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Multicomponet reaction of benzyl halides: Synthesis of [1,2,4]triazolo/benzimidazolo quinazolinones

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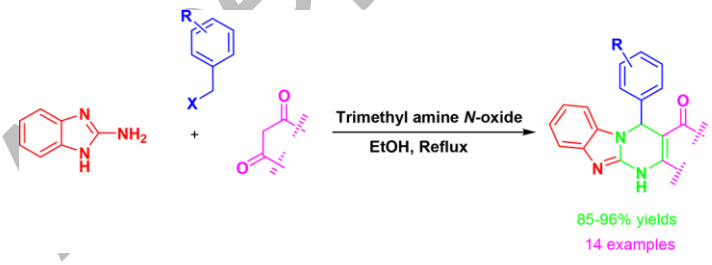
Abstract

We demonstrated a simple and highly efficient new one-pot method to construct triazolo/benzimidazolo quinazolinones through a cascade of oxidation, Knoevenagel condensation and Michael addition followed by cyclization and dehydration. This protocol tolerates easily available benzyl halides, 2-amino benzimidazole/3-amino-1,2,4-triazole and α-hydroxy C-H acids as starting materials using trimethyl amine *N*-oxide in ethanol. To the best of our knowledge, this is the first example of synthesis of triazolo/benzimidazolo quinazolinones directly from benzyl halides in one pot. Simple procedure, environmental friendly, mild reaction condition and high yield are the attractive features of this method.



KEYWORDS: Quinazolinone, Triazole, Benzimidazole, Trimethyl amine *N*-oxide and Multi component reaction

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INTRODUCTION

Multi-component reactions (MCRs) have been refined in recent years as powerful and necessary tools in synthetic organic and medicinal chemistry. This powerful tool combines both the environmental and economic aspects of organic chemistry that are essential for industrial and academic applications. MCRs offer remarkable advantages like convergence, reduction in the number of workup, operational simplicity, separation and purification process, hence minimize waste production and rendering the green transformations.[1-5]

The synthesis of quinazolinone analogues is a significant synthetic reaction in organic chemistry as these scaffolds are found to be a very important core structure in various natural products[6,7] and a wide range of biologically active synthetic compounds.[8,9] Many commercially available drugs (Fig. 1) including Ispinesib (anticancer), Dacomitinib (anticancer), Methaqualone (antimalarial), Albaconazole (antifungal activity), Balaglitazone (antidiabetic and hypolipidimic property) and Anagrelide (for the treatment of essential thrombocytosis) are derived from quinazolinone core entities.[10] Quinazolinone moieties exhibit a variety of biological activities such as antitumor,[11] antiviral,[12] anticancer,[13] antileishmanial,[14] antimicrobial,[15] anti-inflammatory,[16] antitubercular,[17] antimalarial,[18] antifungal[19] and antibiotic.[20] Hence, the synthesis of quinazolinone has evoked much interest, as a result of which a variety of synthetic methodologies have been reported.[21-23] The most important approaches are (i) one-pot condensation of aromatic aldehydes, 2-amino benzimidazole/3-amino-1, 2, 4-triazole and

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α-hydroxy C-H acids[24] (ii) three-component reaction of 2-amino benzamides, aryl halides, and isocyanides[25] (iii) one-pot reaction with *o*-amino benzamides and primary alcohols[26] (iv) cascade synthesis of phenylamino substituted quinazolinones from urea derivatives and *tert*-butyl isocyanide[27] [v] oxidative radical skeletal rearrangement induced by oxygen[28] (vi) synthesis of quinazolinone and quinazoline from aerobic oxidative C(sp3)−H amination/C−N cleavage.[29] Other methods have also been developed within the last three decades.[30] In the past years, a few methods have described the one-pot multicomponent synthesis of quinazolinones based on catalysts such as NH_2SO_3H,[31] thiamine hydrochloride,[32] CuCl,[33] chitosan,[34] nafion-H®,[35] Mg-Al-CO_3,[36] silica gel[37] and $H_6P_2W_{18}O_6 \cdot 18H_2O$[38] from the reaction of aromatic aldehydes, 2-amino benzimidazole/3-amino-1,2,4-triazole and *α*-hydroxy C-H acids. Nevertheless, these methods have some significant limitations like restricted to benzaldehyde, harsh reaction conditions, required long reaction time, tedious work-up, low yields, use of metal and moisture sensitive catalysts. Hence, the development of a simple and high yielding environmentally kind procedure for the one-pot multicomponent synthesis of quinazolinone analogues is still reasonable.

