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A Review on 4(3H)-quinazolinone synthesis

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ABSTRACT: Quinazoline and 4(3H)-quinazolinone is a commonly seen a fused nitrogen containing heterocyclic scaffold with broad biological applications including anticonvulsant, fungicidal, antimicrobial, antimalarial, antitumor, and anti-inflammatory. This review article will briefly outline the different paths and strategies like Niementowski reaction, using benzoxazinone intermediate,oxidative heterocyclization by conventional way or microwave irradiation for the synthesis of valuable 4(3H)-quinazolinone with wide biological applications together with antimicrobial, fungicidal, anticonvulsant, antitumor, antimalarial, and anti-inflammatory. Utilization of quinazolinone core for the design and synthesis of new agents raised momentum. The current advance in the synthesis of 4(3H)-quinazolinone analogues, which is an honoured scaffold in the medicinal community for their therapeutic potential in handling a number of illnesses.

KEYWORDS: 4(3H)-quinazolinone, anticonvulsant, fungicidal, antimicrobial, antimalarial, antitumor, anti-inflammatory.

I. INTRODUCTION:

Heterocyclic compounds, and in particular nitrogen containing heterocycles, found a remarkably diverse, and a correspondingly important class of molecules. The pool of heterocyclic compounds offers different chemical space for exploration of medicinal potential.Quinazolinone are an honoured class of nitrogen heterocyclic skeletons that have been found to show a wide-ranging spectrum of pharmacological activities, including anti-inflammatory, antitubercular, and antiviral activities.[1]

1. Quinazolinone:

4(3H)-Quinazolinone and its derivatives constitute an important class of fused heterocycles that are found in more than 100 naturally occurring alkaloids[2]. The first 4(3H)-quinazolinone compound 1 (fig.1) was obtained as early as 1869 from anthranilic acid and cyanogen[3]. Intense search for biologically active substrate in this series was stimulated in the early 1950s with the elucidation of an alkaloid, febrifugine 2 (fig.1), which is an ingredient of a traditional Chinese herbal remedy, effective against malaria[4].Themethaqualone 3 (fig.1) was synthesized and it is the most well-known 4(3H)-quinazolinone based drug and has sedative and muscle relaxant effects[5].

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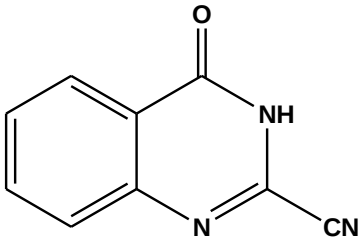
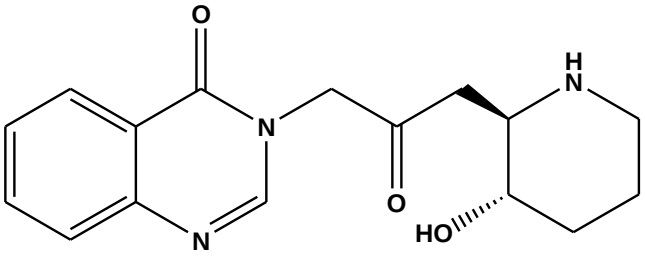
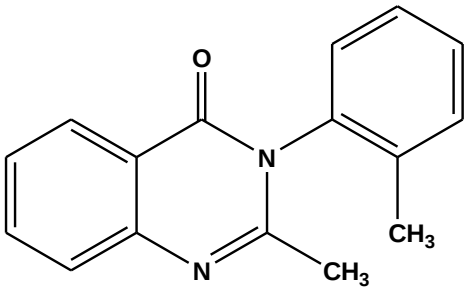


2-Cynoquinazolinone
(1)



Febrifugine
(2)



Methaqualone
(3)

Fig.1 synthetic quinazolinones

The 4(3H)-quinazolinone systems are now known to have a wide range of useful biological properties, e.g., anticancer,antiviral, anti-inflammatory, anti-microbial cholinesterase inhibitor, antifolate, antitumor, protein kinase inhibitor and many others[6].A few illustrative examples of quinazolinones that show important pharmacological activities[7, 8] are listed in fig.2. In this regards an overview of the synthetic paths and approaches for recently described highly potential 4(3H)-quinazolinones.

Synthetic path of 4(3H)-quinazolinone and derivatives

Niementowski quinazolinone synthesis

The furthermost common way for 4(3H)-quinazolinone synthesis is based on the Niementowski reactionby the fusion (130–150 ^{0}C) of anthranilic acid analogues with amides, proceeding via an o-amidobenzamide intermediate (Scheme 1)

