CHAPTER II
LITERATURE REVIEW
CHAPTER II

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LITERATURE REVIEW

The goal of drug discovery is to identify an effective therapeutic agent with less toxicity against a disease. Following the discovery, several structural modifications have been made to the quinazoline nucleus in order to increase the biological activities and ultimately furnish a candidate drug suitable for appropriate pharmacological studies and further clinical evaluation.
1. QUINAZOLINE DRUGS IN MARKET

1.1. Anticancer agents

Lapatinib (Fig 1) is used as a treatment for women's breast cancer in patients who have HER2-positive advanced breast cancer that has progressed after previous treatment with other chemotherapeutic agents, such as anthracycline, taxane derived drugs or trastuzumab (Herceptin, Genentech). In the year of 2006 GSK made a clinical trial on female breast cancer previously being treated with those agents (anthracycline, a taxane and trastuzumab) demonstrated that administrating lapatinib in combination with capecitabine delayed the time of further cancer growth compared to regime that use capecitabine alone. The study also reported that risk of disease progression was reduced by 51%, and that the combination therapy was not associated with increases in toxic side effects. The results from studies like these leave lapatinib with its somewhat complex and rather specific indication-use only in combination with capecitabine for HER2-positive breast cancer in women whose cancer have progressed following previous chemotherapy with anthracycline, taxane and trastuzumab. A number of studies are underway attempting to evaluate the efficacy of lapatinib as a first-line therapy for HER2-positive cancer.

Fig 1
**Erlotinib hydrochloride** (Tarceva) is a drug used to treat non-small cell lung cancer (Fig 2), pancreatic cancer and several other types of cancer. It is a tyrosine kinase inhibitor, which acts on the epidermal growth factor receptor (EGFR). Genentech is marketed this drug in US.

![Erlotinib](image)

**Gefitinib** (Iressa) is a drug used in the treatment of certain types of cancer. Gefitinib (Fig 3) is an EGFR inhibitor, like erlotinib, selectively targeting proteins in malignant cells. It is marketed by AstraZeneca and Teva.

![Gefitinib](image)
Cediranib (Fig 4) (Recentin) is a potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases. It is being developed as a possible anti-cancer chemotherapeutic agent for oral administration. Beginning in 2007, it is undergoing Phase I clinical trials for the treatment of non-small cell lung cancer, kidney cancer, and colorectal cancer in adults, as well as tumors of the central nervous system in children. Phase I trials of interactions with other drugs used in cancer treatment are also underway.

![Figure 4](image)

Vandetanib (Zactima) is an antagonist of the vascular endothelial growth factor receptor (VEGFR) (Fig 5) and the epidermal growth factor receptor (EGFR). It is a tyrosine kinase inhibitor. The drug is target to inhibits RET-tyrosine kinase activity, an important growth driver in certain types of thyroid cancer.

![Figure 5](image)

Nolatrexed (Fig 6) is, like raltitrexed, a selective inhibitor of thymidylate synthase. It is under investigation as an antimetabolites antineoplastic for the treatment of hepatocellular carcinoma. It is also under investigation in combination therapy for other solid tumours.
1.2. Analgesic and antipyretic agents

Diproqualone has some alpha\textsubscript{1}-antagonist and histamine H\textsubscript{1}-antagonist properties, but the clinical significance of these is controversial and Diproqualone (Fig 7) used as an analgesic.

Proquazone and Fluproquazone (Tormosyl) (Fig 8) is a quinazolinone derivative with potent analgesic and antipyretic effects and also anti-inflammatory action. It has been shown to be effective in a variety of animal species after both oral and parenteral administration, and has duration of action of several hours. The compound is much potent than acetylsalicylic acid and clinically generally resembles ibuprofen and indoprofen in its pharmacological effects, but with less ulcerogenic activity. It is mainly used in the treatment of arthritis and post-operative pain (Fig 9).
1.3. Antihypertension agents

Doxazosin mesylate (Fig 10), a quinazoline compound sold by Pfizer under the brand names Cardura and Carduran, is an alpha blocker used to treat high blood pressure and benign prostatic hyperplasia, the USFDA approved a sustained release form of doxazosin, to be marketed as Cardura XL. It is an alpha\textsubscript{1} adrenergic receptor blocker that inhibits the binding of norepinephrine to alpha receptors in the autonomic nervous system. The primary effect of this blockage is relaxed vascular smooth
muscle tone (vasodilation), which decreases peripheral vascular resistance, leading to decreased blood pressure.

![Chemical structure of Fenquizone](image)

**Fenquizone** (Fig 11) is a diuretic, part of the class of low-ceiling sulfonamide diuretics. Fenquizone is used primarily in the treatment of oedema and hypertension.

![Chemical structure of Prazosin](image)

**Prazosin** is selective for the alpha<sub>1</sub> receptors on vascular smooth muscle. The alpha<sub>1</sub> receptors leads vasoconstrictive action, which would normally raise blood pressure. By blocking these receptors, prazosin reduces blood pressure. Prazosin (Fig 12), trade names Minipress, Vasoflex and Hypovase, is a sympatholytic drug used to treat high blood pressure (hypertension). Which lower blood pressure by relaxing blood vessels.
Terazosin (marketed as Hytrin) is a selective α₁ antagonists used for treatment of symptoms of an enlarged prostate (BPH). It also acts to lower the blood pressure, and is therefore a drug of choice for men with hypertension and prostate enlargement. It works by blocking the action of adrenaline on smooth muscle of the bladder and the blood vessel walls. Most common side effects include dizziness, drowsiness, headache, constipation, loss of appetite, fatigue, nasal congestion or dryness, but they generally go away after only a few days of use. Therapy should always be started with a low dose to avoid first dose phenomenon. Sexual side effects are rare, but may include priapism or erectile dysfunction.
1.4. Hypnotics and sedatives agents

**Mebroqualone** (Fig 14) is an analogue of mecloqualone, which presumably has similar sedative and hypnotic properties to its parent compound. Mebroqualone differs from mecloqualone by having a bromine atom instead of chlorine on the 3-phenyl ring.

![Mebroqualone structure](image)

**Methaqualone** (Fig 15) is a quinazoline derivative with hypnotic and sedative properties. It has been given by mouth in the short-term management of insomnia but the use of methaqualone for this purpose is no longer considered appropriate. It has also been given with diphenhydramine for an enhanced effect.

![Methaqualone structure](image)

1.5. Antidiuretic agents

**Metolazone** is a thiazide diuretic (Fig 16) (or, rather, a thiazide-like diuretic because it acts similarly to the thiazides but does not contain the benzothiadiazine molecular structure) marketed under the brand names Zaroxolyn and Mykrox. It is primarily used to treat congestive heart failure and high blood pressure. Metolazone indirectly
decreases the amount of water reabsorbed into the bloodstream by the kidney, so that blood volume decreases and urine volume increases. This lowers blood pressure and prevents excess fluid accumulation in heart failure. Metolazone is sometimes used together with loop diuretics such as furosemide or bumetanide, but these highly effective combinations can lead to dehydration and electrolyte abnormalities.

![Chemical Structure of Metolazone](image)

**Fenquizone** (Fig 17) is a diuretic, part of the class of low-ceiling sulfonamide diuretics. Fenquizone is used primarily in the treatment of oedema and hypertension.

![Chemical Structure of Fenquizone](image)

### 1.6. Antidiabetic agents

**Dipeptidyl peptidase-4 inhibitors** (DPP-4 inhibitors) are enzyme inhibitors (Fig 18) that inhibit the enzyme dipeptidyl peptidase-4 (DPP-4) and are a potent treatment for type 2 diabetes. Inhibition of the DPP-4 enzyme prolongs and enhances the activity of incretins that play an important role in insulin secretion and blood glucose control regulation. Type 2 diabetes is a chronic metabolic disease that can be caused by
pancreas β-cell dysfunction, deficiency in insulin secretion, insulin resistance and/or increased hepatic glucose production. It is one of the fastest growing health concerns in the world.

![Diagram of Trimetrexate molecule]

**Fig 18**

1.7. Pneumocystis, pneumonia agents

Trimetrexate (Fig 19) is a quinazoline derivative. It is a dihydrofolate reductase inhibitor. It has been used with leucovorin in treating pneumocystis pneumonia. It has been investigated for use in treating leiomyosarcoma
1.8. 5-HT antagonist agents

**Ketanserin** (Fig 20) is a serotonin antagonist with a high affinity for peripheral serotonin-2 (5-HT\(_2\)) receptors and thus inhibits serotonin induced vasoconstriction, broncho constriction, and platelet aggregation and **Diproqualone** also has some alpha\(_1\)-antagonist and histamine H\(_1\)-antagonist properties (Fig 21)
1.9. Sympatholytic agents

The drug Trimazosin (Fig 22) exhibit sympatholytic effect

![Chemical structure of Trimazosin](image)
2. COMPOUNDS UNDER CLINICAL TRAILS

2.1. Sedative and hypnotic agents

**U-90042** is a sedative and hypnotic drug (Fig 23) used in scientific research. It is like benzodiazepine drugs, but structurally different that's why it was classed under a nonbenzodiazepine hypnotic. U-90042 is a GABA\(_A\) agonist acting primarily at the \(\alpha_1\), \(\alpha_3\) and \(\alpha_6\) subtypes, with a Ki of 7.8nM at \(\alpha_1\), 9.5nM at \(\alpha_3\) and 11.0nM at \(\alpha_6\). It produces sedation and ataxia and prolongs sleeping time in mice, rats and monkeys, but does not produce amnesia and blocks the amnestic effect of diazepam, reflecting its different subtype affinity compared to benzodiazepine drugs.

![Fig 23](image)


2.2. Anxiolytic and antidepressant agents

**ATC-0175** is a drug (Fig 24) used in scientific research, which is a selective, non-peptide antagonist at the melanin concentrating hormone receptor MCH\(_1\). In animal studies it has been shown to produce both anxiolytic and antidepressant actions, but without sedative or ataxic side effects.

