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Research Article

Synthetic Strategies to Quinazolinones

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ABSTRACT

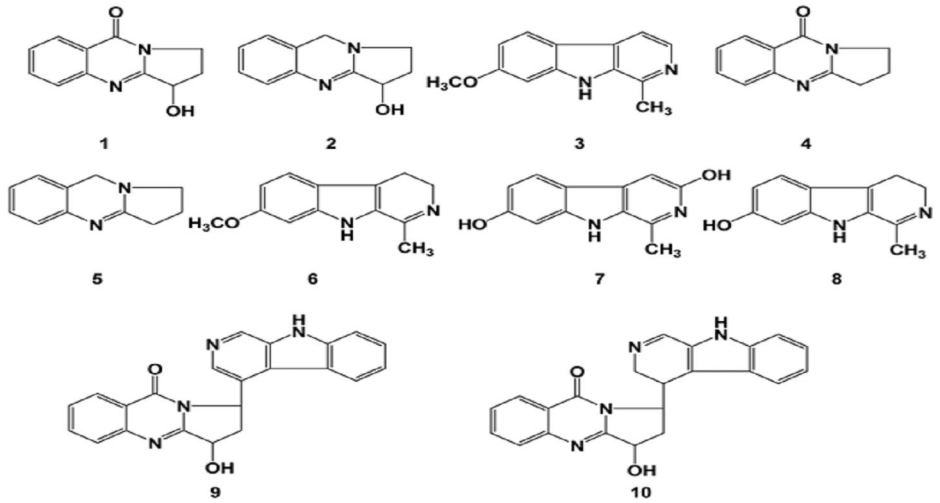
Alternative methods to obtain substituted quinazolinones are reported in the present communication. Novel catalysts such as montmorollinate K10, Ferric chloride, Silicagel are used in the reactions. Microwave conditions are effectively utilized in the reactions.

Keywords: Quinazolinones, Organic synthesis, Medicinal Chemistry, anti-inflammatory drugs.

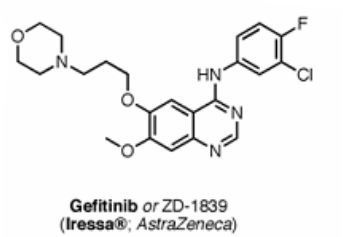
INTRODUCTION

Quinazolinones are one of the most important core structures present in many natural products as well as synthetic drugs. 4-(3H)-quinazolinone is frequently encountered heterocyclic moeity in medicinal chemistry known for more than a century. Quinazolinone derivatives attract a widespread interest due to the diverse biological activities[1] associated with them. They are pharmaceutically important as antituberculars[2], antibacterial[3], antiparkinsons[4], antihelmintics[5], and they also show blood platelet antiaggregatingactivity.[6] Formation of 2-alkyl-4(3H)-quinazolinones by condensation of anthranilic acid or substituted anthranilic acid and amides is designated as the Niementowski reaction.[7] Pyrazolones are associated with broad spectrum of biological activities including antifungal, antibacterial, anti-inflammatory properties.[8-10] Hydrazide derivatives have been extensively used as a good precursor for the synthesis of these derivatives.[11]

The quinazolinone alkaloids form small but important group of naturally occurring bases which have been isolated from a number of different plant families. For instance the following are few compounds isolated from seeds of *P. nigellastium Bunge* and other plant sources, where most of them have the quinazolinone nucleus incorporated in them.

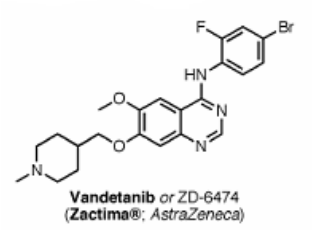


Molecules based on quinazolinones & quinazolines exhibit a multitude of interesting pharmacological and biological activities applications including antiviral, antibacterial, antifungal, anti-inflammatory and anticonvulsant ,anti-malarial, anti-diabetic , anti-cancer , hypnotic, broncho-dialatory activities. Following are some of the drugs which are in current use containing quinazoline core structure. This prompted us to investigate the studies on quinazolinone and related molecules.



Gefitinib *or* ZD-1839
(**Iressa®**; *AstraZeneca*)

18



Vandetanib *or* ZD-6474
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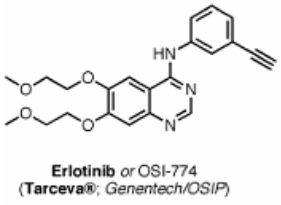

Erlotinib *or* OSI-774
(**Tarceva®**; *Genentech/OSIP*)

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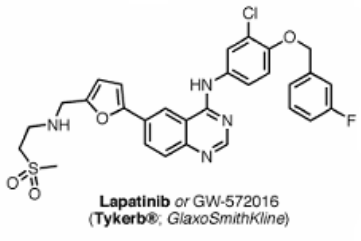