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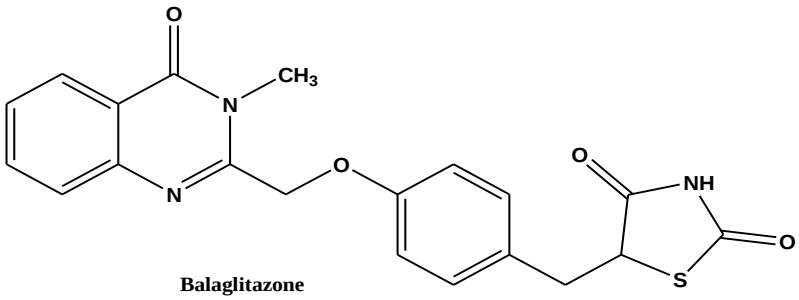
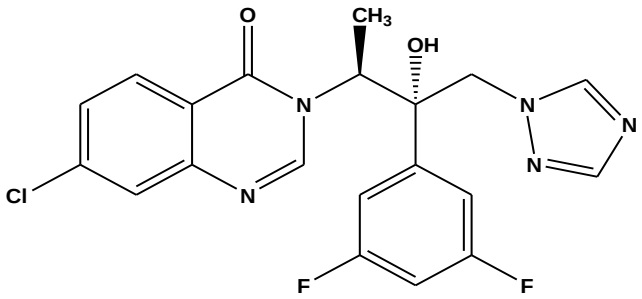
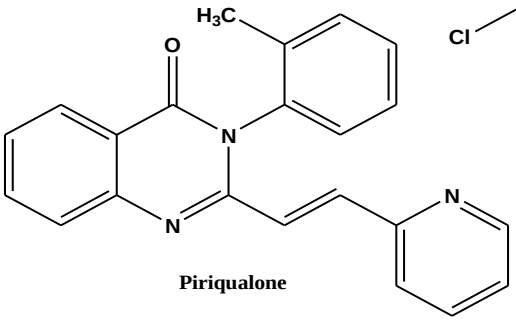


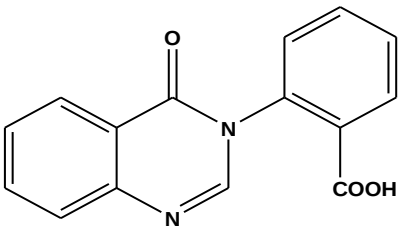
Balaglitazone



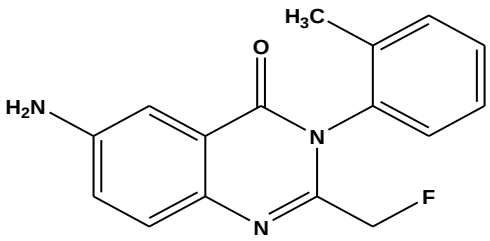
Albaconazole



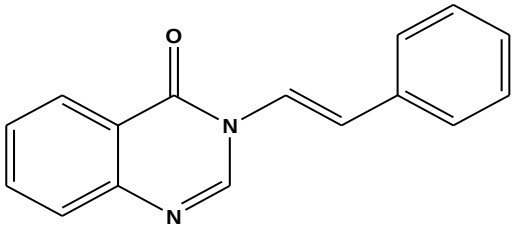
Piriqualone



3-(2-Carboxyphenyl)-4(3H)-quinazolinone



Afloqualone



(E)-bogorin

Fig.2 Some examples of quinazolinones that show potentially pharmacological activities

Bessonet al.[9] have re-investigated the Niementowski synthesis of the 4(3H)-quinazolinone using microwave irradiation and have enhanced the yields and speedy the reaction

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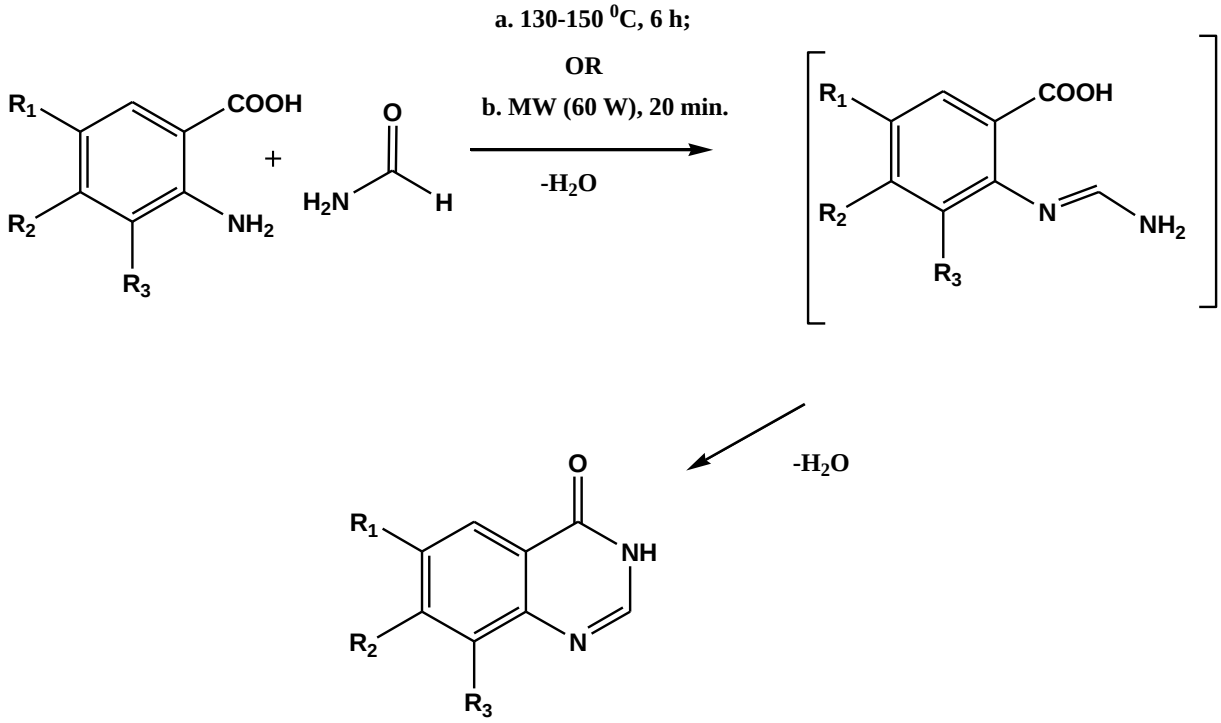
time. By using microwave techniques, new effective routes to novel fused quinazolinones (Scheme 2) have been established[10, 11].



