated as the (Z)-β-enaminone derivatives were obtained in moderate to excellent yields (29–90% respectively). The study revealed the limitations of the isomerization, with sterically hindered aryl substituents having a negative impact on the percent yield. It was suggested that sterically hindered functional groups near the propargylic position, proved unfavorable for the overall yield of the (Z)-β-enaminones developed.

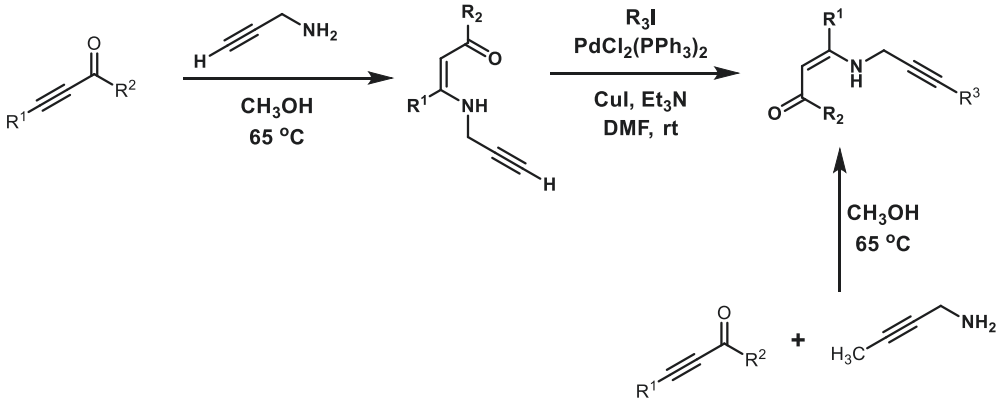
b. Enaminones As Synthetic Intermediates

The commercial production of complex organic molecules is often one of the biggest hurdles that must be overcome when bringing a new drug to market. The production of drug molecules is often an expensive endeavor and the identification of affordable intermediates that can simplify the process is a vital pursuit. To this end, enaminones are ideal synthetic building blocks that can be employed to allow for high potential savings. Enaminones are utilized in organic interactions because of the presence of delocalized nucleophilicity with the delocalized electrophilicity of enones.3.

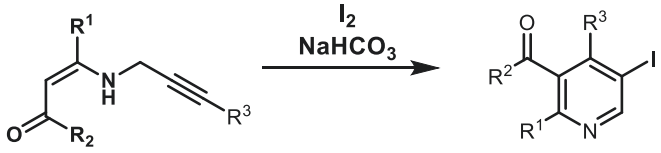
Enaminones intermediates are used for the development of pharmacological relevant heterocycles. Iodopyridines can be used as building blocks to undergo conversion into such heterocycles



Scheme 12. *Gayon* et al. *catalytic isomerization to synthesize (Z)-β-enaminones.*



Scheme 13. *Synthesis of N-propargylic β-enaminones.*



Scheme 14. *Synthetic strategy for the synthesis of iodopyridines from N-propargylic β-enaminones.*

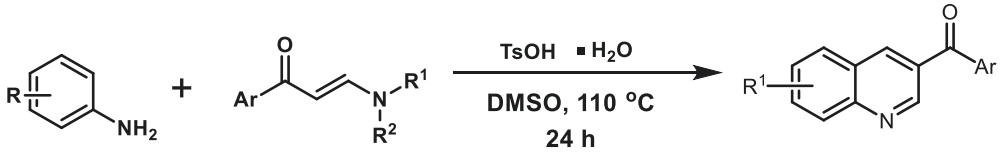
that are used in drug design and development. Karabiyikoglu and colleagues reported a facile synthetic conversion of N-propargylic β-enaminones into iodo substituted pyridines in moderate to good yields.42 The author's state there were no prior reports of the direct synthesis of monocyclic iodopyridines from N-propargylic β-enaminones.42 In this study, the authors employed an electrophilic cyclization and treated N-propargylic β-enaminones with molecular iodine in the presence of sodium bicarbonate to yield iodopyridines. Scheme 13 shows the synthetic route to generate N-propargylic β-enaminones.

The initial synthetic step was the preparation of N-propargylic β-enaminones from α, β-alkynic ketones. A conjugated addition of propargylamine to an α, β-alkynic ketone via a reflux in methanol (MeOH) was used to produce the enaminone derivatives. The β-enaminones would undergo a Sonogashira cross-coupling with aryl iodides to functionalize the enaminones. When the β-enaminones were reacted with aryl iodides under palladium-catalyzed conditions in the presence of copper iodide (CuI) and triethylamine (Et_3N) at room temperature, the result was generation of arylated β-enaminones. The N-propargylic β-enaminones would serve as an intermediate for the synthesis of iodopyridines as shown in Scheme 14.

