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Review Article

Microwave assisted one-pot Total synthesis of some natural Quinazoline alkaloids- a review

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The current review mainly concern with the greener approach for the synthesis of quinazoline alkaloids. Due to the important role in lead optimization as well as for the synthesis of derivatives, effective and convenient methods are a serious need for medicinal chemistry. Synthesis of complex quinazoline alkaloid moiety is difficult, time consuming and increase the cost of synthesis. So, by applying Microwave assisted one-pot synthesis above problems can be overcome. It is try to include as many as possible quinazoline moiety which are fused or attached with some different heterocycles. The review contains 2,3-disubstituted quinazolin-4-ones, quinazoline fused with pyrrole, pyrroloquinoline, piperazine and benzodiazepin ring. Included reactions in review are simple and efficient for the synthesis of natural quinazoline alkaloids.

Key words- *Quinazoline alkaloids, Leutonin, Deozyvasisinone, Microwave, One –pot raection*

Introduction

Quinazoline alkaloids are a small group of secondary natural compounds, which passes a number of biological activity. For this reason it attracts a number of scientists to work on quinazoline heterocycle. Quinazoline alkaloids attract the scientist since 1888, with the discovery of the first natural representative of them - (+)-peganine (vasicine) [1]. Scientist had work on these alkaloids and synthesized them in to the laboratory. Synthesis of natural product involves complex multi-step procedures, harsh reaction conditions, longer reaction times, expensive reagents, anhydrous solvents and cumbersome experimental/ work-up procedures. In this review we try to compile the microwave synthesis of natural Quinazoline alkaloids, Because microwave is a less time consuming, avoid multi-step procedures and Good yield of product with purity. Quinazoline fused with some other heterocycles show prominent phramcological activity like Lutonin (Cytotoxic activity), Isaindigottone (anti-oxidant), Fumiquinazoline (Cytotoxic activity) etc. A number of work has been

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published in journals which mention the chemistry of natural alkaloids [2] and there chemical distribution in nature with some other heterocyclic[1].In spite of there therapeutic value, less availability and low yield it is difficult to synthesis Quinazoline alkaloids on large level. We have attempted to compile some Quinazoline alkaloids synthesis with the help of microwave. Some are them are one pot and some contains number of steps for synthesis of a complex alkaloids. The present review contain-

1) One pot synthesis of 2,3-disubstituted quinazolin-4-ones
2) One pot synthesis of quinazolinones with pyrrole ring
3) One pot synthesis of quinazolinones with pyrroloquinoline ring
4) One pot syntheses quinazoliopiperazine ring
5) One pot syntheses of quinazolinobenzodiazepin ring

One-Pot Synthesis of 2, 3-Disubstituted Quinazolin-4-ones

2,3 disubstituted quinazoline show potent pharmacological activity e.g. Glycosminine anti-malarial) methaqualone (sedative and piriqualone (anticonvulsant). The general method of Quinazoline synthesis includes hypnotic), chloroquinalone (antitussive), and reaction of anthranilic acid with acylchloride or with carboxylic acid which generates the benzoxzinone. and further reaction with aniline or substituted amine groups which gives 3-substituted quinazolinones derivatives. A number of synthesis methodology are applied for sunthesis of Quinazoline alkaloids such as Glycosminine (*Glycosmis arborea*) and arborine (G. arborea) were synthesized by Kametani et al.[3] by reaction between phenylacetamide with sulfinamide anhydride Glycosminine produced and N-methylsulfinamide anhydride used inplace of phenylcetamide which gives arborine. **Scheme I**

In the One pot synthesis of 2,3 –disubstiuted quinazolinone first anthranilic acid and benzoyl-chloride mix with pyridine which stirred at room temperature and then Cyclohexyl-amine and $P(PhO)_3$ were then added and the mixture was microwave irradiation at $>200^0$ c. Where $P(PhO)_3$ act as a coupling agent. **Scheme II** [4].