Scheme 1: The Niementowski reaction: (a) 130–150 C, 6 h; (b) Besson's microwave conditions: MW (60 W), 20 min.

Vanelle et al. have investigated the Niementowski reaction could be easily and speedily performed[12], giving the intermediate 2-chloromethyl-6-nitroquinazolin-4(3H)-one in decent yield (Scheme 3). These analogues act as a substrate for the synthesis of somenovel quinazolines, having several substituents in position 2.

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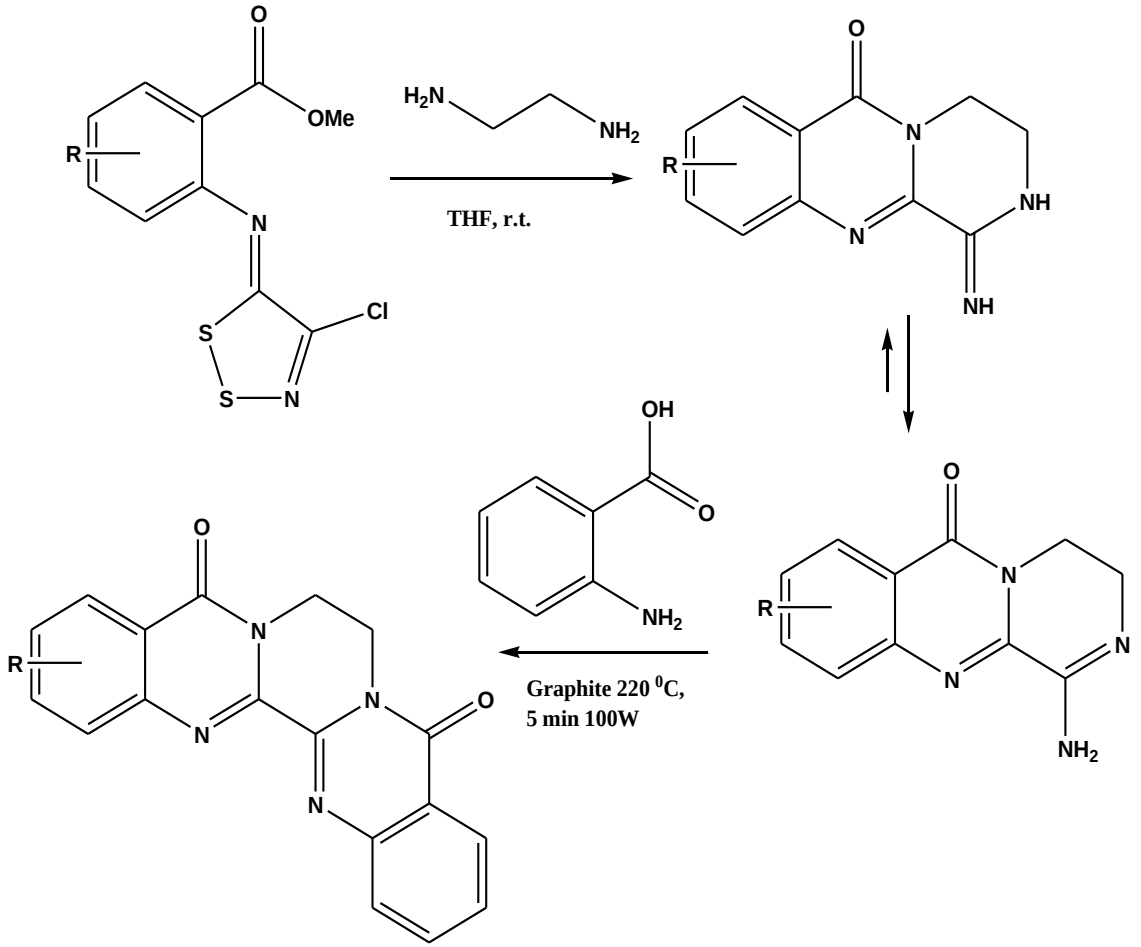
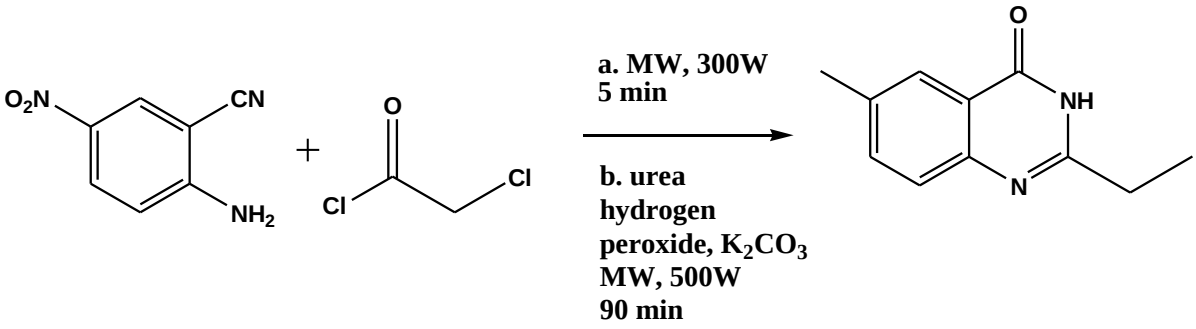


Scheme 2: Microwave-assisted Niementowski reaction.