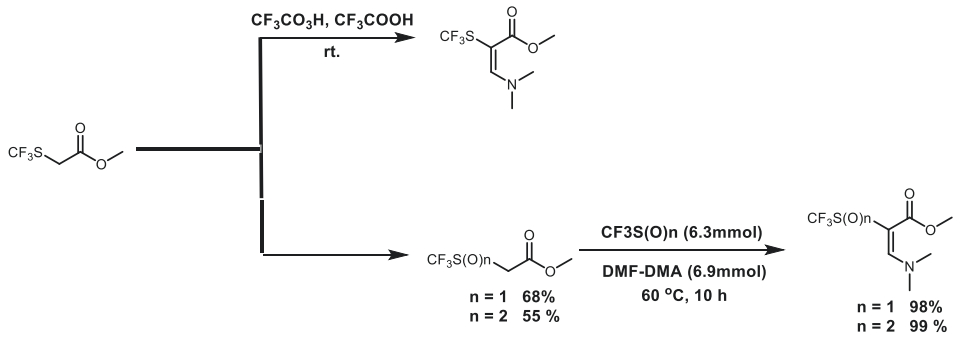
From the optimized reaction conditions, the authors showed that refluxing the β-enaminone with molecular iodine in the presence of sodium bicarbonate afforded the iodopyridines in good yields (up to 80%) [42].

Enaminones have been used extensively as intermediates for the synthesis of heterocycles. Jiang et al. reported a para-toluenesulfonic acid catalyzed, metal free synthesis of 3-keto quinolines from enaminones, DMSO and anilines [43]. Scheme 15 shows the synthesis employed to produce the desired bicyclic compound..

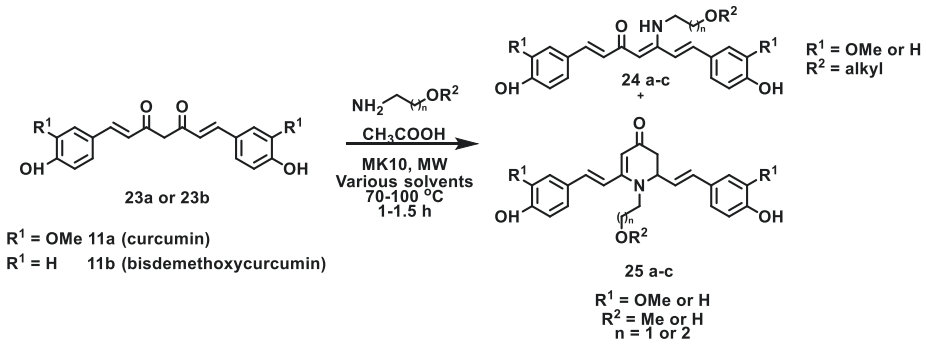
With the optimized reaction conditions, a library of enaminones with electron withdrawing or electron donating groups were



Scheme 15. *Jiang* et al.*, synthesis of 3-keto quinolines from enaminones.*



Scheme 16. *Synthesis of enaminones as intermediates for cyclization of urea and thiourea.*



Scheme 17. *Synthesis of curcumine β-enaminones.*

utilized to produce 3-keto quinolines in moderate to good yields (49%–72%). Results of the study showed that enaminone derivatives that contained iodine or a free hydroxyl functional group were key handles that would undergo further transformation to yield the desired product [43]. This methodology was expanded to other heteroaryl, alkyl and N, N-disubstituted enaminones. Heteroaryl enaminones, pyridine and thiophene, produced the desired 3-keto quinoline in moderate yields [43].

Sokolenko and coworkers developed synthetic methodology utilizing enaminones as intermediates for the synthesis of heterocyclic compounds. The authors strategy involved insertion of a trifluoromethylsulfenyl-, sulfinyl- or sulfonyl functional groups at the α-position of the enaminone, as shown in Scheme 16 [44].

Sokolenko and co-workers reported the enaminones utilized in this study, were efficient intermediates that could undergo synthesis with compounds such as aromatic and aliphatic amidines, urea and thiourea to yield a diverse class of heterocyclic derivatives.. [44]. Cyclization of the enaminones with urea and thiourea, would afford uracil and 2-thiouracil, organic compounds with biological activity [44].

i. Problematic Substrates in the Development of Enaminones

Incorporation of enaminones into natural products have been reported. Curcumin is the active organic compound found in turmeric and is used in herbal medicines. Curcumin is reported to have an extensive bio-active profile having anti-microbial, anti-inflammatory, anti-Alzheimer, and anti-cancer activity. Although curcumin is deemed to be biological active, it presents challenges with limited bioavailability *in vivo* and *in vitro,* low solubility, rapid cell metabolism and rapid clearance from the body.

Theppawong and co-workers, reported structural modifications of curcumin to improve its water solubility, thereby improving the bioavailability of curcumin (Scheme 17) [45]. The authors employed synthetic methodology to modify (bisdemethoxy) curcumin at its β-diketone moiety, by incorporation of β-enaminones into the curcumin molecule. In this study, a series of curcumine β-enaminones that contained a polar side chain to address solubility issues were developed.