As part of our continuing efforts on the development of new methods for the construction of biologically active compounds,[39] we have reported synthesis of pyran-based heterocycles via one-pot reaction of benzyl halides, *α*-hydroxy C-H acids and active methylene compounds.[40] Herein, we investigated a new and straightforward approach for the synthesis of triazolo/benzimidazolo quinazolinones which involved an *in situ* oxidation of benzyl halides with trimethyl amine *N*-oxide in to corresponding aldehydes,

which they undergo a three-component reaction with α-hydroxy C-H acids and 2-aminobenzimidazole/3-amino-1,2,4-triazole without addition of any other catalyst. The wider scope and synthetic utility of trimethyl amine *N*-oxide for the synthesis of heterocyclic compounds in one pot has not been explored even though this reagent has been used as an oxidizing agent[41,42]. This procedure developed the known reaction using the novel methodology, while not limiting one of the substrates to an aldehyde.[43]

RESULTS AND DISCUSSION

To set up the optimal reaction conditions for the construction of quinazolinone analogues, our preliminary experiments were focused on a one-pot reaction involving 3-cyanobenzyl bromide (1 equiv), 2-amino benzimidazole (1 equiv), and dimidone (1 equiv) in the presence of trimethyl amine *N*-oxide (2 equiv) as an oxidizing agent. For a low hazard and eco-friendly process, ethanol is used as a preferred solvent for all the optimization experiments. The reactions were performed heating at 70 ^{o}C. It was found that the yield of the product was relatively superior. However, the yield decreased when the reaction proceed to room temperature or over 70 ^{o}C. Based on above results, a reaction of 3-cyanobenzyl bromide (1 equiv), 2-amino benzimidazole (1 equiv) and dimidone (1 equiv) in the presence of trimethyl amine *N*-oxide (2 equiv) stirring in ethanol at 70 ^{o}C was considered as a standard and a model reaction (Scheme 1) to optimize the reaction conditions for the one-pot synthesis of other triazolo/benzimidazolo quinazolinones.[44]

In order to evaluate the effect of organic solvents to optimize the reaction conditions using trimethyl amine *N*-oxide as an oxidizing agent for the synthesis of quinazolinone

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analogues (Table1), ethanol was replaced with other polar solvents such as THF, acetonitrile, DMF, water, acetic acid and methanol (entry 4, 6, 7, 8, 9 and 10). The results showed that using ethanol as the solvent gave the best yield of the respective product with higher reaction rate (entry 5). The use of non polar solvents such as toluene, chloroform, dioxane afforded the desired product in traces (entries 1, 2 and 3). Therefore, ethanol was selected as a suitable medium to run the further reaction trimethyl N-oxide as a oxidant.

The scope of present protocol was further investigated by the replacement of dimidone with ethylacetoacetate. To our observation, the reaction underwent successful condensation under similar reaction conditions to give the corresponding quinazolinone analogues in excellent yields (Table 2, entries 8, 9). Reactions were also carried out by replacing 2-amino benzimidazole with 3-amino-1,2,4-triazole. The reaction underwent smooth cyclisation to give respective quinazolinone derivatives in virtually high yields (Table 2, entries 10-14). Thereafter, a series of different substituted quinazolinone analogues were synthesized from different benzyl halides containing electron-withdrawing and electron-donating groups using trimethyl amine *N*-oxide in ethanol at 70 ^{o}C in high yields[45] (Table 2). In general, the overall yield ranged from 96% for 3,3-dimethyl-12(4-nitro-phenyl)-1,2,3,4,5,12-hexahydrobenzo [4,5]imidazo[2,1-*b*]quinazolin-1-one (**4h)** (entry 8) to 85% for 6,6-dimethyl-9-(4-hydroxy-phenyl)-5,6,7,9-tetrahydro-4*H*-1,2,4-triazolo[5,1-*b*] quinazolin-8-one (**4m**) (entry 13).