Scheme 3: preparation of 2-substituted quinazolines.

Wang and co-workers reinvestigates the highly accelerated acid catalyzed coupling of anthranilamides or anthranilic acids with amides (Scheme 4)[13]. They mention in their paper substituted quinazolin-4-one derivatives were obtained in an average time of 10 min under microwave irradiation using various power inputs (60 W, 300 W or 500 W) in a modified domestic oven adapted for refluxing.

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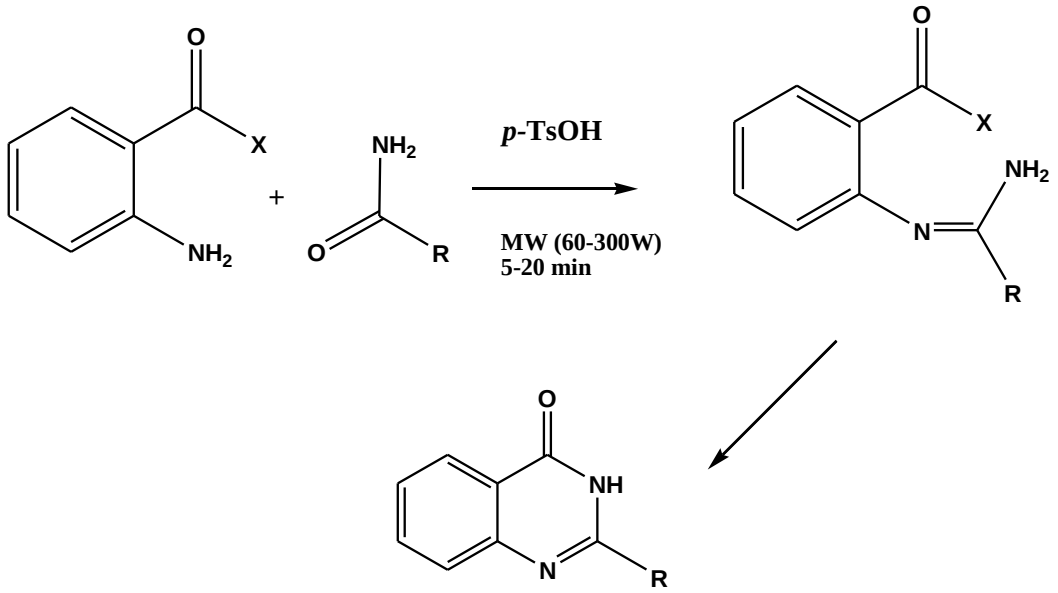
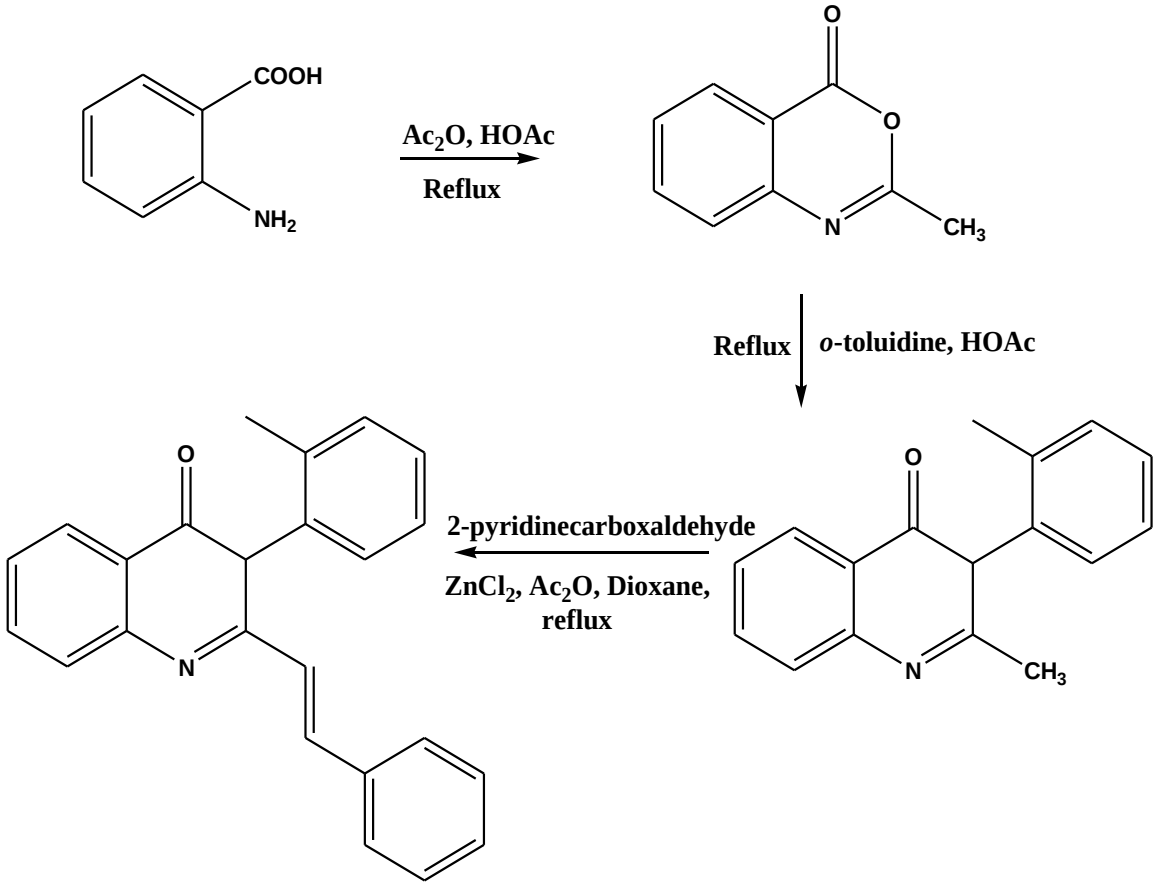