This synthetic method was achieved utilizing hydroxy or methoxy alkylamines, as replacements for the diketone moiety of curcumin or bisdemethoxy curcumin. Initially, the authors investigated a reaction of curcumin with 5–10 equivalents of ethanolamine or propanolamine, in the presence of 2.4 equivalents of acetic acid and 1.6 equivalents montmorillonite K10 clay (MK10 clay) as a catalyst for the reaction. The synthesis was carried out in 2-methyl-THF and under microwave irradiation conditions at 70–80 °C for 1–1.5 h. It was stated, the reaction of ethanolamine with curcumin did not proceed with ease, thus investigation of an alternative polar solvent was conducted. Upon optimization of the reaction conditions, ethanol was chosen as the solvent to carry out the synthesis of the curcumine β-enaminones. Although the reaction produced the desired compound, the synthetic methodology presented challenges as the product was generated in low yields. However, the major problem in the conversion of the starting reagents into the final product was establishing optimal reaction conditions to generate the β-enaminone derivatives. The work-up step to purify the final product proved to be problematic also, as several β-enaminone derivatives underwent numerous purification techniques to isolate the pure product. The highest yield obtained for the N-methoxyalkyl β-enaminone analogs was 40% using 10 equivalents of 2-methoxy ethylamine in ethanol at 100 °C for 1 h under microwave irradiation conditions. Perhaps an alternative starting reagent to undergo reactivity with curcumin derivatives

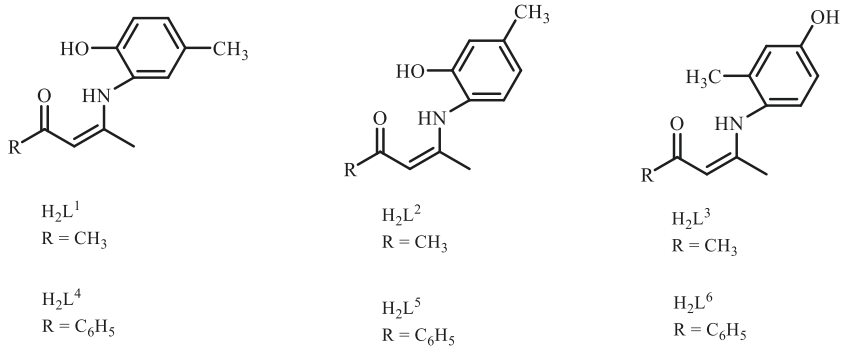


Fig. 5. Antibacterial aminophenol enaminones.

could be explored [45].

c. Structure Activity Relationships (SAR) of Enaminones

In medicinal chemistry, the biological activity of a potential drug molecule changes with modifications on the pharmacophoric elements. The versatility of enaminones in drug development is extensive. In this section we discuss enaminone SAR as it relates recent developments in different therapeutic areas. The goal of this section is to highlight the importance of how the structure of the enaminone moiety relates to activity of various analogs in drug development.

i. Antibacterial

Enaminones and their analogs have been investigated for antibacterial activity. M. Cindric et al. explored acyclic enaminones linked to methyl substituted aminophenols and their antibacterial and cytotoxicity activities [8]. By utilizing simple structural rearrangement of hydroxyl and methyl groups, they were able to design and synthesize six novel enaminone analogs and evaluate their antibacterial activities. All six enaminones H_2L [1] – H_2L [6] (Fig. 5) were tested against THP-1 and HepG2 cells for cytotoxicity and against four common bacterial strains (*Staphylococcus aureus, Enterococcus faecalis, Escherichia coli and Moraxella catarrhalis*) for antibacterial activity. The cytotoxicity data for all six enaminones showed IC_{50} values greater than 100 μM in both cells showing that the enaminones do not pose harm to the cells. The antibacterial activity is not as unanimous as the cytotoxicity activity as variations in the structure affected activity in the different bacterial strains. *S. aureus, E. faecalis and E. coli* all possessed minimum inhibitory concentration (MIC) values of greater than 128 μg/mL when compared with *M. catarrhalis* which reported mild antibacterial activities with MIC values ranging from 16 to 64 μg/mL.

An analysis of the antibacterial activities of H_2L [1], H_2L [4] and H_2L [5] vs. H_2L [2], H_2L [3] and H_2L [6] revealed that having a hydroxyl group in *para* position relative to the methyl group on the aromatic ring improves antibacterial activity. Further analysis of the substitution on the enaminone system also showed that a phenyl group rather than a small methyl group is also important for fitting into the binding pocket via proposed hydrogen bonding as seen in H_2L [4] with the lowest MIC value of 16 μg/mL in *M. catarrhalis*. This discovery also confirms that a hydroxyl group needs to be in the 2-position relative to the enaminone, as lower antibacterial activity is observed in compounds H_2L [3] and H_2L [6] which possess a hydroxyl group in the 4-position to the enaminone. This study concludes that modification of the enaminone structure with the properly substituted aromatic groups could enhance the antibacterial activities of this class of enaminones [8].