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The proposed mechanism (Figure 2) is similar to the well-known mechanism reported in the literature.[46-49] In the first step, oxidation proceeds via nucleophilic substitution of the benzyl halide with the oxygen of the trimethyl amine *N*-oxide to give a *N*-alkoxy salt. Afterwards, proton elimination at the carbon carrying the oxygen leads to the formation of an .aldehyde giving trimethyl amine hydrogen halide salt which in turn would, in the second step, able to acid catalyse Knoevenagel condensation between aldehyde and α-hydroxy C-H acid gives the heterodiene. The third step is the Michael addition of the amino compound on the heterodiene, followed by cyclisation and dehydration in the presence of acid to afford the desired product.

CONCLUSION

In conclusion, we have developed a new and straight forward methodology for the one pot synthesis of quinazolinone analogues via trimethyl amine *N*-oxide catalyzed *in situ* oxidation of benzyl halides into benzaldehydes followed by the three component reaction with α-hydroxy C-H acids and amine compounds. Mild reaction condition, one pot operation, easy isolation of product and broad functional group tolerance are the main advantages of this reaction.

EXPERIMENTAL

General Information:

All the reagents were purchased commercially and were used directly without further purification. The melting points were measured by the open capillary tubes using electric melting point equipment and are uncorrected. The Infrared (IR) spectra were obtained

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using Agilent Cary 630 FT-IR Spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker spectrometer using DMSO-d_6 as solvents and tetramethylsilane (TMS) as an internal standard at IISC, Bangalore. The chemical shifts were given on the δ scale (ppm). The purity of the compounds was checked by thin layer chromatography (Merck silica gel 60 F254 pre coated aluminium sheets). The CHN analysis was performed on an Elemental Vario Micro Cube CHN Rapid Analyzer. All the synthesized compounds gave agreeable elemental study.

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Typical Procedure For The Synthesis Of 12(3-Cyanophenyl)-3,3-Dimethyl-1,2,3,4,5,12-Hexahydrobenzo[4,5]Imidazo[2,1-*B*]Quinazolin-1-One (4a)

Trimethyl amine *N*-oxide (290 mg, 3.0 mmol) was added to a solution of 3-cyanobenzyl bromide (290 mg, 1.5 mmol), dimidone (210 mg, 1.5 mmol) and 2-aminobenzimidazole (200 mg, 1.5 mmol) in ethanol (10 mL) in a round-bottomed flask. The resulting reaction mixture was heated at 70 ^{o}C in an oil bath for 70 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The solid was collected by filtration at pump, washed with ethanol and recrystallised from hot ethanol to obtain pure product.

12(3-Cyano-Phenyl)-3,3-Dimethyl-1,2,3,4,5,12-Hexahydrobenzo[4,5]Imidazo [2,1-*B*]Quinazolin-1-One (4a).

Yield 94%; White solid; mp >300^{o}C; IR (ATR, cm^{-1}): 3394 (NH), 2018 (CN), 1660 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.98 (s, 3H, -CH_3), 1.04 (s, 3H, -CH_3), 2.22 (m, J = 4.0 Hz, 2H, -CH_2), 2.48 - 2.64 (m, J = 4.0 Hz, 2H, -CH_2,), 6.50 (s, 1H, CH),

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6.94 - 7.92 (m, 8H, Ar-H), 11.18 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.7, 28.1, 28.4, 32.2, 49.7, 53.6, 105.3, 109.9, 111.0, 117.0, 118.5, 120.7, 122.0, 129.8, 130.9, 131.5, 141.8, 142.8, 145.0, 150.9, 158.1, 159.1, 192.6 ppm; Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21; found: C, 74.82; H, 5.31; N, 15.13.

