Arabian Journal of Chemistry (2023) **16**, 105190

King Saud University

Arabian Journal of Chemistry

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REVIEW ARTICLE

Advances in synthesis and biological activities of quinazoline scaffold analogues: A review

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Received 17 February 2023; accepted 19 July 2023
Available online 28 July 2023

KEYWORDS

Quinazoline;
Synthesis;
Biological activity;
Drug;
Heterocyclic

Abstract Creating effective, ecologically friendly, and commercially viable synthetic routes is crucial in the design and synthesis of organic substances. Quinazoline, a heterocyclic compound with nitrogen, is one of the most significant heterocyclic motifs with diverse chemical reactivities and many biological applications. Its derivatives comprise a family of fused heterocycles in over 200 naturally occurring alkaloids. Over the past few decades, newer, more complex drugs containing quinazolinone structures have been discovered, with enormous progress in designing various efficient protocols to construct these pharmacologically active scaffolds. This review evaluated the recently investigated protocols for synthesizing quinazolines and their derivatives (from 2017 to 2023 till date). The current review paper provides an up-to-date description of recent advancements in straightforward synthetic procedures that result in the creation of quinazoline molecules. In addition, the significant therapeutical activities of numerous quinazoline-based drugs were briefed and assessed in this review. We envisage that this information would assist researchers in designing and synthesizing novel quinazoline analogues as lead compounds.

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.arabjc.2023.105190

1. Introduction

Nitrogen-containing heterocyclic molecules are vital in medical chemistry due to their extensive applications in various fields. Quinazolines are a valuable class of nitrogen-containing heterocyclics with a wide range of biological properties, particularly as anti-bacterial (Ghorab et al., 2013), anti-psychotic (Alvarado et al., 2006), anti-fungal (Al-Amiery et al., 2014), anti-inflammatory (Giri et al., 2009), anti-diabetic (Karan et al., 2021) anti-tuberculosis (Kunes et al., 2000); anti-malarial (Chugh et al., 2020), anti-obesity (Sasmal et al., 2012), anti-viral (Mermer et al., 2021); A_{2A} adenosine receptor antagonists (Bolteau et al., 2022), nematicidal (Wang et al., 2023) agents. Additionally, poly-(ADP-ribose) polymerase (PARP) (Guiles et al., 2009), thymidylate synthase (Liu et al., 2006), tyrosine kinase (Conconi et al., 2013) inhibitors, anti-hepatocellular carcinoma and Radio-sensitizers (Ghorab et al., 2023) characteristics of quinazoline analogues are well documented. Some quinazoline derivatives (Jafari et al., 2016) with diverse biological activities were presented in figure1.

Several quinazoline derivatives are approved drugs, such as Terazosin hydrochloride, Prazosin hydrochloride and Doxazosin mesylate (Kyprianou, 2003). Moreover, due to the promising therapeutic efficacy against human cancers, various quinazoline derivatives like Erlotinib (Moyer et al., 1997), Gefitinib (Wakeling et al., 2002), Lapatinib (Rusnak et al., 2001); Vandetanib (Wedge et al., 2002) and Afatinib (Li et al., 2008) have been approved for cancer therapy in the clinic (figure 2) by the United States Food and Drug Administration (USFDA). Thus, with significant biological activities, quinazoline derivatives have received the utmost importance in organic synthesis and medicinal chemistry research.

Griess produced the first quinazoline moiety, 2-cyano-3,4-dihydro-4-oxoquinazoline (Figure 3), 1869 by reacting cyanogens with 2-aminobenzoic acid. Griess was the first to notice the product's bicyclic character, naming it bicyanoamido benzoyl (Griess, 1869) and using it until 1885.

Bichler and Lang made the parent quinazoline (Figure 4) molecule *via* decarboxylation of the 2-carboxy quinazoline derivative (Bischler and Lang, 1895). Gabriel(1903) developed an improved method for synthesising quinazolines and investigated their characteristics.

Widdege proposed the name quinazoline, which comprises two rings, one of which is benzene and the other one is a pyrimidine. Quinazoline has also been referred to by the names phenamiazine, benzyleneamidine, benzo-1,3-diazine-5,6-benzo pyrimidine, and 1,3-diazanapthaline. Adding a fused benzene ring changes the characteristics of the pyrimidine ring expressively. The extent of conjugation and substituents on the benzene and pyrimidine rings significantly impact the quinazoline derivative properties.

Despite the remarkable progress in quinazoline chemistry, there is still a shortage of terse and efficient protocols for constructing these medicinally significant quinazoline derivatives. Very few reviews addressing the synthesis and properties of these motifs have appeared. For instance, Paul and co-authors (Prashant et al., 2020) described the advances in lead

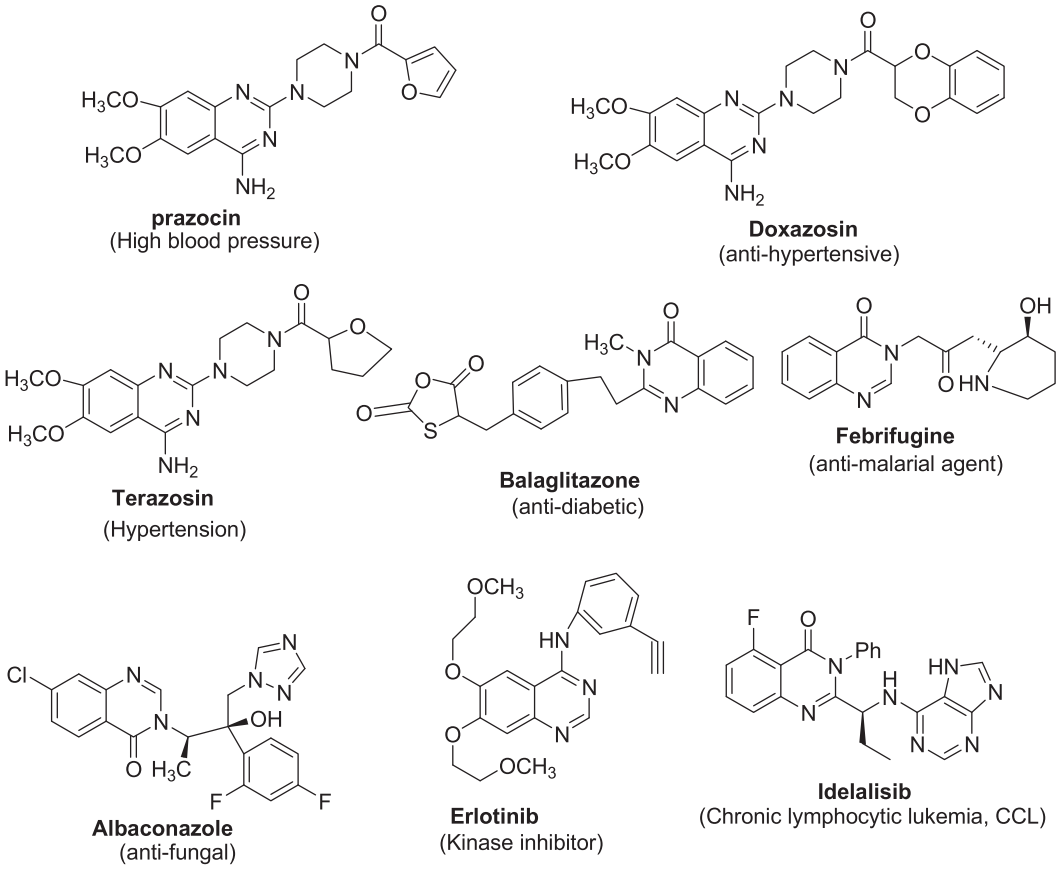


Fig. 1 Some bioactive qunazoline sscaffolds.

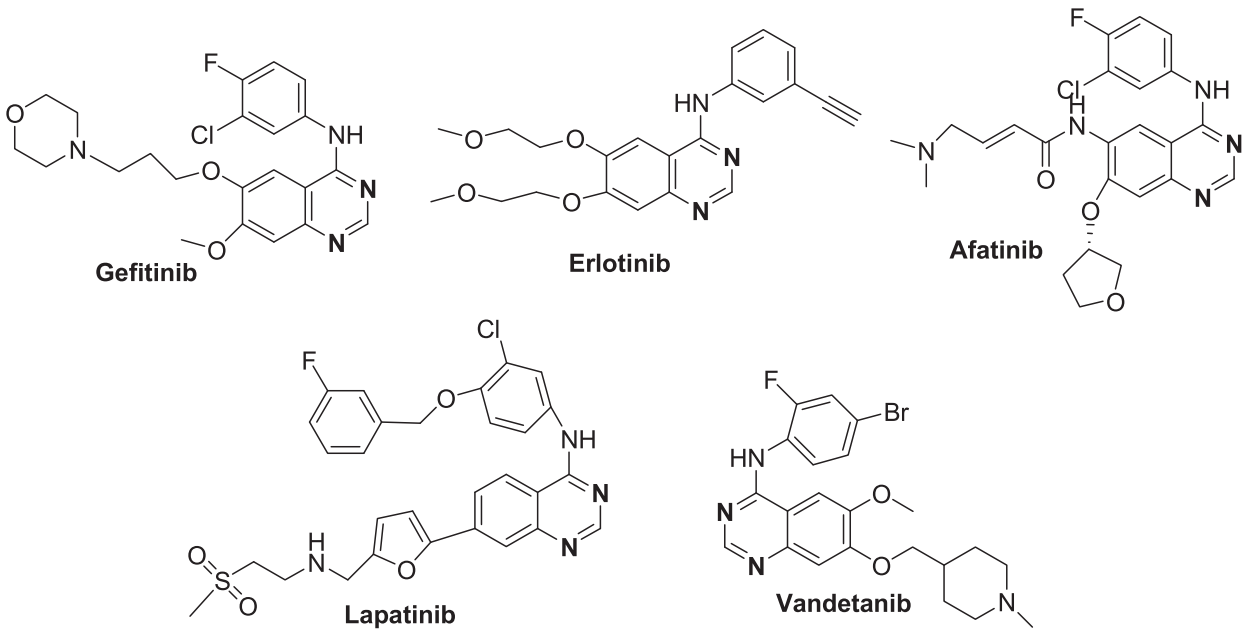


Fig. 2 FDA Approved quinazoline motifs for cancer therapy.

compounds of quinazoline hybrids and their related heterocycles in medicinal chemistry that help to exaggerate the drug development practice. Chen et al. (Chen et al., 2022) provided a comprehensive depiction with emphasis on the structure–activity relationships (SAR) mechanism, agricultural biological activities, and mechanism of action of quinazoline derivatives in the past decade systematically. Yar *et al.* (Haider et al., 2022) summarised the recent advances of quinazoline/quinazolinone scaffold-bearing derivatives as anticancer agents acting through vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR) and dual VEGFR/EGFR inhibitors. Neelima and co-workers (Karan et al., 2021) provided information regarding the latest developments in quinazoline analogues with a broad range of pharmacological activities. Al-Salahi and Abuelizz (Abuelizz and Al-Salahi, 2023) provided an up-to-date account of research findings on the pharmacological activities of benzoquinazoline derivatives and suggested directions for future discoveries. Emami *et al.* (Haghighijoo et al., 2022) presented the relevant information regarding the anti-Alzheimer agents having quinazoline core structure which can promote the discovery and development of novel anti-AD agents. Ionut*et al.* (Şandor et al., 2023) outlined the general principles for developing (2017–2023) potent EGFR TKIs, exploring the impact of structural modulations in critical positions of the quinazoline core on the anticancer effect. Bhagat and coworkers (Bhagat et al., 2022) disclosed patents of synthetics and natural DHFR inhibitors with quinazoline and diaminopyrimidine nuclei during 2001–2021. The review also emphasised the clinical evolution of various DHFR inhibitors established during 2016–21. Gheidari*et al.* (Gheidari et al., 2022) described the multiple methods for synthesising quinazoline-2,4(1H,3H)-diones, such as green methods and heterogeneous or homogeneous catalysts from various precursors under different conditions. Joshi and co-authors (Parveen et al., 2022) described the biological significance of quinazoline and its derivatives. They used the diverse nano catalysts (2015–2022) to synthesise various quinazoline derivatives with emphasis on the catalytic performances and synthetic protocols that afford an idea for the coherent designing of efficient, novel and efficient nanocatalysts. Quinazoline and its derivatives have been incessantly evaluated as potent bioactive compounds in recent decades. Table 1 summarises some of the most effective bioactive compounds (Giang et al., 2020; Zhang et al., 2021; Qin et al., 2022; Ghorab et al., 2021; Malasala et al., 2020; Romero et al., 2019; Moreira et al., 2023; Zuzana et al., 2023) with quinazoline nuclei reported in recent years.

Giang*et al.* (Giang et al., 2020) prepared and evaluated the quinazoline-triazole hybrid motifs as acetylcholinesterase inhibitors to treat Alzheimer's disease (AD). The biological assay outcomes revealed that 6-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-N-benzylquinazolin-4-amine (Compound I, Table 1) is the most potent with IC_{50} (AChE) value 2.6 ± 0.1 9 μM. Zhang *et al.* (Zhang et al., 2021) synthesised a series of quinazoline derivatives containing substituted anilide and-sulfamoylphenyl fragments as dual EGFR/CAIX inhibitors. In the obtained compounds, 5-((7-methoxy-4-((3-(trifluoromethyl)phenyl)amino)quinazolin-6-yl)oxy)-N-(4-sulfamoylphenyl)pentanamide (Compound II, Table 1) was identified as the most potent with $EGFR^{WT}$ IC_{50} = 27.0 nM, $EGFR^{T790M}$ = 9.2 nM, and CAIX IC_{50} = 115 nM. Qin *et al.* (Qin et al., 2022) prepared a library of 2–substituted–4–amino-quinazolines and evaluated their anti-fungal activity against four invasive fungal strains. The antimicrobial screening revealed that compound *N*-((1E,3E)-penta-1,3-dienyl)-2-p-tolylquinolin-4-amine hydrochloride (Compound **III**, Table 1) have good anti-fungal activity with MICs 4–16 μg/mL. Ghorab *et al.,* (Ghorab et al., 2021) synthesised a series of iodoquinazolinones with benzenesulfonamide moiety as human carbonic anhydrase (hCA) inhibitors. The screening outcome revealed that 2-(3,4-dihydro-6-iodo-4-oxo-3-(4-(trifluoromethylsulfonyl)phenyl)quinazolin-2-ylthio)-N-(pyridin-4-yl)acetamide (Compound **IV**, Table 1) is identified as the most potent candidate against hCA IX and hCA XII., on MTT assay, it

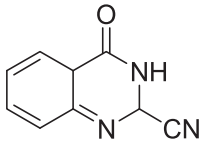


Fig. 3 Structure of 2-Cyano-3,4-dihydro-4-oxoquinazoline.

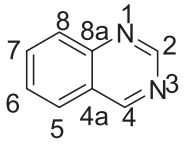


Fig. 4 Structure of quinazoline.

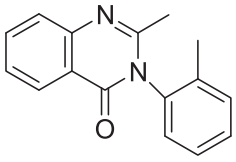


Fig. 5 Structure of Methaqualone.

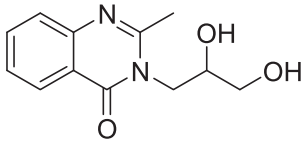


Fig. 6 Structure of Diproqualone.

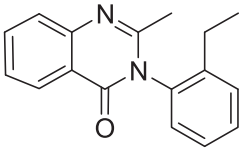


Fig. 7 Structure of Etaqualone.

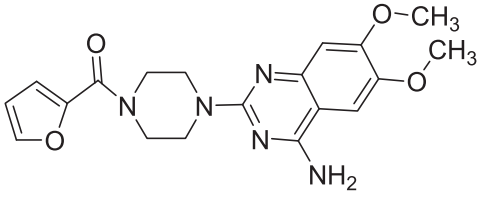


Fig. 8 Structure of Prazosin.

exhibited potent activity against HepG-2 and MCF-7 cells with IC_{50} values of 2.53 μM and 4.58 μM. Satyaveni *et al.* (Malasala et al., 2020) synthesised 2-arylquinazoline benzamide derivatives and screened against *Mycobacterium tuberculosis* H37RV strain, the Compound *N1*-(5-bromo-2-chlorophenyl)-N4-(2-phenylquinazolin-4-yl)benzene-1,4-dia mine (Compound **V**, Table 1) exhibits selective and potent antimycobacterial activity with MIC value 4 mg/mL. Romeo *et al.,* (Romero et al., 2019) prepared a series of 2-aryl-

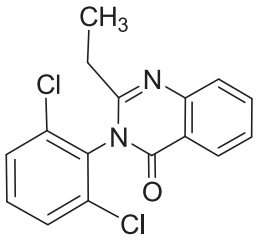


Fig. 9 Stucture of Cloroqualone.

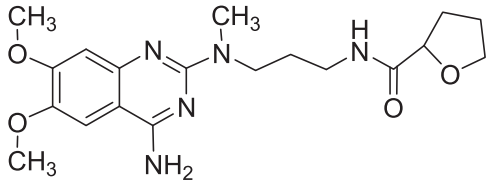


Fig. 10 Structure of Alfuzosin.

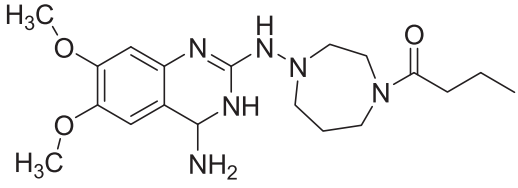


Fig. 11 Structure of Bunazosin.

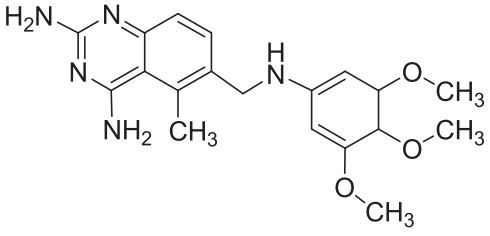


Fig. 12 Structure of Trimetrexate.

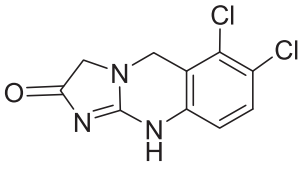


Fig. 13 Structure of Anagrelide.

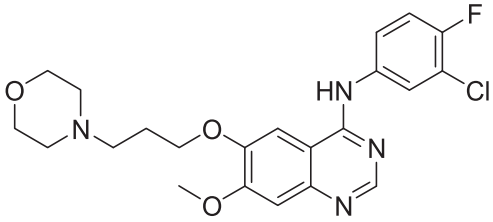


Fig. 14 Structure of Gefitinib.

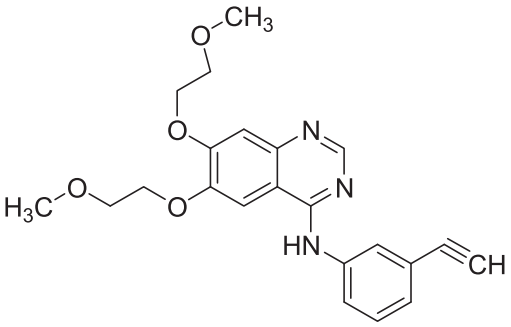


Fig. 15 Structure of Erlotinib.

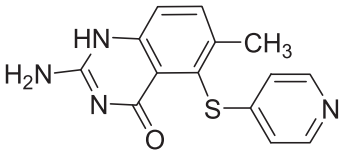


Fig. 16 Structure of Nolatrexed.

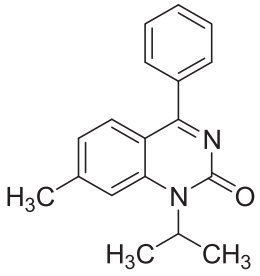


Fig. 17 Structure of Proquazone.

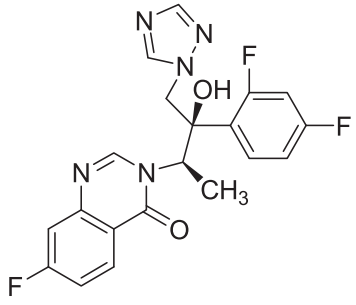


Fig. 18 Structure of Albaconazol.

quinazolin-4(3H)-ones as leishmania folate inhibitors. The biological screening result revealed that 2-(3-methoxyphenyl)qui nazolin-4(3H)-one (Compound **VI**, Table 1) is identified as a potent antileishmanial agent with ID_{50} vales 11.04–29.34 μM. Moreira group (Moreira et al., 2023) described the synthesis of Pyrrolo[1,2-*c*]quinazolines and Pyrrolo[2,1-*a*] isoquinolines *via* a C(sp^3)–H functionalisation of 4-methylquinazolines and 1-benzylisoquinolines with α-substituted β-nitrostyrenes mediated by inexpensive Cu $(OAc)_2$. The biological activity of the 2-(furan-2-yl)-3-methyl H-pyrrolo[1,2-c]quinazoline (Compound **VII**, Table 1)was found to have promising antiplasmodial action against

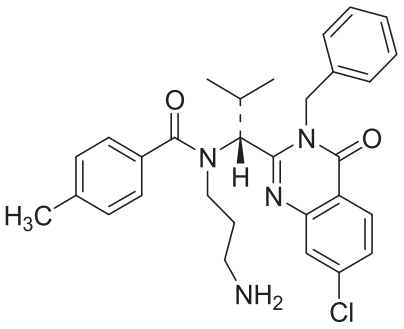


Fig. 19 Structure of Ispinesib.

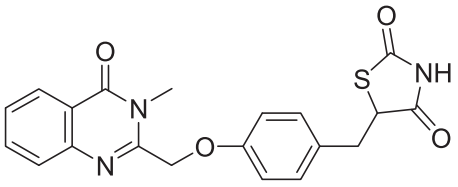


Fig. 20 Structure of Balaglitazone.

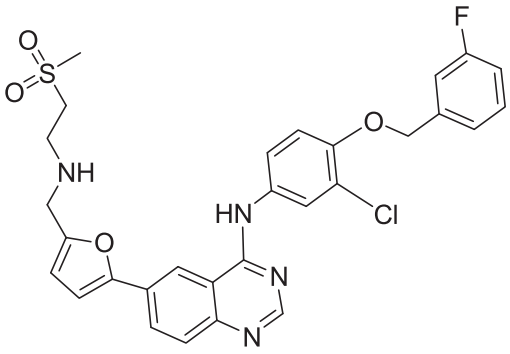


Fig. 21 Structure of Lapatinib.

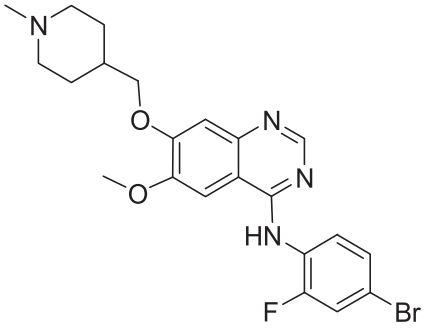


Fig. 22 Structure of Vandetanib.

Plasmodium falciparum. Zuzana and group (Zuzana et al., 2023) reported various 2-Substituted quinazolines as partial agonistic and antagonistic ligands of the constitutive androstane receptor (CAR) among the prepared compounds 2-(4-bro mophenyl)quinazoline-4-thione (Compound **VIII**, Table 1) exhibited significant CAR antagonistic activity with EC_{50} value of 0.055 μM.