Scheme 4: syntheses of 2-Substituted (3H)-Quinazolin-4-Ones



Scheme 5: The synthetic route to piriqualone.

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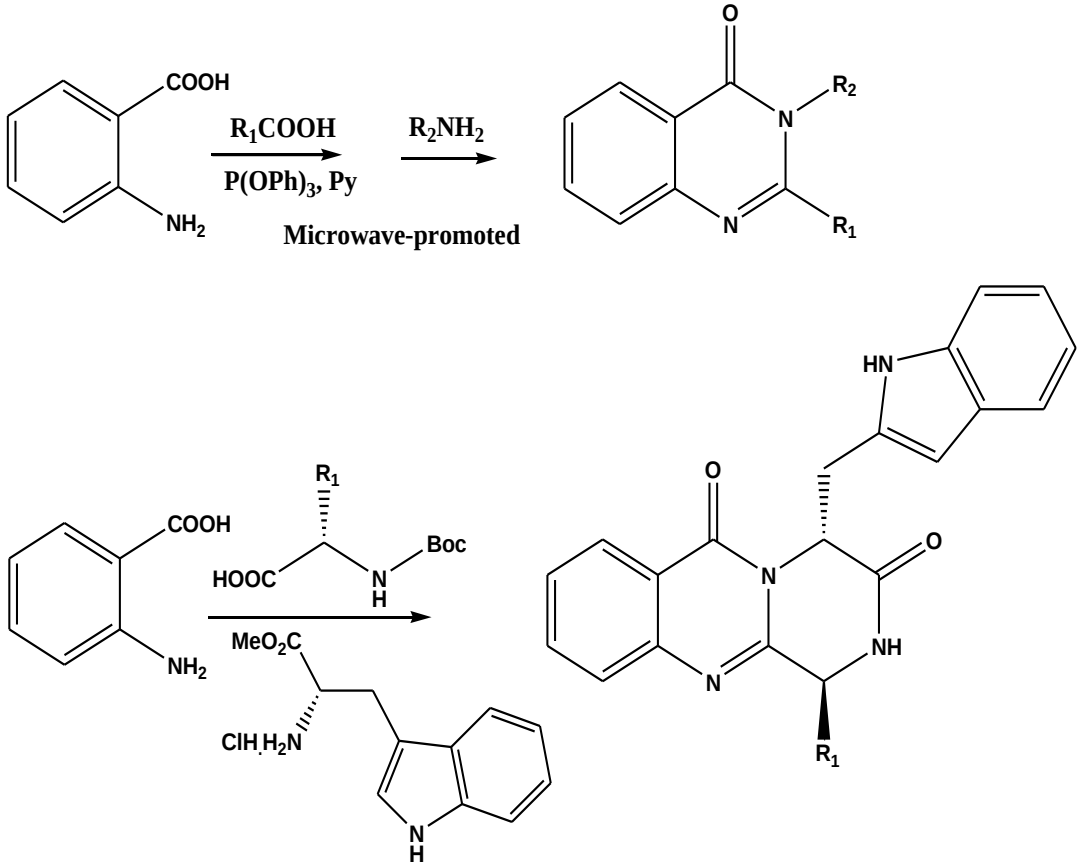
Quinazolinone synthesis via benzoxazinone intermediate

4(3H)-quinazolinone syntheses via benzoxazinone intermediates have become very prevalent Chenard et al. has stated a brief SAR program that led to the finding of piriqualone CP-465022, a potent antagonist that interacts with the receptor over an allosteric site. The synthetic route to piriqualone (Scheme 5)[14] combines 3 steps: anthranilic acid is converted to benzoxazin-4-one with hot acetic anhydride in acetic acid. Subsequent reaction with a suitable aniline fragment in refluxing acetic acid installed the ortho toluidine ring. Lastly, condensation of 2-methyl-3-aryl-quinazolin-4-one with pyridine-2-carboxaldehydes yieldsthe target compounds.



Scheme 6: Microwave-promoted synthesis of quinazolinones via benzoxazinone intermediate

A microwave-promoted synthesis of 2,3-disubstituted 3Hquinazolin 4-ones with broad scope was developed by Liu and co-workers.[15, 16] The key step is the one-pot, two-step reaction sequence combining anthranilic acids, carboxylic acids, and amines providing efficient access to the desired heterocycles (Scheme 6).