![Fig 24](image)


2.3. TRPV\(_1\) antagonist

The TRPV1 receptor is an ion channel that has been implicated in mediation of many types of pain and therefore studied most extensively. The first competitive antagonist, capsazepine is described in the 1990, since then development of novel TRPV1 antagonists has come a long way. This is led to find the TRPV1 antagonists and its entered in clinical trials as analgesic agents. Should these new chemical entities
Relieve symptoms of chronic pain then this class of compounds may offer one of the first novel mechanisms for the treatment of pain, in many years.

![Chemical structure](image)

Fig 24

As of late 2009 vanilloid receptor ligands availability is nil market. The public information suggests that quite a few are in clinical trials. In biotechnology and pharmacy field companies are developing TRPV1 ligands and the emphasis seems to be on both agonists and antagonists. Although the agonists appear to be further along in clinical development. Agonists NeurogesX (Fig 25 and 26) three Phase III clinical studies are successfully completed for Qutenza (NGX-4010) that met studies primary endpoints. Qutenza is known for synthetic trans capsaicin and drug delivery is by a rapid-delivery patch application system NeurogesX plans to launch Qutenza in the United States in the first half of November 2010. The company like anesiva, has completed two Phase III trials of Adlea (ALGRX 4975), an injectable capsaicin. Adlea is promising as a pain reliever and both trials showed that Adlea's safety profile of adverse events, wound healing, and wound sensory function were similar to placebo over the study duration. TRPV1 antagonists are seven orally active substances have progressed into clinical development and several more are in preclinical development. The Eli Lilly-Glenmark introduced ligand GRC 6211, is the most advanced and it is currently in phase IIb clinical trials. Amgen and AstraZeneca is all developing TRPV1 antagonist and all are developing substances that have completed phase I trials successfully.
2.4. DPP-4 antagonist

Linagliptin (expected trade name Ondero Ondero) (Fig 27) is a DPP-4 inhibitor developed by Boehringer Ingelheim undergoing research for type II diabetes. It is currently in a Phase III clinical trial.

Fig 25

Fig 26
Fig 27
3. SYNTHESIS OF QUINAZOLINE NUCLEUS

In this review, which covers the literature up to the end of Feb-2010, we describe the new and improved methods for the construction of quinazoline skeleton, with a particular emphasis on the substituted analogues. Some of these procedures have clear technical advantages over older methods in terms of yield and versatility, but do not employ new chemistry in the construction of the ring systems. The use of combinatorial microwave enhanced synthetic processes and new catalytic methods in the preparation of these heterocycles are a clear indication that significant advancement has been made in recent years. Interest in the quinazolinic structure (Witt 2003 and Michael 2005) has led to a number of different synthetic pathways (e.g., Niementowski’s synthesis, Bischler’s synthesis, and Riedel’s synthesis). In 1905, Riedel obtained a patent for the synthesis of quinazoline (Robert 1957) from o-nitro benzaldehyde by reacting with formamide to the o-nitrobenzylidene diformamide. Reduction of the above with zinc and dilute acetic acid gave quinazoline (Fig 28) in good yield. Later Bogertm, McColm and Marr have improved the over-all yield up to 65%. This is the best method of obtaining quinazoline.

![Fig 28](image1)

This method suffers only from the difficulty of obtaining o-nitrobenzaldehyde and especially substituted o-nitrobenzaldehyde. In 1939, Fetscher and Bogert only synthesized 6,7-dimethoxyquinazoline (Fig 29), through the intermediate 6-nitro veratraldehyde.

![Fig 29](image2)
Chapter II  

Synthesis of Quinazoline Nucleus

The alkyl or aryl quinazoline (Fig 30) are obtained in high yields by reacting o-acyl amino benzaldehydes or phenyl ketones with ammonia. When the substituted amino ketones are available, this constitutes the best method of obtaining the quinazoline nucleus substituted with an alkyl or aryl group in the 2\textsuperscript{nd} or 4\textsuperscript{th} position.

![Fig 30]

Schofield passes the ammonia through a fusion of the o-acyl amino ketone with ammonium acetate at 165-175\textdegree C results in improved yields and avoids the use of sealed tubes.

![Fig 31]

Dianilides are obtained by condensation of o-amino aceto or benzo phenone with oxalyl chloride, which on ring closure give 2,2'-biquinazolines (Fig 31).
Schofield has surveyed the most efficient methods for the preparation of 4-phenylquinazoline (Fig 32) and concludes that the best one is represented by the following sequence.

There are many syntheses known, for 2 and 4 quinazolones (Per Wiklund 2004) unlike most quinazoline derivatives, which has limited methods of preparation. The majority of these proceeds from anthranilic acid or a derivative of anthranilic acid (Buckley 2005, Rao 1999 and Rani 2002) as the original starting compound and continue through the N-acylanthranilamide, which is generally not isolated. Generally there are three types of quinazolones. 1. 2-Quinazolones, 2. Benzoyleneurea, 3. 4-Quinazolones. The only known method of forming a 2-quinazolone (Fig 33) involves the condensation of an o-aminobenzaldehyde or phenyl ketone with urea. Synthesized 4-methyl 2-quinazolone by heating o-aminoacetophenone and an excess of urea at 190°C for 20 min with 60% yield (Bischler 1891).
Chapter II  Synthesis of Quinazoline Nucleus

Bogert, Scatchard and Lange, Sheibley synthesized Benzoyleneurea (Fig 34, 35) from anthranilic acid by different catalysts.

The 4-quinazolone (Fig 36) is most commonly synthesized by (Niementowski 1895) method in which; anthranilic acid is heated in an open container with excess formamide at 120°C.
Many of the literature (Rad Moghadam 2006, Correa 2002, Gilchrist 2001 and Sirisoma 2010) synthetic methods for elaboration of this simple ring structure are, however, time consuming tedious and often low yielding. Thus, considering the importance of this class of compounds (Fig 37) and authors developed both a microwave-assisted and a conventional thermal heating protocol for the preparation of quinazolines from a mixture of 2-aminobenzonitrile, o-ester, and ammonium acetate under solvent-free conditions. The authors did not inform the microwave equipment used in the reaction. The reactants were used in a molar ratio of 2:1:1, respectively. The excess of o-ester was necessary to diminish the side reactions. The microwave-assisted synthesis furnished products in 82-89% yields and for 5-7 min, and in the conventional thermal heating method was observed that the yields were slightly superior (83-92%), although it required 30-80 min. The authors also performed the reaction in refluxing ethanol for 180-240 min to furnish the products in 71-81% yields.

The synthesis of 1,2,3,4-tetrahydroquinazolines (Fig 38) from the reaction of 2-aminobenzylamine and benzaldehydes using two different methods, grinding and oil bath. In the first method, the reactants were used in a molar ratio of 1:1:1 respectively, while in the second, equimolar amounts were used. In both methodologies used, the conversion of the reactants into the products (Sirisoma 2010).
A photochemically (Chandregowda 2009) induced Fries rearrangement of anilides gave several o-amino acyl benzene derivatives that were acylated (Fig 39).

![Chemical structure of quinazoline](image)

**Fig 39**

A tandem palladium-catalyzed arylation-ester amidation (Ferrin 2007) sequence allows the synthesis of various quinazolinedione (Fig 40) products by reaction of o-halo benzoates with mono alkyl ureas. The reactions are regioselective for the formation of 3-N-alkyl isomers.

![Chemical structure of quinazolinedione](image)

**Fig 40**

MIT (Fig 41) have developed a protocol for the synthesis of quinazolines (Mohammad 2006) via electrophilic activation of secondary amides utilizing 2-chloropyridine (2-ClPyr)
in combination with Tf$_2$O and subsequent reaction with weakly nucleophilic nitriles. Whereas electron rich N-vinyl and aryl amides afforded the corresponding pyrimidine derivatives at room temperature, microwave heating to 140°C was necessary for less reactive substrates. Additionally, one example was presented where a primary amide was employed instead of nitrile under the same microwave conditions giving the quinazoline$^{20}$ (R$^1$ = Ph, R$^2$ = H, R$^3$ = OMe, R$^4$ = C$_6$H$_{11}$) in 74% yield.

A three-component reaction to form 2-alkylquinazolines from the reaction of amidines with ammonia (Erba 1999). In the first step, an aldehyde is reacted with morpholine and subsequently, with an aryl azide to afford the thiazoline in acceptable yields, (Fig 42). On exposure to a saturated ethanolic solution of ammonia in a sealed vessel at 150°C or, alternatively, in ammonium acetate in boiling toluene, the triazolines were converted into the desired quinazoline products in approximately 30 min. The ring-closure step worked well for the triazolines affording the 2-alkyquinazolines (Fig 43) in 92 and 95% yield, respectively. In comparison, the triazolines and only gave moderate yields of 38 and 37%. Overall, this procedure is characterized by the use of readily available starting materials for the synthesis of 2-substituted- quinazolines that bear electron-withdrawing groups.
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Synthesis of Quinazoline Nucleus

Fig 42

\[
\begin{align*}
\text{R}_1 &= \text{Me, Et, Bn, C}_{10}\text{H}_{21} \\
\text{X} &= \text{CN, NO}_2 \\
\text{R}_3 &= \text{NO}_2, \text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_3 &\xrightarrow{\text{EtOH, 150°C}} \\
\text{R}_1 &= \text{Et, Me, Bn, C}_{10}\text{H}_{21} \\
\text{R}_3 &= \text{NO}_2
\end{align*}
\]

Fig 43

\[
\begin{align*}
\text{R} &= 4\text{-C}_{10}\text{H}_{21}\text{C}_6\text{H}_4, 4\text{-Br C}_6\text{H}_4
\end{align*}
\]
A condensation of cyano and nitro activated o-fluoro Benzaldehydes with amidines to give a variety of quinazoline derivatives in good yields (Kotsuki 1999). This method involves tandem imine formation with the aldehydes function and an intramolecular nucleophilic aromatic substitution at the fluorine-substituted carbon centre, (Fig 44). The reaction is carried out in refluxing acetonitrile with potassium carbonate in the presence of powdered molecular sieves, and the crude product is purified by chromatography.