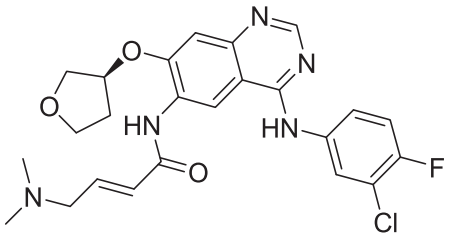


Fig. 23 Structure of Afatinib.

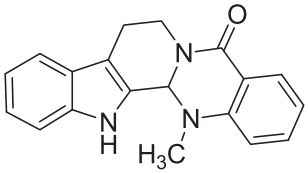


Fig. 24 Structure of Evodiamine.

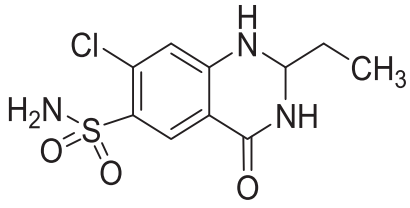


Fig. 25 Structure of Quinethazone.

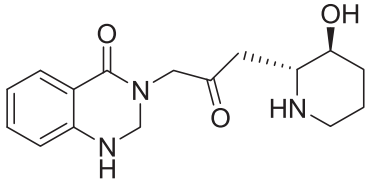


Fig. 26 Structure of Febrifugine.

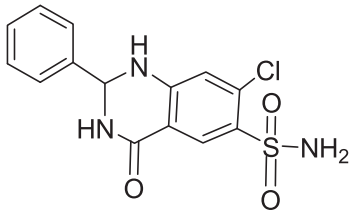


Fig. 27 Structure of Fenquizone.

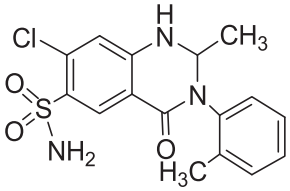


Fig. 28 Structure of Metolazone.

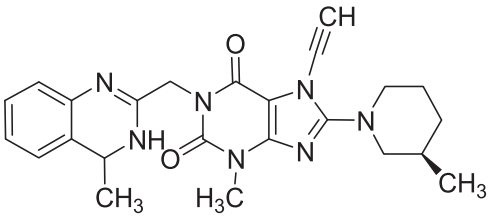


Fig. 29 Structure of Linagliptin.

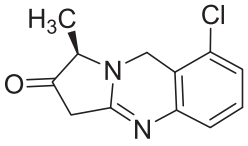


Fig. 30 Structure of Quazinone.

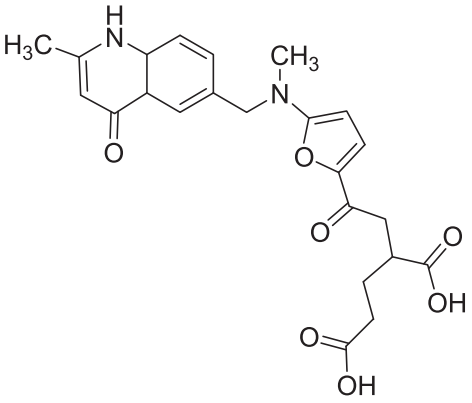


Fig. 31 Structure of Raltitrexed.

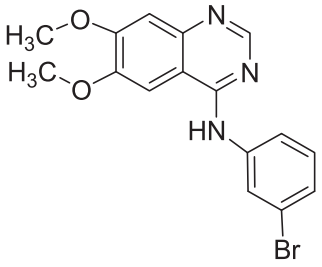


Fig. 32 Structure of EBE-A22.

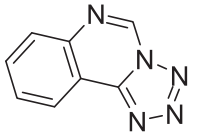
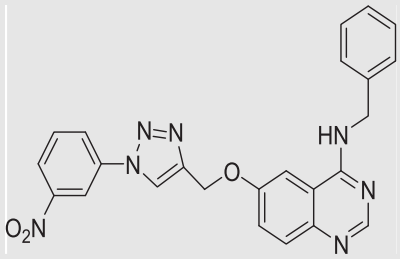
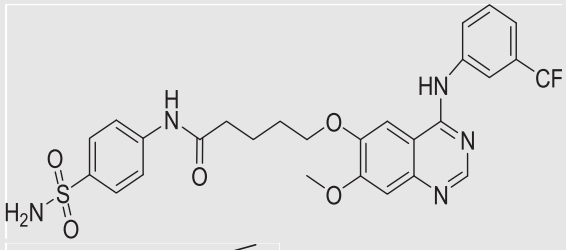
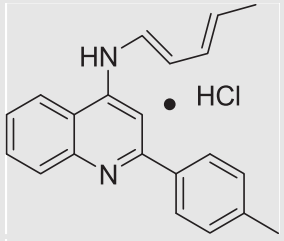
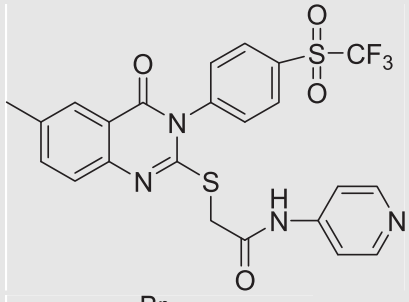
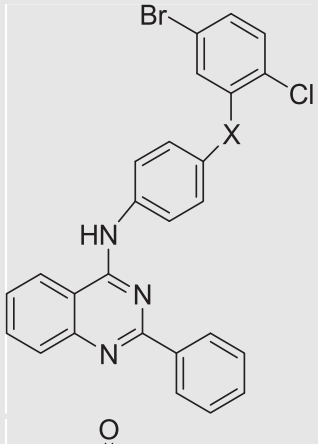
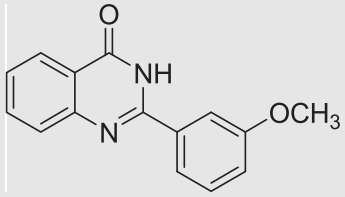


Fig. 33 Structure of NSC127213.

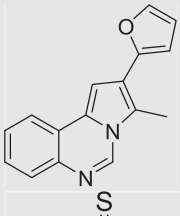
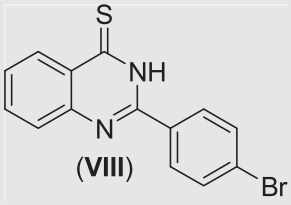
Due to the extensive range of applications of Quinazolines in different fields, the authors believed that the collection of the recent advances in synthetic methods for the construction of Quinazoline scaffolds and reported synthetic protocols of quinazoline-based drug molecules along with its therapeutic

Table 1 Recently reported bioactive quinazoline scaffolds.

Entry	Compound	Biological Activity	Ref. No
1		Anti-Alzheimer's activity	(Giang et al., 2020)
2		Dual EGFR/CAIX inhibitor	(Zhang et al., 2021)
3		Anti-fungal agent	(Qin et al., 2022)
4		Human carbonic anhydrases IX/XII inhibitors	(Ghorab et al., 2021)
5		Anti-tubercular agent	(Malasala et al., 2020)
6		Antileishmanial activity	(Romero et al., 2019)

(*continued on next page*)

Table 1 (*continued*)

Entry	Compound	Biological Activity	Ref. No
7		Antiplasmodial activity	(Moreira et al., 2023)
8	 (VIII)	CAR antagonistic activity	(Zuzana et al., 2023)

application would be exceptionally helpful for the young researchers to spotlight on Quinazoline construction and its applications. In this review, we afforded to collect the recent progressions in synthesizing different quinazoline derivatives from 2017 to till date in 2023 and the pharmacological significance of new quinazoline-based drug moieties along with the developed synthetic pathways towards those drugs. The information presented in this manuscript is beneficial for medicinal chemistry researchers to open inventive channels towards constructing several highly efficient lead quinazoline molecules.

2. Synthesis of quinazoline

The first quinazoline compound was generated in 1869 using anthranilic acid and cyanogens (Griess, 1869). Since then, the field attracted various researchers developing multiple conventional techniques for synthesising quinazoline analogues (Sharma and Kaur, 1989; Moore et al., 1969; Cai et al., 2002; Asakawa and Matano, 1979; Connolly et al., ,2005; Su and Yang, 2002).Most of these approaches use the Niementowski reaction, which fuses the analogues of anthranilic acid with amides (Scheme 1) at temperatures between 130 and 150 °C *via* the formation of an *o*-amidobenzamide intermediate (Niementowski, 1895).However, this approach results in low yields and contaminants that are generally difficult to remove by column chromatography or recrystallisation. Besson *et al.,* (Alexandre et al., 2002) used microwave irradiation to re examine the Niementowski synthesis of the 4(3H)- quinazolinones to improve yields and speed up response times. The condensation of anthranilamide (2-aminobenzamide) derivatives with carbonyl compounds and the one-pot three-component reaction of aldehydes, isatoic anhydride and amines (Kim and Cheon, 2014; Zhang et al., 2015; Li et al., 2015; Lobo et al., 2012; Mekala et al., 2017) are two additional significant procedures for the synthesis of quinazolines (Scheme 1).

Transition metal-catalysed C–H activation and functionalisation routes are the most promising approaches. The transition metal-catalysed C–H activation processes arepromising and display an excellent future for organometallic chemistry. Compared to the traditional method, the transition metal-catalysed C–H activation and functionalisation is simple. With no requirement for pre-functionalising the starting material, waste generation is minimised. Significant progress has been achieved in creating heterocycles via C-N and C–C bonds in the last five years. The monograph provides a concise summary and review of the recent literature on the metal-catalysed generation of quinazolines *viaC–H* activation and *C–N* coupling reactions over the past fiveyears.

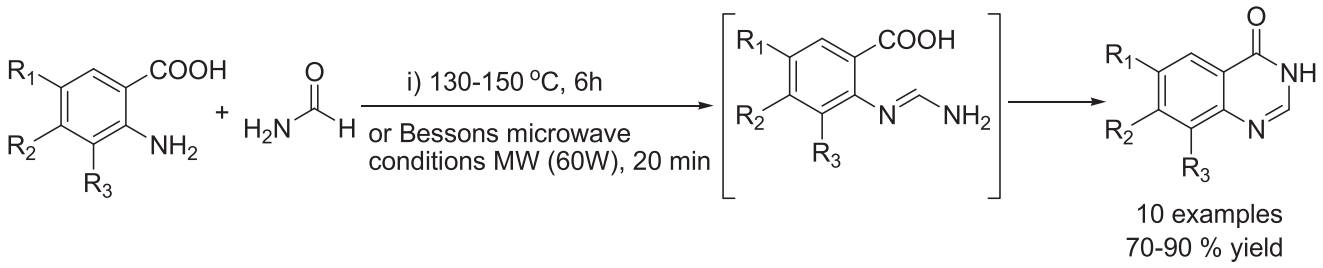
Paul and coauthors reported (Chakraborty et al., 2019) a simple atom-efficient reaction of nitriles with 2-aminobenzyl alcohol to obtain quinazolines in good yields *via* the biomimetic dehydrogenative condensation/coupling process (Scheme 2). Singlet diradical Ni(II) with two antiferromagnetically connected singlet diradical diamine type ligands catalyses this reaction.

Catalytic system from the cationic ruthenium−hydride complex [(C_6H_6)- (PCy_3)(CO)RuH]+ BF_4^- (precatalyst) with 4-(1,1-dimethylethyl)-1,2- benzenediol (Ligand) was found to give the highest activity and selectivity for the coupling of 2-(aminophenyl)ethanone with 4-methoxybenzylamine in yielding the quinazoline product (Scheme 3) by Yi and group (Arachchige and Yi, 2019). The reactions work without using any reactive reagents or forming any toxic byproducts.

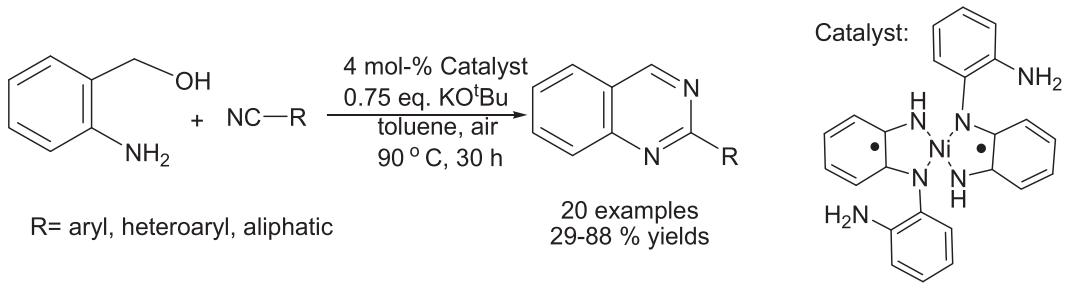
Chen and coworkers (Chen et al., 2018) described a competent synthesis of quinazolines through a Fe(II) catalysed C (sp^3)-H oxidation and intramolecular *C−N* bond formation (Scheme 4). Initially, the reaction of 2-alkylamino benzonitriles with various organometallic reagents led to 2-alkylamino *N–H* ketimine species. Next, the $FeCl_2$-catalysed C(sp^3)-H oxidation of the alkyl group employing *tert*-BuOOH, intramolecular *C−N* bond formation and aromatisation afforded a wide variety of 2,4-disubstituted quinazolines in good to excellent (43–86 %) yields.

Chen *et al.* reported (Hu et al., 2018) an efficient Pd-catalysed one-pot three-component tandem reaction of 2-aminobenzonitriles, aldehydes, and arylboronic acids. The reaction proceeds through the cyano group's carbopalladation, generating a wide range of quinazolines (Scheme 5). The significant feature of this protocol is tolerance of bromo and iodo groups, broad substrate scope with remarkable chemoselectivity.

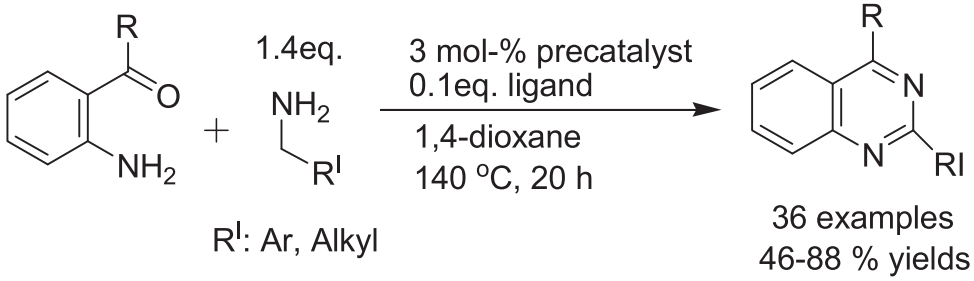
Bhanage*et al.* (Raut et al., 2017)produced cuprous oxide nanocubes as a heterogeneous nano-catalytic system and used



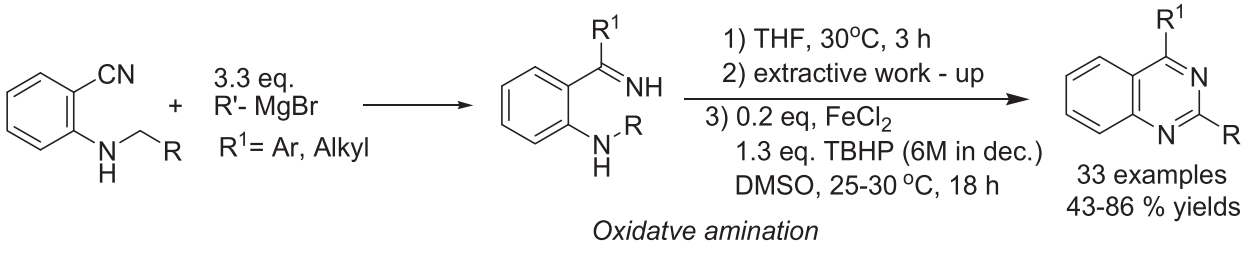
Scheme 1 Synthesis of quinazoline by Niementowski reaction or by Besson's microwave conditions.



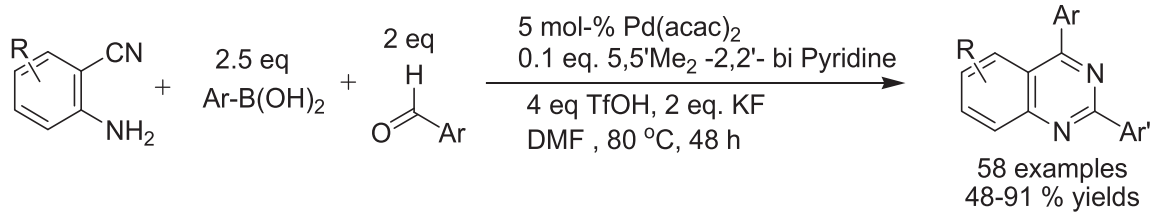
Scheme 2 Singlet diradical diamine Ni(II) catalysed the synthesis of arylquinazolines.



Scheme 3 Cationic ruthenium–hydride complex catalysed synthesis of quinazolines.



Scheme 4 Ferrous chloride catalysed synthesis of quinazolines.



Scheme 5 Palladium-catalysed catalysed synthesis of arylquinazolines.

one-pot tandem cyclisation of 2-bromobenzaldehyde derivatives with amidine hydrochlorides without the use of ligands. This simple, eco-friendly method can produce quinazoline frameworks in excellent isolated 81–95 % yields Within a few minutes (Scheme 6). The cuprous oxide nano catalytic system could also be recycled and regenerated up to four times without significantly losing its catalytic effectiveness.

Fan *et al*. recently described (Guo et al., 2018) the production of quinazolines in moderate to good isolated yields (40–72%) using the Cu-catalysed aerobic oxygenation of 2-(2-amidoaryl)-1Hindoles, followed by intramolecular cyclisation under acidic conditions (Scheme 7). This method features controlled selectivity and a simple operational procedure.

The construction of quinazoline derivatives from I_2 catalyzed reaction of 2-aminobenzaldehydes or 2-aminobenzophenones with benzyl-amines was recently described by Bhanage*et al*. (Deshmukh and Bhanage, 2018) With a sample range of functionalised 2-aminobenzaldehydes or 2-aminobenzophenones, many functionalised hetero-aryl or aryl amines were examined to produce quinazolines in 49–92% yields (Scheme 8). The method is more environmentally benign and cost-effective due to using O_2 as a safe oxidant without transition metals, additives, and solvents. The absence of an aqueous workup also increases the efficiency of this process.

Wu *et al*. (Wu et al., 2018) presented a rhodium-catalysed direct and distinctive process through annulation of ketones and 2-arylimidazoles,for a library of 5- arylimidazo[1,2-c] quinazolines in 49–95 % yields (Scheme 9). This approach is distinguished by (i) being devoid of halo functionalisation handles and (ii) using readily available starting materials.

Wang and Jiao documented (Wang and Jiao, 2016) the synthesis of biologically active quinazolines by reacting imidate derivatives with alkyl azides. The novel [4 + 2] carbon-hydrogen bond activation and annulation was co-catalysed by Cu and Rh. Simple alkyl azide derivatives are usefully used in this aerobic oxidative process to produce *N*-heterocycles, with water and nitrogen as byproducts(Scheme 10).

While employing inexpensive 2-aminobenzonitriles, aryl boronic acids and aldehydes, Chen *et al*. (Kun et al., 2018) demonstrated Pd-catalysed three-component, one-pot tandem assembly for quinazolines. The technique exhibits astounding chemoselectivity and a broad substrate range (Scheme11). This method stands out for its tolerance of iodo and bromo moieties allowing flexibility for future modifications.

The same team reported the reaction of aryl boronic acids with 2-(quinazolinone-3(4H)-yl)benzonitriles (Zhang et al., 2018) in another approach. This tandem synthesis produced the quinazoline scaffolds in good to exceptional isolated yields (31–93%) through nucleophilic addition, intramolecular cyclisation, and subsequent ring-opening (Scheme 12).

Another interesting study by Chen *et al*. (Zhu et al., 2018) describes the synthesis of 2,4-disubstituted quinazoline derivatives using 1,10-phen and trifluoroacetic acid in THF at 80 °C in the Pd-catalyzed reaction of aryl boronic acidswith *N*-(2-cyanoaryl)benzamides (Scheme 13). With *N*-(2-cyanoaryl) benzamides, the reaction showed a wide range of functional group tolerance, encompassing electron-deficient and electron-rich aryl boronic acids.

In 2021, Senadi*et al*. (Philips et al., 2021) reported an atom economical and environmentally benign Cu-promoted oxidative coupling strategy towards the construction of 4(3H)-quinazolinones and benzoimidazoquinazoline utilising 0.25–0.5 equivalent D-glucose as renewable C_1 synthon in the open air for 12– 24 h at 120 °C (Scheme 14). Biomass-derived platform chemical as carbon synthon; synthesis of naturally occurring alkaloids and precursors are the significant features of this method.

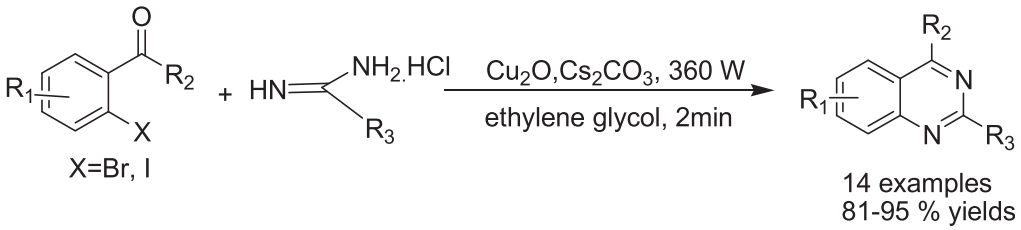
To find a new fungicide to combat Rhizoctoniasolani, Lei and coworkers reported (Lei et al., 2022) a library of novel quinazolinone scaffold-containing pyrazole carbamide derivatives (Scheme 15). Initially, the substituted quinazolinone wasobtained from anthranilic acid and formamidine acetate in ethylene glycol monomethyl ether at 95–130 °C to get the quinazolin-4-ones (Scheme 16). The key intermediate *N*-(2-(chloromethyl)phenyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide was obtained in 75% yield by dissolving 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid in DMF followed by the addition of triethylamine and thionyl chloride at room temperature (Scheme 17). Next, the targeted quinazolinone-scaffold-containing pyrazole carboxamides were achieved in 41–83 % yield by the reaction of quinazolin-4-ones and *N*-(2-(chloromethyl)phenyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide in DMF under alkaline conditions (Scheme 15).

Tskhovrebov and group demonstrated (Osmanov et al., 2022) an efficient method for the synthesis of 2-selenoxo-1,2,3,4-tetrahydro-4-quinazolinone *via* cyclisation reaction between methyl anthranilate and isoselenocyanates (Scheme 18). The latter compounds readily undergo oxidation with H_2O_2 to produce the appropriate diselenides in high yields (Scheme 19). Additionally, all chalcogen bonding (ChB) interactions were established by DFT calculations, followed by the topological analysis of the electron density distribution.