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Table 1. Optimization of solvents for the synthesis (**4a)**

Entry	Solvents	Time (min)	Yield (%)
1	Toluene	95	trace
2	$CHCl_3$	95	trace
3	Dioxane	90	traces
4	THF	80	55
5	**Ethanol**	**70**	**96**
6	Acetonitrile	75	86
7	DMF	80	78
8	Water	80	68
9	Acetic acid	80	65
10	Methanol	70	70

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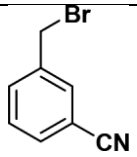
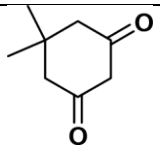
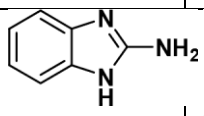
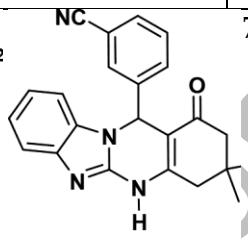
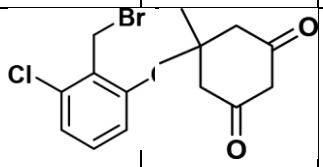
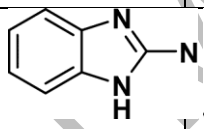
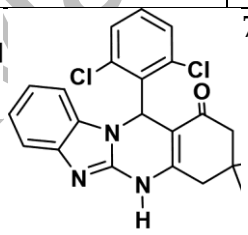
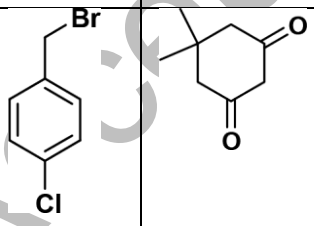
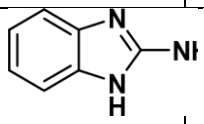
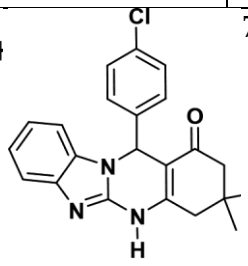
Table 2. Synthesis of quinazolinone analogues (**4a**–**n**)

Entry	Benzyl halides	α-Hydroxy C-H acids	Amine source	Quinazolinones	Time (min)	Yield (%)	Obs. mp (^{O}C)	Lit. mp (^{O}C)^{Ref}
1				 4a	70	94	>300	
2				 4b	70	92	>300	
3				 4c	70	92	>300	>300 [31]

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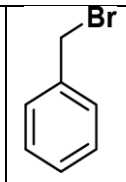
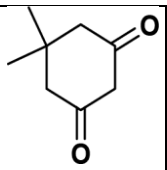
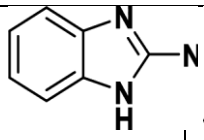
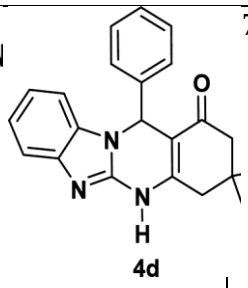
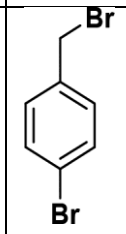
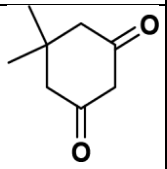
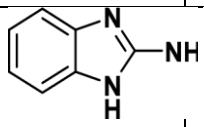
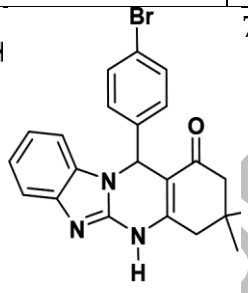
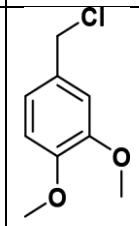
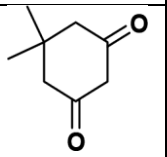
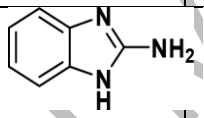
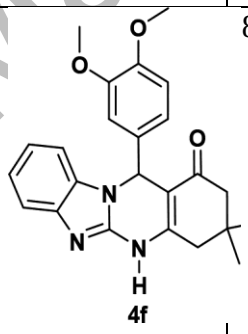
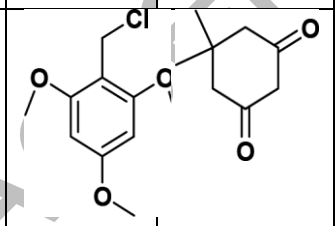
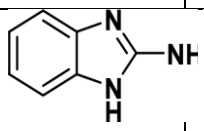
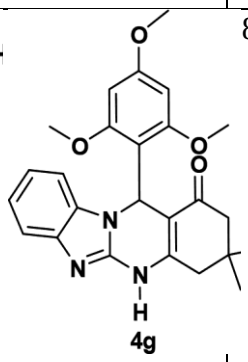
4				 4d	75	90	>300	>300 [31]
5				 4e	70	92	>300	>300 [31]
6				 4f	85	88	>300	>300 [50]
7				 4g	85	88	>300	