4-Chloroquinazolines (Shreder 2004) are important synthetic intermediates as they can be derivatives further through nucleophilic attack at the C-4 position. This is illustrated in the synthesis of an intermediate, a quinazoline-derived photo affinity probe for epithelial growth factor receptor (EGFR) (Fig 45).
A thiomethyl substituent can also be used to activate the 4-position towards nucleophilic substitution (Rewcastle 1996). The formation of thiomethyl ether is achieved in two steps by treating the corresponding quinazolinone with Lawesson’s reagent ($P_2S_5$) to yield a quinazoline thione (Fig 46). Subsequent lithiation and methylation lead to the formation of the thioether, which can then be treated with a nucleophile to give the 4-substituted quinazoline.
The 2-amino-N-arylbenzamides furnished the 4-arylaminoquinazolines in good yields (Szczepankiewicz 1998 and Szczepankiewicz 2000) (70-92%) when heated with 85% formic acid, although the reaction can only be applied to the synthesis of 2-unsubstituted 4-arylaminoquinazolines. (Fig 47).

In May 2003, the US Food and Drug Administration (FDA) approved the first epidermal growth factor receptor inhibitor, (Barker 2001), for the treatment of lung cancer, further highlighting the importance of the 4-anilinoquinazolines in medicine (Fig 48).
An efficient method for the synthesis of 4-anilinoquinazolines. 5-Nitroanthranilidonitrile was condensed with DMF acetal to yield (Tsou 2001). Heating this compound with 3-bromoaniline in acetic acid yielded the desired quinazoline in excellent yield, (Fig 49). An advantage of this approach is the formation of the quinazoline ring and the incorporation of the 4-anilino group in the one step. Yoon et al. reported the reaction of N,N-dimethylamidinobenzamide with benzylamine (Yoon 2004) to give 4-aminoquinazoline under the conditions of microwave (MW) irradiation, (Fig 50)
A novel palladium complex catalyzed synthesis of quinazoline derivatives by employing an intermolecular reductive N-hetero cyclization (Watanabe 1995). A palladium complex of \( \text{PdCl}_2(\text{PPh}_3)_2 \) with \( \text{MoCl}_5 \) showed high catalytic activity for the N-hetero cyclization of 2-nitrophenyl ketones with formamide to afford the corresponding 4-substituted quinazolines (Fig 51).

![Fig 51](image)

In the absence of the palladium complex, 2-nitrobenzaldehyde reacted with formamide to give the corresponding N-[1-formylamino-1-(2-nitro-phenyl)-methyl]-formamide. When formamide was treated in the presence of the catalyst under CO pressure at 100°C for 16 h, the quinazoline was produced in 29% yield, (Fig 52). This suggests that N-[1-formylamino-1-(2-nitro-phenyl)-methyl]-formamide is a possible intermediate in the reductive N-hetero cyclization.

![Fig 52](image)

The suggested mechanism for this process begins with the carbonyl group of the 2-nitrophenyl ketone condensing with the formamide to give the corresponding bisamide, (Fig 53). A nitrene intermediate is generated by deoxygenation of the nitro group with
carbon monoxide. It is proposed that the Lewis acidic MoCl$_5$ coordinates to the oxygen atoms of the nitro group, weakening the N-O bond and thereby facilitating the deoxygenation process. An intramolecular nucleophilic addition of the nitrene to the carbonyl group of the bisamide follows to generate the metal acyclic intermediate, which subsequently undergoes decarboxylation. Finally, the reductive elimination of the 3,4-dihydro-4-(N-formylamino)quinazoline regenerates the active catalyst and dehydro amidation of furnishes the desired quinazoline.

This novel route to biologically important compounds represents the first transition-metal-complex-catalyzed intermolecular reductive N-hetero cyclization and offers a new synthetic method for preparing quinazoline derivatives, albeit in moderate yields (19-44%). The solid-phase synthesis reported by Wilson enabled the preparation of 2,4-diamino quinazolines (Fig 54) in good yields and purities (Wilson 2001). This was accomplished using an acyl iso thiocyanate resin with functionalized 2-inobenzonitriles and amines as the key building blocks in the synthesis.

A microwave-promoted synthesis of 4-aminoquinazolines (Seijas 2000) by reacting cyano aromatic compounds with anthranilonitrile in a domestic microwave oven (Fig 55). As an example, anthranilonitrile, 2-thiophenenitrile and potassium tert-butoxide were added to a test tube and heated for 1 min to afford 4-amino-2-(2-thiophenyl)-quinazoline in 90% yield. It was found that this method was superior to the traditional methods of synthesis for this class of compound. As a comparison, 4-amino-2-benzylquinazoline was prepared in 73% yield after 3 min by microwave irradiation, whereas the same compound was obtained in only 40% yield after refluxing for 48h in isopropanol. A dramatic reduction in reaction time, the absence of solvents and the use of only a catalytic amount of base are appealing features of this approach.
Fig 53
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Synthesis of Quinazoline Nucleus

Fig 54

R = Ph, CH₃,
The synthesis of 2,4-dihydroxyquinazolines using 2-aminobenzonitriles and carbon dioxide in the presence of DBU under mild conditions was developed by (Mizuno 2000). Carbon dioxide reacts with 2-aminobenzonitriles. In the presence of the suitable base to generate the carbamate salts. This is followed by nucleophilic cyclization with attack of the carbamate oxygen on the nitrile functionality. A rearrangement then occurs to afford the intermediate, which is protonated to yield the desired 2,4-dihydroxyquinazoline, (Fig 56). This experimentally convenient procedure can be used to prepare the unsubstituted 2,4-dihydroxyquinazoline in high yield and purity. Excellent yields (90-97%) were also obtained in the presence of both methoxy- and nitro substituted 2-aminobenzonitriles.

The thermolysis of 5-methoxy- and 5-diethylamino-(3H)-1,4-benzodiazepines to give 4-methoxy- and 4-diethylaminoquinazolines (Kaname 1999) by a ring contraction mechanism (Fig 57). On heating the 5-methoxy-(3H)-1,4-benzodiazepines 254 in diphenyl ether at 160-170°C for 6h, the 4-methoxyquinazolines were furnished as the sole products in moderate yields (41-46%). Similarly, 5-diethylamino-(3H)-1,4-benzodiazepines were treated with sodium methoxide at room temperature to give the corresponding 4-diethylaminoquinazolines in acceptable yields, (Fig 58).
Fig 56

Fig 57

R = Me, Ph
Fig 58
The behavior of the 2-phenyl derivative differed from its 2-methyl analogue as an approximate 1:1 mixture of the benzodiazepine and the expected quinazoline was obtained. An increase in the chemical yield 60% was observed on refluxing the 2-phenyl-benzodiazepine in xylene or by further treatment with sodium methoxide.

Fig 59
A possible mechanism to account for the products obtained involves a thermal electrocyclization to produce aziridine type compounds, (Fig 59). These undergo ring opening
to give the corresponding N-ylides and subsequent fission of the N-C bond yields the required quinazolines.

Okada employed 5,7-bis-(trifluoroacetyl)-8-quinaolylamin as a convenient building block for the synthesis of quinoline-fused quinazolines bearing a trifluoromethyl functionality (Okada 1999). The C-2 substituent in each case was derived from the corresponding aldehyde and aqueous ammonia was used as the N-3 source in a straightforward synthesis of the desired compounds, (Fig 60). The benzaldehyde derivatives reacted with the quinolone starting material to afford 2-aryl-1,2-dihydropyridoquinazolines in 60-88% yields with recovery of the unreacted substrate. It was noted that prolonged heating (48-96 h) resulted in the formation of the unexpected 2-aryl-a,4-bis(trifluoromethyl)-pyrido[3,2-H]quinazoline-6-methanols in 18-46% yield. Treatment of the quinazoline products with DDQ at room temperature for 1h furnished the fluorine-containing pyrido[3,2-H]quinazolines in 85-95% yield, (Fig 61). The alcohols could also be converted in excellent yields (82-94%) by oxidation into the quinazoline derivatives using DDQ. This route enables access to products that are not easily obtained by other methods.
The reaction of organo lithium reagents with 2,4-dichloroquinazoline (Harden 1998) was regioselective, resulting in predominant substitution at the 4-position (Fig 62).

The differential reactivity of 2,4-dichloroquinazoline derivatives as part of their structure activity relationship studies of phosphodiesterase inhibitors (Lee 1995). The 6-substituted quinazoline-2,4-diones were readily prepared from the anthranilamides by treatment with phosgene (Fig 63).
Alternatively, the reaction of anthranilic acids band potassium cyanate followed by ring cyclization could be employed. In the light of commercial interest in quinazoline antihypertensive agents, a similar procedure for the synthesis of kilogram quantities of the substituted quinazoline-2,4-dione was developed by (Hammen 1987). The substituted 2,4-dichloroquinazoline was prepared in excellent yield by refluxing the 6-substituted quinazoline-2, 4-dione in phosphorus oxychloride. Replacement of the 4-chloro group by a primary amine such as benzylamine afforded the desired intermediate. An imidazole group was subsequently introduced at the 2-position to furnish the required 2,4-diaminoquinazoline in 63% yield. It was found that the 4-
benzylamino fragment imparted a greater activity than the 4-anilino series in the study of PDE inhibitors. In addition, the 2-position imidazolyl substituents gave a slightly higher potency than the corresponding 2-pyridyl analogues. This method demonstrates how assisted drug design technology can identify potentially causal relationships between structural fragments and biological activity.