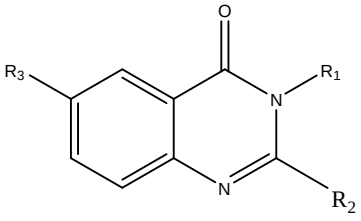
Lapatinib *or* GW-572016
(**Tykerb®**; *GlaxoSmithKline*)

21

Various commercially available anti cancer drugs

RESULTS AND DISCUSSION

In the recent years, the chemistry of quinazolinone and their derivatives has received considerable attention owing to their synthetic and effective biological importance. Because of these manifold reasons much attention is being paid for the synthesis of quinazolinone derivatives. In continuation of our interest in the synthesis and biological activity studies of quinazoline based compounds, we have attempted various reaction conditions to improve the reaction conditions and yields of the quinazolinone derivatives and are being reported in this communication. The quinazolinones bear the following general structure, wherein, R1, R2, and R3 are chosen from various substitutions.



Although numerous classes of quinazolines have been conventionally synthesized, their synthesis have been suffered due to the multiple steps that sometimes have described in their preparation and also their chemical transformations that have been taken hours or even days to be completed. However microwave energy can offer numerous benefits for performing synthesis of organic compounds including reduced pollution, increased reaction rates, yield enhancements, and cleaner chemistry. Hence we have developed very environment friendly and mild conditions for substituted quinazolinones.

1. The synthesis has been carried out using readily available starting materials and under simple laboratory conditions.The compounds synthesized were further characterized by m.p, TLC & spectral analysis like 1HNMR. Successful preparation of 6-nitro quinazolinone was carried out by fusing 5-nitro-anthranilic acid in excess formamide in presence of silica gel and ferric chloride by subjecting to microwave irradiation for 5 mins. TLC page. The NMR data [7.89 (doublet,

Ar.H), 8.16 (singlet, Ar.H), 8.58 (doublet, Ar.H), 9.17 (singlet, Ar.H), 9.84 (broad singlet, NH)] indicated the formation of the product **22**.

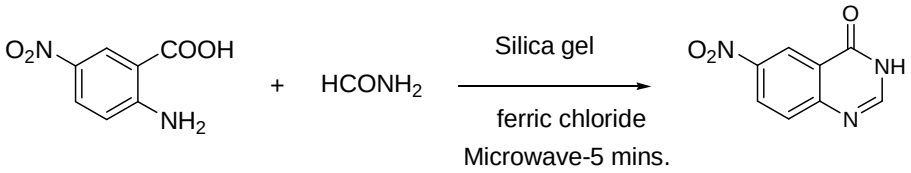
2. The same reaction when carried out in presence of clay 22 and acetic acid.
3. When 5-nitro-anthranilic acid was mixed with excess of formamide and subjected to microwave irradiation (medium 2 mins, low 5 mins, medium 3 mins) resulted in formation of 6-nitro quinazolinone which was further confirmed by TLC and NMR analysis **22** [7.87 (doublet, Ar.H), 8.3 (singlet, Ar.H), 8.55 (doublet, Ar.H), 8.8 (singlet, Ar.H), 12.8 (broad singlet, NH)].
4. The combination of 5-nitro-anthranilic acid with formamide in presence montmorollinite clay and ferric chloride at 150^0 C resulted in the product 6-nitro quinazolinone. Further the NMR analysis confirmed the formation of the product **22** [7.87 (doublet, Ar.H), 8.3 (singlet, Ar.H), 8.5 (doublet, Ar.H), 8.8 (singlet, Ar.H), 12.7 (broad singlet, NH)].

EXPERIMENTAL

All the chemicals and reagents are purchased from standard sources like Aldrich, Fluka, Merck etc. TLC was checked on precoated silicagel on aluminium foil. LR grade solvents are used for reactions and purifications and used as such without distillation or drying. 1NMR was recorded on Bruker Instrument.

Synthesis of 6-Nitro-4-(3H)quinazolinone using the following routes

1) 5-nitro anthranilic acid (0.5 gms) in excess formamide (10 mL) was taken and silica gel (1 gm), ferric choloride (0.2 gms) was added and subjected to microwave heating for 5 mins. Ethyl acetate and water are added to the reaction mixture and ethyl acetate layer was collected, dried over anhyd sodium sulfate, and concentrated and dried. To obtain 0.3g (55% yield). Product was characterized by 1HNMR in CDCl3.



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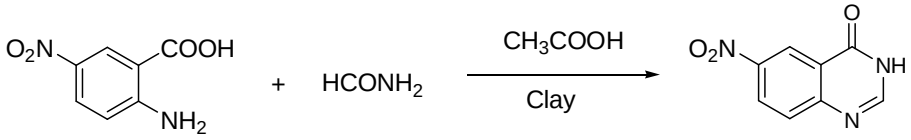
2) 5-nitro anthranilic acid (1 gm) in excess formamide, clay (2 gms), acetic acid (0.2 mL) was added and heated in microwave in low mode for 10 mins. The reaction mixture was decanted into separate beaker and ice cubes were added. The solid obtained was filtered and dried to obtain 0.6g in 60% yield. 1HNMR in CDCl3 was recorded.