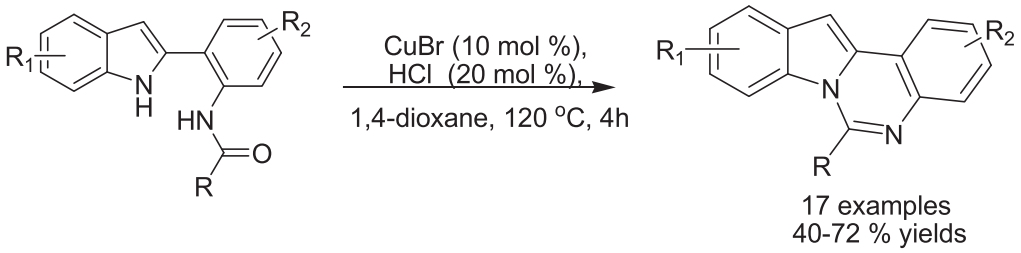
Al-Tel' group (Ravi et al., 2023) reported a metal-free, stereo-divergent build/couple/pair strategy that allows access to a unique collection of benzo[5,6][1,4]) (oxazino[4,3-*a*]quinazoline, quinolino[1,2-*a*]quinazoline scaffolds (Scheme 20) with total diastereo control and wide distribution of molecular architectures. This metal-free protocol proceeds through the desymmetrisation of phenol derivatives. The cascade connects Mannich with aza-Michael addition reactions, providing hasty entries to different classes of molecular shapes in a single operation.

Gil and team (Victor et al., 2020) described a simple method for the synthesis of substituted 3-benzyl-1-(4-(trifluoromethyl)benzyl)quinazolin-2,4(1H,3H)-diones (Scheme 21). Initially, 3-benzylquinazolinediones were obtained by reacting 2-aminoaryl esters and aryl isocyanates *via* method A or B. Further, the obtained 3-benzylquinazolinedione in DMF combines with 4-(trifluoromethyl) benzyl chloride in the presence of $NaHCO_3$ and the reaction mixture is heated to 130 °C overnight to produce the consecutive 3-benzyl-1-(4-(trifluoromethyl)benzyl)- quinazolin-2,4(1H,3H)-diones in 10–71 % yields.

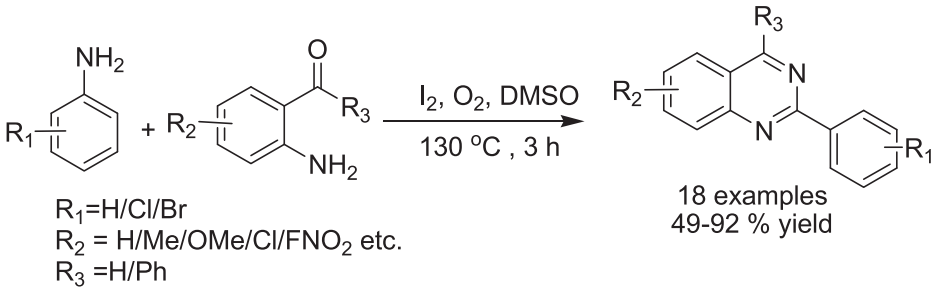
Chang and coauthors presented (Wang et al., 2023) the metal-free synthesis of quinazolinone-fused polycyclic skeletons from 2-aminobenzamide precursors *via* an iodine-promoted intramolecular sp^3 C–H amination reaction (Scheme 22). The reaction progressed well with crude 2-aminobenzamide derivatives, permitting the synthesis of the products from tetrahydroisoquinolines and simple 2-aminobenzoic acids without purification of the 2-aminobenzamide intermediates. This reaction has a broad sub-



Scheme 6 Cu_2O–catalysed synthesis of quinazolinone derivatives.

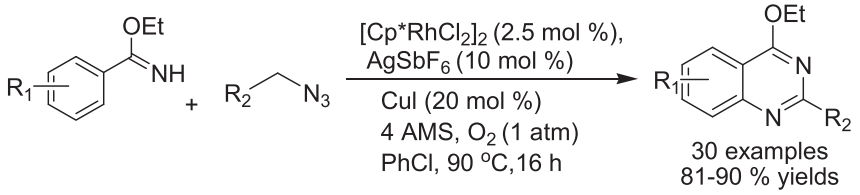


Scheme 7 CuI -catalysed synthesis of quinazoline derivatives.

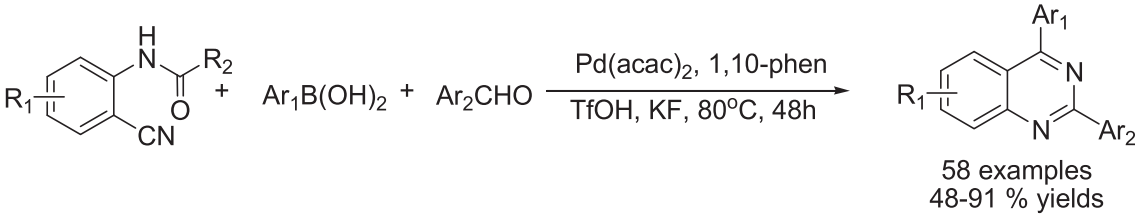


Scheme 8 Molecular iodine catalysed reaction of benzyl-amines with 2-amino benzophenones or 2-aminobenzaldehydes.

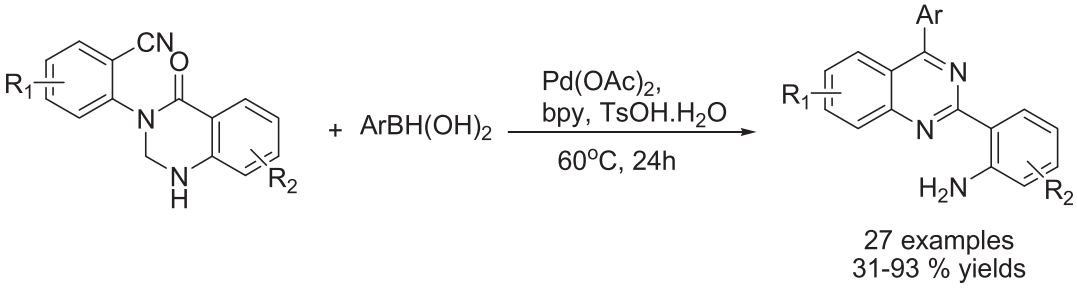
Scheme 9 Rhodium-catalysed annulation of C–H bonds.



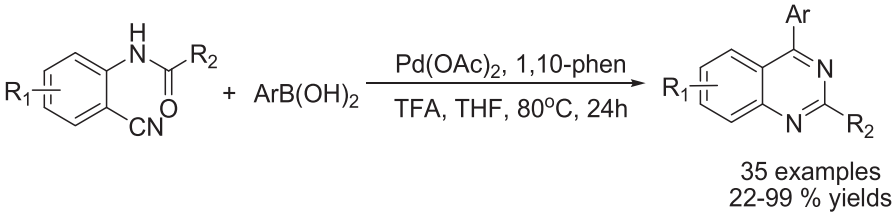
Scheme 10 Rh-catalyzed protocol for the formation of quinazoline skeletons.



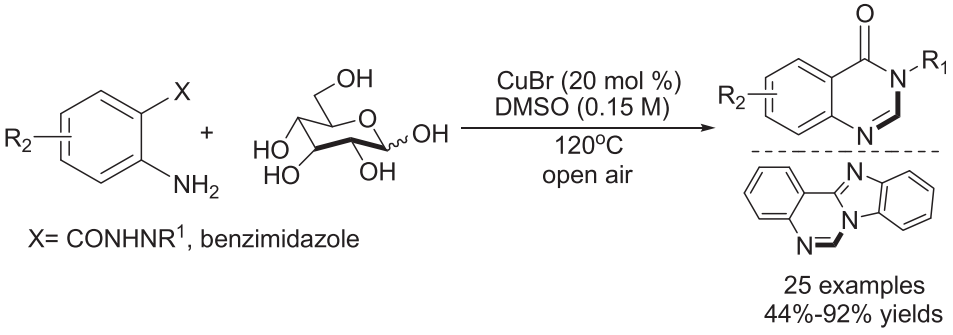
Scheme 11 Pd-catalyzed synthesis of quinazolinones.



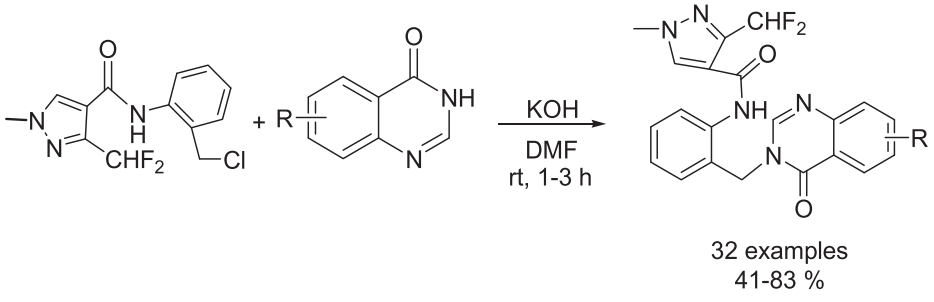
Scheme 12 Pd-catalysed synthesis of multi-substituted quinazolines.



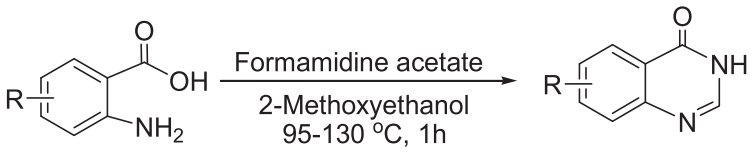
Scheme 13 Pd-catalysed synthesis of quinazolinones.



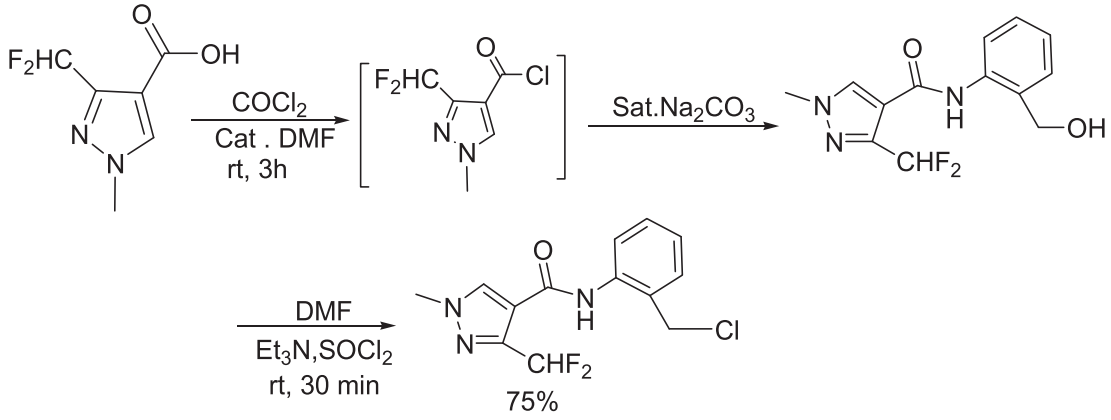
Scheme 14 Cu promoted synthesis of 4(3H)-quinazolinones and benzoimidazoquinazoline.



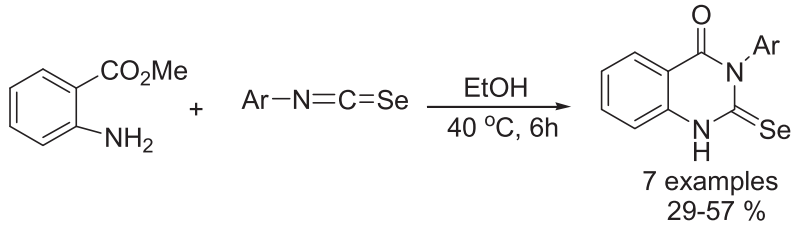
Scheme 15 Synthesis of quinazolinone containing pyrazole carbamide derivatives.



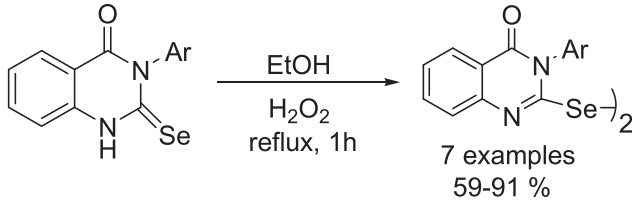
Scheme 16 Synthesis of quinazolin-4-one derivatives.



Scheme17 Synthesis of *N*-(2-(chloromethyl)phenyl)-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide.



Scheme 18 Synthetic path for2-selenoxo-1,2,3,4-tetrahydro-4-quinazolinones.



Scheme 19 Synthetic route for2,2′-diselane-1,2-diylbis(3-arylquinazolin-4(3*H*)-ones.

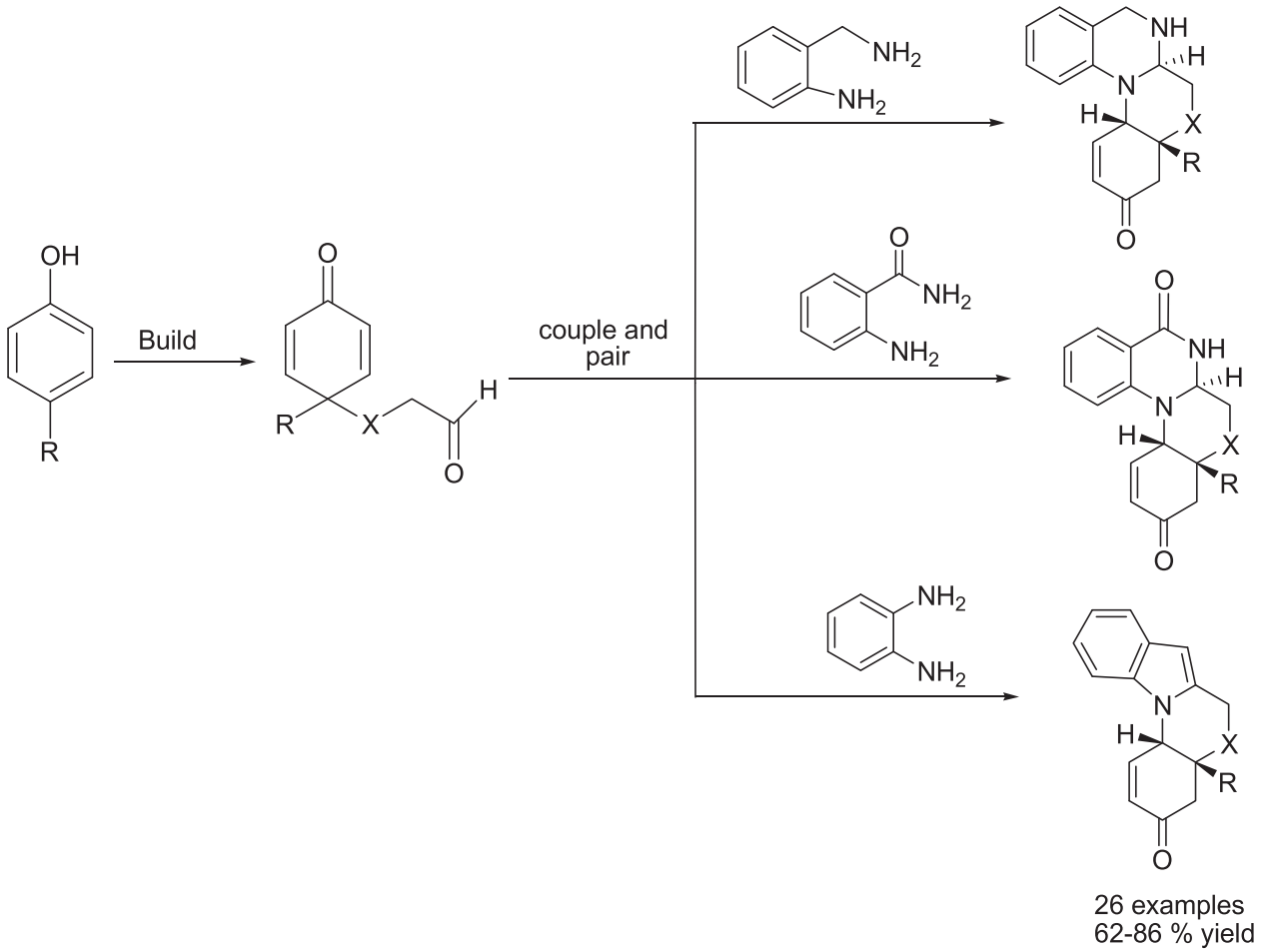
strate scope and can be used on a gram scale under optimal reaction conditions.

Tabatabai group reported (Hejazi et al., 2020) a series of new quinazoline-4(3*H*)- one derivatives with varying steric and electronic properties synthesised from 4-nitrobenzaldehyde and anthranilamide (Scheme 23). Initially, the mixture of 4-nitrobenzaldehyde and anthranilamide in DMSO was irradiated under ultrasound irradiation for 3h in an open flask to produce the 2-(4-nitrophenyl)quinazoline-4 (*3H*)-one that reacts with sodium dithionite in 1:9 H_2O-DMF at 90 °C with stirring to obtain the 2-(4-aminophenyl) quinazoline-4(3*H*)-one. This intermediate, stirring with consequent anhydrides or acyl chlorides under an argon atmosphere at 0 °C to room temperature, followed by adding water, produced the target quinazoline-4(3H)-one derivative in 62–95 % yields.

Chang and coauthors (Wu et al., 2023) reported a mild metal-free protocol towards the construction of quinazolines scaffolds from 2,2,2–trichloroethyl imidates hydrochloride as nitrogen source and 2-aminophenyl ketones in the presence of sodium acetate (Scheme 24). This protocol afforded several quinazoline derivatives, especially 2-substituted quinazolines, in moderate to high yields. This approach has advantages like readily available starting materials and gram-scale synthesis.

Ding and coauthors reported an efficient metal-/solvent-free protocol (Tan et al., 2022) towards the construction of quinazolines by elemental sulfur-promoted oxidative condensation of 2-(aminomethyl)anilines and nitriles (Scheme 25). The method tolerates a broad range of functional groups to obtain the consecutive products in 56–91% yield and can also be achieved on a gram scale.

Lu and group (Pan et al., 2022) prepared a series of novel 4-aminoquinazoline derivatives. Initially, 7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate and sulfuryl dichloride were added into *N, N*-dimethylformamide dropwise under nitrogen



Scheme 20 Synthetic protocols for functionalised Quinazoline Scaffolds.

atmosphere to obtain 4-chloro-7-methoxyquinazolin-6-yl acetate, that reacts with ammonia in CH_3OH, produced 4-chloro-7-methoxyquinazolin-6-ol. Next, the obtained 4-chloro-7-methoxyquinazolin-6-ol reacts with 2-(pyrrolidin-1-yl)ethan-1-ol in THF under DTAD and PPh_3 produced 6-(2-(pyrrolidin-1-yl)ethoxy)-4-chloro-7-methoxyquinazoline. Finally, in the presence of 4-methylbenzene-1-sulfonic acid and propan-2-ol, the compounds 6-(2-(pyrrolidin-1-yl)ethoxy)-4-chloro-7-methoxyquinazoline reacts with various N^1-benzylbenzene-1,4-diamines and 4-(aryloxy)benzenamine to obtain the consecutive target compounds N^1-(6-(2-(pyrrolidin-1-yl)ethoxy)-7-methoxyquinazolin-4-yl)-N^4-arylbenzene-1,4-diamines and 6-(2-(pyrrolidin-1-yl)ethoxy)-N-(4-(benzyloxy)phenyl)-7-methoxyquinazolin-4-amine(Scheme 26). Similarly, N^1-(6-(2-(1H-pyrrol-2-yl)ethoxy)-7-methoxyquinazolin-4-yl)-N^4-arylbenzene-1,4-diamines were obtained by the reaction of 6-(3-(1H-pyrrol-2-yl)butyl)-4-chloro-7-methoxyquinazoline with N^1-benzylbenzene-1,4-diamines (Scheme 27).

Raju Dey *et al.* (Hima et al., 2023) described a transition metal-free protocol towards constructing quinazoline derivatives starting from aryl amides and 2-aminobenzyl alcohols through a potassium tertiary butoxide-promoted alcohol dehydrogenation strategy (Scheme 28). This method tolerates a range of functional groups affording simple access to diverse quinazolines with good to excellent yields.

3. Drugs having quinazoline and its derivatives as a scaffold

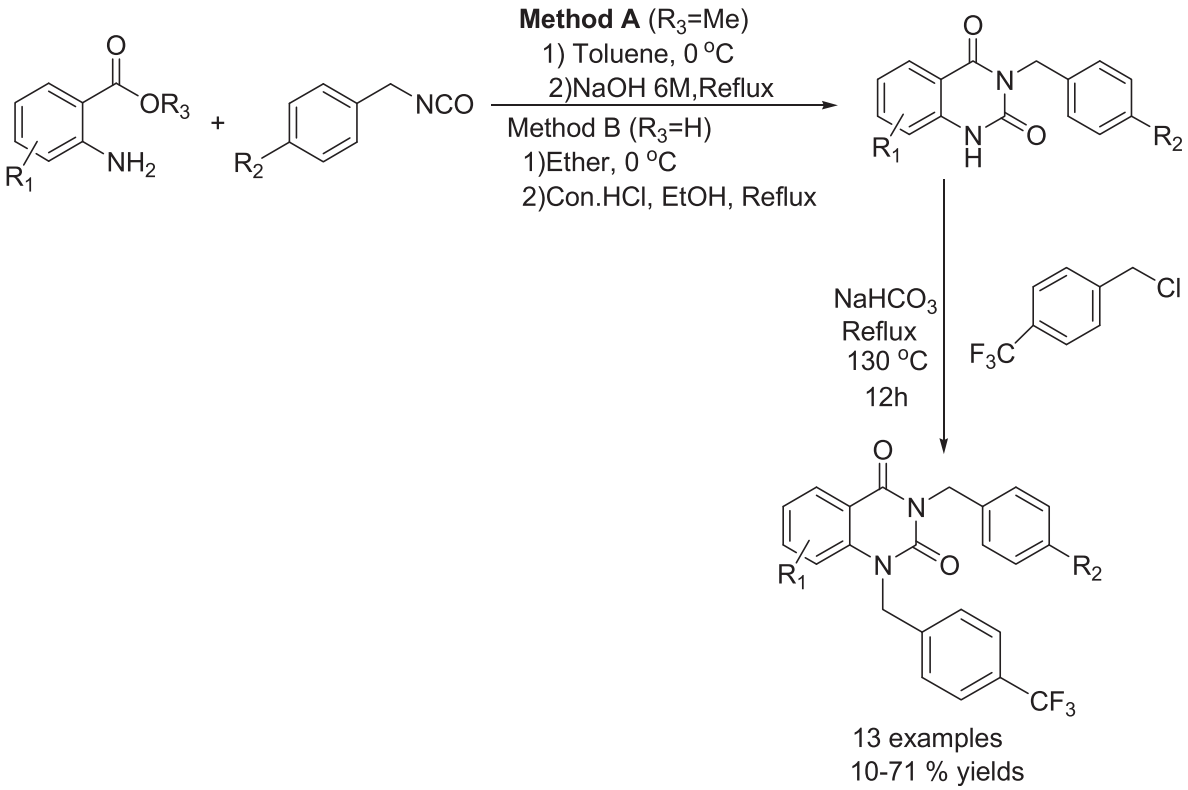
In 1968, only two quinazoline derivatives, Methaqualone (soporific and anticonvulsant) and Quinethazone (diuretic), by 1980, over 50 derivatives with varied biological properties such as sedative, tranquillising, analgesic, anticonvulsant, antitussive, myorelexant, antirheumatic, hypotensive, antiallergic, bronchodilating, antidiabetic, cholagogue, diuretic, cystatic, anti-malarial and spermicidal have been reported.