A series of quinazolines was prepared in order to evaluate their usefulness as a possible treatment for obstructive pulmonary disease such as asthma (Charpiot 1998). Protection of the aminophenol starting material was required in order to allow the efficient alkylation of the hydroxyl functionality, (Fig 64). Deprotection and subsequent reaction with the isocyanate afforded intermediate. It was found that the yield from the cyclization reaction with phosphorus oxychloride was dependent on the nature of the 6- and 7-substituents (80% and 10%).

Fig 64
A Stille coupling resulted in exclusive reaction at the 4-chloro substituent in 2,4-dichloroquinazoline derivatives (Mangalagiu 1996), since this position is the most electrophilic, (Fig 65). Lastly, substitution at the remaining 2-position by both organotin and organozinc reagents was possible using similar cross-coupling methodology, Alcohols, thiols or amines in the presence of sodium hydroxide could also be used to replace the 2-chloro substituent, to produce in yields of 50-90%, (Fig 66).

\[
\begin{align*}
R_1, R_2 & = \text{H} \\
R_3 & = \text{3,5-dibenzyloxy-phenyl, 3,5-dicyclopropylmethoxy-phenyl}
\end{align*}
\]

\[
\begin{align*}
R = \text{Et, n-Bu, 2-thiophenyl, 3,5-dicyclopropylmethoxy-phenyl}
\end{align*}
\]
By exploiting the inherent reactivity of 2,4-dichloroquinazoline, it was possible to access a large number of biologically relevant products. This reactivity may also be exploited for the elaboration of 2,4-quinazolines with trimethylalane and tri-isobutylalane and tetrakis (triphenylphosphine) palladium as catalyst (Fig 67).

![Reaction Scheme]

After 24 h at reflux, the alkylated products were obtained in good yields (63 and 76%). Addition of another equivalent of the appropriate alane enabled further substitution at the 2-position, with yields varying from 63-80%. This method complements the existing procedures involving organo stannanes, organozinc and organo magnesium reagents for carbo-substitution, allowing region selective modification of biologically important quinazolines. More recently, Weber et al. have exploited this reactivity at the 4-position, while producing a solid-phase library of 2-substituted quinazolinones (Weber 2002 and Weber 2003).

A convenient synthetic route to \(\text{2-(4-allylpiperazin-1-yl)-4-chloroquinazoline}\), a key intermediate in the preparation of \(\text{2-(4-allylpiperazin-1-yl)-4-pentyl-oxyquinazoline}\), a
compound, which is potentially useful in the treatment of dementia (Fig 68). The reaction of quinazoline-2,4-dione with 1,4-diallylpiperazine and 1,4-dimethylpiperazine produced the products in 64 and 74% yield, respectively (Yoshida 1991). The above reaction shows that tertiary amines react selectively at the 2- position of the quinazolinedione in the presence of phosphorus oxychloride (Miki 1982). As previously noted, however, the 4-position of 2,4-dichloroquinazoline is more reactive than the 2-position for nucleophilic attack by primary or secondary amines. This was further demonstrated by the reaction of 1-allylpiperazine and 2,4- dichloroquinazoline in the presence of aqueous sodium hydroxide. The reaction was complete after 30 min at room temperature and furnished 4-(4-allyl-piperazin-1-yl)-2-chloro-quinazoline in 46% yield after recrystallisation (Fig 69).
An investigation into the reaction of 2,4-quinazolinedione with phosphorus oxychloride revealed that the N-methyl pyrrolidine base reacted with intermediate to form a quaternary ammonium salt (Miki 1982), (Fig 70). Under the reaction conditions employed, this ammonium salt degraded to form 2-(4-chloro-N-methylbutylamino)-4(3H)-quinazolinone in 78% yield. Further reaction to facilitate chlorination at the 4-position was also possible, furnishing the product in 87% yield. Interestingly, when a bulky alkyl amine base such as N-sec-butyl or N-tertbutyl pyrrolidine was examined, only 2,4-dichloroquinazoline was isolated. This indicates that the product ratio depends on the bulkiness, rather than the basicity, of the alkyl amine used. An earlier study revealed that tripropyl amine, the base commonly employed in conjunction with phosphorus oxychloride, was sufficiently bulky to enable smooth conversion of the quinazolinedione into the 2,4-dichloro species. When triethyl amine was substituted, however, 4-chloro-2-diethylaminoquinazoline was obtained as the product (Miki 1982). This procedure represents a facile synthesis of 2-(N-alkyl-4-chlorobutyl amino)-4-chloroquinazolines, which are enable to further elaboration at the 2- and 4-positions.

A method to enable the synthesis of 2,4-diaminoquinazolines (Zielinski 1998) by reacting chloro amidines with dialkyl cyanamides. Phenyl isocyanate derivatives with electron-donating and -withdrawing groups were reacted with N,N-diethyl amine to prepare the substituted urea compounds. The subsequent chlorination was facilitated with the use of phosphorus pentachloride. For example, 2-(N,N-diethyl amino)-4-(N,N-dimethylamino)quinazoline was prepared in 79% yield from the cyclization of the intermediate, which was obtained from the reaction of N,N-dimethyl cyanamide with chloro amidine (Fig 71).

Cyclization of the intermediate after reaction with acid chlorides, anhydrides and formates produced the respective quinazolines in moderate to good yields. 2- amino benzonitrile in ether was added drop wise to an ethereal solution of the required organo magnesium reagent. As an example, the reaction of the intermediate with benzoyl chloride and subsequent cyclization furnished 2,4-diphenylquinazoline in 80% yield.
This general approach for the synthesis of 2,4-disubstituted quinazolines is highly flexible and is a useful addition to the existing procedures.

Fig 70
The use of other nitriles such as acetonitrile, benzonitrile, phenyl acetonitrile and cyanamide did not afford the required quinazoline derivatives. (Erba 1997) reported a synthesis of 2-alkyl-4-arylaminoquinazolines by the condensation of arylamines with amidines (Fig 72).

![Chemical diagrams showing the synthesis of quinazoline derivatives](image-url)
As discussed (Bergman 1986 and Wiklund 2003) amidines could be formed by a thermal rearrangement of the triazolines. The reaction of primary arylamines and N-(2-cyanophenyl) amidines was subsequently investigated and two condensations were developed, namely Route A, which involved refluxing the arylamine and the amidine in an organic acid, or Route B, heating the amidine with an equimolar amount of arylamine hydrochloride without any solvent in a sealed tube. Similar results were obtained with each procedure, but high temperatures and the presence of an acid, either an organic acid or its amine salt, were necessary for the successful completion of the reaction. This thermal rearrangement is the method of choice for a straightforward synthesis of functionalized amidines, which can be used to prepare 2-alkyl-4-arylaminoquinazolines in moderate to good yields (30-65%). The research of Bergman et al. demonstrated that 2-aminobenzonitrile reacted with Grignard reagents and the resulting intermediate 293 was useful in accessing a variety of important quinazoline derivatives (Fig 73).
4. BIOLOGICAL ACTIVITY

4.1. EGFR & erbB antagonists

EGFR over expression in gynecologic cancer (Li 2009) has been associated with poor prognosis. Targeted inhibition of EGFR via its tyrosine kinase domain is a successful treatment in lung cancer. However, the results of existing clinical trials in gynecologic cancers do not show a significant clinical response to EGFR inhibit ion alone in unscreened patients. Novel EGFR-TKI might be beneficial for patients with gynecologic cancers. In this article, the in vitro and in vivo effects of a newly synthesized novel EGFR tyrosine kinase inhibitor N-(3-bromophenyl)-N-(7-methoxy-6-(3-morpholino propoxyl)quinazolin-4-yl)-3,3-dimethyl butanamide is being reported. In vitro, Compounds significantly inhibited the growth of four different human gynecologic cancer cell lines in a dose dependent manner. In vivo, quinazolin-4-yl)-3,3-dimethyl butanamide exhibited an inhibitory effect on gynecologic malignancies. While the mechanism of action is still unclear, it might be related to inhibition of EGFR signaling pathway, delay in cell cycle progression and a G1 arrest together with a partial G2/M block and induction of apoptosis. These results suggest that quinazolin-4-yl)-3,3-dimethyl butanamide could be a potential drug candidate for the treatment of human gynecologic malignancies. Breast cancer is the second most common type of cancer after lung cancer and the fifth most common cause of cancer death. Several structural classes of compounds were discovered against tumor, but many of the existing antitumor agents exhibit severe side effects. Hence there is a need to identify a novel chemical entity having a broad range of therapeutic activity with fewer side effects. In this direction, several (Fig 74) imidazolyl-(4-oxoquinazolin-3(4H)-yl)-acetamides (Raghavendra 2009) were screened for their antitumor activity against Ehrlich Ascites Carcinoma (EAC) using in-vitro and in-vivo models. Compounds showed highly significant antitumor activity against EAC in comparison with vincristine as standard.
Doxazosin and related, quinazoline (Kyprianou 2009) based α-adrenoceptor antagonists can induce apoptosis in prostate and various other normal, benign, smooth muscle, endothelial and malignant cells. Such apoptosis-inducing effects occur independently of α--adrenoceptor antagonism and typically require much high concentrations than those required for receptor occupancy. Several studies have invested efforts towards the elucidation of the molecular mechanisms underlying doxazosin-induced apoptosis. These include various tumor cells cardiomyocytes, endothelial cells and bladder smooth muscle cells. While the high concentrations of doxazosin required to induce apoptosis challenge the use of this and related drugs for clinical optimization of apoptosis induction, such quinazoline structure may represent chemical starting points to develop more potent apoptosis-inducing agents free of α-adrenoceptor antagonistic action and suitable for cancer treatment with minimal and well-tolerated side effects. A series of disubstituted 4(3H) quinazolines (Srivastava 2009) were designed for potential application in tumors. Firstly, N-benzoyl anthranilic acid is formed, which undergoes cyclization in the presence of pyridine. Subsequently, nucleophilic attack by semicarbazide on the carbonyl carbon gives 2-substituted 3-carbamido 4(3H) quinazolones, which gives final compound with appropriate substitution. The final as well as intermediate products were confirmed by NMR, FT-IR, and mass spectrometry. In vitro toxicity was performed with different cell lines and showed that the connection of hydrophilic styryl to quinazoline moiety increases its efficacy (Fig 75).
PC-1 (NPP-1) inhibitors may be useful as therapeutics for the treatment of CDDP (calcium pyrophosphate dehydrate) deposition disease and osteoarthritis. A series of potent quinazolin-4-piperidin-4-ethyl sulfamide PC-1 inhibitors (Patel 2009). The series, however, suffers from high affinity binding to hERG potassium channels, which can cause drug-induced QT prolongation. The used hERG homology model to identify potential key interactions between our compounds and hERG, and the information gained was used to design and prepare a series of quinazolin-4-piperidin-4-methyl sulfamides that retain PC-1 activity but lack binding affinity for hERG (Fig 76).
A series of 6, 7-dialkoxy-4-anilino quinazolines (Fig 77) were designed, synthesized by substituting different heterocycles on 6-position and a variety of anilines on 4-position of the quinazoline. These novel quinazoline (Undheim 1998) compounds were screened for their cytotoxic effect on epidermal growth factor receptor over expressing skin epidermoid carcinoma cell line (A431), by using non over expressing tumor cells as negative control (breast adeno carcinoma cell line MCF-7). 2-Butyl-4-chloro-1-{3-[7-methoxy-4-(3(trifluoromethyl) phenylamino)quinazolin-6-yloxy] propyl}-1H-imidazole-5-carboxaldehyde and 2butyl-4-chloro-1-{3-[4-(3-iodophenyl amino)-7-methoxy quinazolin-6-yloxy]ropyl}-1H-imidazole-5carboxaldehyde were found to be more potent against A431 cell line (IC$_{50}$ 3.5 and 3 mM) and their activities are comparable to gefitinib.