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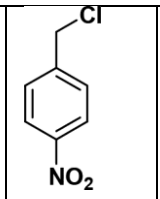
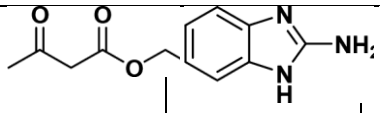
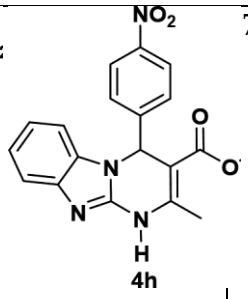
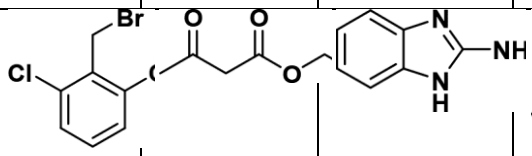
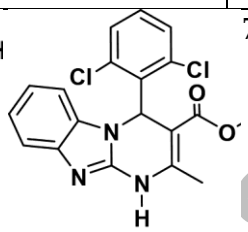
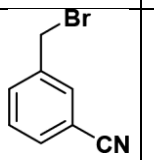
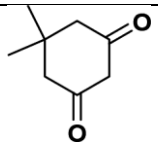
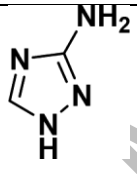
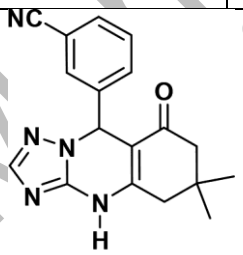
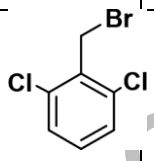
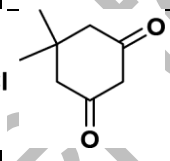
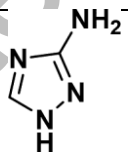
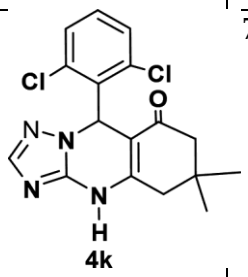
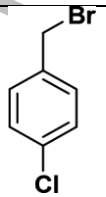
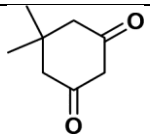
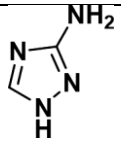
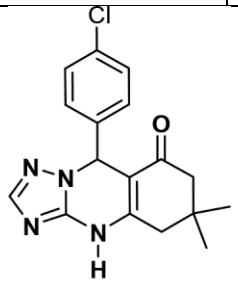
8				 4h	70	96	>300	>300[51]
9				 4i	70	92	>300	
10				 4j	65	94	>300	
11				 4k	70	92	292	
12				 4l	70	92	310	303-305 [31]

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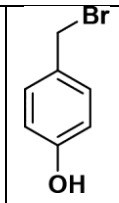
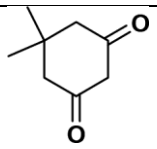
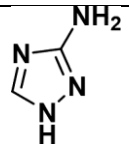
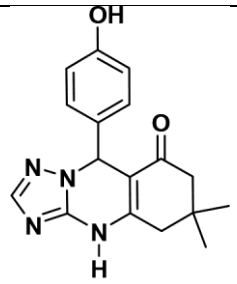
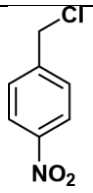
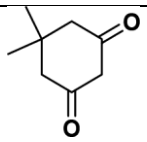
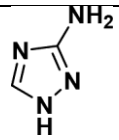
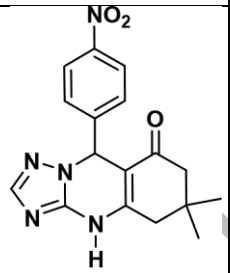
13				 4m	80	85	>300	>300 [31]
14				 4n	65	94	>300	307-309 [31]