3.1. Methaqualone (1954)

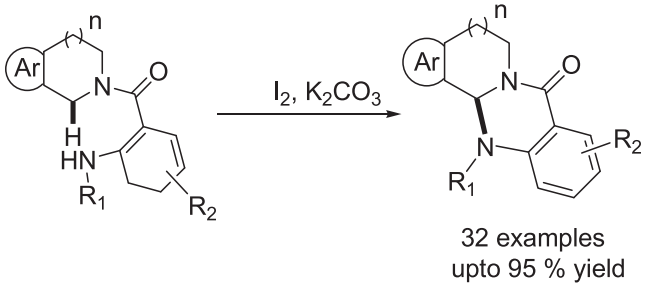
Methaqualone (Fig. 5) is a hypnotic and sedative medicine. It is also used as a muscle relaxant. The drug was marketed under the brand names Quaalude and Sopor. A combination medication Mandrax, which had 250 mg methaqualone and 25 mg diphenhydramine in one tablet, was also promoted (Kacker and Zaheer, 1951). In 1984, commercial methaqualone production was prohibited due to extensive usage.

Synthesis: There are two primary synthetic routes (Van, 2001; Angelos and Meyer, 1985) for manufacturing Methaqualone

Route-1: Two-step preparation- In the first step, N-acetylanthranilic acid (**3**) is synthesised from anthranilic acid



Scheme 21 Synthesis of 3-benzyl-1-(4-(trifluoromethyl)benzyl)quinazolin-2,4(1H,3H)-diones.



Scheme 22 I_2-promoted synthesis of Quinazolinone-Fused Tetrahydro isoquinolines.

(**1**) and acetic anhydride (**2**), followed by condensation of (**3**) with o-toluidine (4) in the presence of phosphorus trichloride in the second step (Scheme 29).

Route-2: One-step process- It is carried out by refluxing a mixture of 2-aminobenzoic acid (**1**), acetic anhydride (**2**), and *o*-toluidine (**4**) to give Methaqualone (**5**). Poly Phosphoric acid may be added to remove water (Scheme 30).

3.2. Diproqualone (1958)

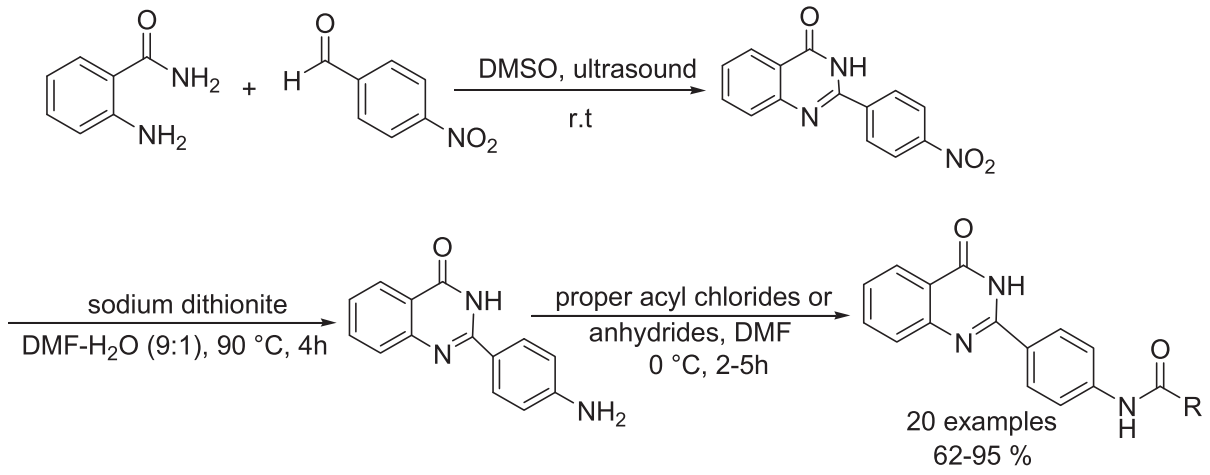
Diproqualone (Fig. 6) belongs to the quinazolinone class of GABAergics and is an analogue of Methaqualone developed by a team at Nogentaise de ProduitsChimiques in the late 1950's, as a result of its agonist activity at the $GABA_A$ subtype, antagonist activity at all histamine receptors, inhibition of the cyclooxygenase-1 enzyme, and possibly agonist activity at both the sigma 1 and sigma 2 receptors. Due to its beneficial anti-inflammatory and analgesic effects and the sedative and anxiolytic effects common to other medicines in this family, diproqualone is the only analogue of Methaqualone that is still widespread in clinical use. Its many benefits are sedative, anxiolytic, antihistamine, and analgesic effects. Also valuable for the treatment of osteo arthritis and rheumatoid arthritis-related inflammatory discomfort. Moreover, it is also used to treat insomnia, anxiety and neuralgia, although not common practice.

Synthesis: Diproqualone is synthesised through a one-pot synthesis of 2-iodobenzoic acid (**6**) and acetamidine hydrochloride (**7**) employing a copper-glucose catalysed quinazolinone reaction as a crucial step (Scheme 31). After the completion of the reaction, the *N*-arylated molecule was obtained by adding 3-chloro-1,2-propanediol to the same flask under reflux conditions. (±)-Diproqualone (**8**) is the end product (Dubey and Kumar, 2018).

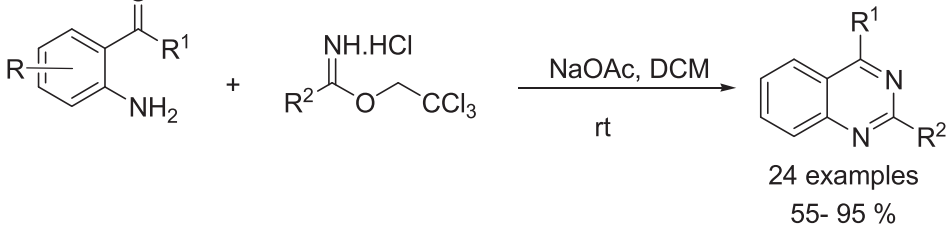
3.3. Etaqualone (1960)

Etaqualone (Fig. 7) is a quinazolinone-class GABAergic that was created in the 1960 s as an equivalent of Methaqualone. The dosage and effects are similar to Methaqualone but have a shorter half-life and milder effect. Aolan, Ethinazone, and Athinazone are some of their other names (Pflegel and Wagner, 1967; GB patent, 1963). It treats insomnia because it possesses sedative, hypnotic, muscle relaxant, and central nervous system depressant characteristics.

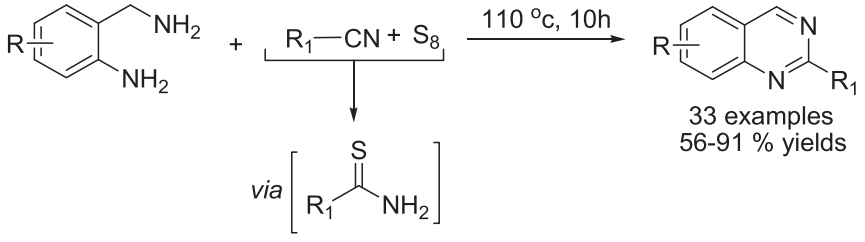
Synthesis: N-Acetylanthranilic acid (**9**) is refluxed at 120 °C with 2-ethylaniline (**10**) in the presence of PCl_3 to give Etaqualone (**11**) as presented in Scheme 32 (Casale and Hays, 2012).



Scheme 23 Synthesis of quinazoline-4(3*H*)- one derivatives.



Scheme 24 Synthesis of quinazolines from 2-aminophenyl ketones and 2,2,2–trichloroethyl imidates hydrochloride.



Scheme 25 Synthesis of Quinazolines by elemental sulphur promoted oxidative condensation.

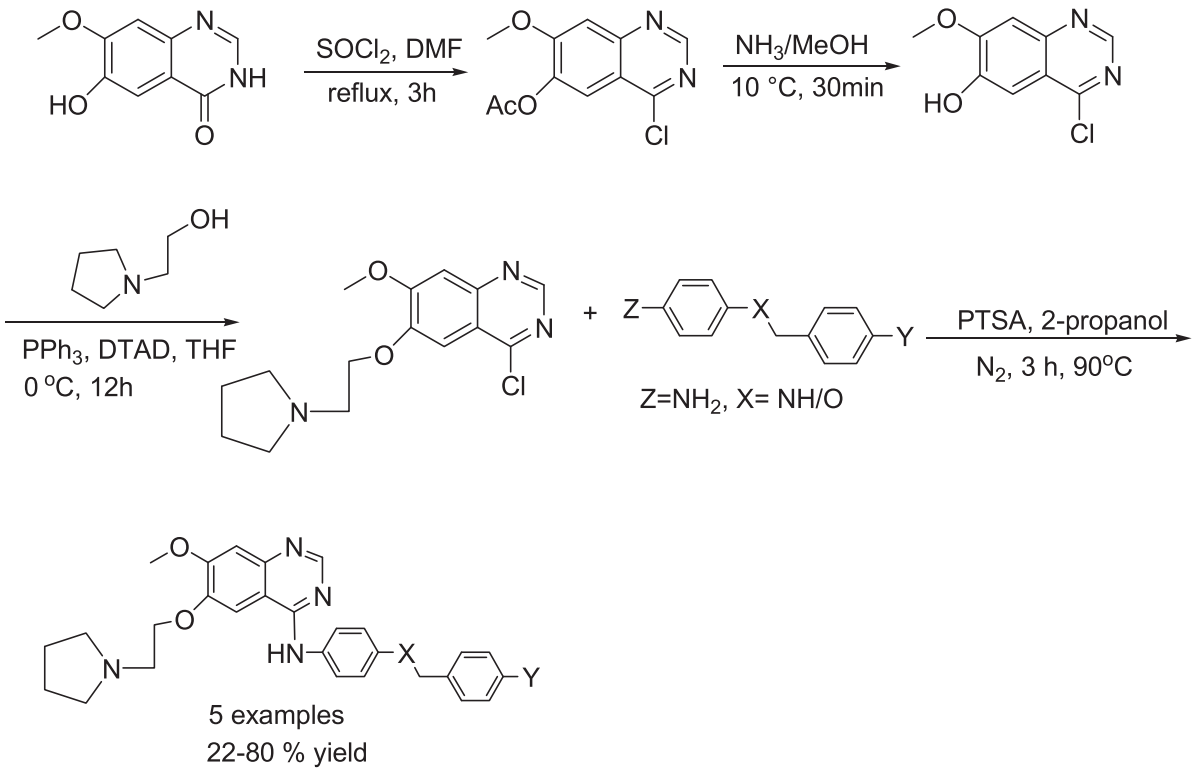
3.4. Prazosin (1974)

2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4amine is the chemical formula for prazosin.(Fig. 8). It's an alpha-adrenergic blocker, which works by relaxing blood arteries to reduce blood pressure. Prazosin is specific for alpha-1 receptors in vascular smooth muscle (Howard, 2008). These receptors mediate the vasoconstrictive action of norepinephrine, which typically elevates blood pressure. Prazosin lowers blood pressure by inhibiting these receptors, a sympatholytic medicine used to treat high blood pressure. It helps to lower blood pressure. Minipress, Vasoflex, Pressin, and Hypovase are some other names.

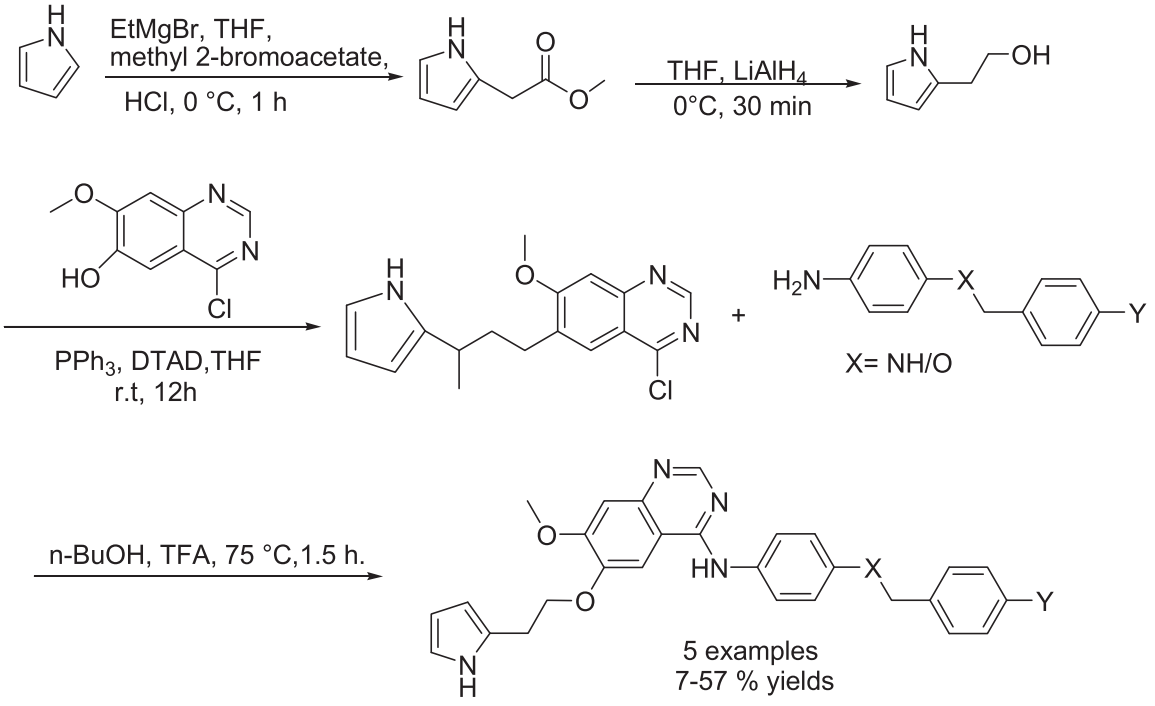
Synthesis: Prazosin is synthesised from 2-amino-4,5-dimethoxybenzoic acid (**12**), which undergoes heterocyclisation into 2,4-dihydroxy-6,7-dimethoxyquinazoline (**13**) when it reacts with sodium cyanate. 2,4-dichloro-6,7-dimethox yquinazoline (**14**) is obtained by replacing the hydroxyl groups with chlorine *via* a reaction with thionyl chloride or a mixture of phosphorous oxychloride and phosphorous pentachloride. The chlorine atom at C4 of the pyrimidine ring is replaced with an amino group in a subsequent reaction with ammonia, resulting in 4-amino-2-chloro-6,7-dimethoxyquinazoline (**15**). Finally, by combining (**15**) with 1-(2-furoyl)piperazine (**16**) is produced Prazosin (**17**) as presented in Scheme 33 (Vardanyan and Hruby, 2006).

3.5. Cloroqualone (1980)

Cloroqualone (Fig. 9) is a quinazolinone-class GABAergic that was established in the 1980's as an analogue of Methaqualone and marketed mostly in France and a few other European nations. Its agonist activity at the subtype of the $GABA_A$ receptor and the sigma-1 receptor gives it soothing and antitussive qualities. It was advertised as a cough treatment alone or in combination with other components. Cloroqualone has a



Scheme 26 Synthetic procedure for quinazoline derivatives.

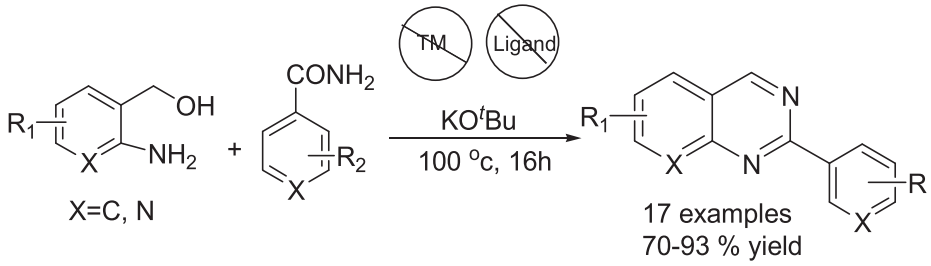


Scheme 27 Synthetic procedure for quinazoline analogues.

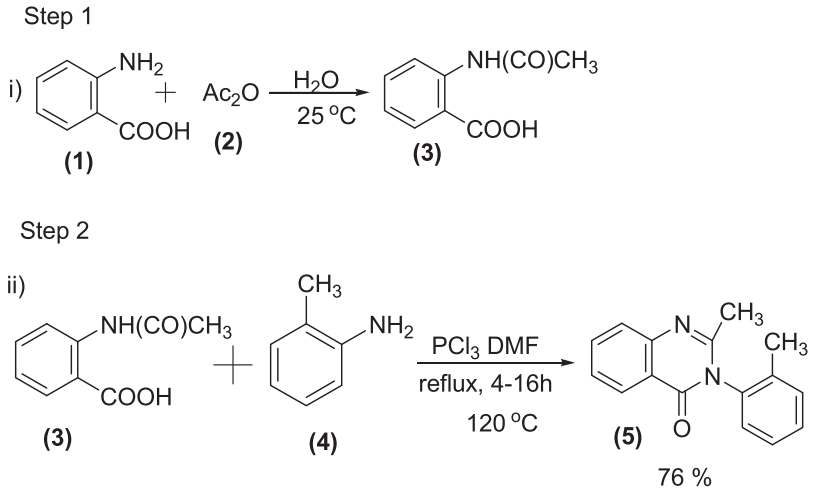
weaker sedative effect than Methaqualone and was recognised for its cough-suppressing characteristics. 3-(2,6-dichlorophe nyl)-2-ethylquinazolin-4-one is its IUPAC name. It possesses sedative and antitussive properties and acts as a cough-suppressing agent.

3.6. Alfuzosin (1988)

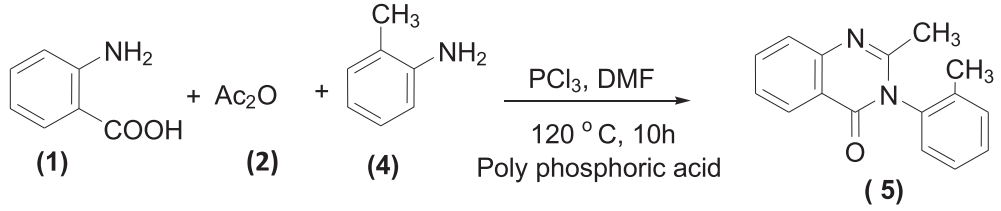
UroXatral; Urion; Xatral; Alfetim are brand names for alfuzosin, which is chemically known as N[3-[(4-amino-6,7-dime



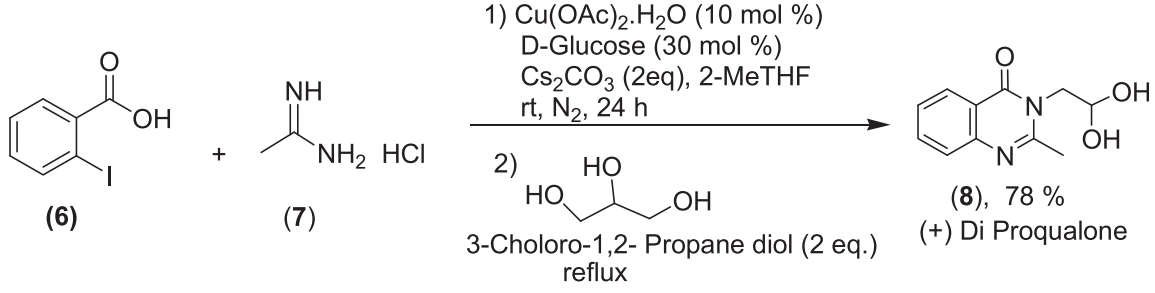
Scheme 28 Metal-free synthesis of quinazoline analogues.



Scheme 29 Phosphorous trichloride mediated synthesis of Methaqualone.

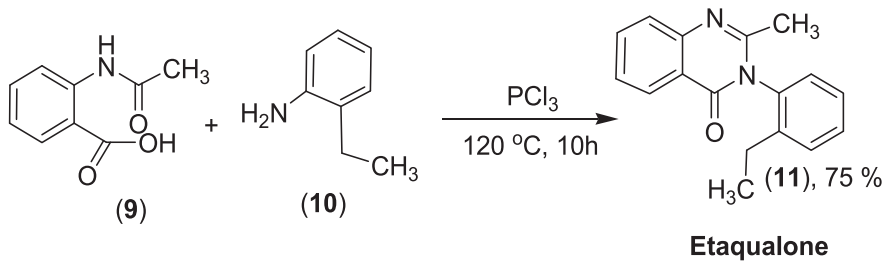


Scheme 30 Phosphoric acid mediated synthesis of Methaqualone.

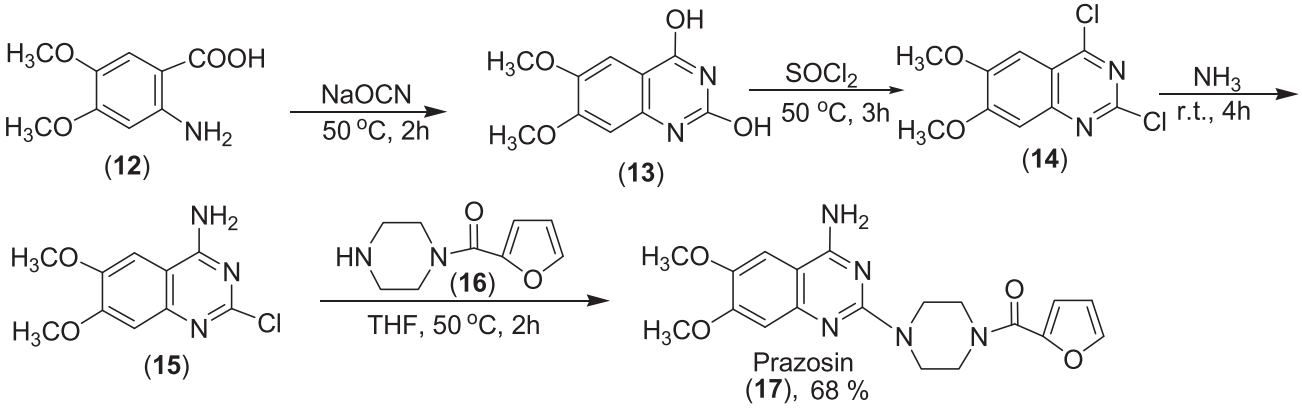


Scheme 31 Phosphoric acid mediated synthesis of Methaqualone.

thoxy-quinazolin-2-yl)-methyl-amino]propyl] tetrahydrofuran-2-carboxamide (Fig. 10). It makes it easier to urinate by relaxing the muscles in the prostate and bladder neck. In patients with severe renal insufficiency, Alfuzosin should be taken with caution. It is not advised for individuals with a QT prolongation history or taking drugs extending the QT interval (Herbert, 2016; Fischer and Ganellin, 2006). It is an α_1 receptor antagonist used to treat benign prostatic hyperplasia (BPH). Additionally, it aids in relaxing the muscles in the prostate and bladder neck, making urination easier.



Scheme 32 Synthesis of Etaqualone.



Scheme 33 Synthesis of Prazosin.