ii. Anti-inflammatory and Analgesic

Studies have shown that enaminones interact with a variety of drug targets. R. Kumar et al. used a target-based drug design strategy to investigate the cyclooxygenase (COX-1 and COX-2) inhibitory activities of novel cyclic enaminone analogs. Drugs that act on this target by inhibiting its effect have been shown to possess anti-inflammatory and analgesic properties such as celecoxib and rofecoxib [46]. With their drug design approach in place, this research group followed the basic template that shows that active COX-2 inhibitors possess α, β-unsaturated carbonyl moieties which is typically one of the starting reagents in the synthesis of enaminones [47,48]. The enaminone system also retains the enone moiety which as reported by the group is essential for binding in the active site of the COX enzyme. An analysis of the binding interactions of some of the designed analogs (Fig. 6) docked inside the COX-2 active site of the crystal structure showed strong hydrogen bonding interactions between the carbonyl oxygen of the enaminone and the hydroxyl groups of Ser 530 and Tyr 385.

For this study, twenty-one enaminone analogs were synthesized and evaluated for inhibitory activity in both COX-1 and COX-2 with 17 compounds showing preference for COX-2 inhibition with compound 7d (Fig. 7) being the most effective (enzyme inhibitory potency: COX-1 = 12.89%; COX-2 = 88.63%). The values interpret higher percent inhibition to represent more active compounds. Further lead optimization of **7d** was carried out to determine ideal structural manipulations for optimal activity. Due to the limited areas of modification on the lead analog **7d**, the group decided that the amine group seems to be the only point of optimization as changes to other portions of **7d**, showed a decrease in COX-2 inhibitory potency. A simple modification of the tert-butoxy and acetyl group resulted in compounds **8** and **9** respectively (Fig. 7).

Both compounds underwent bioevaluation for COX-1 and COX-2

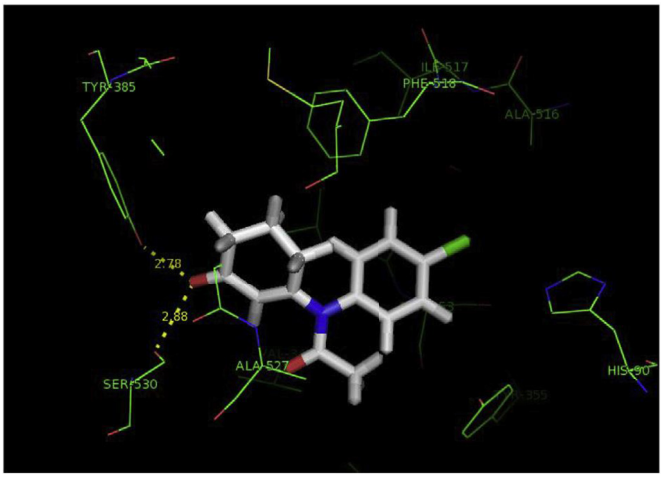


Fig. 6. Docking interaction of compound 9 inside the active site of COX-2 (PDB: 6COX).

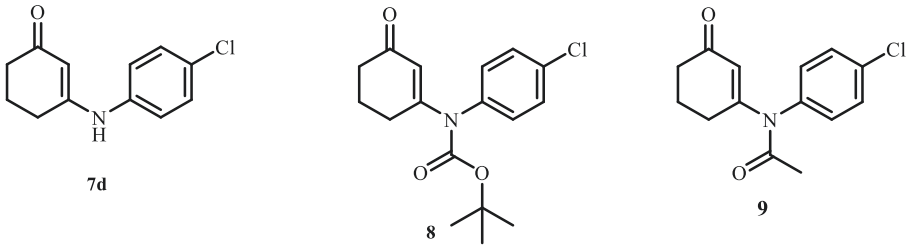


Fig. 7. Enaminones evaluated for COX inhibition.