![Figure 77](image)

Irreversible HER/erbB inhibitors selectively inhibit HER-family kinases (Eckhardt 2008) by targeting a unique cysteine residue located within the ATP-binding pocket. Sequence alignment reveals that this rare cysteine is also present in ten other protein kinases including all five Tec-family members. (Hur 2008), demonstrate that the Tec-family kinase Bmx is potently inhibited by irreversible modification at Cys496 by clinical stage EGFR inhibitors such as CI-1033. This cross-reactivity may have significant clinical implications (Fig 78).
A new series of C-5 substituted indazolyl amino quinazolines (Barlaam 2008) as potent erbB2 kinase inhibitors (Fig 79). The lead compound showed excellent in vitro potency, good physical properties, acceptable oral pharmacokinetics in rat and dog, and low human in vitro clearance. It showed at least equivalent activity dose for dose compared to lapatinib in various erbB2- or EGFR driven xenograft models after chronic oral administration.

4-[4-(N-Substituted-thio-carbamoyl)-1-piperazinyl]-6-methoxy-7-alkoxyaminoquinazoline (Fig 80) derivatives such as have been identified to be potent and selective inhibitors of the phosphorylation of PDGFR (Heath 2004). SAR-investigations are described in the arylamine segment, C-7 appendage, and the thiourea moiety. Bioisosteres of thiourea (cyanoguanidine), and of quinazoline (quinoline-3-carbonitrile) were synthesized and are compared for their in vitro inhibitory activity. PK profiles of the optimized compounds in rat, dog, and cynomolgus monkey are described.

Some substituted 4-alkyl (aryl) thio quinazoline derivatives (Fig 81) were synthesized through thioetherification reaction of 4-chloroquinazolines and thiol compounds refluxed in acetone in the presence of K$_2$CO$_3$. The compounds were evaluated for their anti-proliferative activities against some cancer cells in vitro by MTT method (Yang 2007).
Fig 79

Fig 80

Fig 81

R = Aryl, R₁ = Benzyl

R₁ = H, R₂ = Methoxy phenyl
A series of C-6 or C-3 alkynyl-substituted 4-anilinoquinazoline (Fig 82) derivatives was prepared straightforwardly by a Sonogashira reaction of the corresponding bromo-substituted 4-anilinoquinazolines. Bioactive assay of these compounds for *in vitro* EGFR kinase inhibition (Liu 2007) demonstrated that the novel 6-hydroxypropynyl-4-anilinoquinazoline was a very potent EGFR kinase inhibitor with an IC₅₀ of 14 nM.

The present study identified several 4-alkynyl and 4-alkenylquinazolines that serve as novel and potent EGFR tyrosine kinase inhibitors (Fig 83). The IC₅₀ values of these compounds are in the nanomolar range. In addition, the 4-(4-phenylbut-1-yn/en-yl) quinazolines (Kitano 2007) provided scaffolds for potent enzyme inhibition. Chiral discrimination was observed to occur in one of the 4-alkynylquinazoline derivatives with the (R)-isomer being more than 150 times as potent as the (S)-isomer.
Quantitative structure activity relationship (QSAR) models of inhibiting action of some analogues of dimethoxyquinazoline (Fig 84) on epidermal growth factor receptor tyrosine kinase were constructed using modified ant colony optimization (ACO) method. As a comparison to this method, the evolutionary algorithm (EA) was also tested. It has been demonstrated that the modified ACO is a useful tool for variable selection comparable to EA. In the selected descriptors, electronic descriptor is the most important descriptor in predicting EGFR inhibitory activity (Shi 2007). Electron-donating groups such as Y- substituents enhance the activity as evident by negative. In addition, for quinazoline substituents, nitro group has a large deactivating effect.

Several potent, functionally active MCHr1 antagonists derived from quinolin-2(1H)-ones and quinazoline-2(1H)-ones (Blackburn 2006) have been synthesized and evaluated. Pyridylmethyl substitution at the quinolone 1-position results in derivatives with low-nM binding potency and good selectivity with respect to hERG binding (Fig 85).

A series of novel C-5 substituted anilinoquinazolines (Fig 86), selected on the basis of docking experiments and overlays with ATP in the active site of EGFR tyrosine kinase, have been prepared and found to be potent inhibitors (Ballard 2006). In vivo pharmacokinetics and disease model activity are discussed.
Chapter II

Biological Activity

Fig 85

Fig 86

R₁ = H, Me

R₂ = H, Me
Synthetic modifications on a 6-furanyl quinazoline (Fig 87) scaffold to optimize the dual ErbB-1/ErbB-2 tyrosine kinase inhibition (Petrov 2006) afforded consistent SAR whereby a 4-(3-fluorobenzyloxy)-3-haloanilino provided the best enzyme potency and cellular selectivity. Changes made to the 6-furanyl group had little impact on the enzyme activity, but appeared to dramatically affect the cellular efficacy. The discovery of lapatinib emerged from this work.

The synthesis of 6-(2-chloroethylamino)-4-anilinoquinazolines (Fig 88) designed to block EGFR tyrosine kinase and to damage genomic DNA is described (Rachid 2005). These compounds having fluorescence properties that permitted the quantitation of their
sub cellular uptake by flow cytometry. Fluorescence intensities increased with increasing levels of EGFR in a panel of isogenic and established cell lines.

![Chemical structure of compound](image1)

Starting from a 6,7-substituted quinazoline lead (Fig 89), optimization of 5-substituted quinazolines containing an extended aniline motif led to potent and selective inhibitors of erbB2 receptor tyrosine kinase, and a representative compound inhibited tumour growth (Ballard 2005) in a mouse xenograft model.

![Chemical structure of compound](image2)

\[ R = \text{Cl, } Y = \text{Pyridyl} \]
A series of 6-alkoxy-4-anilinoquinazoline (Fig 90) compounds was prepared and evaluated for \textit{in vitro} inhibition of the erbB2 and EGFR kinase activity (Zhang 2004). The IC$_{50}$ values of the best compounds were below 0.10 uM. Further, several of these compounds inhibit the growth of erbB2 and EGFR over-expressing tumor cell lines at concentrations below 1 uM.

(Micheal 2003) have identified a novel class of 6-thiazolylquinazolines (Fig 91) as potent and selective inhibitors of both ErbB-2 and EGFR tyrosine kinase activity, with IC$_{50}$ values in the nanomolar range. These compounds inhibited the growth of both EGFR (HN5) and ErbB-2 over-expressing human tumor cell lines \textit{in vitro}. Using xenograft models of the same cell lines, we found that the compounds given orally inhibited \textit{in vivo} tumor growth significantly compared with control animals and the evaluation of structure–activity relationships associated with the modification of the quinolinone ring (Fig 91) moiety displaying potent \textit{in vitro} inhibiting activity is described (Angibaud 2003).
A series of 6-arylamino-7-chloro-quinazoline-5,8-diones (Fig 92) were prepared and evaluated for their *in vitro* cytotoxicity in cultured human cancer cell lines (lung cancer), (colon cancer), and (stomach cancer). The preliminary structure–activity relationship has been described for providing further development of potent antitumor (Joo Park 2004) agents.

4-[4-(N-Substituted-thio-carbamoyl)-1-piperazinyl]-6-methoxy-7-alkoxyaminoquinazoline (Fig 93) derivatives such as have been identified to be potent and selective inhibitors of the phosphorylation of PDGFR (Heath 2004). SAR-investigations are described in the arylamine
segment C-7 appendage, and the thiourea moiety. Bioisosteres of thiourea (cyano guanidine), and of quinazoline (quinoline-3-carbonitrile) were synthesized and are compared for their \textit{in vitro} inhibitory activity. PK profiles of the optimized compounds in rat, dog, and cynomolgus monkey are described.

The synthesis and biological evaluations of 4-anilinoquinoline-3-carbonitrile analogues of the three clinical lead 4-anilinoquinazolines (Fig 94) Iressa, Tarceva, are described. The EGFR and HER-2 kinase inhibitory activities (Wissner 2002) and the cell growth inhibition of the two series are compared with each other and with the clinical lead EKB-569.
Described herein is the design and synthesis of indazolyl amino pyrido pyrimidines and quinazolines (Cockerill 2001) as inhibitors of the class1 tyrosine kinase receptor family. Data is presented for N4-(1-benzyl-1H-indazol-5-yl)-N6, N6-dimethylpyrido [3, 4-d] pyrimidine-4,6-diamine (Fig 95). This compound inhibited EGFr and c-erbB-2 enzymes selectively over other kinases. It inhibited the proliferation of a range of tumour cell lines \textit{in vitro} and the growth of BT474 xenografts in SCID mice.