Synthesis: Initially, 4-amino-2-chloro-6,7-dimethoxyquina zoline (**18**) is condensed with 3-methylaminopropionitrile (**19**) in the presence of a polar aprotic solvent chosen from the group consisting of diglyme, dimethyl formamide, *t*-butanol, hexamethylphosphoramide, or mixtures there of to form -(4-amino-6,7-dimethoxyquinazol-2-yl)-*N*-methyl-2-cyanoethylamine (**20**). Using a hydrogenating agent and a pressure of less than 10 kg/cm^2, hydrogenating the *N*-(4-ami no-6,7-dimethoxyquinazol-2-yl)-*N*-methyl-2-cyanoethylamine (**20**) to generate *N*-(4-amino-6,7-dimethoxyquinazol-2-yl)-*N*-methylpropylenediamine (**21**). Moreover, tetrahydrofuran-2-carbonyl chloride (**23**) was obtained by chlorinating the tetrahydrofuran-2-carboxylic acid (**22**) with $POCl_3$ in the presence of a base. Condensing the intermediate (**23**) with the *N*-(4-amino-6,7-dimethoxyquinazol-2-yl)-*N*-methylpropylenediamine (**21**) or with the acid addition salt thereof to generate alfuzosin base (**24**) and optionally converting alfuzosin base to a salt of alfuzosin as presented in scheme 34 (Kankan et al., n.d.).

3.7. Bunazosin (1988)

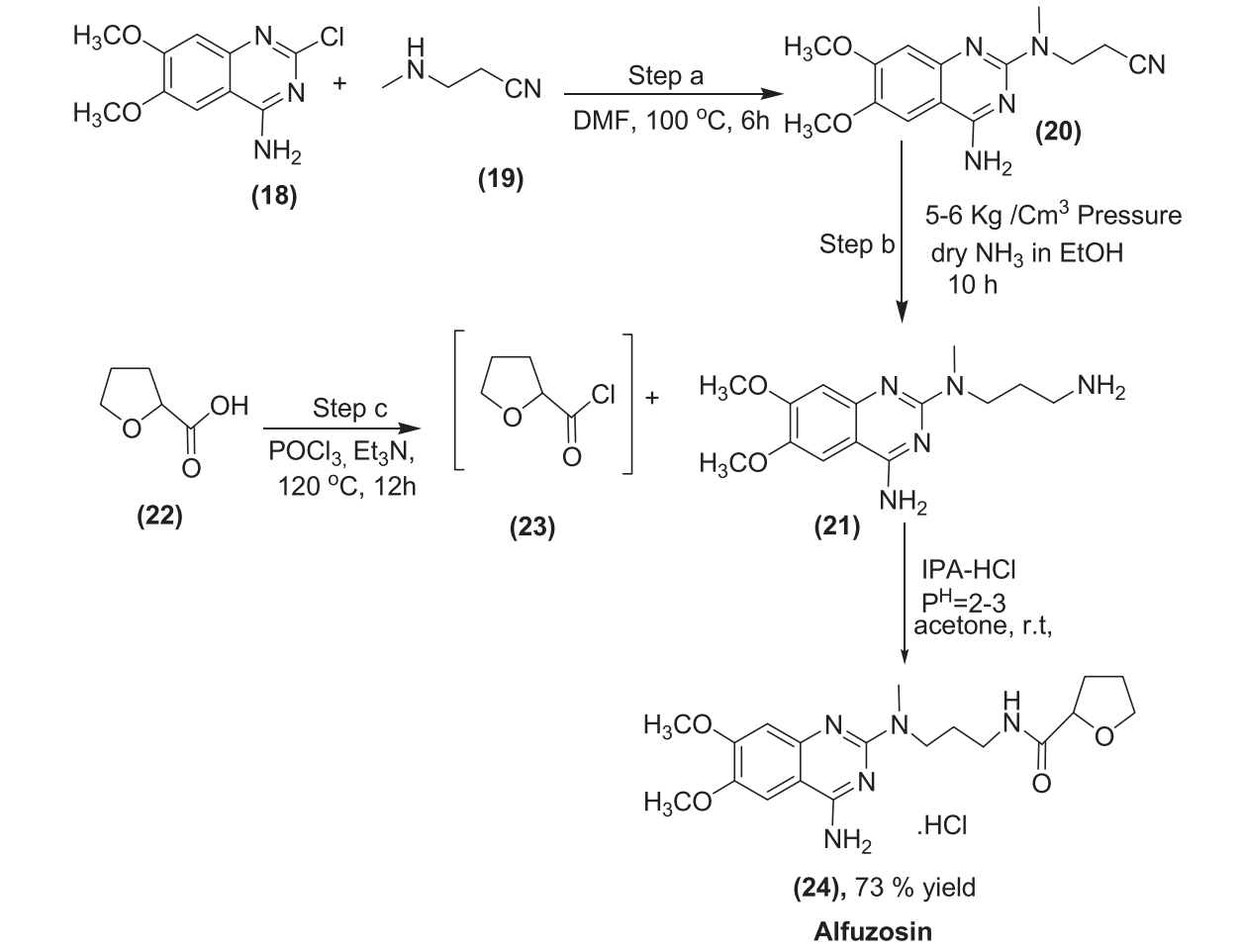
Bunazosin (Fig. 11), also known as andante, is an alpha-1 antagonist with the chemical formula 1-(4-(4-amino-6,7-dime thoxyquinazolin-2-yl)-1,4-diazepan-1-yl)butan-1-one. Bunazosin was created to treat benign prostatic hyperplasia (BPH). The mechanism of action involves lowering intraocular pressure by reducing aqueous outflow through the uveoscleral pathway. Intraoperative Floppy Iris Syndrome was linked to systemic Alpha-1 adrenergic receptor antagonists (IFIS). Bunazosin may have the same effect, but no research proved it as a cataract surgery risk. Its applications include the treatment of benign prostatic hyperplasia (BPH), the treatment of glaucoma, and the improvement of blood flow to the optic nerve.

Synthesis: It is made from 2-amino-4,5-dimethoxybenzoic acid (**25**), which undergoes hetero-cyclisation, producing 2,4-dihydroxy-6,7-dimethoxyquinazoline (**26**) when reacting with sodium cyanate. Next, 2,4-dichloro-6,7-dimethoxyquinazoline is generated by replacing the hydroxyl groups of (**26**) with chlorine using thionyl chloride. The chlorine atom at C_4 of the pyrimidine ring is replaced with an amino group in a subsequent reaction with ammonia, resulting in 4-amino-2-chloro-6,7-dimethoxyquinazoline (**28**). Finally, Bunazosin (**30**) is produced by coupling (**28**) with 1-(1,4-diazepan-1-yl)butan-1-one (**29**) as in scheme 35(Manoury et al., 1986).

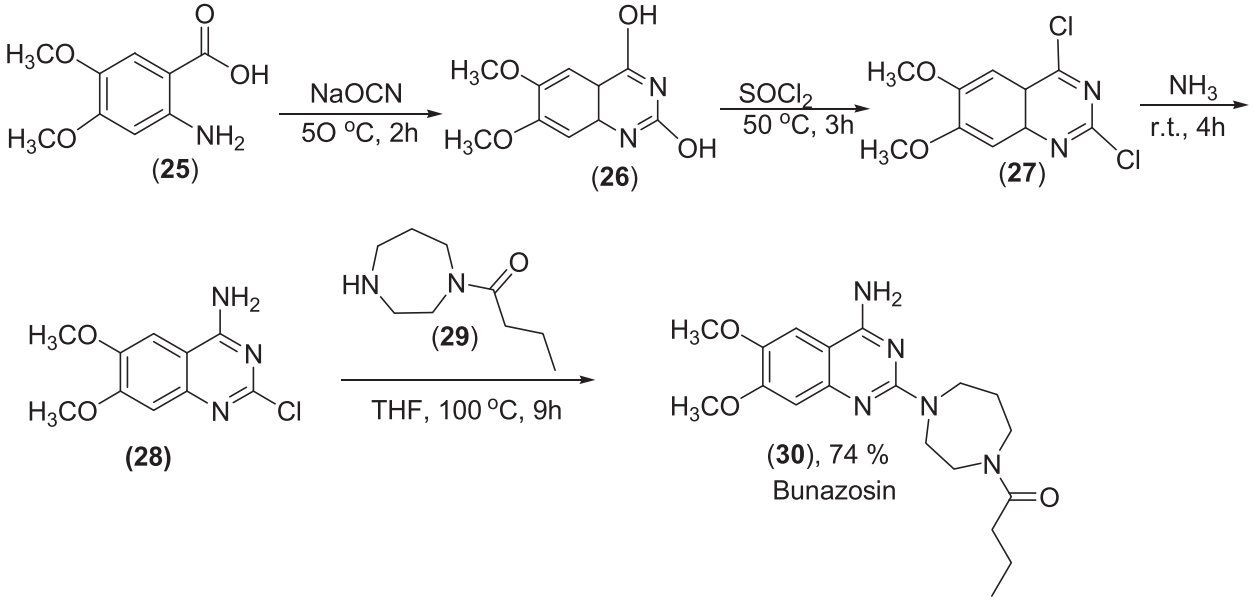
3.8. Trimetrexate (December 1993)

Trimetrexate (Fig. 12), also known as 5-methyl-6-[(3,4,5-trime thoxyphenyl) aminomethyl]quinazoline-2,4-diamine, is a non-classical folic acid inhibitor that works by inhibiting the dihydrofolate reductase enzyme. It treats pneumocystis pneumonia alongside leucovorin and is researched for treating leiomyosarcoma. Trimetrexateisa methotrexate (MTX) derivative that works against transport-deficient MTX-resistant tumor cells, overcoming methotrexate resistance both acquired and natural (Wong et al., 1990; Smith et al., 2002). It is an antineoplastic and antiparasitic agent to treat pneumocystis pneumonia in AIDS patients and skin lymphoma.

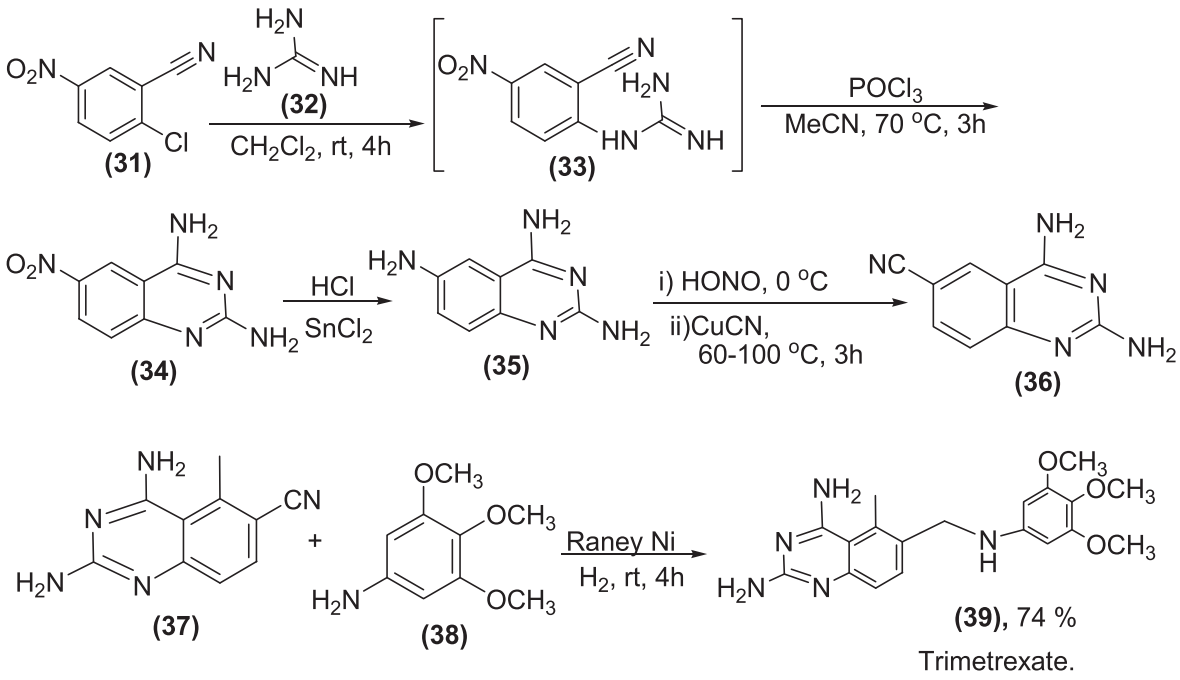
Synthesis: To obtain Trimetrexate (**39**), the 2,4-diamino-6-quinazolinecarbonitrile (**37**) is reduced over raney nickel in the presence of benzneamine (**38**) at a pressure of 50 psig (Elslager et al., 1983) as represented in below scheme 36.



Scheme 34 Synthesis of Alfuzosin.



Scheme 35 Synthesis of Bunazosin.



Scheme 36 Synthesis of Trimetrexate.

3.9. Anagrelide (1997)

Agrylin/Xagrid, Shire, and anagrelide are brand names, and the chemical name is 6,7-dichloro1,5-dihydroimidazo(2,1-b)q uinazolin-2(3*H*)-one (Fig. 13). Anagrelide works by preventing platelets from megakaryocytes from maturing. Although it is known to be a PDE inhibitor, the specific mechanism of action is unknown. It is a strong phosphodiesterase-II inhibitor (IC_{50} = 36 nM). PDE-3 and phospholipase A2 are both inhibited by it. According to a randomised experiment conducted by the Medical Research Council in 2005, hydroxyurea with aspirin is superior to anagrelide and aspirin for treating essential thrombocytosis (ET). Myelofibrosis, arterial thrombosis, and bleeding decreased in the hydroxyurea group, although venous thrombosis was somewhat higher (Voglova et al., 2006). It is used to treat ET, or excessive blood platelet production. It also has been used in the treatment of chronic myeloid leukemia.

Synthesis: When 1,2-dichloro-4-nitro-3-propylbenzene (**40**) is combined with the ethyl ester of glycine to form an alkylated product (**41**). The nitro group is reduced to form aniline and converted to cyanamide (**42**) by reacting it with cyanogen bromide. The aliphatic would then undergo cyclisation, resulting in the development of a quinazoline ring (**44**). Whatever the intricacies of the sequence, amide creation between the newly generated imide and the ester would next suffice to construct the imidazolone ring, yielding anagrelide (**45**).Scheme 37 represents the total synthetic route (Hitoshi and Fumiyoshi, 1981).

3.10. Gefitinib (May 2003)

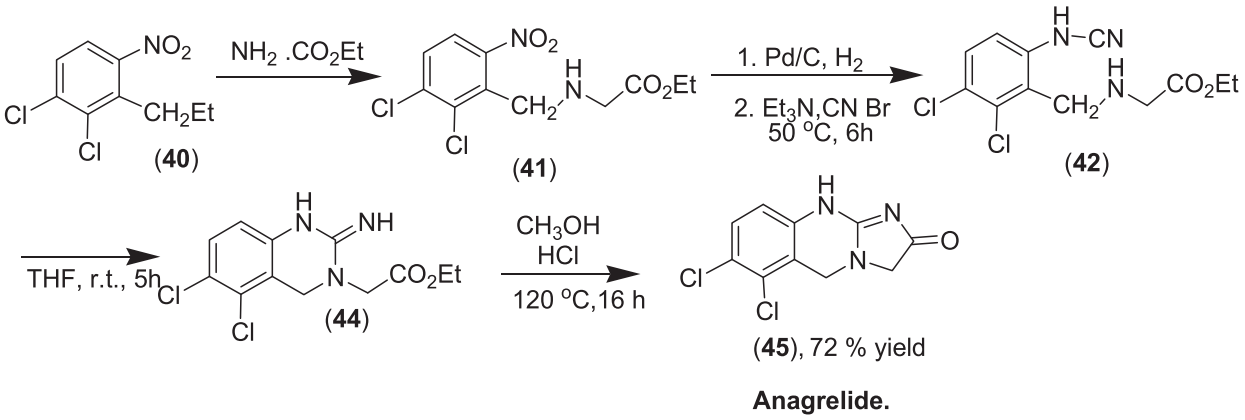
Gefitinib (Fig. 14), a quinazoline-containing medication, has been approved by the US Food and Drug Administration (FDA). AstraZeneca's medication is an inhibitor of the protein kinase of the epidermal growth factor receptor (EGFR). It binds to the EGFR ATP-binding site, inactivating the anti-apoptotic ras signal transduction cascade and stopping cancer cells from growing further (Sordella et al., 2004). The drug is used to treat non-small-cell lung cancer if platinum- and taxane-based chemotherapies have failed.

Synthesis: Methyl 3-hydroxy-4-methoxybenzoate (**46**) on alkylation with 1-bromo-3-chloropropane (**47**) produced the intermediate (**48**) in 94.7 percent yield. Compound (**49**) was obtained by nitrating the intermediate (**48**) with nitric acid in acetic acid, which was then reduced by powdered iron in acetic acid to provide Compound (**50**) with an acceptable yield of 77 %. Even after long reaction periods, catalytic hydrogenation using Raney/Ni or 5% Pd/C yielded partial conversions. Compound (**53**) is obtained by cyclising (**50**) with formamidine acetate and chlorinating it with thionyl chloride after two reactions with various amines, Gefitinib (**54**) was created (Scheme 38) (Li et al., 2007).

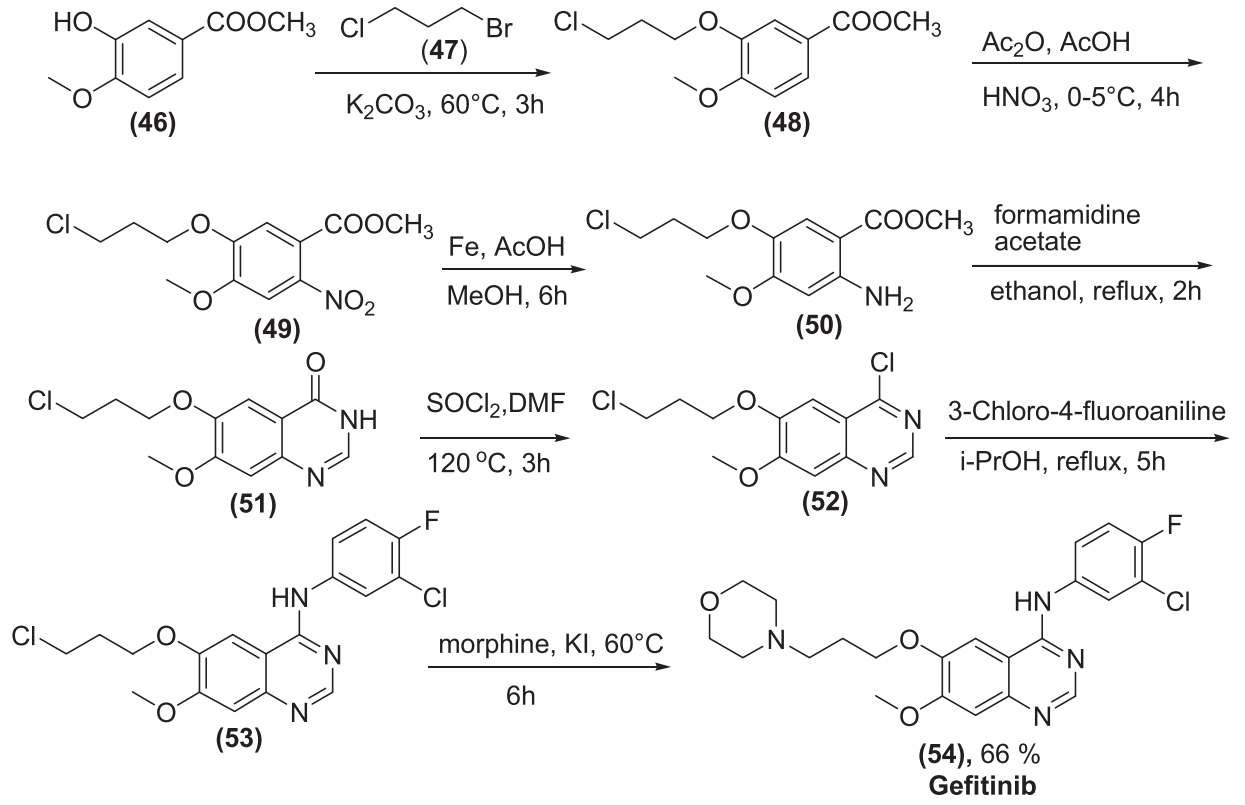
3.11. Erlotinib (2004)

Tarceva is the brand name for erlotinib (Fig. 15). N-(3-ethynyl phenyl)6,7-bis(2-methoxyethoxy)quinazolin-4-amine is its chemical name. It is used to treat NSCLC that has progressed to other parts of the body and contains mutations in the epidermal growth factor receptor (EGFR), either an exon 19 deletion (del19) or an exon 21 (L858R) substitution mutation (Martin et al., 2015). It treats non-small cell lung cancer, advanced unresectable metastatic prostate cancer, and pancreatic cancer.

Synthesis: Erlotinib hydrochloride (**63**) was manufactured in seven stages, starting with 3,4-dihydroxy benzoic acid (**55**), as shown in Scheme 39. One essential modification in this work is reducing the 6-nitrobenzoic acid derivative (**59**) to the 6-aminobenzoic acid derivative (**60**). In the presence of palladium/charcoal (Pd/C), a cheap reagent, ammonium formate was utilised as an *in situ* hydrogen donor instead of hydrogen



Scheme 37 Synthesis of Anagrelide.



Scheme 38 Synthesis of Gefitinib.

gas at high pressure to obtain intermediate (**61**), that on cyclisation and chlorination produced the precursor (**62**), that couples with 3-ethynylaniline to afford the Erlotinib hydrochloride (**63**) as a final product (Zhang et al., 2015).