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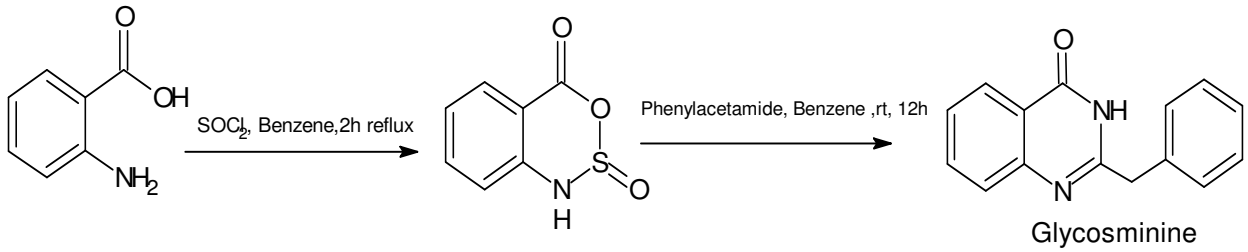
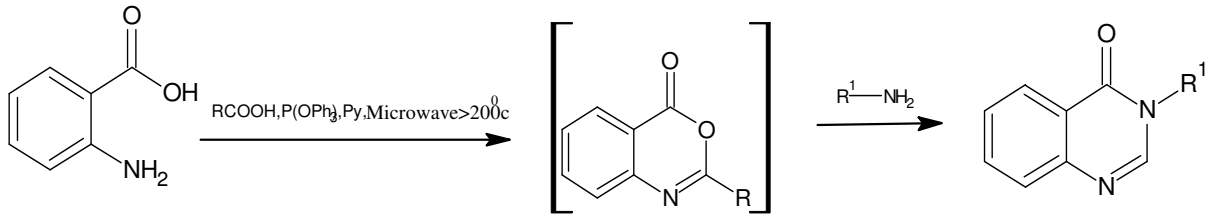


Scheme I – Conventional synthesis of Glycosminine



Scheme II- Microwave assisted synthesis of 3-substituted Quinazoline synthesis

One Pot Synthesis of quinazolinones with Pyrrole Ring [5]

A number of methods have been reported for the synthesis of deoxyvasicinone, Mackinazolinine and Isaindigotone. These include transition-metal-catalyzed reductive N-heterocyclization, [6] coupling of O-methylbutyrolactim with anthranilic acid, [7] cycloaddition of anthranilic acid iminoketene to a methyl butyrolactam (via sulfonamide anhydride), [8] intramolecular aza-Wittig reactions using PPh_3 and PBu_3,[9] the cycloaddition of anthranilamide with succinic anhydrides, [10] and solvent-free microwave-assisted reactions between isatoic anhydride and pyrrolidone.

Ji-Feng Li et al. 2005 [11] reported synthesis anthranilic acid with 4-(tert-butoxycar-bonylamino) butyric acid in the presence of $P(OPh)_3$ in pyridine at 200 °C for 10 min, followed by addition of 4-hydroxy-3,5-dimethoxybenzaldehyde and microwave irradiation at 230 °C for 12 min gives isaindigotone

Mackinazolinone was synthesized by Ji-Feng Li 2005 using anthranilic acid with 5-(tert-butoxycarbonylamino) pentanoic acid in the presence of $P(OPh)_3$ in pyridine under microwave irradiation at 220 °C for 10 min afforded Mackinazolinine, while using 4-(tert-butoxycarbonylamino) butyric acid with Microwave irradiation at 150°C gives Deoxyvasicinone. Yadav and Reddy 2002

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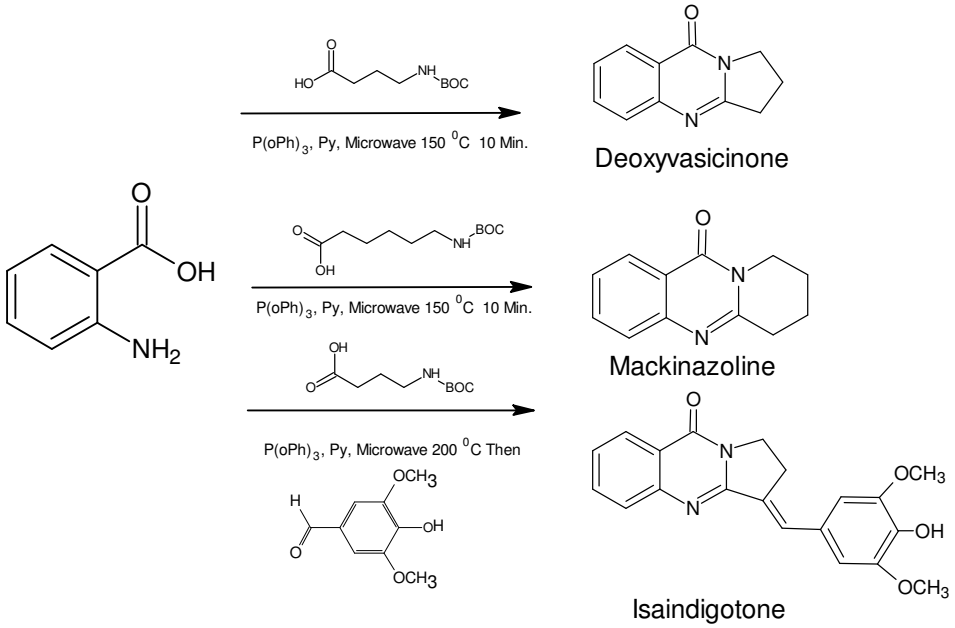
also reported solvent-free microwave-assisted synthesis of deoxyvasicinone by reaction between isatoic anhydride and pyrrolidone.