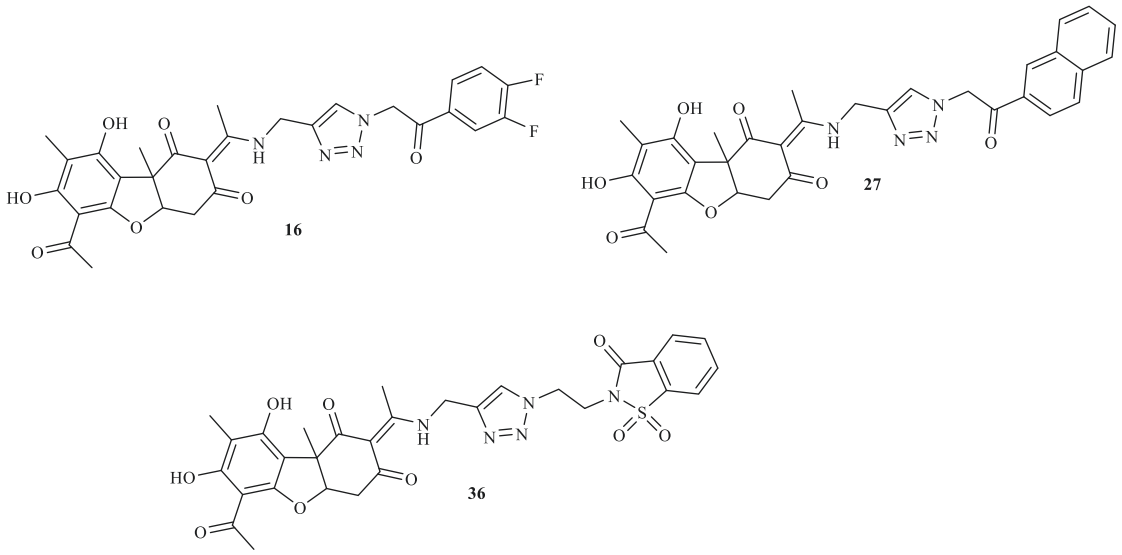


Fig. 8. Enaminone triazoles with antitubercular activity.

inhibition. Compared to the parent compound **7d**, compound **8** containing the tert-butoxy group showed a decrease in COX-2 inhibition (88.63–73.46%), while COX-1 inhibition was moderate (12.89%–30.50%). The results of COX-1 inhibition could be ascribed to the bulky nature of the substituent thereby, decreasing its interaction with the target's active site. Compound 9 on the other hand emerged as the most potent and selective COX-2 inhibitor (COX-2: 96.94%; COX-1: 10.80%). This inhibition data is almost comparable to celecoxib, which shows a 100% COX-2 inhibition.

The analgesic properties of the lead compounds were also evaluated with compound **9** showing the most efficacy in comparison celecoxib at comparable doses. This activity is a valid response due to the pre-determined anti-inflammatory activities on COX-2 inhibition since response to pain stimulus is induced by a cascade of second messengers found in the inflammatory pathway. The conclusion from this study was the discovery of a new potent class of COX-2 inhibitors containing the enaminone scaffold which will pave the way for more research in the future [9].

iii. Antitubercular

Bangalore et al. described the conjugation of usnic acid enaminones conjugated to 1,2,3-triazoles containing heterocycles [10]. The research was focused on optimizing the antitubercular properties of usnic acid which is a secondary metabolite of lichens, a natural product. The other half of the hybrid molecule is the 1,2,3-triazole scaffold which is one of the most utilized scaffolds in medicinal chemistry. The group synthesized a total of 35 (10–44) novel usnic-enaminone analogs for bioevaluation of both antitubercular and antibacterial activities. An overview of the assay results shows that most of the novel usnic-enaminone triazoles are active above a concentration of 10 μM. Among these derivatives, compound **36** (Fig. 8), with an O-sulfobenzimidinyl group (saccharin), was found to be active on *M. tuberculosis* (Mtb) H37Rv with an MIC value of 2.5 μM, slightly better than Isoniazid with an MIC value of 2.9 μM.

Even with the high potency of compound **36** in Mtb H37Rv, it lacked activity in the antibacterial activity studies. Compounds **16** (3,4-difluorophenacyl) and **27** (2-acylnaphthalenyl) (Fig. 8) also proved to be potent, with MIC values of 5.4 and 5.3 μM, respectively which is still comparable to marketed drug (ethambutol with an

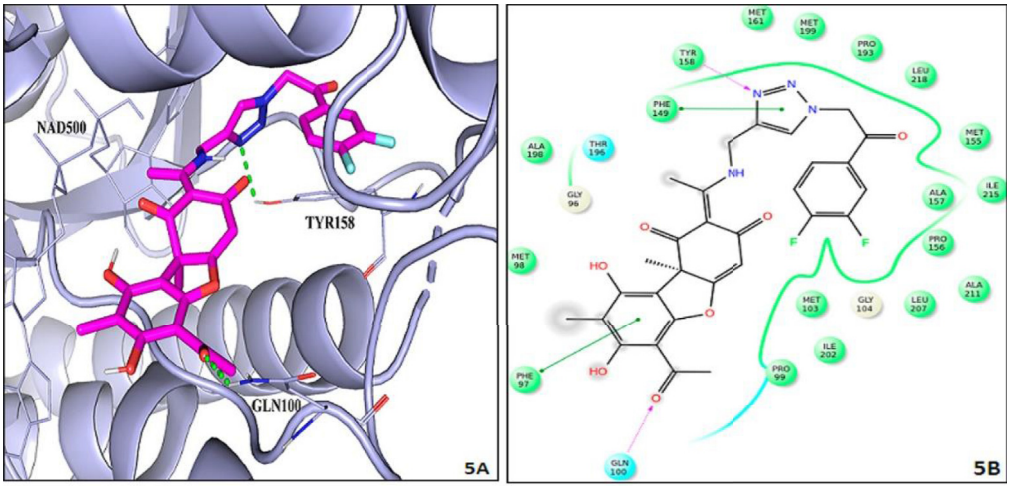


Fig. 9. 3D, and 2D representations for compound 16.