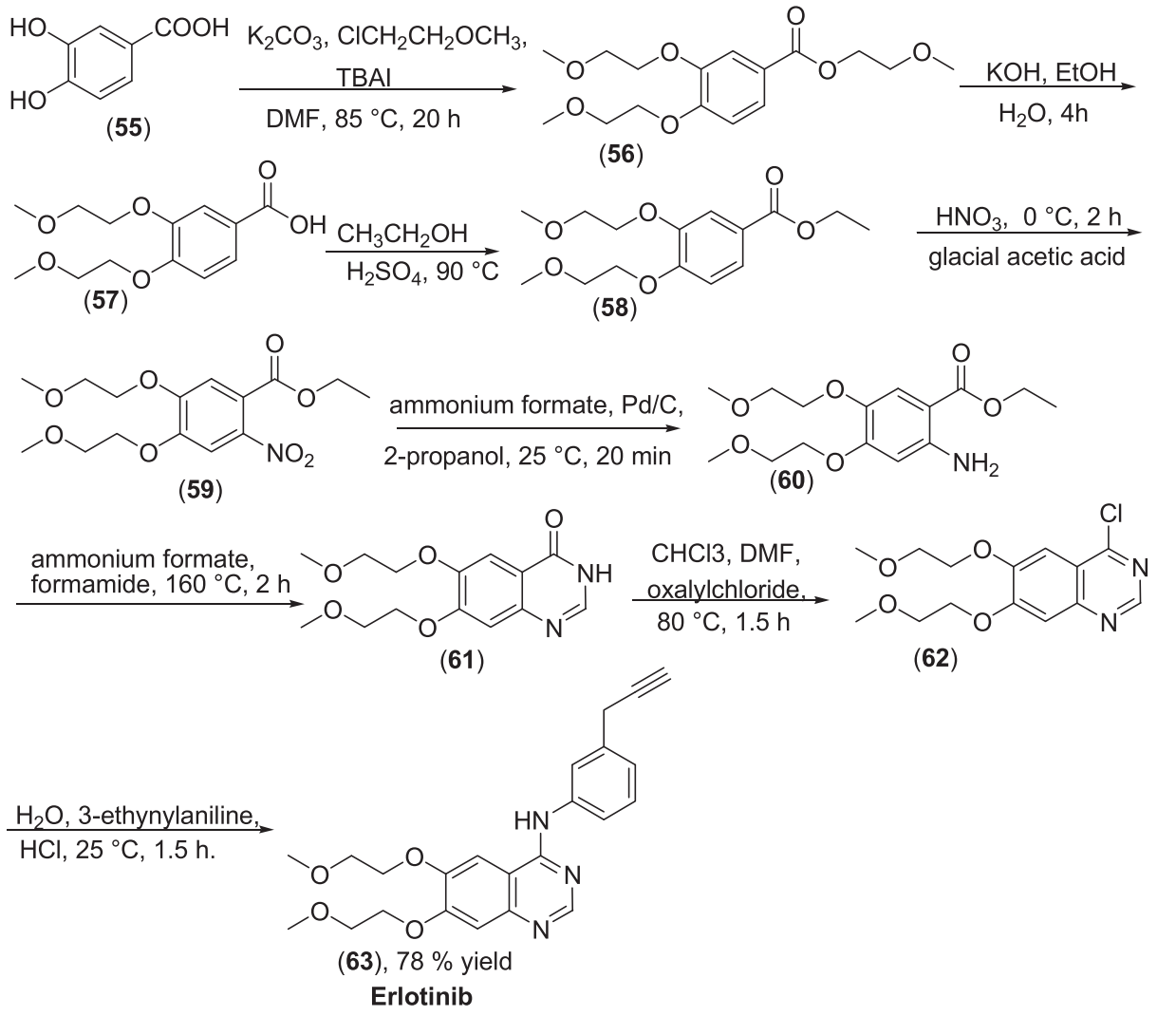
3.12. Nolatrexed (2005)

Nolatrexed (Fig. 16) has the chemical name 2-Amino-6-methyl-5-(4-pyridylthio)-1H-quinazolin-4-one. Nolatrexed is a thymidylate synthase inhibitor. Used for the treatment of liver cancer (Hughes et al., 1999).

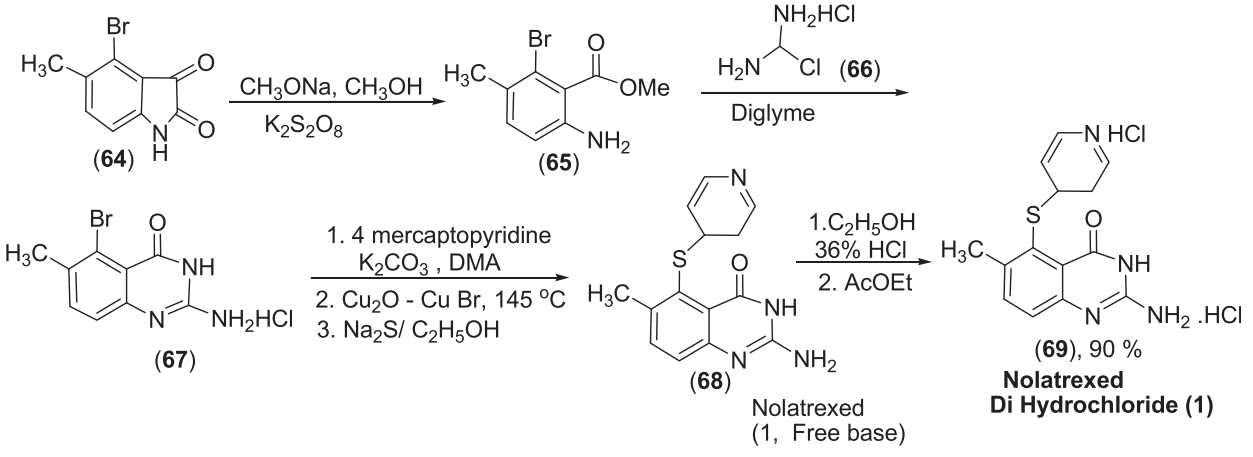
Synthesis: The synthesis was carried out in three phases. The first step included converting 4-bromo-5-methylisatin(**64**) to methyl anthranilate(**65**) using potassium peroxydisulfate/-sodium methoxide. In the final Ullmann reaction, potassium carbonate was used instead of sodium hydride, and copper catalysts were used in much smaller amounts. Furthermore, instead of using hydrogen sulfide/methanol under very acidic conditions, sodium sulphide solution was used to extract copper efficiently in almost neutral conditions (Scheme 40). These adjustments prepared nolatrexed dihydrochloride (**69**) in high yield and purity (Zhao et al., 2010).

3.13. Proquazone (2005)

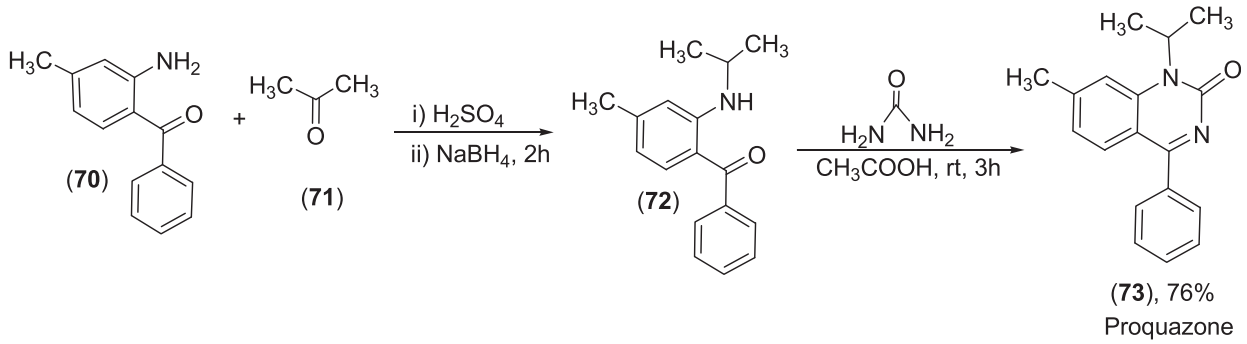
Its trade name is Biarison is chemically known as 1-isopropyl-7-methyl-4phenylquinazolin-2(1H)-one. Proquazone (Fig. 17)



Scheme 39 Synthesis of Erlotinib.



Scheme 40 Synthesis of Nolatrexed.



Scheme 41 Synthesis of Proquazone.

is a non-steroidal anti-inflammatory drug. Its uses are cyclooxygenase inhibitors and analgesics.

Synthesis: Proquazone is prepared (https://pharmaceutical-substances.thieme.com/ps/searchresults?docUri=KD-16-0230, n.d.) as presented in scheme 41. 2- amino-4-methyl benzophenone (**71**) undergoes reductive coupling with acetone in the presence of sodiumborohydride to form 2-(isopropylamino)-4 -methylphenyl)(phenyl)methanone (**72**) that, on cyclisation with urea produced the proquazone (**73**) in good yield.

3.14. Albaconazole (2005)

Albaconazole (Fig. 18) is an anti-fungal triazole with a wide range of effects. Its IUPAC name is 7-Chloro-3-[(2R,3R) -3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-y l] quinazolin-4-one (Karsdal, 2009). Its anti-fungal properties include toenail fungus, distal onychomycosis, and subungual onychomycosis. It has also completed early clinical trials for the treatment of tinea pedis.

Synthesis: The Albaconazole (**84**) is made from 1,3-thiazolo [4,5-*g*]quinazolin-8(7H)-one (**83**). Intially,7-bromo-3H-quina zolin-4-one(**75**) is obtained by interacting 4-bromo-2-nitrobenzoic acid (**74**) with formamide under microwave irradiation. Further, the intermediate (**75**) from appropriate chemical transformations afford the thiazolo[4,5-g]quinazolin-8 (7H)-one(**82**) that couples with 1-(((2R,3S)-2-(2,4-difluorophe nyl)-3-methyloxiran-2-yl)methyl)-1H-1,2,4-triazole (**83**) to obtain the Albaconazol(**84**) as shown in Scheme 42(Guillon et al., 2013).

Reagents and conditions: (a) H_2NCHO, $InCl_3$, 150 °C (mW), 40 min, 81%, (b) HNO_3, H_2SO_4, 100 °C, 1 h, 76%, (c) NaH, benzyl bromide, DMF, 80 °C (mW), 30 min, 84%, (d) Fe, AcOH, EtOH, reflux, 1 h, 93%, (e) Appel salt, CH_2Cl_2, pyridine, rt, 3 h, 58%, (f) $AlCl_3$, toluene, 65 °C, 30 min, 90%, (g) CuI, pyridine, 115 °C (mW), 15 min, 86%, (h) HBr (48%), 115 °C (mW), 30 min, 93%. Albaconazole is produced by reacting the above synthesised (**82**) with (**83**).

3.15. Ispinesib (2006)

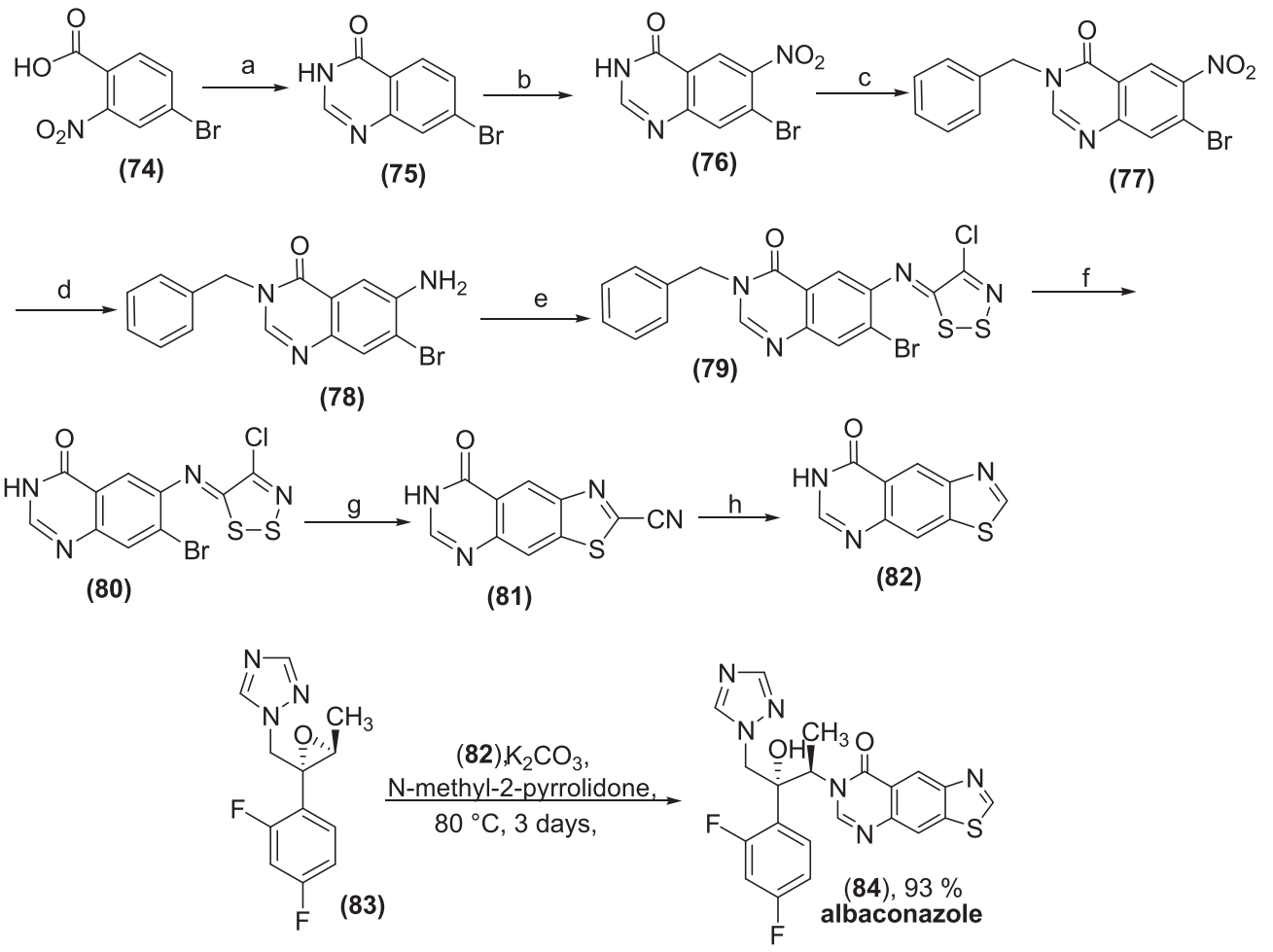
Ispinesib (Fig. 19) inhibits the mitotic motor protein kinesin spindle protein (KSP), causing mitotic spindle construction to be hindered, cell cycle arrest during the mitotic phase to be induced, and cell death in actively dividing tumour cells. Ispinesib may be less likely to cause peripheral neuropathy than tubulin-targeting drugs since KSP is not engaged in non-mitotic activities such as neuronal transport. IUPAC name- N-(3-aminopropyl)-N-[(1R)-1-[7-chloro-4-oxo-3-(phenylmethyl)-2-quinazolinyl]-2-methylpropyl] -4-methylbenzamide (Wang et al., 2013). It has anti-cancer characteristics and is used to treat breast cancer.

Synthesis: Swern oxidation was used to convert optically active alcohol (**85**) from L-valine to R-phthalimidyl aldehyde **(86)**. The aldehyde (**86**) converted to oxime (**87**) was reacted with NCS to obtain C-chlorooxime. C-chlorooxime was then coupled with aldimine (**88**) by [3 + 2]-cycloaddition in the presence of Et_3N to yield 4,5-dihydro-1,2,4-oxadiazole **(89)** as a 1:1 diastereomixture. Aerobic treatment of each isomer of (**89**) produced quinazolinone **(90)** in 62% and 50% yields, respectively, with partial racemisation (87 % ee each). The phthalimido moiety of **(90)** was further deprotected with hydrazine, resulting in the essential precursor amine **(91)**, which couples with *p*-methylbenzoyl chloride to form the targeted drug Ispinesib(**92**) in good yield (Scheme 43) (Agrawal et al., 2012).

3.16. Balaglitazone (October 2006)

The antihyperglycemic drug balaglitazone (Fig. 20) is a thiazolidinedione derivative. Balaglitazone is a partial agonist for the peroxisome proliferator-activated receptor (PPAR) gamma and appears to have fewer negative effects than complete PPAR gamma agonists. 5-[[4-[(3-methyl-4-oxoquinazolin-2-y l)methoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione is its IUPAC name (Su and Yang, 2002). Among the applications it plays a key role in controlling insulin, triglycerides, and lipid metabolism; it's a promising target for Type 2 diabetes treatment; and Balaglitazone is a partial agonist of PPAR. Balaglitazone inhibits PPAR activity to a maximum of 52 %. As a result, Balaglitazone is considered to have fewer negative effects. In numerous animal models, it is effective at lowering blood glucose levels.

Synthesis: In the presence of a base, 2-(chloromethyl)-3-me thylquinazolin-4(3H)-one(**93**) combines with *p*-Hydroxybenzaldehyde (**94**) to produce ether compound (**95**). Balaglitazone is formed when ether (**95**) connects with thiazolidine-2,4-dione(**96**) to generate precursor(**97**), which is then reduced with hydrogen on palladium carbon to form Balaglitazone(**98**) as presented in scheme 44(Lohray et al., n.d.).



Reagents and conditions: (a) H_2NCHO, $InCl_3$, 150 °C (mW), 40 min, 81%, (b) HNO_3, H_2SO_4, 100 °C, 1 h, 76%, (c) NaH, benzyl bromide, DMF, 80 °C (mW), 30 min, 84%, (d) Fe, AcOH, EtOH, reflux, 1 h, 93%, (e) Appel salt, CH_2Cl_2, pyridine, rt, 3 h, 58%, (f) $AlCl_3$, toluene, 65 °C, 30 min, 90%, (g) CuI, pyridine, 115 °C (mW), 15 min, 86%, (h) HBr (48%), 115 °C (mW), 30 min, 93%. Albaconazole is produced by reacting the above synthesised (9) with (10).

Scheme 42 Synthesis of Albaconazole.

3.17. Lapatinib (March 2007)

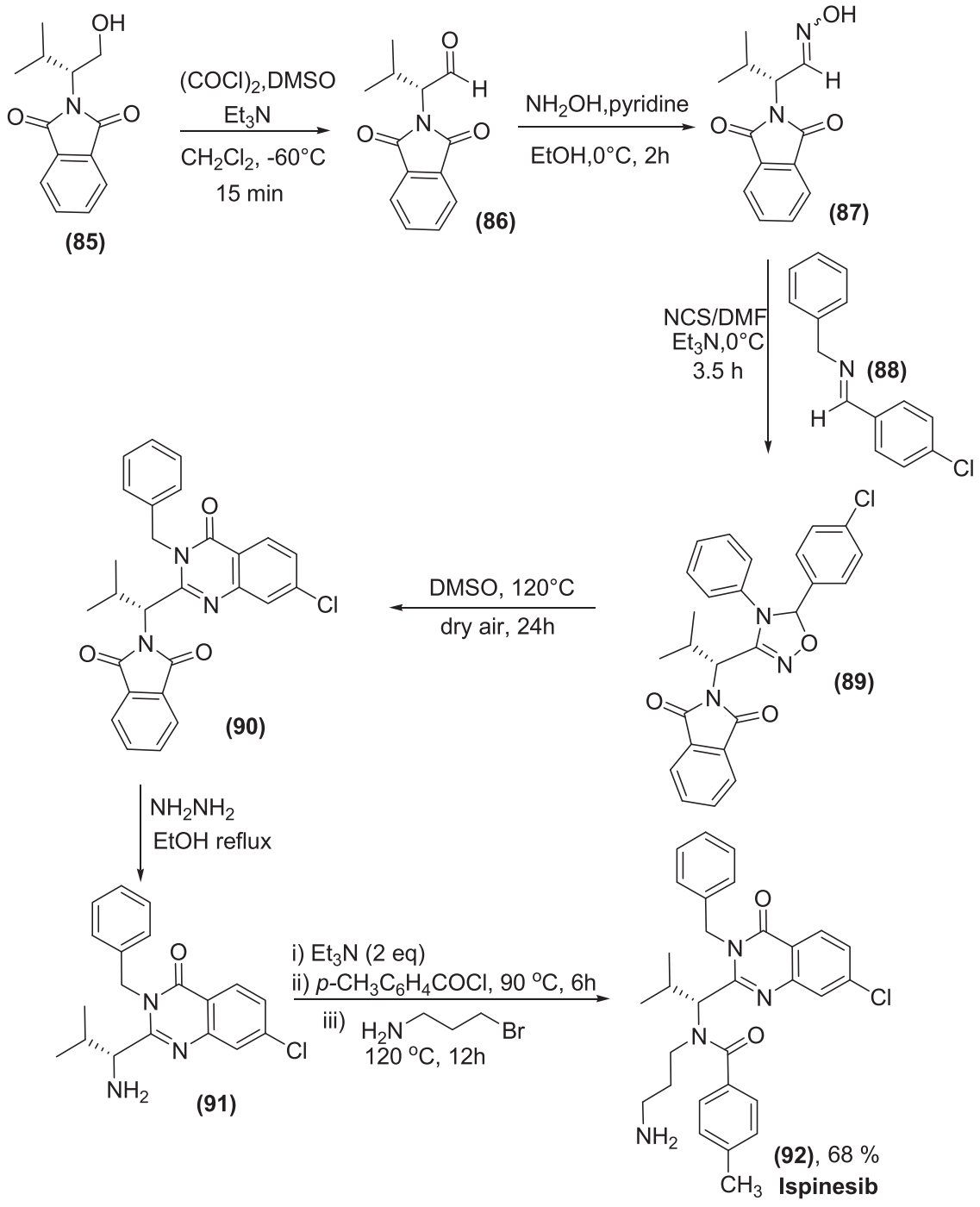
The FDA has approved Lapatinib (Fig. 21) in combination therapy for breast cancer patients already taking capecitabine (Xeloda). The medicine is marketed by GlaxoSmithKline (GSK) under the brand names Tykerb (primarily in the United States) and Tyverb (mainly in Europe) (mostly Europe and Russia). The tyrosine kinase activity of two oncogenes, EGFR (epidermal growth factor receptor) and HER2/neu, is inhibited by Lapatinib (human EGFR type 2). Overexpression of the HER2/neu gene in women has been linked to some forms of high-risk breast cancers. Lapatinib treats a specific form of breast cancer (HER2-positive). It acts by slowing or preventing cancer cell proliferation (Erickson et al., 2014).

Synthesis: The total synthesis of Lapatanib was presented in scheme 45(Erickson et al., 2014).

The key intermediate 6-bromo-*N*-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)quinazolin-4-amine(**103**)was obtained from 2-amino-5-bromobenzoic acid (**99**) through suitable chemical transformations shown in scheme 45. Next, the palladium catalysed regioselective arylation of furfural(**104**) with 6-bromo-*N*-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)quinazolin-4-amine(**103**) yield the Lapatanib (**108**) (Scheme 45). This crucial step is an atom-inefficient Suzuki cross-coupling reaction, resulting in a considerable reduction in synthesis time.