One Pot synthesis of Quinazolinones with pyrroloquinoline

Luotonin A is a cytotoxic alkaloid first isolated in 1997 from the plant *Peganum nigellastrum* The six luotonins can be classified into three categories: luotonins A, B, and E are pyrrolo-quinazolinoquinoline alkaloids, luotonin F is a 4(3H)-quinazoline alkaloid, and luotonins C and D are canthin-6-one alkaloids. Jing Lu Liang, et al 2011 [12] present a review in recent advances of Luotonins and its derivatives. The review contain synthesis of lutonins by formation of the pyridine core (ring B), the pyrrole core (ring C), the pyrimidinone core (ring D), the 5H-pyrrolo[4,3-b]pyridine core (rings B and C), the pyrrolo[1,2-a]pyrimidin-4(6H)-one core (rings C and D), and the pyrido[2'3':3,4]pyrrolo[1,2-a]pyrimidin-4(6H)-one core (rings B,C,D) as the final step.

Lutonin is synthesized by Batey [13] (10%yield in eight steps) and Zhou[14-15] (47%yield in five steps). *Ming C. T. et al* ***2011*** [16] Synthesized leutonin A and its analogues by Lewish acid ($Yb(OTf)_3$) catalyzed intamoleuclar aza dies alder cyclization in one pot synthesis and tested for cytotoxicity in vitro against the murine leukemia P-388 cell line with an IC_{50} value of 6.3 μM. Yadav and Ready synthesized

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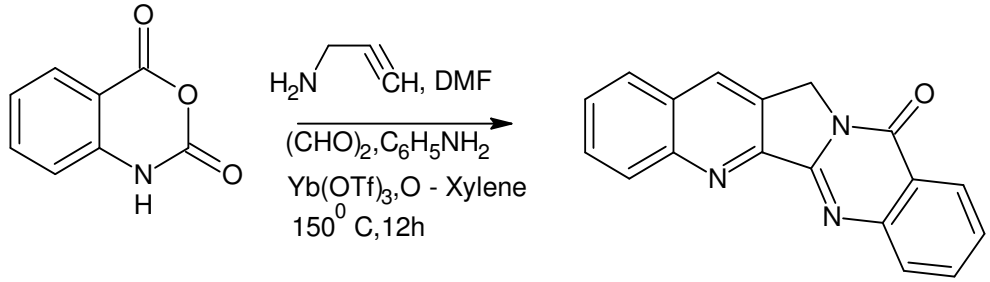
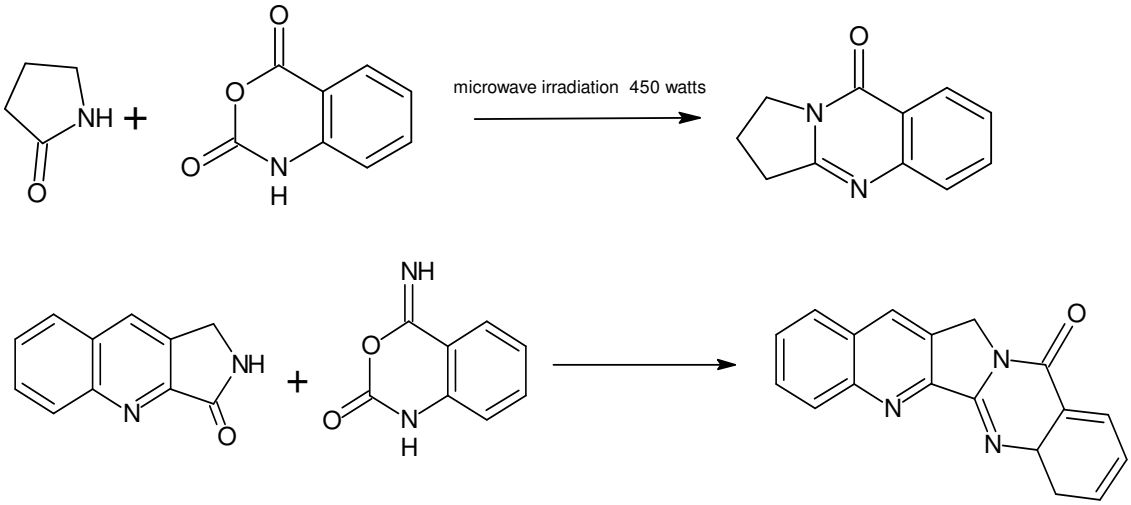
lutonin A by subjected to microwave irradiation at 450 watts to 3-oxo-1H-pyrrolo[3,4-b]quinoline and isatoic anhydride for 6 min.