Gupta et al. (2013) reported the biological activity and their synthesis of some new quinazolin-4(3H)-ones derivatives (Scheme7) as anticonvulsants[17]. The first step is the condensation of anthranilic acid and benzoyl chloride in the presence of pyridine. The treatment of the obtained 2-phenylbenzo[d][1,3]oxazin-4-one with hydrazine hydrate yielded 3-amino-2-phenyl-1H-quinazolin-4-one. Using the similar method, Alagarsamy and saravanan obtained eighteen novel quinazolin-4(3H)-one derived pyrazole analogs[18].

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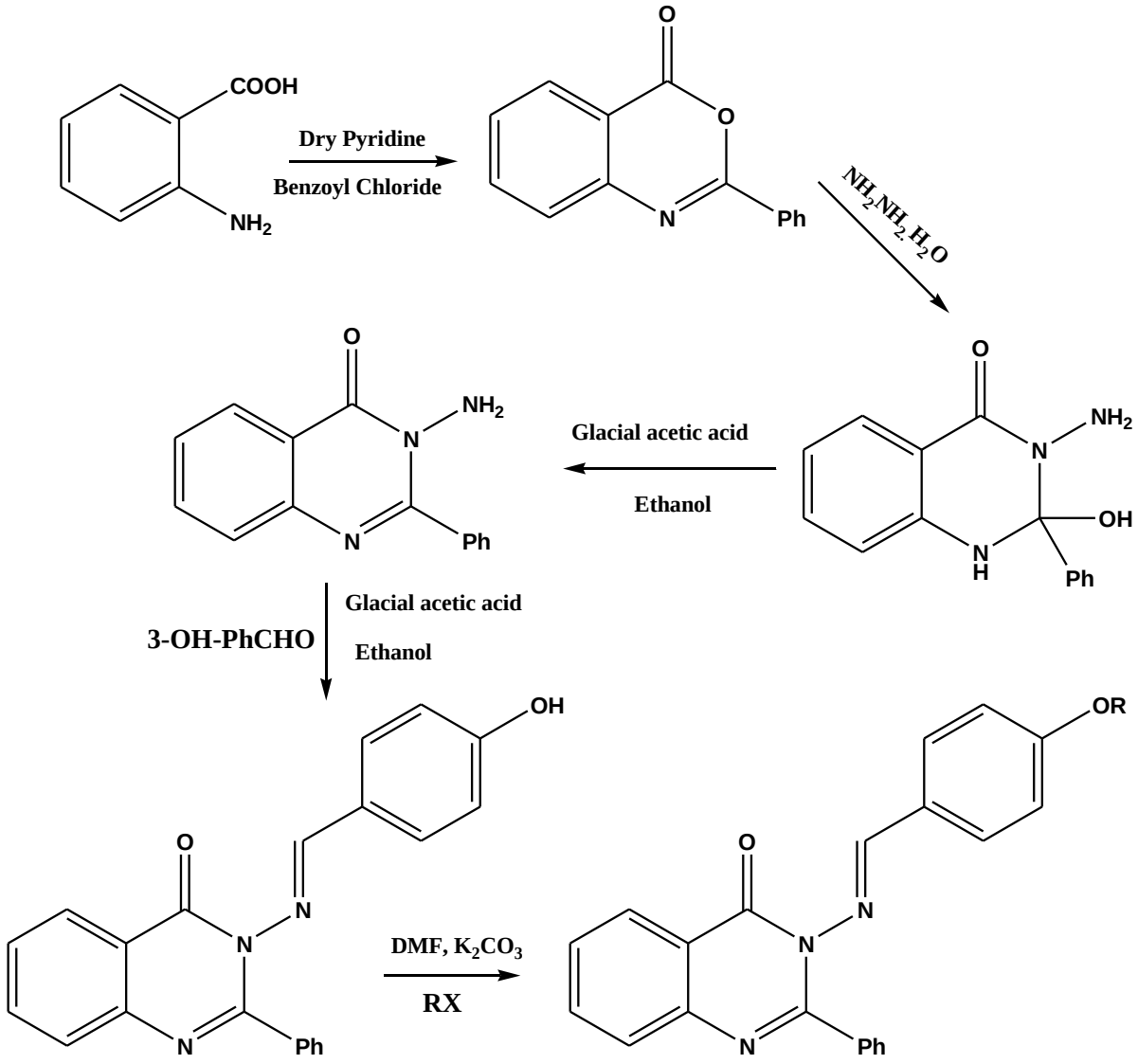

Scheme 7 Synthesis of quinazolinone derivatives.

Effective microwave assisted synthesis in order to make a series of 2,3-disubstituted quinazolin-4-ones, Besson and co-workers shown that microwave assisted rapid decomposition of formamide under controlled conditions is a convenient source of ammonia for the creation of 2-substituted quinazolin- 4-ones and other rings[19] (Scheme 8).