3.18. Vandetanib (April 2011)

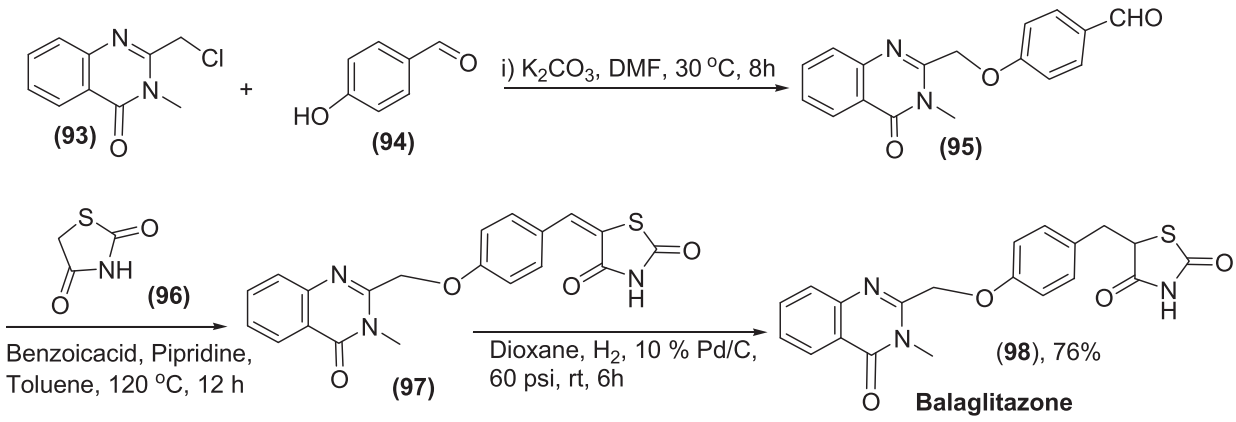
Vandetanib's (Fig. 22) marketing name is Zactima, and its chemical name is N-(4bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy] quinazolin-4-amine. It is a vascular endothelial growth factor receptor (VEGFR) and epider-



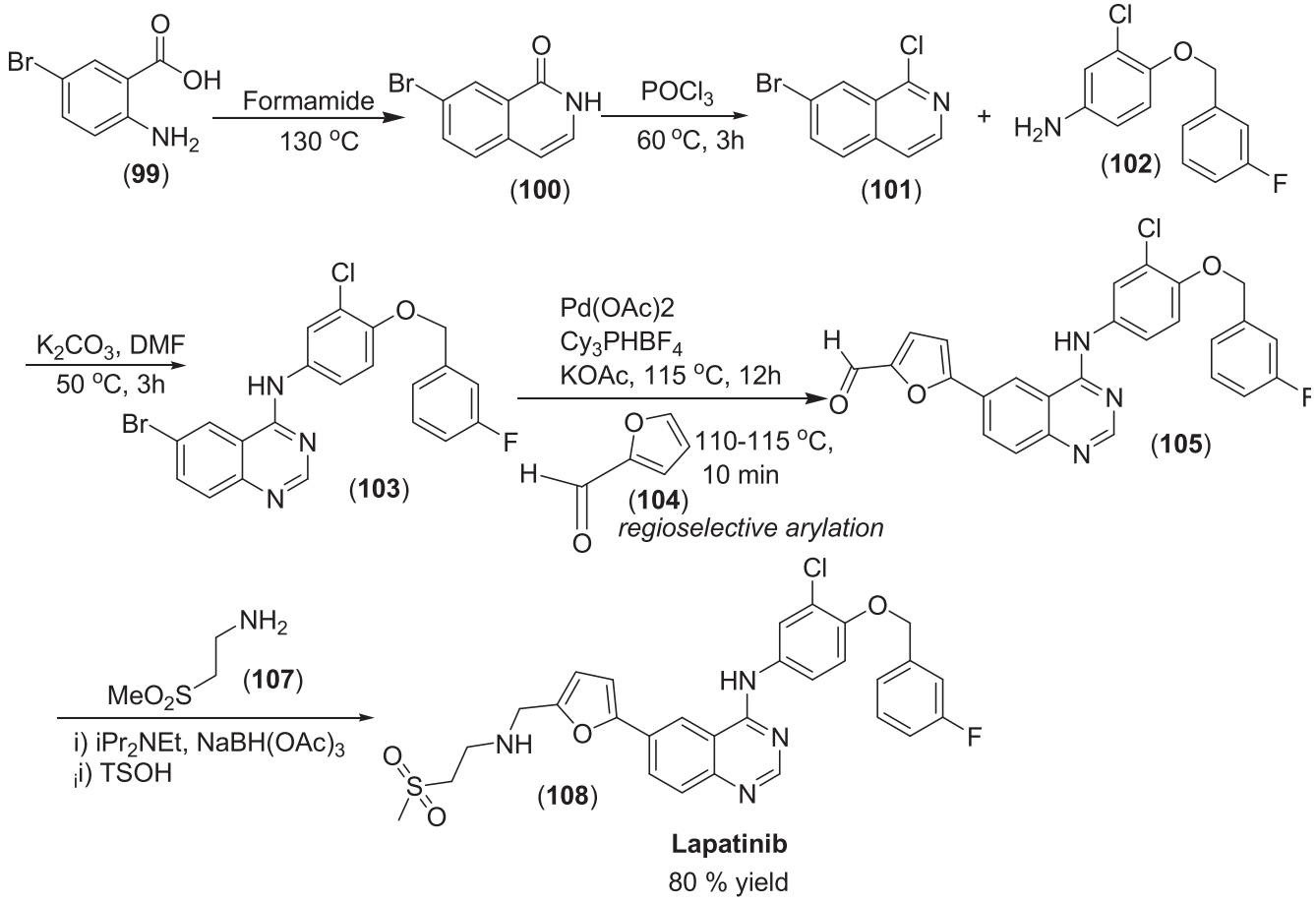
Scheme 43 Synthesis of Ispinesib.

mal growth factor receptor (EGFR) antagonist (EGFR). It works by inhibiting tyrosine kinases. The drug also has a third target: it inhibits the activity of RET-tyrosine kinase, a crucial growth driver in particular thyroid cancer (Selvam and Kumar, 2011). It treats patients with unresectable locally advanced or metastatic illnesses with symptomatic or progressing medullary thyroid carcinoma.

Synthesis: Synthesis is carried out utilising an unstable 4-chloroquinazoline scaffold, which necessitates the use of strong chemicals as well as sequential protection and deprotection processes. 7-(benzyloxy)-4-chloro-6-methoxyquinazoline hydrochloride (**109**) on appropriate chemical transformation produce the precursor (**115**) that on N-methylation affords the target Vandetanib in good yield. Vandetanib was synthesised using the Dimroth rearrangement in the primary quinazoline-producing step. The precursor7-((piperidin-4-yl) methoxy)-N-(4-bromo-2-fluorophenyl)-6-methoxyquinazolin-4-amine was obtained. The total synthesis for Vandetanib was presented in Scheme 46(Brocklesby et al., 2017).



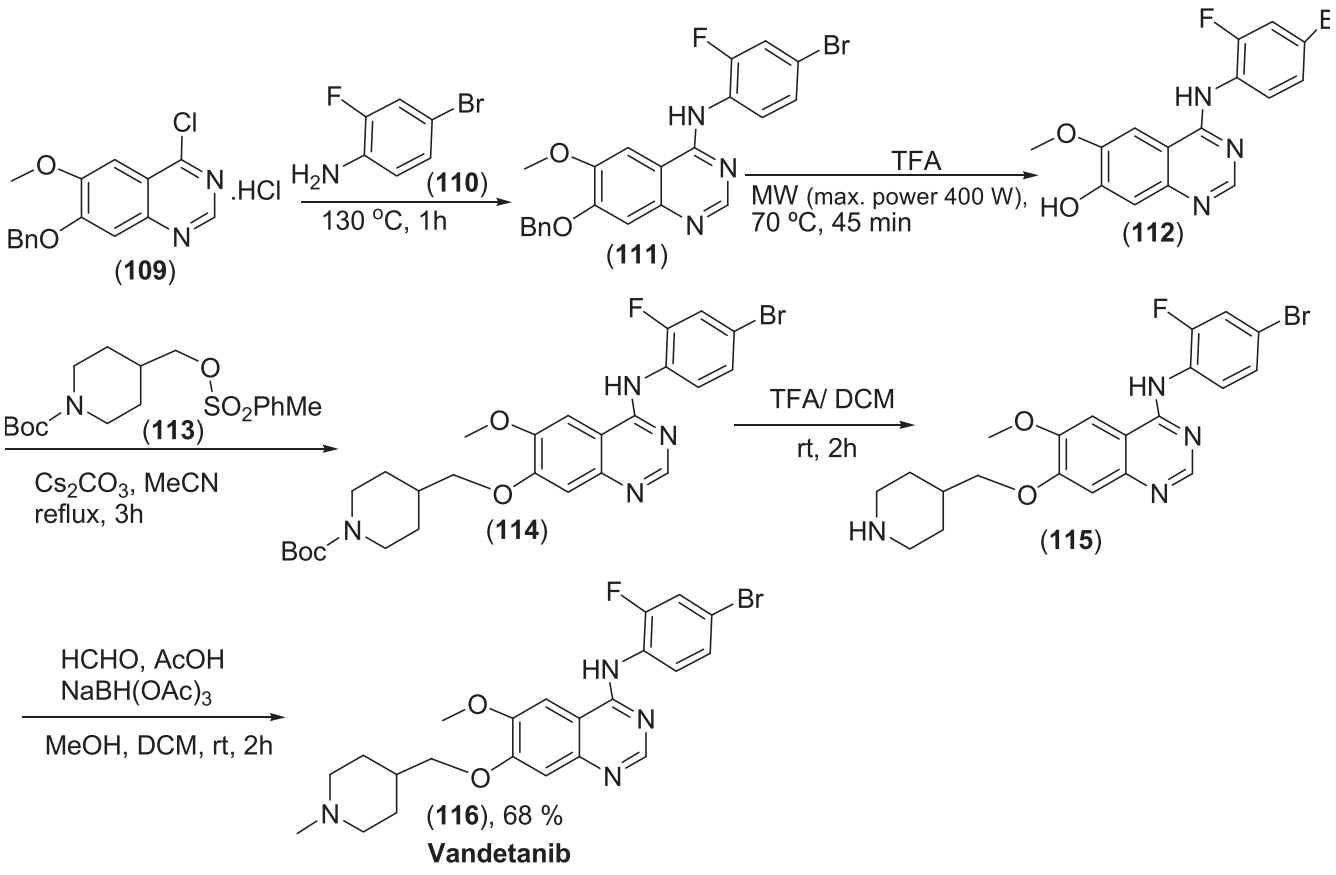
Scheme 44 Synthesis of Balaglitazone.



Scheme 45 Synthesis of Lapatinib.

3.19. Afatinib (2013)

Afatinib (Fig. 23) treats non-small cell lung cancer. It is available under the trade names Gilotrif and others (NSCLC) (Ghorab et al., 2013; Alvarado et al., 2006; Al-Amiery et al., 2014). It belongs to the class of drugs known as tyrosine kinase inhibitors. Afatinib, like Lapatinib and Neratinib, is a protein kinase inhibitor that inhibits human epidermal growth factor receptor 2 (Her2) and epidermal growth factor receptor (EGFR) kinases irreversibly. Afatinib is effective against EGFR mutations targeted by first-generation TKIs like Erlotinib or Gefitinib and against less prevalent mutations resistant



Scheme 46 Synthesis of Vandetanib.

to these medicines (Selvam and Kumar, 2011). It treats non-small cell lung, breast cancer, and cancers resistant to Gefitinib and Erlotinib.

Synthesis: Scheme 47 illustrates the total synthesis of Afatanib (Kovacevic et al., 2018). The desired intermediate (**121**)was synthesised from commercially available 4-fluoro anthranilic acid (**117**), which was iodinated with potassium iodide and sodium periodate to yield **(118)**, and the 4-quinazolinone ring was closed conventionally using formamide acetate to produce intermediate **(119)**. Next, the etherification and introduction of 3-chloro-4-fluoroaniline to intermediate (**119**) afforded the key intermediate (**121**), which on Cu promoted *C-N* coupling with trans-*N,N'*-dimethyl-1,2-cyclohexanediamine procured the desired Afatanib (**123**) in 56 % yield.

Reagents and conditions: (a) KI, $NaIO_4$, NaCl, AcOH, H_2O, r.t., 16 h, 86%, (b) formamide acetate, ethylene glycol monomethyl ether, reflux, 3 h, 95%, (c) (3S)-tetrahydrofuran-3-ol, NaH; 130 °C, 30 min, 89%, (d) $SOCl_2$, DMF, 90 °C, 3 h, (e) 3-chloro-4-fluoroaniline, *i*-PrOH, 90 °C, 3 h, 94%, (f) CuI, K_3PO_4, trans-N,N'-dimethyl-1,2-cyclohexanediamine, dioxane, 100 °C, 48 h, 56%.

3.20. Evodiamine (1915)

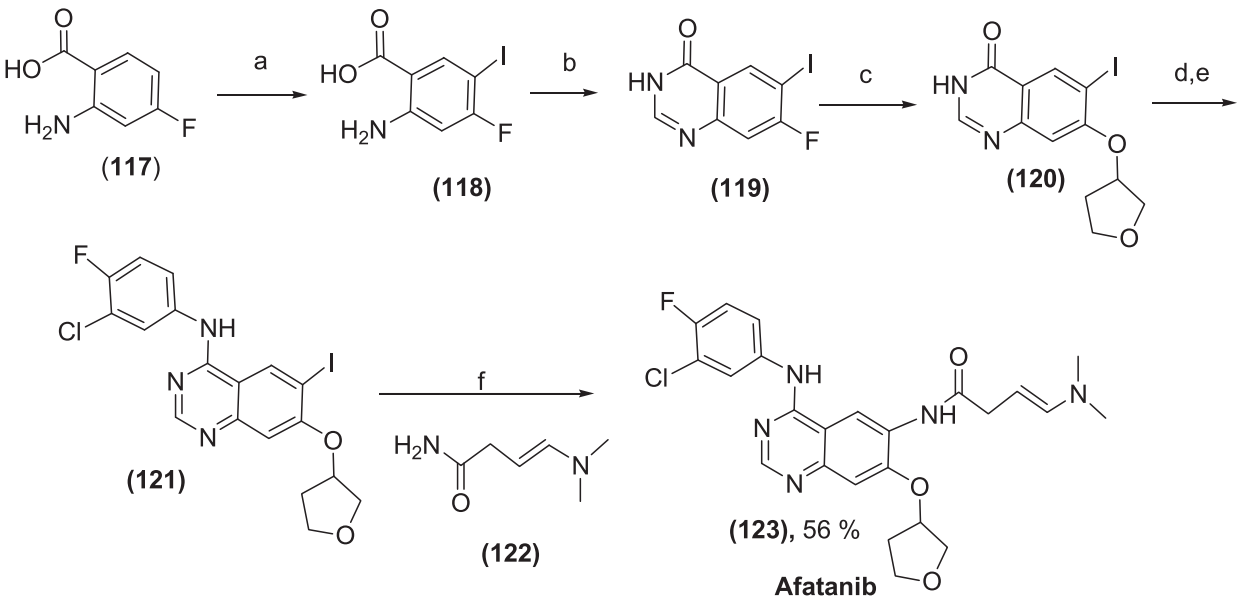
21-methyl-3,13,21-triazapentacyclo [11.8.0.02,10.04, 9.015,20] henicosa-2(10),4,6,8,15,17,19-heptaen-14-one is its chemical name. Evodiamine (Fig. 24) is made from the Evodia spp. plant family, and proved to lower fat intake in the mouse trials. This substance has been found in various over-the-counter bodybuilding supplements, but neither its fat-burning benefits nor possible hazards and side effects have been empirically established (Viola, 2016). Its properties include increasing body warmth and inhibiting the growth of some cancer cells. Furthermore, when taken with certain medicines, it alters your metabolism and impacts catecholamine output from your adrenal glands.

Synthesis: The synthetic path for constructing the drug Evodiamine(**126**) was shown in scheme 48(Wang et al., 2018), with triethoxymethane as a cosolvent, one-pot synthesis of evodiamine from tryptamine (**124**) and *N*-methylisatoic anhydride (**125**). The transformation proceeded efficiently in dimethylacetamide (DMA) at 100 °C with the addition of 1.0 equiv of TFAA and 1.5 equiv of 1,4-diazabicyclo[2.2.2] octane (DABCO) as shown in below scheme 48.

3.21. Quinethazone (1960)

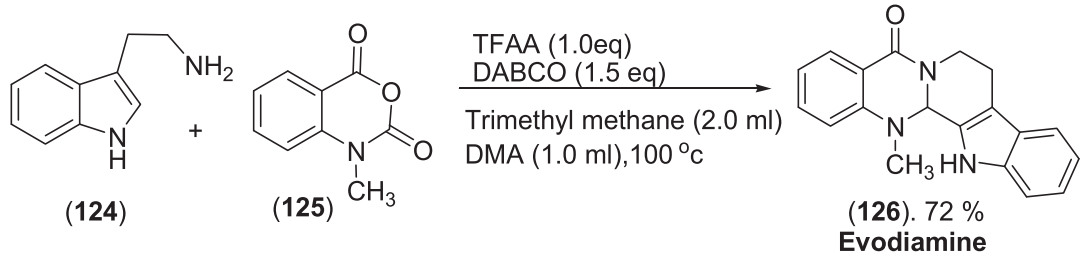
The drug chemically known as 7-chloro-2-ethyl-4-oxo-1,2,3,4-etrahydroquinazoline-6-sulfonamide is marketed as Hydromox (Fig. 25). Common side effects include dizziness, dry mouth, nausea, and low potassium levels (Kobayashi et al., 2001). It is used as a thiazide diuretic to treat hypertension.

Synthesis:The total synthesis of quinethazone is shown in Scheme 49 (Cohen et al., 1960). The 5-chloro-o-acetotoluide (**128**) was produced by the acetylation of 5-chlorotoluidine (**127**). Then it was chlorosulfonated and then treated with aqueous ammonia to generate 5-chloro-4-sulfamyl-o-acetoto luidide (**129**), which on oxidation with permanganate,afford the 4-chloro-5-sulfamyl-N-acetylanthranilic acid (**130**). Next,

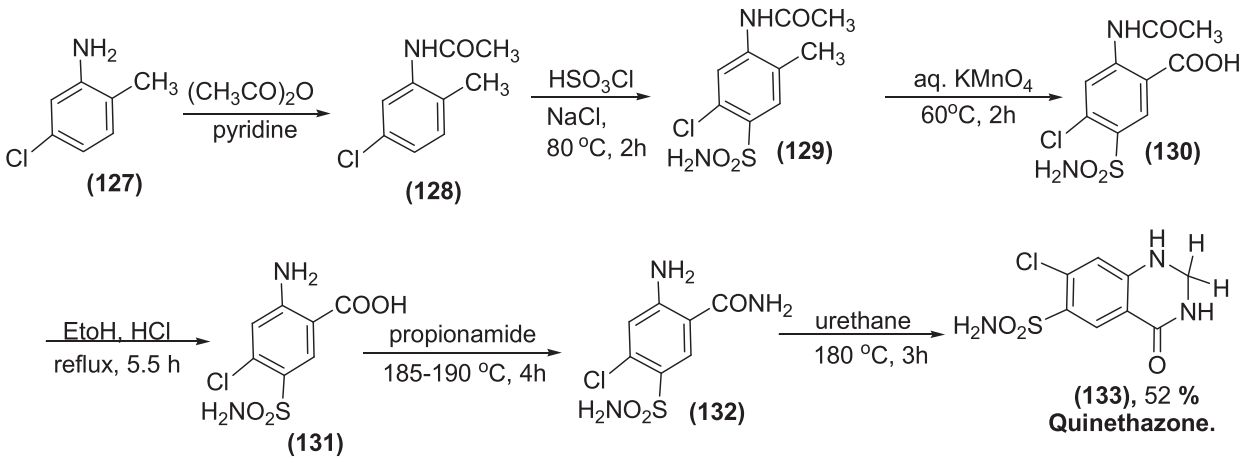


Reagents and conditions: (a) KI, $NaIO_4$, NaCl, AcOH, H_2O, r.t., 16 h, 86%, (b) formamide acetate, ethylene glycol monomethyl ether, reflux, 3 h, 95%, (c) (3S)-tetrahydrofuran-3-ol, NaH; 130 C, 30 min, 89%, (d) $SOCl_2$, DMF, 90 C, 3 h, (e) 3-chloro-4-fluoroaniline, *i*-PrOH, 90 °C, 3 h, 94%, (f) CuI, K_3PO_4, trans-N,N'-dimethyl-1,2-cyclohexanediamine, dioxane, 100 C, 48 h, 56%.

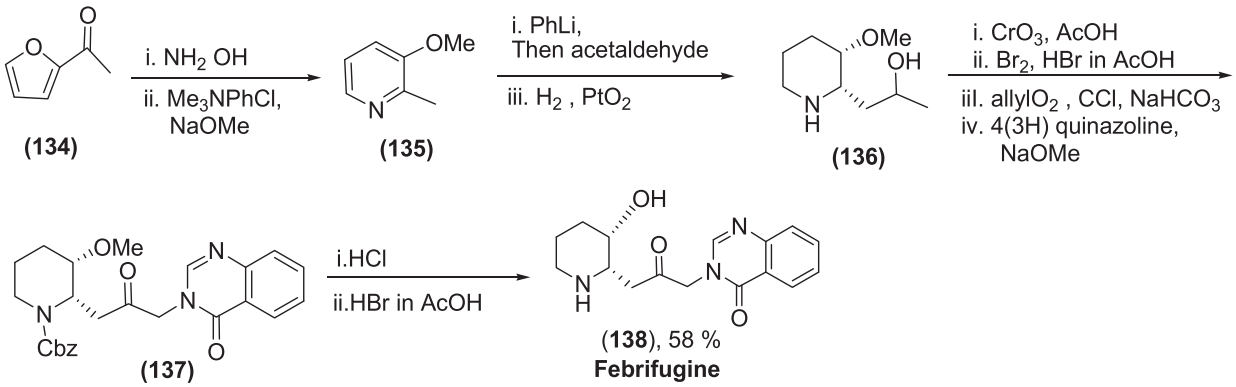
Scheme 47 Synthesis of Afatinib.



Scheme 48 Synthesis of Evodiamine.



Scheme 49 Synthesis of quinethazone.



Scheme 50 Synthesis ofFebrifugine.

intermediate (**130**)on deacetylation with a base or an acid, 4-chloro-5-sulfamylanthranilic acid (**131**) is produced. Finally, fusing(**131**) with propionamideand cyclising with urethane give the target quinethazone(**133**) in good yield.

3.22. Febrifugine (1949)

3–3-[(2S,3R)-3-Hydroxypiperidin-2-yl]-2-oxo propyl quinazolin-4(3H)-one is the chemical name for Febrifugine (Fig. 26). The quinazolinone alkaloid was discovered from the Chinese herb Dichroa febrifuge. However, it is also present in the garden plant Hydrangea (McLaughlin and Evans, 2010). It possesses anti-malarial effects, and it's halogenated derivative, halofuginone, is utilised as a coccidiostat in veterinary medicine.

Synthesis: Scheme 50 presents the total synthesis of Febrifugine (Smullen et al., 2018). The 2-acetyl furan (**134**) was transformed to the pyridine (**135**), which on treatment with NH_2OH and methylation, produced the intermediate (**135**), which combined with acetaldehyde and hydrogenated with PtO_2 to afford *cis*-piperidine (**136**). Next, it was oxidised to the ketone, alpha- brominated, N-protected and reacted with 4-(3H)-quinazolinone to furnish the N,O protected Febrifugine. Finally,the *N,O*-deprotection gave access to Febrifugine (**138**).

3.23. Fenquizone (1969)

Idrolone is a diuretic that belongs to the low-ceiling sulfonamide diuretic class. Its chemical name is 7-chloro-4-oxo-2-phenyl-1,2,3,4 tetrahydroquinazoline-6-sulfonamide. Fenquizone (Fig. 27) is most commonly used to treat oedema and hypertension.

Synthesis: Fenquizone(**141**) was generated in good yields in water under neutral conditions by the reaction of anthranilamide (**139**)withbenzaldehyde (**140**) mediated by *β*-cyclodextrin (Scheme 51). With a slight loss of enzymatic activity, *β* -cyclodextrin can be recovered and reused (Ramesh et al., 2012).

3.24. Metolazone (1970)

It is sold under the brand names Zytanix, Metoz, Zaroxolyn, and Mykrox and is a thiazide-like diuretic. Metolazone (Fig. 28) reduces the quantity of water reabsorbed into the bloodstream by the kidney in an indirect manner, resulting in a drop in blood volume and an increase in urine volume. Metolazone reduces blood pressure and prevents extra fluid from building up in heart failure patients. Metolazone is sometimes used with loop diuretics like furosemide or bumetanide, although these combinations can cause dehydration and electrolyte imbalances (Fischer and Ganellin, 2006). Furthermore, it is primarily utilised to treat congestive heart failure and hypertension.