As a continuation of our efforts to discover and develop apoptosis inducing (Fig 96) N-methyl-4-(4-methoxyanilino) quinazolines (Armarego 1967) as novel anticancer agents, we explored substitution at the 5, 6, 7 positions of the quinazoline and replacement of the quinazoline by other nitrogen-containing heterocycles. A small group at the 5-position was found to be well tolerated. At the 6-position a small group like an amino was preferred. Substitution at the 7-position was tolerated much less than at the 6-position. Replacing the carbon at the 8-position or both the 5- and 8-positions with nitrogen led to about 10-fold reductions in potency.
4.2. Histamine antagonists

The optimization of affinity and selectivity in a novel series of dual 5-HT5A/5-HT7 receptor ligands (Fig 97) is described. Brain penetrant 2-aminodihydro quinazolines (Peters 2008) with low nanomolar affinities were identified.

Design and synthesis of highly potent and selective non-imidazole (Fig 98) inverse agonists for the histamine H₃ receptor is described. The study validates a new pharmacophores (Roche 2007) model based on the merging quinazoline moiety.
A series of novel 1-substituted-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-ones (Alagarsamy 2005) were synthesized (Fig 99) by the cyclization of 2-hydrazino-3-phenylquinazolin-4(3H)-one with various one carbon donors. The starting material 2-hydrazino-3-phenylquinazolin-4(3H)-one 6, was synthesized from aniline by a novel innovative route. When tested for their in vivo H-antihistaminic activity on conscious guinea pigs all the test compounds protected the animals from histamine induced bronchospasm significantly, whereas the compound 1-methyl-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one (percentage protection 70.7%) was found to be equipotent with the reference standard chlorpheniramine maleate (percentage protection 71%). These compounds show negligible sedation (5%) when compared to the reference standard (26%). Hence they could serve as prototype molecules for future development.

Two new synthetic analogues of luotonins, 7-acetylaminoluotonin and 3-[3H(quinazolino-4-one)]quinolone (Fig 100) were synthesized. The new analogues, along with four natural quinazoline–quinoline alkaloids, luotonins and a synthetic deoxoluotonin showed cytotoxic activity (IC$_{50}$ 1.8–40.0 mg/mL) and DNA topoisomerase II (Ma 2004) inhibition at a concentration of 25 mM.
A new series of [4-(2-phenylethenesulfonylmethyl) phenyl] quinazolin-4-yl-amines (Fig 101) was prepared and tested for its \textit{in vitro} cytotoxic activity against a panel of 12 human cancer cell lines. Compounds showed good \textit{in vitro} activity and were further tested for their \textit{in vivo} efficacy in the HT-29 human colon adeno carcinoma xeno graft model (Sharma 2004). Compound exhibited promising activity in this model. Dose response studies for this compound against HT-29 human colon adeno carcinoma xenografts at 100, 200 and 400 mg/kg doses were performed and the quinazoline (Rahman 2003) structure may represent a pharmacologically-active conformation of these agents, and the aryl biguanides were found more lipid soluble than their aryl guanidine counterparts at physiological pH.
4.3. PDE antagonists

In a continuing effort to discover novel PDE5 inhibitors (Fig 102), (Choi 2009) have successfully found quinazolines with 4-benzylamino substitution as a potent and selective PDE5 inhibitors. Initial lead compound was found to be easily metabolized when incubated with human liver microsomes mainly through C6 amide hydrolysis. Blocking of this metabolic hot spot led to discovery of (CKD533) which is highly potent, selective and orally efficacious in conscious rabbit model for erectile dysfunction and now is undergoing preclinical toxicology study.

The increasing life expectancy in our population makes Parkinson’s disease (PD) a growing public health problem. There is a great need to find a way to prevent and delay the disease. It was shown that selective phosphodiesterase 1 (PDE1) inhibitors and
anti-inflammatory agents (Laddha 2009) might be effective in treating PD. Therefore, a novel quinazolin-7-one and quinazolin-8-one (Fig 103) derivatives were synthesized by reported method and investigated for their ability to inhibit PDE1. Most of the synthesized compounds have shown good activity against PDE1 and were less effective than 3-isobutyl-1-methylxanthine. All the compounds were also tested for their in vitro anti-inflammatory activity by carrageenan-induced oedema in rats. In addition, ulcerogenic activity was determined. The combined anti-inflammatory data from in vitro animal model showed that compounds exhibited even more potent anti-inflammatory activity and low gastric ulceration incidence compare to reference standard Indomethacin.

Fig 103

(Kim 2008) have successfully identified a series of 6,7,8-substituted quinazolines (Fig 104) as potent inhibitors of PDE5 with high level of isozyme selectivity, especially against PDE6 and PDE11. PDE5 potency and isozyme selectivity of quinazolines were greatly improved with substitutions both at 6- and 8-position. The synthesis, structure–activity relationships and in vivo efficacy of this novel series of potent PDE5 inhibitors are described. In an effort to minimize side effects associated with low selectivity against PDE isozymes.
4.4. Clk4 & Cdk4 antagonists

A series of substituted 6-arylquinazolin-4-amines (Mott 2009) were prepared and analyzed as inhibitors of Clk4. Synthesis, structure–activity relationships and the selectivity of a potent analogue against a panel of 402 kinases are presented. Inhibition of Clk4 by these agents at varied concentrations of assay substrates (ATP and receptor peptide) highly suggests that this chemo type is an ATP competitive inhibitor. Molecular docking provides further evidence that inhibition is the result of binding at the kinase hinge region. Selected compounds represent novel tools capable of potent and selective inhibition of Clk1, Clk4, and Dyrk1A (Fig 105) NMR spectroscopy, X-ray crystallography and molecular modeling studies indicate that N,N-disubstituted-1,4-diazepane (Cox 2009) orexin receptor antagonists exist in an unexpected low-energy conformation that is characterized by an intramolecular p-stacking interaction and a twist-boat ring conformation. Synthesis and evaluation of a macro cycle that enforces a similar conformation suggest that this geometry mimics the bioactive conformation.

The inhibition of cyclin-dependent kinase (Bathini 2005) causes cell cycle arrest and restores a checkpoint that is absent in the majority of tumor cells (Fig 106). Compounds that inhibit Cdk4 selectively are targeted for treating cancer. Appropriate substitution of aminoquinazoline is demonstrated to produce high levels of selectivity for Cdk4 versus closely related serine-threonine kinases.
Quinazolines (Sielecki 2001) have been identified as inhibitors of CDK4/D1 and CDK2/E (Fig 107). Aspects of the SAR were investigated using solution-phase, parallel synthesis. An X-ray crystal structure was obtained of quinazoline bound in CDK2 and key interactions within the ATP binding pocket are defined.
4.5. CCR antagonists

The pyrrolidine moiety of N-(4-chlorophenyl)-6,7-dimethoxy-2-(4-pyrrolidin-1-yl)piperidin-1-yl)quinazolin-4-amine (Fig 108) with a 3-(hydroxymethyl) piperidine and the resulting compound (10-{4-[[4-chlorophenyl] amino]-6,7-dimethoxyquinazolin-2-yl]-1,40-bipiperidin-3-yl)methanol was a strong inhibitor of human/mouse chemotaxis. Oral administration showed anti-inflammatory activity in a murine model of acute dermatitis (Yokoyama 2009).

![Chemical structure](image)

A series of CC chemokine receptor-4 (CCR4) antagonists (Yokoyama 2008) were examined in a previous report in an attempt to improve metabolic stability in human liver microsomes. In this study, the cycloheptylamine moiety of N-cycloheptyl-6,7-dimethoxy-2-(4-pyrrolidin-1-yl)piperidin-1-yl)quinazolin-4-amine (Fig -109) was replaced with the p-chloroaniline moiety, and the resulting compound, N-(4-chlorophenyl)-6,7-dimethoxy-2-(4-pyrrolidin-1-yl)piperidin-1-yl)quinazolin-4-amine, retained its potency ([35S] GTPcS binding inhibition and CCL22-induced chemotaxis in humans/mice). Based on the structure–activity relationships (SAR), a homology model was constructed for CCR4 to explain the binding mode. Overall, there was good agreement between the docking pose of the CCR4 homology model and the human [35S] GTPcS assay results.
Administration of in a murine model of acute dermatitis showed anti-inflammatory activity (oxazolone-induced contact hypersensitivity test).

A series of CC chemokine receptor-4 (CCR4) antagonists were examined in a previous report in an attempt to improve metabolic stability in human liver microsomes. In this study, the cycloheptylamine moiety of N-cycloheptyl-6,7-dimethoxy-2-(4-pyrro lidin-1-yl piperidin-1-yl)quinazolin-4-amine (Fig 110) was replaced with the p-chloroaniline moiety,
and the resulting compound, N-(4-chlorophenyl)-6,7-dimethoxy-2-(4-pyrrolidin-1-ylpiperidin-1-yl)quinazolin-4-amine (Yokoyama 2008), retained its potency ([35S]GTP cS binding inhibition and CCL22-induced chemotaxis in humans /mice). Based on the structure activity relationships (SAR), a homology model was constructed for CCR4 to explain the binding mode. Overall, there was good agreement between the docking pose of the CCR4 homology model and the human [35S] GTPcS assay results. Administration of compound in a murine model of acute dermatitis showed anti-inflammatory activity (oxazolone-induced contact hypersensitivity test).