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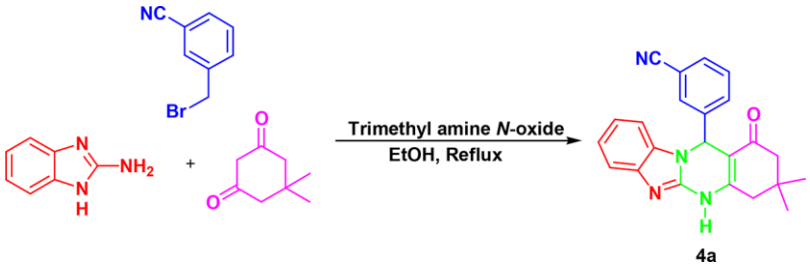
Scheme 1. Synthesis of 12(3-cyanophenyl)-3,3-dimethyl-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo [2,1-b]quinazolin-1-one (**4a)**.



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Scheme 2. A plausible reaction mechanism for the formation of quinazolinone derivatives.

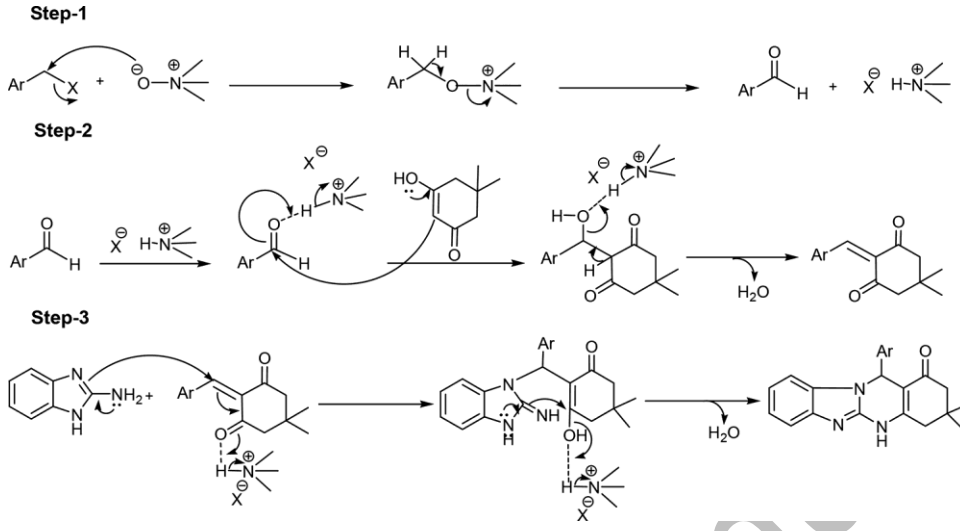

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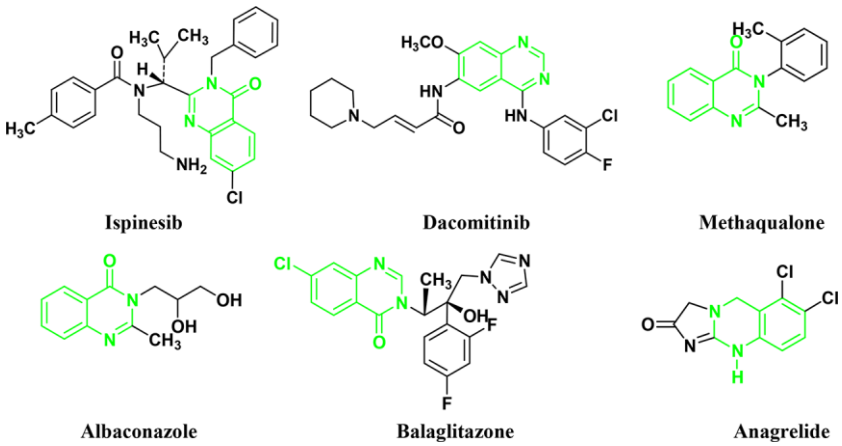
Figure 1. Quinazolinone derived commercially available drugs.



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