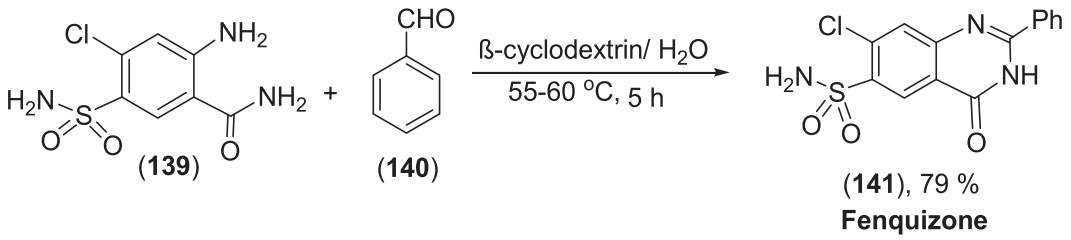
Synthesis: Metolazone is produced from5-chloro-2-methylaniline (**142**), which on treatment with Ethyl chloroformate, acylates the amino group, yielding 5-chloro-N-ethoxycar bonyl-2-methylaniline (**143**). Following a reaction with chlorosulfonic acid and ammonia, the intermediate (**143**) is converted into 4-sulfonamido-5-chloro-N-ethoxycarbonyl-2-methylaniline (**144**). On oxidation with potassium permanganate, the methyl group of this molecule yields 5-sulfona mido-4-chloro-N-ethoxycarbonyl anthranilic acid (**145**). It cycles into the corresponding anhydride (**146**) after being treated with thionyl chloride. When this comes into contact with *o*-toluidine, it forms 2-amino-5-aminosulfonyl-4-chloro-o-toluol benzamide (**147**). Finally, metolazone (**148**) is produced by reacting the intermediate with dimethylacetal acetic acid (Scheme 52) (Vardanyan and Hruby, 2006).

3.25. Linagliptin (2011)

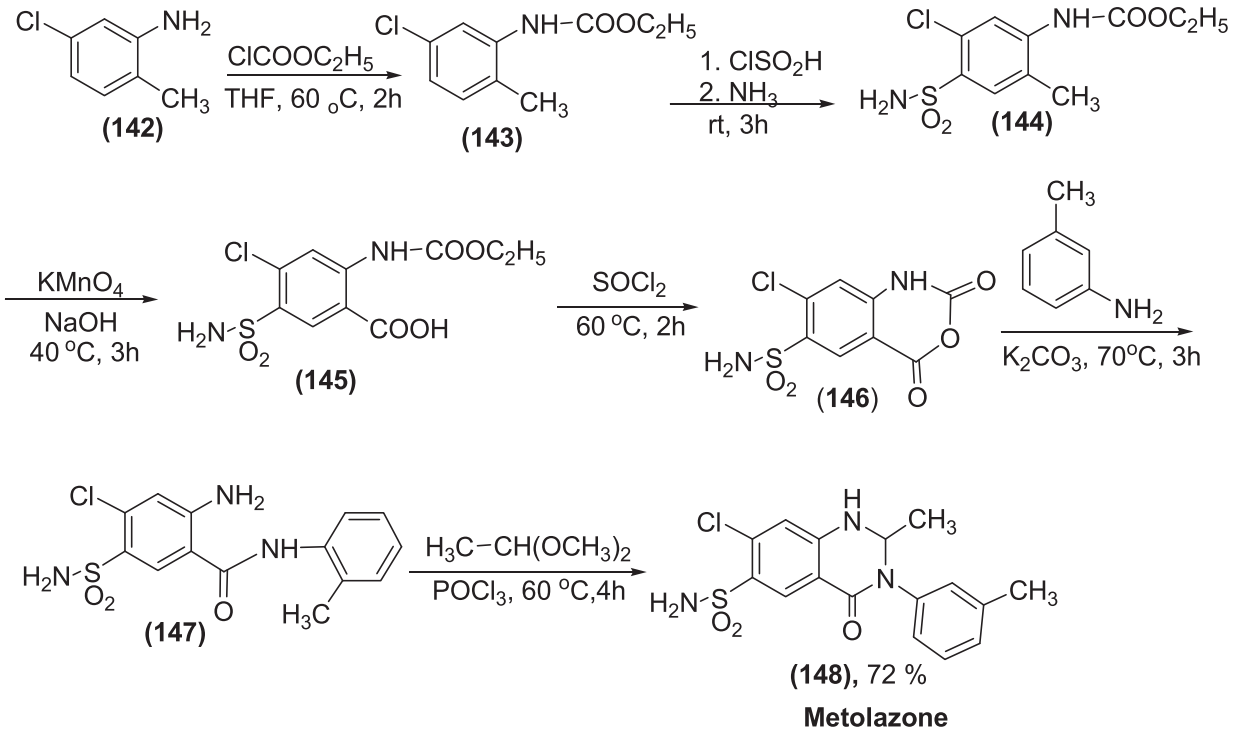
Ondero is its brand name, and its chemical name is 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2yn-1-yl)-3-methyl-1-[(4-methyl quinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione. It's a DPP-4 inhibitor produced by Boehringer Ingelheim for type 2 diabetes research. A Phase III clinical trial of linagliptin (Fig. 29) found that the medicine effectively lowers blood sugar levels (Huang et al., 2016).

Synthesis: The synthesis of Linagliptin (**155**)involves (Scheme 53) cyclisation of 1-(2-aminophenyl)ethanone (**149**) with 2-chloroacetonitrile in the presence of HCl to afford 2-(chloromethyl)-4-methylquinazoline (**150**). The compound (**150**) is condensed with 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1H-purine-2,6(3H,7H)-dione (**151**) in the presence of Na_2CO_3 as a basic reagent, giving 8-bromo-7-(but-2-yn-1-yl)-3-methyl-1-((4-methylquinazolin-2-yl)methyl)-1H-purine-2,6(3H,7H)-di one (**152**).

Regent and Conditions: (a) HCl, 1,4-dioxane, 60 °C, 2 h, 74%–85%; (b) Na_2CO_3, *N*-methyl-2-pyrrolidone (NMP), 140 °C, 2 h, 76%–83%; (c) diisopropanolamine, NMP,



Scheme 51 Synthesis of Fenquizone.



Scheme 52 Synthesis of Metolazone.

140 °C, 2 h, 90%–94%;(d) ethanolamine, THF/H_2O, 60 °C, 3 h, 81.9%.

Subsequently, the condensation of **(152)** with (R)-2-(piperi din-3-yl)isoindoline-1,3-dione (**153**) and D-tartaric acid using diisopropylethylamine as a basic reagent provided (R)-7-(bu t-2-yn-1-yl)-8-(3-(1,3-dioxoisoindolin-2-yl) piperidin-1-yl)-3-m ethyl1-((4-methylquinazolin-2-yl)methyl)-1H-purine-2,6(3H,7 H)-dione(**154**). Finally, Compound **(154)** was converted to the desired Linagliptin (**155**) in 82 % yield *via* aminolysis using ethanolamine as the aminolysis agent(Scheme 53).

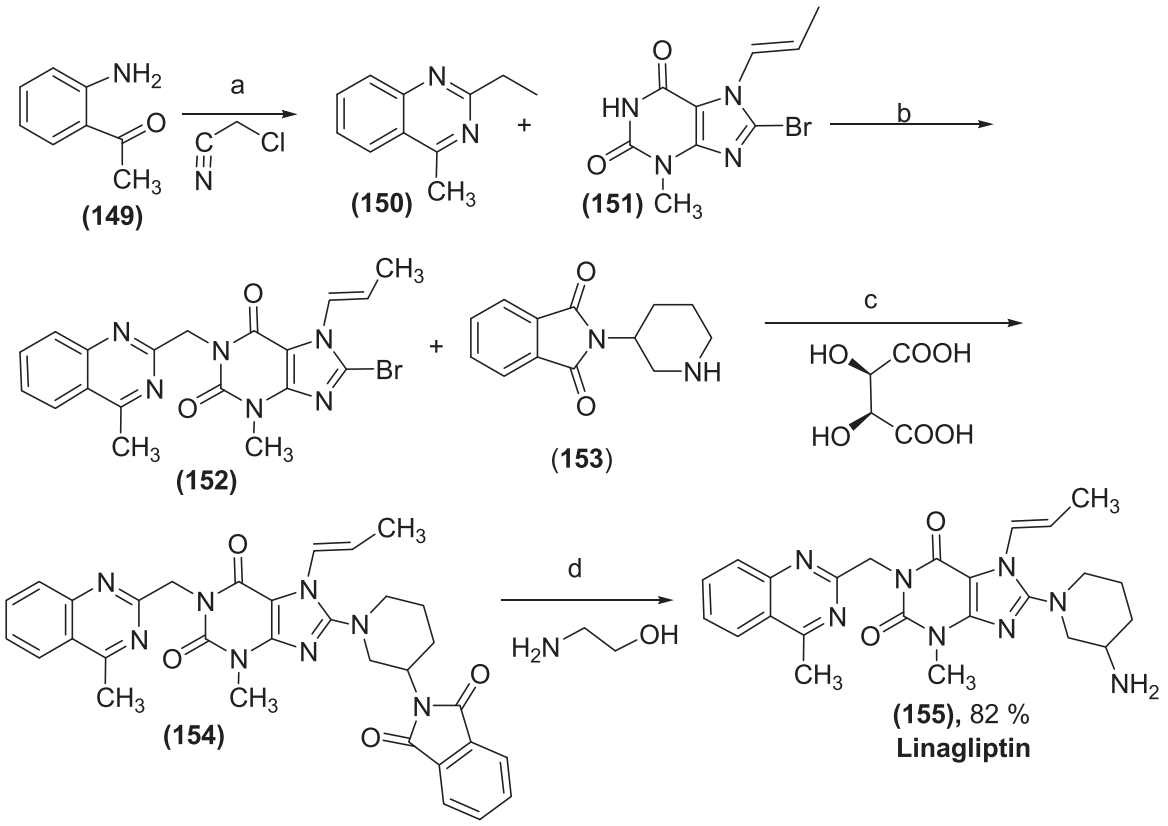
3.26. Quazinone (1980)

Quinazone (Fig. 30 was developed and marketed in the 1980's for the treatment of heart disease under the brand name Dozonone, which is chemically known as (3R)-6-chloro-3-methyl-5,10dihydroimidazo[2,1-b] quinazolin-2(3H)-one. It works as a selective PDE3 inhibitor (Daly et al.,1985; Belz et al., 1985). It's a cardiotonic and vasodilator medication.

Synthesis: Quinazone was prepared by combining 1-chloro-(2-chloromethyl)nitrobenzene (**156**) with (*S*)-ethyl-2-aminopropanoate (**157**) to form **(158)**, then hydrogenating the nitro group to form NH_2 to form intermediate (**159**). The intermediate reacts with cyanogen bromide followed by cyclisation resulting in the formation of the product Quazinone (**161**) (Scheme 54) (Chodnekar and Kaiser, n.d.).

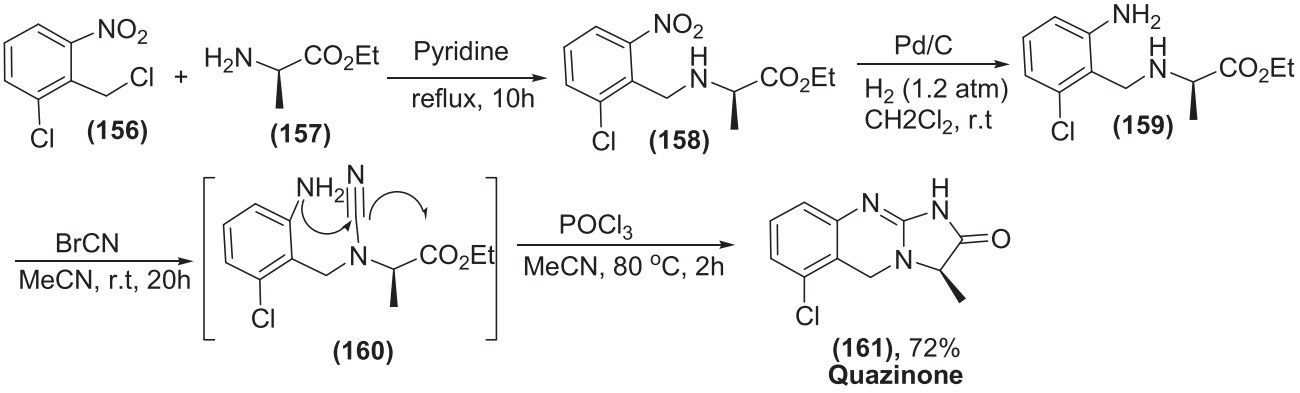
3.27. Raltitrexed (1996)

Tomudex is the commercial name for N-[(5-{methyl[(2-methyl-4-oxo-1,4dihydroquinazolin-6-yl)methyl]amino}-2-thienyl)car bonyl]-L-glutamic acid, and is manufactured by AstraZeneca. Raltitrexed (Fig. 31) is a chemotherapeutic medication chemically related to folic acid and belongs to the folate antimetabolites class. It prevents the formation of thymidylate by inhibiting dihydrofolate reductase, an enzyme involved in generating tetrahydrofolate. After polyglutamylation, Raltitrexed is fully functional. Raltitrexed hinders the production of DNA



Regent and Conditions: (a) HCl, 1,4-dioxane, 60 °C, 2 h, 74%–85%; (b) Na_2CO_3 ,*N*-methyl-2-pyrrolidone (NMP), 140°C, 2 h, 76%–83%; (c) diisopropanolamine, NMP, 140°C, 2 h, 90%–94%;(d) ethanolamine, THF/H_2O, 60°C, 3 h, 81.9%.

Scheme 53 Synthesis of Linagliptin.



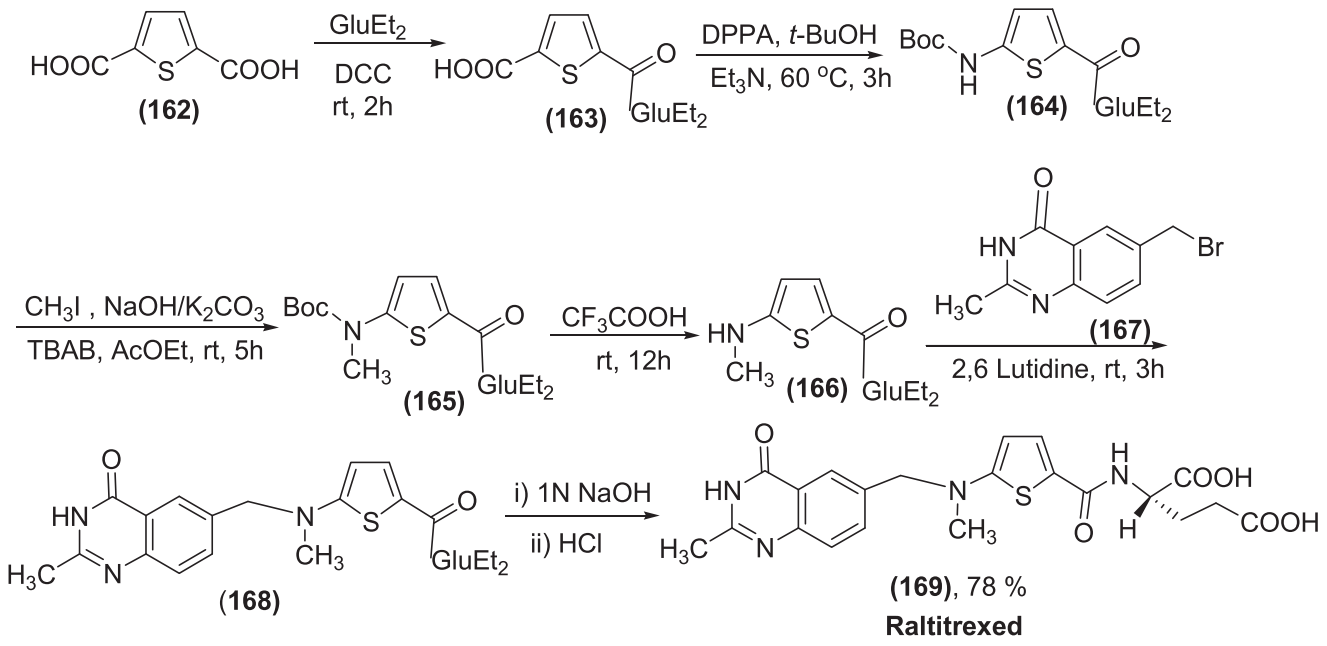
Scheme 54 Synthesis of Quazinone.

and RNA, which are necessary for the growth and survival of both normal and malignant cells, by blocking the formation of precursor pyrimidine nucleotides. It is an antimetabolite medicine used in cancer chemotherapy; it is a thymidylate synthase inhibitor. Raltitrexed has been employed in treating colorectal cancer since 1998.

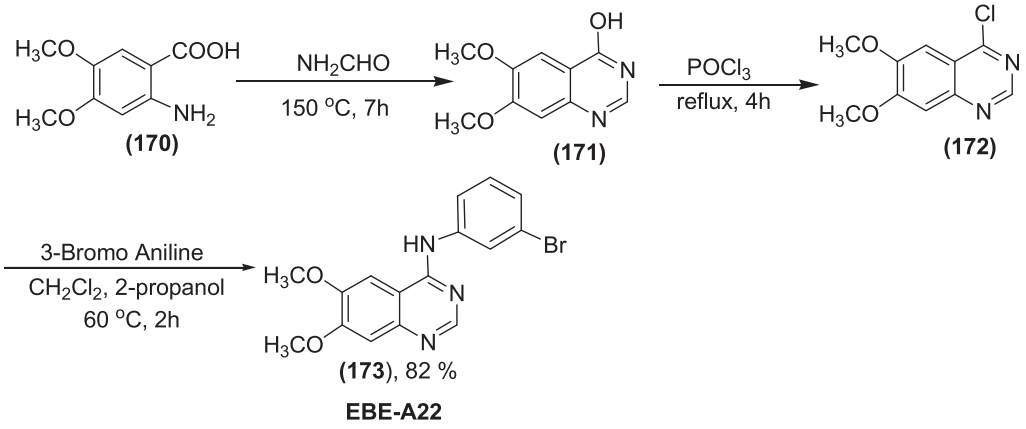
Synthesis: The synthesis of Raltitrexed (**169**) was presented in Scheme 55(Cao et al., 2003). Initially, monocoupling 2,5-thiophenedicarboxylic acid (**162**) with diethyl L-glutamate. Next, the intermediate (**162**)on consecutive modified Curtius reaction,*N*-methylation, deprotection of BOC, condensation with (bromomethyl)quinazolinone, and saponification reactions afford the targeted drug molecule Raltitrexed (**169**).

3.28. EBE-A22 (2011)

PD153035 is another name for EBE-A22 (Fig. 32), which is chemically known as N-(3-bromophenyl)-6,7-dimethoxyquina



Scheme 55 Synthesis of Raltitrexed.



Scheme 56 Synthesis of EBE-A22.

zolin-4-amine (Selvam and Kumar, 2011). It is an antineoplastic and intercalating agent (capable of insertingitself between DNA bases). These are employed in DNA research.

Synthesis: The synthetic path for EBE-A22 was shown in scheme 56 (Johnström et al., 1998). Initially, formamide was heated with 2-amino-4,5-dimethoxybenzoic acid(**170**) to 150 °C for 7 h. The obtained brown solid (**171**) was refluxed with $POCl_3$ for 4 h. Excess $POCl_3$ should be vaporised before adding $CHCl_3$ and NaOH to the wash residue. Compound (**172**) was produced by heating 3-bromoaniline and a minor amount of 3-bromoaniline hydrochloride with CH_2Cl_2 and 2-propanol for 2 h at 60 °C (Scheme 56).

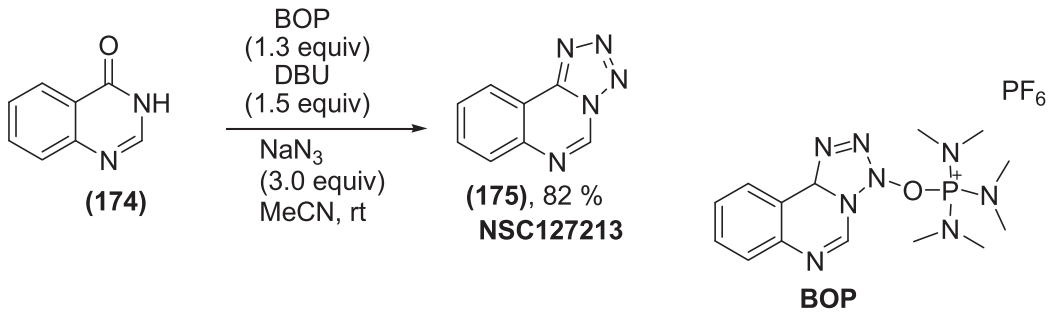
3.29. NSC127213 (2015)

Tetrazolo [1,5-c]quinazoline is the chemical name for NSC127213. NSC127213 (Fig. 33) can treat or prevent inflammatory, autoimmune, allergy, and ophthalmic illnesses by inhibiting H1R and H4R (Selvam and Kumar, 2011).

Synthesis: The synthesis of the fused tetrazole NSC127213 (Wan et al., 2010) was achieved by treating quinazolin-4 (3H)-one (**174**) with 0.5 equivalents of BOP reagent in the presence of DBU and sodium azide as the nitrogen nucleophile(Scheme 57). The reaction proceeds *via* BOP-promoted homo-dimerisation of 3,4-dihydro-4-methylenequinazoline to obtain the targeted fused tetrazole NSC127213(**175**).

4. Conclusions

Quinazoline and its derivatives play a crucial role in medicinal chemistry, evident in the chemical makeup of a wide range of FDA-approved medications, clinical candidates, and bioactive compounds. The findings state that several strategies have been designed to create these scaffolds. However, there is still an opportunity to develop highly effective protocols for synthesising and biological assessment of vari-



Scheme 57 Synthesis of NSC127213.

ous quinazoline derivatives. The development of molecular hybrids of quinazolines with a wide range of therapeutic values is receiving a lot of interest these days. Additionally, understanding presently prescribed quinazoline-based medications, their therapeutic value, and the methods for developing them is crucial for any researcher in medicinal chemistry. Substantial synthetic advancements have been made in meeting this requirement. In this review, we presented a precise account of recent advancements and noteworthy developments in synthesising different novel quinazoline analogues (2017–2023) focusing on design and therapeutic activity. We briefed the synthetic protocols of significant quinazoline-based drugs currently in use. We have also demonstrated how these skeletons can serve as artificial substrates for further alterations. Considering that quinazoline and quinazolinone compounds exhibit various biologically significant characteristics, this review will be beneficial for medicinal chemistry research and future drug development from the straightforward and varied nature of synthetic methods for producing quinazoline- and quinazolinone-based heterocycles.

Author contributions

The authors S.N.M.B. and H.B.B. designed the project; R.K. V.P., G.B.K., H.S.S., and N.R. helped prepare the manuscript, while S.N.M.B, H.B.B. and S.B.J. provided scientific guidance and helped to draft the manuscript. All authors have read and agreed to the submission of the manuscript.

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

Dr. S. N. Murthy Boddapati thanks the University of KwaZulu- Natal authorities for the fellowship. All the authors thank the Acharya Nagarjuna University, for the constant support and motivation. H. S. Saini expresses his gratitude to CSIR for its SRTP program 2020.

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