Scheme III- One Pot synthesis by using $Yb(OTf)_3$



Scheme-IV –Lutonin A synthesis by one pot reaction

One-Pot Total Syntheses Quinazoliopiperazine ring system [17]

Quinazoliopiperazine ring containing natural alkaloids such as anacine ,(+)-verucine,Glyantrypine, Fumiquinazoline A-I, Fiscalin A-C are show some of pharmacological activity.A microwave-promoted three-component one-pot reaction has been developed by Ji-Feng L., et al 2005 to provide access to the core pyrazino[2,1-b] quinazoline-3,6-dione. Microwave irradiation of anthranilic acid with N-Boc-glycine followed by the addition of D-tryptophan methyl ester hydrochloride and microwave heating at 150 °C for 10 min provided glyantrypine in 55% yield. While reaction of anthranilic acid with N-Boc-L-alanine and then addition of D-tryptophan methylester hydrochloride (microwave heating, 220 °C, 1.5 min) gives

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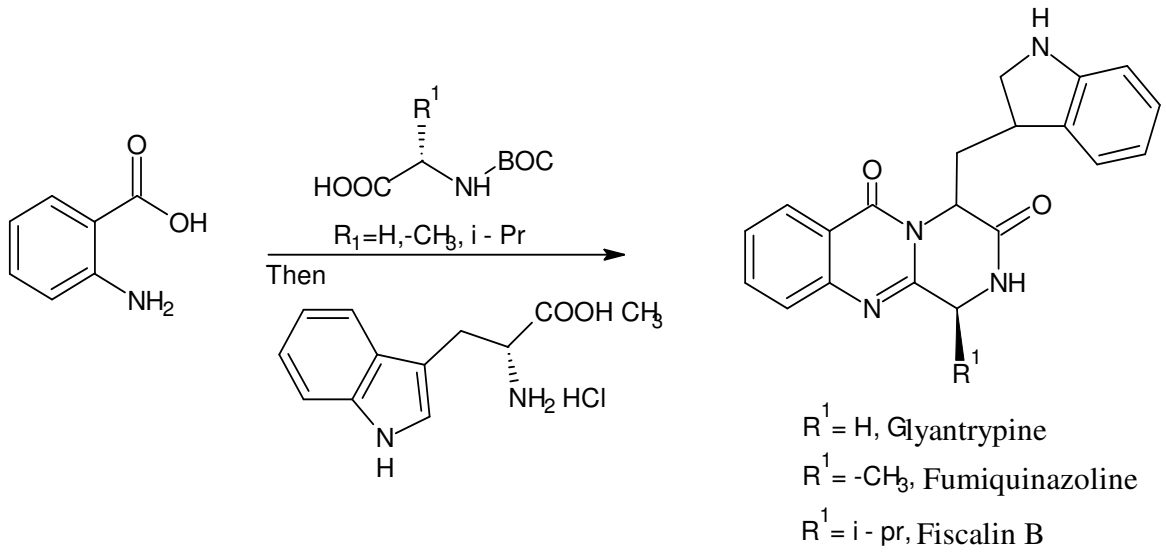
Fumiquinazoline 39% and anthranilic acid , Boc-L-valine and triphenyl phosphite along with anhydrous pyridine heating at 55 ^{0}c for 16hrs. then addition of D-tryptophan methyl ester hydrochloride and microwave heating at 220°C for 1.5 min give sFiscalinB