A new series of quinazolines (Fig 111) that function as CCR4 antagonists were discovered during the screening of our corporate compound libraries. Subsequent compound optimization elucidated the structure–activity relationships and led the identification of 2-(1,4-bipiperidin-1-yl)-N-cycloheptyl-6,7-dimethoxyquinazolin-4-amine (Yokoyama 2008), which showed potent inhibition in the [35S]GTP cS-binding assay (IC$_{50}$ = 18 nM). This compound also inhibited the chemotaxis of human and mouse CCR4-expressing cells (IC$_{50}$ = 140 nM, 39 nM).
4.6. NMDA antagonists

A novel series of kynurenic acid amides, ring-enlarged derivatives of indole-2-carboxamides (Fig 112), was reported and identified as *in vivo* active NR2B subtype selective NMDA receptor antagonists (Borza 2007). The synthesis and SAR studies are discussed.

A series of novel protein geranyl transferase-I (PGGTase-I) inhibitors (Fig 113) based on a benzoyleneurea scaffold has been synthesized. Using a benzoyleneurea scaffold as a mimic for the central dipeptide, (Carrico 2005) have developed peptidomimetic inhibitors that selectively block the activity of PGGTase-I over the closely related enzyme protein farnesyl transferase. In this new class of PGGTase-I inhibitors, compound with X = L-phenylalanine displayed the highest inhibition activity against PGGTase-I. A new set of 5,6-dihydro-pyrazolo[1,5-c]quinazoline-2-carboxylates bearing different substituents (COOEt, Cl, Br, CH₃, and COOH) at position-1, were synthesized in order to investigate the influence of various groups at this specific position on Gly/NMDA receptor affinity and/or selectivity. All the herein reported compounds were evaluated for their binding at the Gly/NMDA, AMPA, and KA receptors. Some selected compounds were also tested for their functional antagonistic activity at both the AMPA and NMDA receptor-ion channels. The results obtained in this study have highlighted that a C-1 lipophilic substituent on the pyrazolo quinazoline-2-carboxylate core shifts selectivity toward the Gly/NMDA receptor, while a C-1 anionic carboxylate residue is able to increase affinity toward this receptor subtype. In particular, the 2-carboxylic
acids 15 and 16, bearing a chlorine atom at position-1, are not only potent (Ki = 0.18 and 0.16 µM, respectively), but also highly Gly/NMDA versus AMPA selective (selectivity ratio > 500). Furthermore, the 1,2-dicarboxylic acids are endowed with the highest Gly/NMDA receptor binding activity (Varano 2005).

The synthesis and Gly/NMDA, AMPA and KA receptor binding activities of some 3-hydroxy-quinazoline-2,4-dione (Colotta 2004) derivatives are reported (Fig 114). The Binding data, together with functional antagonism studies, showed that the 3-hydroxy-quinazoline-4-dione moiety can be considered a useful scaffold to obtain selective Gly/NMDA and AMPA receptor antagonists. In fact, introduction of chlorine atom on precise position of the benzo fused moiety yielded Gly/NMDA selective antagonists, while the presence of the 6-(1,2,4-triazol-4-yl) group shifted the affinity and selectivity towards the AMPA receptor.
4.7. MCH antagonists

(Arienzo 2007) reported 2-aminoquinoline (Fig 115) to provide two novel series of MCH-1R antagonists. Representative compounds from the quinazoline and benzimidazole series have been shown to be potent and selective, with promising in vitro ADME profiles.

Optimization of a series of 4-(dimethylamino) quinazoline antagonists of the melanin-concentrating hormone receptor (MCH-R1) is described (Fig 116). The combination of the elaboration of both the linker portion and the terminal phenyl ring provided N-(cis-4-{[4-(dimethylamino)quinazolin-2-yl]amino}cyclohexyl)-3,4-difluorobenzamide hydrochloride, which showed excellent antagonist activity at the MCH-R1 (IC$_{50}$ = 3.4 nM) as well as good selectivity over the Y5 and the α2A receptors (Kanuma 2005).
(Palanki 2003) have developed novel orally active quinazoline (Fig 117) analogues as inhibitors of AP-1 and NF-kB mediated transcriptional activation. Among the derivatives prepared, 1-[2-(2-thienyl)quinazolin-4-ylamino]-3-methyl-3-pyrrolidine-2,5-dione showed significant activity in an adjuvant-induced arthritis rat model by reducing the swelling by 65% in the non-injected foot. (Tobe 2003) investigated the roles of substituents on the terminal phenyl ring at the C(4)-position of the quinazoline (Fig 118) core to complete the structure activity relationships (SARs) of our NF-kB activation inhibitors. Among them, compound afforded highly potent inhibitory activity toward NF-kB transcriptional activation with IC\textsubscript{50} value of 2nM, along with an excellent \textit{in vivo} efficacy by reducing the edema formation seen in carrageenan-inflammation of the rat hind paw.
4.8. Aurora antagonists

New class of 1-acetanilide-4-aminopyrazole-substituted quinazoline (Foote 2008) aurora kinase inhibitors has been discovered possessing highly potent cellular activity. Continuous infusion into athymic mice bearing tumors of the soluble phosphate derivative led to dose-proportional exposure of the des-phosphate compound (Fig 119) with a high-unbound fraction. The combination of potent cell activity and high free-drug exposure led to pharmacodynamic changes in the tumor at low doses, indicative of aurora B-kinase inhibition and a reduction in tumor volume. A novel series of 5-aminopyrimidinyl quinazolines has been developed from anilino-quinazoline (Fig 120), which was identified in a high throughput screen for aurora A. Introduction of the pyrimidine ring and optimization of the substituents both on this ring and at the C7 position of the quinazoline led to the discovery of compounds that are highly specific aurora kinase inhibitors. Cocrystallisation of one of these inhibitors with a fragment of aurora A shows the importance of the benzamido group in achieving selectivity (Heron 2006). (Webb 2003) recently reported the discovery of numerous new compounds (Fig 121) that are selective inhibitors of all of the subtypes of the adenosine receptor family via a pharmacophore database searching and screening strategy. During the course of this work we made the unexpected discovery of a potent A2B receptor antagonist, 4-
methyl-7-methoxyquinazolyl-2-(2-amino-4-imidazolinone), which showed selectivity for this receptor and functioned as an antagonist.

![Figure 119](image1)

R = OCH₃, CH₃
R₁ = CH₃, OH
R₂ = OCH₂CH₃

![Figure 120](image2)

![Figure 121](image3)
4.9. Tk antagonists

(Fernandes 2007) developed novel SPECT radio ligands for EGFR positive tumours (Fig 122), new potentially irreversible tyrosine kinase (TK) inhibitors are being explored. The radio iodination of N-4-[(3-chloro-4-fluorophenyl) aminquinazoline-6-yl-3-bromopropionamide, a novel EGFR-TK inhibitor synthesized in our laboratory, was accomplished via halogen exchange. Purification by RP-HPLC gave \([^{125}\text{I}]\)-N-{4-[(3-chloro-4-fluorophe-nyl) amino] quinazoline-6-yl]-3-iodopropionamide with a radiochemical purity higher than 95% and a high specific activity. \textit{In vitro} studies indicate that both iodinated quinazoline and its bromo precursor inhibit A431 cell growth and also possess higher potency than the parent quinazoline to inhibit the EGFR auto phosphorylation. \textit{In vivo} stability studies suggest metabolism of the radio iodinated quinazoline indicating a short biological half-life. The \textit{in vitro} results point out that these quinazoline derivatives could be promising candidates for SPECT imaging of EGFR positive tumors provided that they are selectively modified in order to achieve better \textit{in vivo} radio chemical stability.

![Fig 122](image)

Anilinoquinazolines (Wright 2001) currently of interest as inhibitors of tyrosine kinases have been found to be allosteric inhibitors of the enzyme fructose 1,6-bisphosphatase (Fig 123). These represent a new approach to inhibition of F16BPase and serve as leads for further drug design. Enzyme inhibition is achieved by binding at a unidentified allosteric site.
This paper describes the development of the epidermal growth factor receptor tyrosine kinase inhibitor (Fig 124) from a lead series of 4-anilinoquinazoline compounds. ZD1839 has suitable properties for use as a clinically effective drug and shows activity against human tumours (Barker 2001).

Novel quinazoline type compounds (Fig 125) were designed as inhibitors of the parasite specific enzyme trypanothione reductase (TR), and their biological activities were evaluated. Some of our compounds inhibited TR, showed selectivity for TR over human glutathione reductase, and inhibited parasite growth in vitro. (Cavalli 2009), propose that
the quinazoline framework is a privileged structure that can be purposely modified to design novel TR inhibitors. Furthermore, the use of privileged motifs might emerge as an innovative approach to antiparasitic lead candidates.

![Chemical Structure]

**4.10. TNF antagonists**

(Tobe 2003) synthesized various 6-fluoro-7-(1-piperazino) quinazolines (Fig 126) based on the structure and evaluated their inhibitory activities toward both TNF-a production and T cell proliferation responses. The compounds 3,4-(methylenedioxy)phenyl moiety at the C(4)-position of the quinazoline ring, showed both inhibitory activities. Furthermore, the oral treatment exhibited an anti-inflammatory effect in rats with adjuvant arthritis as well as an inhibitory activity toward LPS-induced TNF-a production.
4.11. TS antagonists

The α-FR has been reported to be over expressed in many carcinomas, in particular those of the ovary and uterus. The high expression of α-FR in some tumors compared with normal tissues has been exploited over the last decade for folate-mediated targeting of macromolecules, anticancer drugs, imaging agents and nucleic acids to cancer cells. A cyclopenta quinazoline-based inhibitor of thymidylate synthase (Fig 127) (TS), has been reported to have high affinity for the receptor and selectivity for α-FR over expressing tumour cell lines. In this study, the structural features of the molecule, in particular modifications at the 2-position, have been investigated with respect to TS inhibition, affinity for the α-FR and reduced folate carrier (RFC) and activity in A431FBP cells (transfected with human α-FR) compared with neo-transfected A431 cells. Compounds were synthesized utilizing multistep sequences. It was found that the 2-substituent does not affect the affinity for the α-FR; however, it greatly affects selectivity for A431-FBP cells, and suggests that there are factors other than TS inhibition and α-FR affinity that are important for the activity of these compounds. Compound (2-CH2OH derivative) displayed the highest selectivity (Henderson 2006) for the A431-FBP cells compared with A431 cells.
Cyclopenta quinazoline (Fig 128) based inhibitors of thymidylate synthase (TS) possess a chiral centre at the 6-position of the molecule. The effect of this chirality on the inhibition of TS was investigated by synthesizing compounds (Bavetsias 2001).
4.12. Tcf antagonists

The synthesis and SAR of a series of 2,4-diamino-quinazoline (Chen 2009) derivatives as b-catenin/Tcf-4 inhibitors (Fig 129) are described. This series was developed by modifying the initial lead, which was identified by screening of our compound library and found to inhibit the b-catenin/Tcf-4 pathway. Replacement of the biphenyl moiety in compound with the N-phenylpiperidine-4-carboxamide chain resulted in a number of new analogues, which are potent inhibitors of the b-catenin/Tcf-4 pathway.