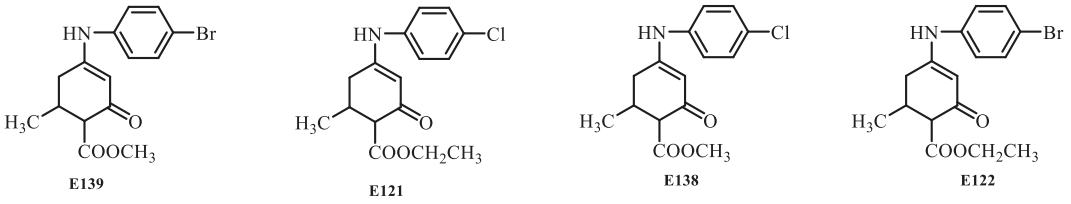


Fig. 10. Anilino enaminone esters evaluated for antinociceptive and analgesic activity.

MIC of 7.6 μM).

In addition, these two compounds also possessed antibacterial activity. SAR assessment of the analogs and their biological activities shows us that the presence of the fluorine atoms in **16** might be a contributing factor for the increased potency of the molecule when compared with other halogens, such as chlorine and bromine which have higher MIC values. Naphthalene-substituted triazole **27** displayed similar activity to that of **16**, indicating that the meta- and para-positions of the fused ring should be occupied for optimal antitubercular activity. To investigate the potential mechanism of action, docking studies were carried out in the *Mtb* enzyme enoyl reductase (Fig. 9). The results revealed that compound **16** (3,4-difluorophenacyl) showed hydrogen bonding with TYR158 and GLN100 and π−π stacking with PHE97 and PHE149. This interaction patterns were also seen with **17** and **36**. These results made the group to propose that the antitubercular property of the active compounds may be via inhibition of InhA enzyme. The conclusion of the study was that compounds **16** and **27** look promising for future drug discovery and development and could be further expanded upon for optimal activities [10].

iv. Antinociceptive and Analgesic

Enaminones have been shown to produce their anticonvulsant activity by the enhancement of extracellular GABA levels in the brain. Enaminones have also shown the same activity as antinociceptive, by acting indirectly to inhibit GABA-T or the reuptake of GABA thereby enhancing extracellular GABA levels. Masocha et al. reported the evaluation of previously synthesized enaminone derivative **E139,** among other analogs **(Fig. 10)**, that were shown to have anticonvulsant activity [49] in the evaluation of antinociceptive activities using the formalin and hot plate tests in mice [1]. Out of the five anilino enaminones evaluated only **E139** and **E138** had significant antinociceptive activity in both phase 1 and 2 of the formalin test. Compound **E139** was also the only active aniline enaminone with activity in the hot plate test. The activity of the compounds are due to the structural similarity of the analogs except for the presence of a 4-chloro group as opposed to a 4-bromo group in **E139**.

Another difference noted by the authors is the ClogP values. The authors mentioned that it might not have significant effect but also deduced that an optimal ClogP value of about 4.00 is responsible for antinociceptive effects. This is in comparison of ClogP values of compounds **E121** and **E138** which only differs in the ester substituent on the cyclic enaminone ring showing 4.44 and 3.91, respectively. **E138,** with a ClogP value closer to 4.00 seems to have activity in both phases of the formalin test while **E121** has activity only in phase 1. The authors concluded that since the antinociceptive activity of **E139** in the hot plate test was blocked by a $GABA_A$ and $GABA_B$ receptor antagonists, then the antinociceptive effects of **E139** are partly due to the activation of both GABA receptors, possibly by raising the levels of endogenous GABA. Thus, this anilino enaminone may serve as lead compound for further research and development into novel analgesic agents [1].

v. Antitumor and Anticancer

Enaminones are also used as hybrid linkers for molecular hybridization in drug design. Molecular hybridization is a technique used in medicinal chemistry to connect important pharmacophoric elements, to form a new analog with increased efficacy and a better side effect profile [50]. M.M Ghorab et al. utilized this methodology to develop a new class of potential anticancer agents that act on the vascular endothelial growth factor receptor 2 (VEGFR2) [12]. This design was based on utilizing the pharmacophore of two common VEGFR2 inhibitors; Sorafenib and Sunitinib to create a novel class of analogs, that were tested for both antitumor and anticancer activities. The acyclic enaminone system contained some of the important elements required for binding to the VEGFR2 receptor, such as a hydrogen bond donor-acceptor and was found to be the best candidate to act as a linker. The enaminone system was conjugated in two orientations to the terminal aromatic ring of the