Scheme-V one pot synthesis of Glyantrypine, Fumiquinazoline, Fiscalin B

One pot synthesis of Quinazolinobenzo-diazepine ring [18]

In recent past year some of quinazolinobenzodiazepine alkaloids were isolated from the various species of fungus like *Aspergillus ochraceus* (Circumdatins A-G) *Penicillium sclerotigenum* (Sclerotigenin) . A larger number of synthetic procedures are available for the synthesis of diazpine ring fused with Quinazoline like N-sulfinylanthraniloyl chloride is used as a precursor for synthesis of Circumadatin F & C[19] some other used aza-witting cyclization for synthesis of sclerotegenin and Circumadatin F [20].

Circumdatin F and some of quinazolinobenzodiazepine were synthesized by Ji-Feng Liu et al 2005 using anthranilic acid , N-Boc-alanine and triphenyl phosphite along with 1 mL of anhydrous pyridine. The sealed vial was irradiated in the microwave for 20 min at 230 °C. which provide Circumdatin F at yield 32%.

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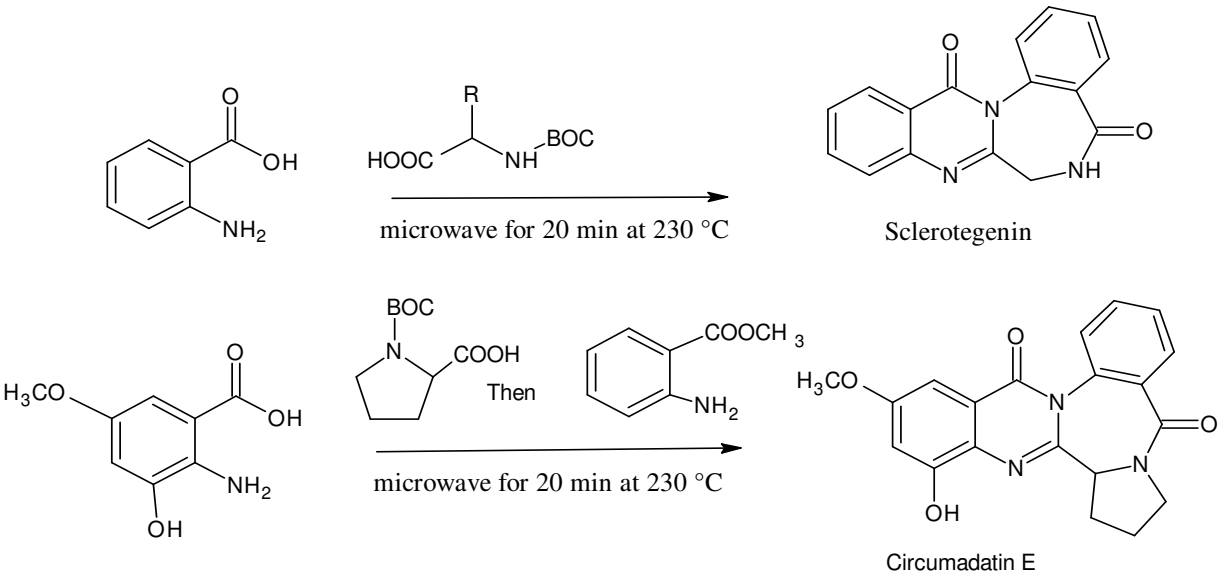

Scheme VI- Three component one pot synthesis of some Benzodiazepine fused quinazolinones.

Summary

The present review describe one-pot synthesis methodology and there advancement by one-pot synthetic method.

A number of synthetic methods are available for the synthesis of Quinazoline alkaloids but, Due to natural product involves complex multi-step procedures, harsh reaction conditions, longer reaction times it was much convenient to synthesis through Microwave method applying Green approach for synthesis. Quinazoline Moiety passes a number of therapeutic value. The synthesis of these alkaloids with advance technique and new derivatization can generate a more effective derivative. We feel that alkaloids which contain Quinazoline or contain other heterocycles will show potent activity or may be used as a lead for discovery of new components

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