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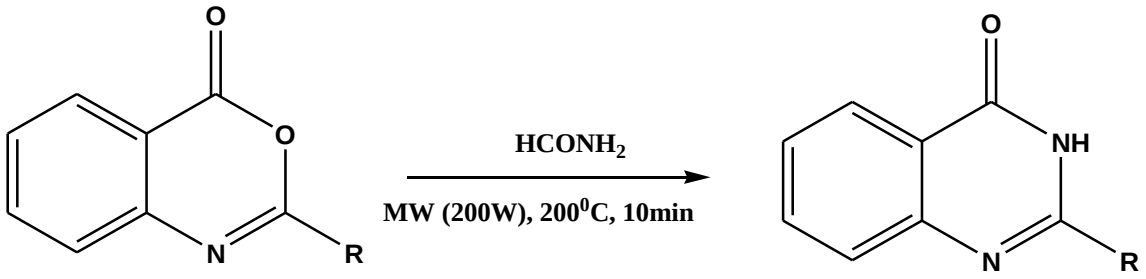
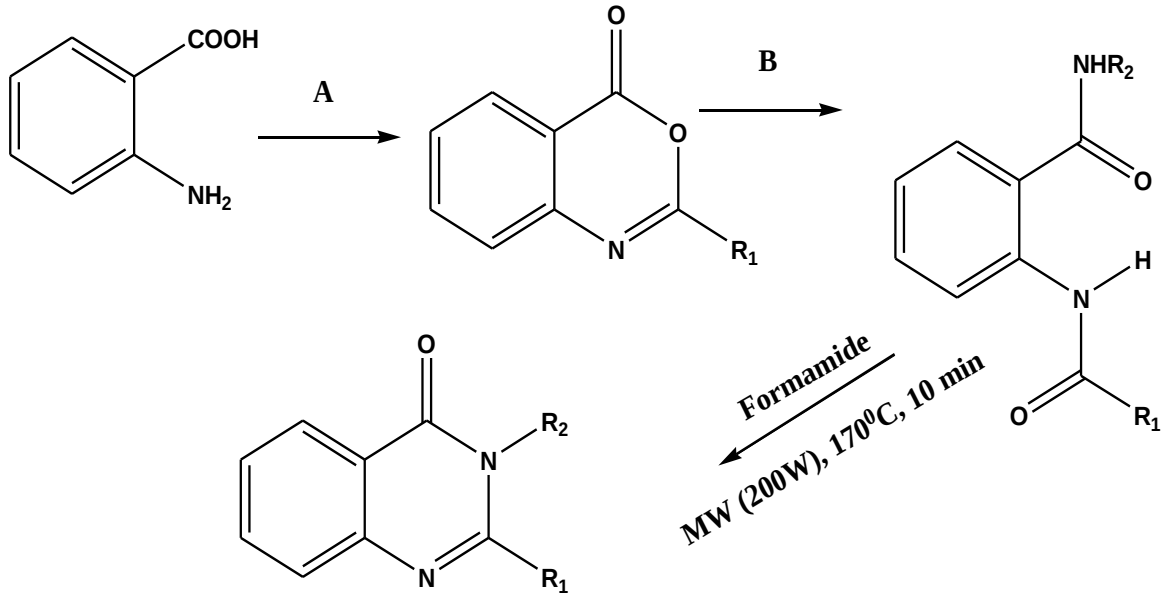


R = Me, Et

Scheme 8 Synthesis of 2-substituted quinazolin-4-ones derivatives.

Liu and co-workers described the microwave assisted synthesis of 2,3-disubstituted 3H-quinazolin-4-ones from anthranilic acids[20] in a one-pot-two steps order, first step combined anthranilic acids and carboxylic acids, or the equivalent acyl chlorides, for 10 min at 150°C. Upon consumption of the acid, an amine was added and the reaction mixture was heated for 3-6 min at 250°C (Scheme 9). The mechanism of the reaction proposes benzoxazin- 4-ones which were not isolated**.**



A) acetic or propionic anhydride, MW (200W), 130^{0}C, 10min
B) Aliphatic amine, CH_2Cl_2 r.t. 10- 40 min

R_1 = Me, Et
R_2= Me, *n*-Bu, CH_2NEt_2

Scheme 9 synthesis of 2,3-disubstituted 3H-quinazolin-4-ones in a one-pot-two steps sequence

Quinazolinone synthesis Cyclocondensation of anthranilic acid, ortho esters (or formic acid), and amines

Khosropour et al. have demonstrated condensation with high to excellent yields of the 4(3H)-quinazolinones[21]. The notable features of

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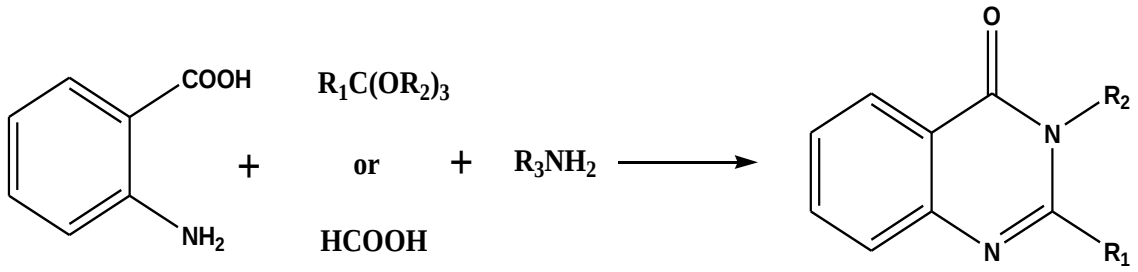
this procedure are mild reaction conditions (room temperature), clear reaction profiles, improved yields for both anilines and primary amines, enhanced rates and simplicity in operation. Moreover, the reusability, stability and non-toxicity of the catalyst and ionic liquid are other noteworthy advantages of this method.Multi-component reactions, one-pot condensation of anthranilic acid, ortho esters (or formic acid) and amines is one of the most straightforward procedures for the preparation of 4(3H)-quinazolinones (Scheme 10)



Scheme 10 One-pot condensation of anthranilic acid, ortho esters (or formic acid) and amines.