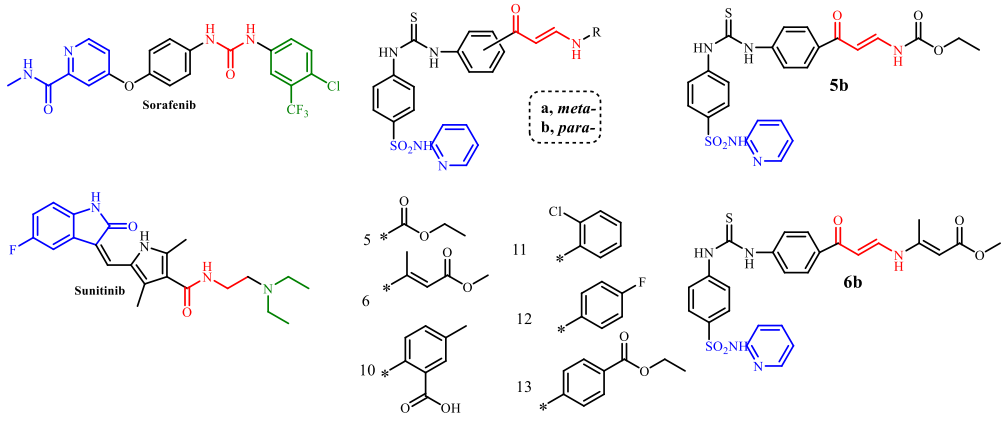


Fig. 11. Acyclic enaminone substituted VEGFR2 candidates 5b and 6b

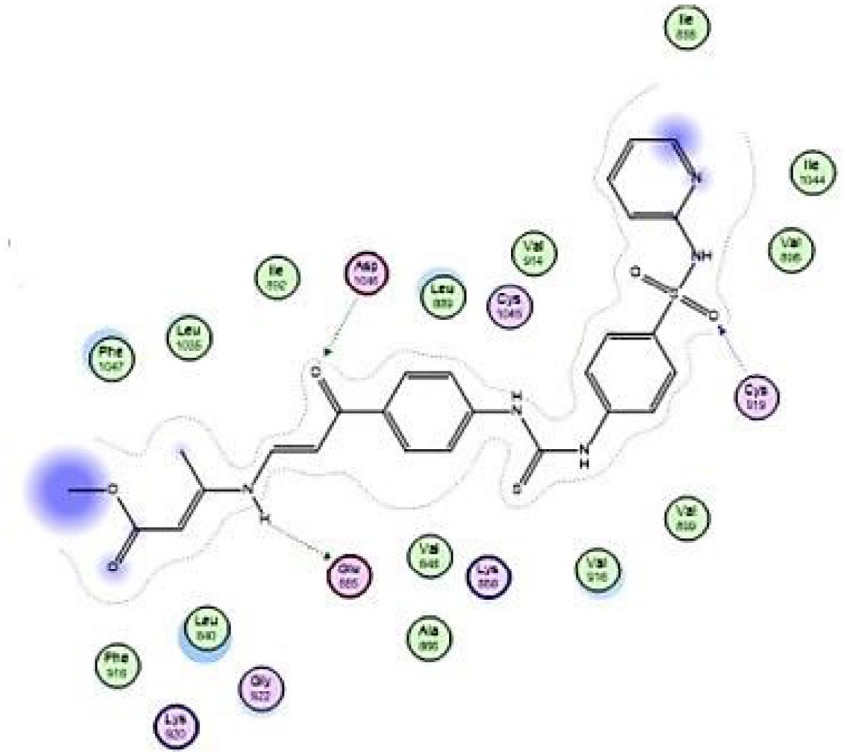


Fig. 12. 2D interaction map of compound 6b in VEGFR-2 active site.

sulfapyridine ring consisting of *meta* and *para* linkages to study SAR patterns. Ghorab and colleagues, synthesized a total of 24 analogs with an equal amount of *meta* and *para* substituted enaminone linkers.

The analogs were screened for biological activity and six of the twenty-four compounds (Fig. 11), were identified to be the most potent. It is interesting to note that all six analogs were the *para* substituted enaminones. SAR analysis of the active analogs showed that compounds **5b** and **6b** possessing a linear ester terminal substituent had greater activity in the initial *in-vitro* anticancer screening with IC_{50} values of **5b** (IC_{50} = 0.12 μM) and **6b** (IC_{50} = 0.29 μM) compared to Sorafenib (IC_{50} = 1.06 μM). This could be ascribed to the presence of more hydrogen bond donor-acceptors, which was also enhanced by the presence of the enaminone system.

For further confirmation on the biological activity of the analogs, the enzymatic inhibition of the most potent of the six lead compounds, were studied *in vitro* for their inhibitory action against the VEGFR-2 enzyme, using Sorafenib as a reference drug. As with the initial screening for anticancer activity, **5b** and **6b** seemed to be more active than their aromatic substituted counterparts, with the ethyl ester derivative **(5b)** having the best activity in additional advanced tests. The six analogs were docked in the VEGFR-2 active site to understand their binding mode. The docking studies showed how the linear ester substituents were able to interact with essential amino acid residues that are necessary for activity. An analysis of the docking poses of compounds **5b, 6b, 10b, 11b** and **13b** revealed that the pyridinyl sulfonamide moiety is embedded in the ATP binding site, while the enaminone linker acts as an essential hydrogen bond donor and acceptor for binding with Glu885 and Asp1046 (Fig. 12); which are the two amino acid residues the urea linker in sorafenib binds to. The results from this study revealed the significance of the enaminone pharmacophore in drug development [12].