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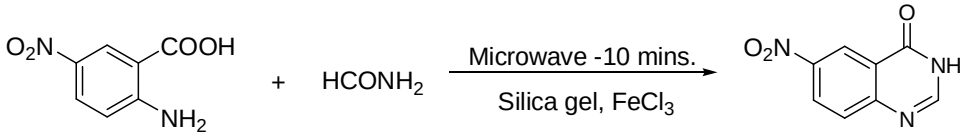
3) 5-nitro anthranilic acid (1gm) in excess formamide, silica gel (1gm), ferric chloride (0.4 gms) was added and microwave for 10 mins (medium -2 mins, low – 5mins, medium – 3 mins). To the reaction mixture water was added and filtered. The residue was collected in methanol and methanol was distilled off. To the contents water and ethyl acetate was added and ethyl acetate layer was collected, dried, concentratedto obtain 0.3g in 30% yield.



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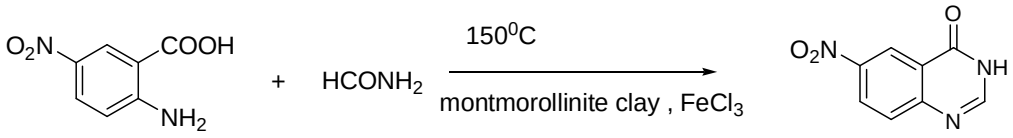
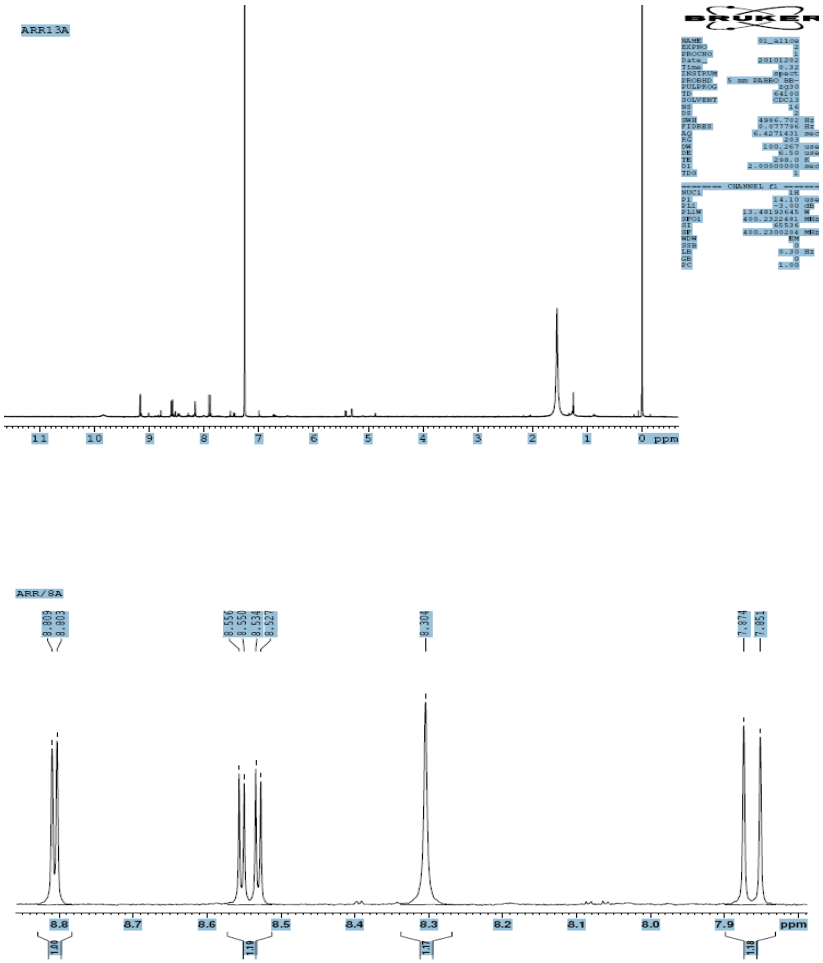
4.) 5-nitro anthranilic acid (0.2 gms), formamide (1.5 mL) montmorollinite clay (0.25 gms) and ferric chloride (0.1 gm) were mixed and heated at 150^0 C for 2.5 hours. The reaction mixture was purified by passing through silica gel column. The fraction (DCM : Methanol, 8:2) was collected and water in DCM were added. The DCM layer was then collected, concentrated and dried to obtain 0.15g in 70% yield.



2.5 hours

22



1HNMR of 6-Nitro quinazolinone in $CDCl_3$ Solvent

CONCLUSION

In conclusion, we have reported herein novel reaction conditions for the synthesis of substituted and unsubstituted quinazolinones. We strongly believe that the methods will find extensive use as quinazolinones are important intermediates in pharmaceutical industry and are core structures in many natural products of medicinal importance.

ACKNOWLEDGEMENTS

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