Wang et al. found that $SrCl_2.6H_2O$ could be used as an efficient and recyclable catalyst in one-pot condensation of anthranilic acid, ortho esters and amines leading to the formation of 4(3H)-quinazolinone derivatives in good yields at room temperature under solvent-free conditions[22]. The method offers several advantages including simple work-up, mild conditions, commercially available catalyst, and the relatively clean procedureA different approach to the facile synthesis of 2-substituted-quinazolin- 4(3H)-ones and its derivatives using the condensation reaction of substituted 2-aminobenzamide and ortho esters is reported by Huang in 2011[23]. Remarkably, the reaction proceeds without organic solvent and in the absence of basic or acidic catalyst.

Oxidative heterocyclization for 4(3H)-quinazolines synthesis

In 2008, Seidel et al. reported the syntheses of deoxyvasicinone and rutaecarpine by the potassium permanganatepromoted oxidation of aminals, which in turn were obtained from the condensation of o-aminobenzaldehydes and simple secondary amines (Scheme11)[24].

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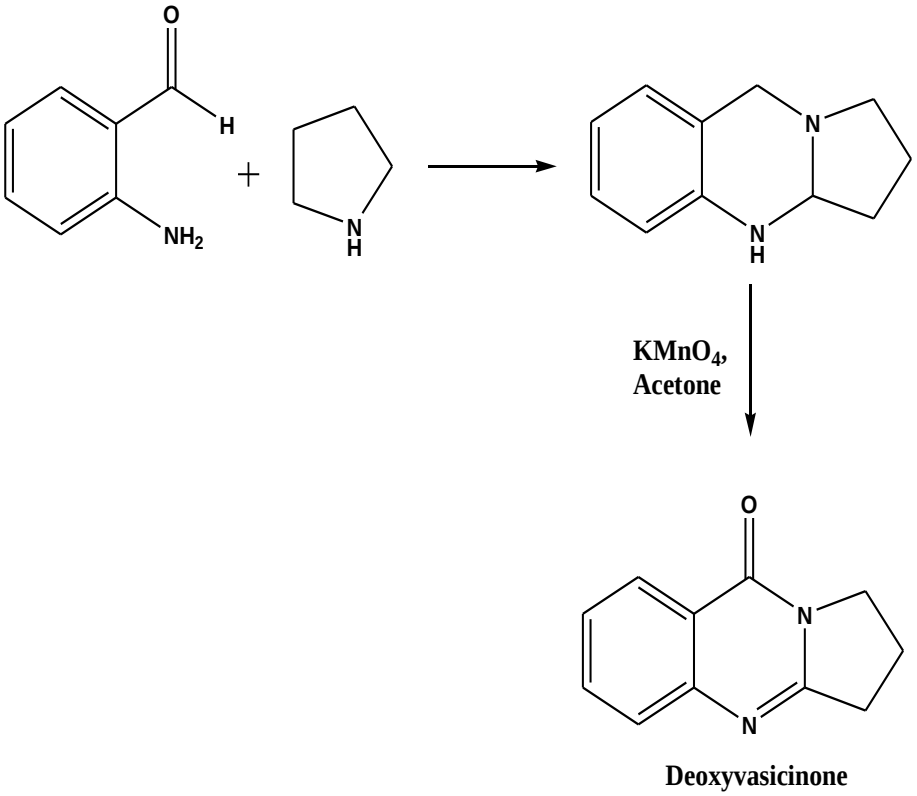
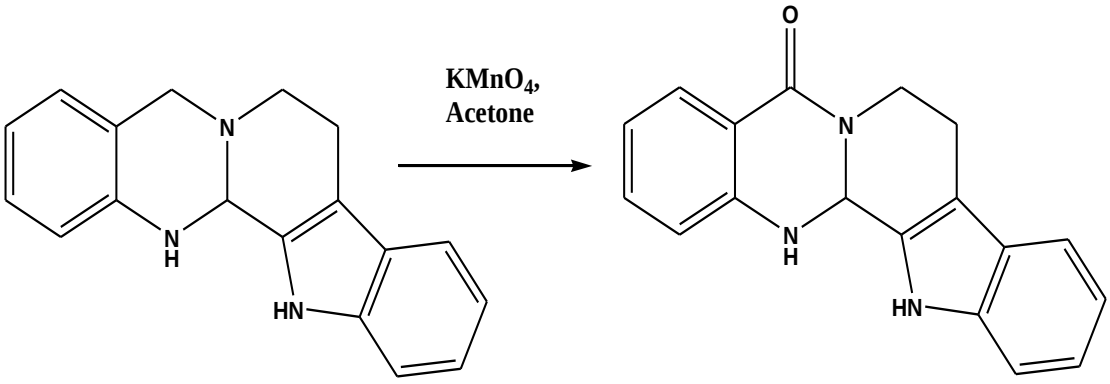


Deoxyvasicinone



Rutaecarpine

Scheme 11 syntheses of deoxyvasicinone and rutaecarpine

II. CONCLUSION:

Quinazoline and 4(3H)-quinazolinone derivatives are the developing pharmacophore which has drawn an emergent interest in the field of drug designing and development. In last year, many publications were recorded on the quinazolinone derivatives only. This review article will contribute to the design strategies based on the pharmacophore Quinazoline and 4(3H)-quinazolinone.

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Abbreviations:Not Applicable

Conflicts of Interest

The author declared no conflict of interests.

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