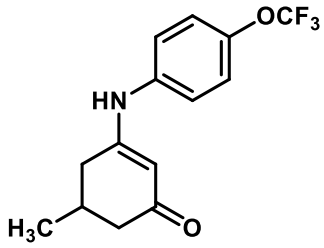


Fig. 13. Anticonvulsant KRS−5-Me−4−OCF3.

vi. Anticonvulsant

Our research lab is focused on elucidating the anticonvulsant properties of fluorinated N-benzamide cyclic enaminones. In our previous studies, we found the enaminone system to be an excellent pharmacophore for anticonvulsant active analogs [16,25,26]. Previous work by Wang et al. showed the positive neuronal activity of *para* and *meta*-substituted anticonvulsant aniline enaminone derivatives on mitral cells in an olfactory bulb brain slice preparation using whole-cell patch-clamp recordings [51]. The lead compound from this study was KRS−5-Me−4−OCF_3 (Fig. 13).

Using lead-based drug design methods, we hypothesized that optimizing the KRS−5-Me−4−OCF_3 analog with an amide bridge functionality between the cyclic enaminone and the aromatic ring, while maintaining the fluorinated groups on the benzene ring, will allow the analogs to retain anticonvulsant activity, with better efficacy and little to no neurotoxicity.

SAR studies led us to the design and synthesis of 14 novel mono and disubstituted fluorinated N-benzamide enaminones (**Fig. 14**).

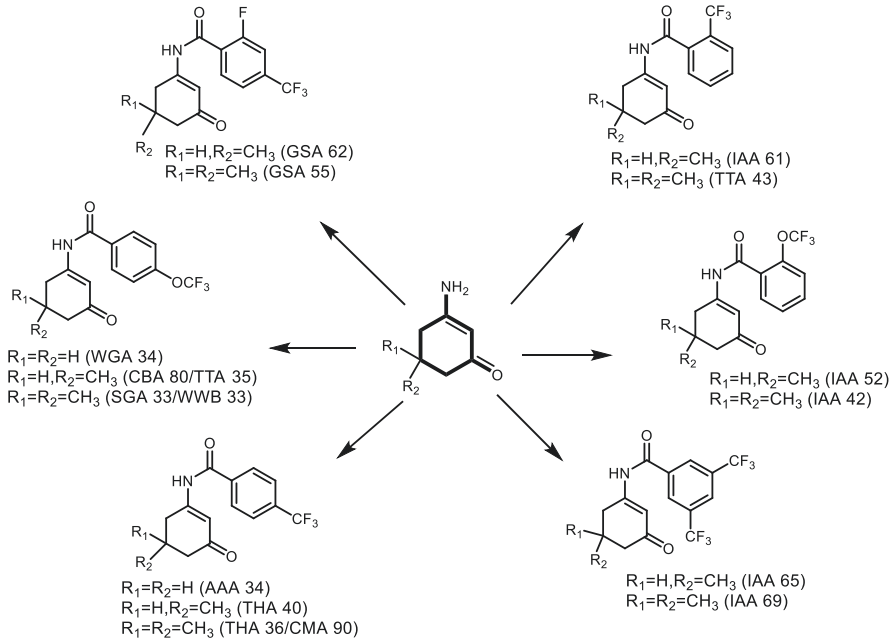


Fig. 14. Cyclic enaminone benzamides evaluated for anticonvulsant activity.

Test analogs (**GSA 62, TTA 35, SGA 33, WWB 67, and THA 36**) showed minimal to no activity in the Maximal Electroshock (MES) test, and moderate to excellent seizure protection in the 'psychomotor' 6-Hz 44 mA-test with no neurotoxicity. The 'psychomotor' 6 Hz anticonvulsant acute animal model of drug resistant epilepsy. Previously, there had been no reports of N-benzamide enaminones having activity in the 6-Hz 44 mA acute seizure rodent model. Hence, our group was the first to report this activity. *In vivo* data for the mono- and di-substituted N-benzamide analogs that were previously synthesized in our lab showed protection in the MES and 6-Hz 44 mA seizure rodent models with no neurotoxicity. Interestingly, we identified three lead analogs (**WWB 67, SGA 33, and GSA 62**) that showed protection in the rodent drug-resistant model, which is a new result that potentially has clinical implications. We were able to conclude from the electrophysiology studies that one probable mode of action for the lead analogs is the inhibition of the voltage-gated sodium channel. Other seizure-related molecular targets require further studies. The next steps are (1) to further explore the inhibitory sodium channel effects of the anticonvulsant analogs by conducting concentration dependent studies *in vitro*, and (2) to determine the inhibitory mechanism of these compounds on voltage-gated sodium channels, and whether they may target different subunits of the channels selectively [11].

3. Conclusion

The unique properties of the enaminone system makes it an exceptional versatile scaffold that can serve as an essential pharmacophoric element for several compounds. Exploring this quality has proven to be a vital contributor to diverse chemical methods and the development of new potential therapeutics. The purpose of this review article was to shed light on the recent advances of the chemistry and utilization of enaminones.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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