![Fig 129]

4.13. IKKb antagonists

An IKKb inhibitor (Fig 130) reported to block NF-kB transcriptional activities (Chen 2009) in Jurkat T cells was found to enhance NF-kB translocation in HUVEC cells. These studies suggested a non canonical NF-kB signaling pathway independent of IKKb in HUVEC cells.
4.14. TRPV$_1$ antagonists

A focused SAR exploration of the lead 4-aminoquinazoline (Blum 2008) TRPV1 antagonist led to the discovery of compound (Fig 131). In rats, compounds are readily absorbed following oral dosing and demonstrate excellent *in vivo* potency and efficacy in an acute inflammatory pain model.
4.15. HIV-1 antagonists
A series of unique 3,3a-dihydropyrano[4,3,2-de]quinazolin-2(1H)-ones (Fig 132) and 5-dihydro-2H-thieno[4,3,2-de]quinazo-line-4(3H)-thione were found to be HIV-1 non-nucleoside reverse transcriptase inhibitors (Corbett 2001).

4.16. AlK-5 antagonists
Starting from quinazoline, (Gellibert 2009) designed potent and selective ALK5 inhibitors (Fig 133) over p38MAP kinase from a rational drug design approach.

\[ \text{Fig 132} \]

\[ \text{Fig 133} \]

\( R_1 = \text{Phenyl, Chlorophenyl} \)
based on co-crystal structures in the human ALK5 kinase domain. The quinazoline exhibited also \textit{in vivo} activity in an acute rat model of DMN-induced liver fibrosis when administered orally at 5 mg/kg (bid).

**4.17. CXCR3 antagonists**

The evaluation of the CXCR3 antagonist AMG 487 in clinic trials was complicated due to the formation of an active metabolite. In this Letter, (Liu 2009) discuss the further optimization of the quinazolinone series that led to the discovery of compounds devoid of the formation of the active metabolite that was seen with AMG 487 (Fig 134). In addition, these compounds also feature increased potency and good pharmacokinetic Properties and also discuss the efficacy of the lead compound in a mouse model of cellular recruitment induced by bleomycin.

![Fig 134](image)

**4.18. LPA$_2$ antagonists**

The LPA$_2$ protein is over expressed in many tumor cells. Hilary et al, report the optimization of a series of LPA$_2$ antagonists using calcium mobilization assay (Beck 2008) that led to the discovery of the first reported inhibitors selective for LPA$_2$. Key
compounds were evaluated \textit{in vitro} for inhibition of LPA2 mediated Erk activation and proliferation of HCT-116 cells. These compounds could be used to evaluate the benefits of LPA2 inhibition both \textit{in vitro} and \textit{in vivo} (Fig 135).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig135}
\caption{VR\textsubscript{1} antagonists}
\end{figure}

\subsection*{4.19. VR\textsubscript{1} antagonists}
A focused quinazolinone natural product-templated (Liu 2006) library was designed and synthesized. Compounds from this privileged structure-based library were identified as anti-mitotic agents (Fig 136) acting through destabilization of tubulin polymerization. Bioisosteric replacement of piperazine with an aryl ring in lead VR\textsubscript{1} antagonist (Zheng 2006) led to the biarylamide series. The development of B-ring SAR led to the conformationally constrained analog (Fig 137). The resulting aminoquinazoline represents a novel VR1 antagonist with improved \textit{in vitro} potency and oral bioavailability.
4.20. GABA antagonists

A systematic approach through computer assisted design to identify novel quinazolines (Goel 2005) having anxiolytic and GABAergic activity has been reported (Fig 138).
4.21. IMPDH II antagonists

The synthesis and biological activity of a novel series of 7-methoxy-6-oxazol-5-yl-2,3-dihydro-1H-quinazolin-4-ones (Fig 139) are described. Some of these compounds were found to be potent inhibitors of inosine 5-monophosphate dehydrogenase type II (IMPDH II) (Birch 2005).

![Fig 139](image)

4.22. c-Src antagonists

A series of 5,7-disubstituted quinazolines (Fig 140), bearing 4-heteroaryl substituent such as 2-pyridinylation or 2-pyrazinylation, has been synthesized and evaluated as c-Src kinase inhibitors (Barlaam 2005).

![Fig 140](image)

Highly potent inhibition, high selectivity and physical properties suitable for oral dosing were achieved within this series were identified as sub-0.1 IM inhibitors in a c-Src-driven cell proliferation assay and displayed adequate rat pharmacokinetics after oral administration.
4.23. Dopamine agents

In an attempt to identify novel ligands for the dopamine transporter, a series of 4-substituted-2-phenylquinazolines were synthesized and evaluated. The compound 4-[(diphenylmethyl) amino]-2-phenylquinazoline (Fig 141) was identified as a novel partial inhibitor binding to the dopamine transporter and a partial inhibitor of [3H] dopamine uptake (Ananthan 2002).

![Fig 141](image)

4.24. FTI antagonists

Based on the structure of (Tipifarnib, Zarnestra), a series of farnesyl transferase inhibitors FTI (Fig 142) have been synthesized by modification of the 2-quinolinone motif and transposition of the 4-chlorophenyl ring to the imidazole or its replacement by 5-membered rings. This has yielded a novel series of potent farnesyl transferase inhibitors (Angibaud 2007).

4.25. mGlu5 antagonists

A high-throughput cell-based screen identified a series (Felts 2009) of 6-substituted-4-anilinoquinazolines (Fig 143) as noncompetitive antagonists of metabotropic glutamate receptor 5 (mGlu5). This Letter describes the SAR of this series and the profile of selected compounds in selectivity and radio ligand binding assays.
4.26. DPP-4 antagonists

Systematic variations of the xanthine scaffold in close analogs of development compound led to the class of 3,5-dihydro-imidazo[4,5-d]pyridazin-4-ones (Fig 144) which provided, after substituent screening, a series of highly potent DPP-4 inhibitors (Peters 2008).
4.27. PDGFR antagonists

4-[4-(N-Substituted-thio-carbamoyl)-1-piperazinyl]-6-methoxy-7-alkoxyaminoquinazoline derivatives such as have been identified to be potent and selective inhibitors of the phosphorylation of PDGFR (Heath 2004). SAR-investigations are described in the arylamine segment, C-7 appendage, and the thiourea moiety. Bioisosteres of thiourea (cyanoguanidine) and of quinazoline (quinoline-3-carbonitrile) were synthesized and are compared for their in vitro inhibitory activity. PK profiles of the optimized compounds in rat, dog, and cynomolgus monkey are described.

4.28. TDR antagonists

This paper describes the design, synthesis and evaluation of a series of 2,4-diaminoquinazolines (Fig 146) as inhibitors of leishmanial and trypanosomal dihydrofolate reductase. Compounds were designed by generating virtual library of
compounds and docking them into the enzyme active site. Following their synthesis, they were found to be potent and selective inhibitors of leishmanial dihydrofolate reductase (Khabnadideh 2005). The compounds were also found to have potent activity against trypanosoma brucei rhodesiense, a causative organism of African trypanosomiasis and also against Trypanosoma cruzi, the causative organism of Chagas disease. There was significantly lower activity against *leishmania donovani*, one of the causative organisms of leishmaniasis.

![Chemical structure](image)

**Fig 146**

4.29. **Mitochondrial complex antagonists**

Several quinazoline derivatives (Fig 147) were made as mitochondrial complex inhibitors. Compound showed an IC$_{50}$ of 11.3 Nm. The analogs (Purohit 2007) was injected in the rat and showed high and rapid heart uptake, fast liver clearance, and low blood uptake.

4.30. **FPT antagonists**

A series of (4-chlorophenyl)-a-(1-methyl-1H-imidazol-5-yl) azoloquinolines (Fig 148) and quinazolines was prepared. These compounds displayed potent Farnesyl Protein transferase (FPT) inhibitory activity and tetrazolo[1,5-a]quinazolines (Angibaud 2003) are promising agents for oral *in vivo* inhibition.
4.31. DNA-based biosensor agents

A disposable electrochemical DNA-based biosensor was developed and applied as a screening device to detect an effect of a synthetically prepared quinazoline (Fig 149) derivative (Labuda 2009) on the surface-attached double stranded calf thymus DNA. Screen-printed carbon electrodes without and with multi walled carbon nanotubes interface served as the signal transducer. The quinazoline interaction with DNA was investigated voltammetrically using DNA-bound electrochemical indicators such as $[\text{Co(phen)}_3]^{3+}$, $\text{Ru (bpy)}_3^{2+}$, methylene blue, the $\text{K}_3[\text{Fe(CN)}_6]$ complex present in the solution phase as well as by electrochemical impedance spectroscopy. A severe
damage to DNA at the incubation of the biosensor in quinazoline solution was found which leads to the loss of DNA from the electrode surface. Agarose gel electro phores is was used to verify the results.

4.32. Polyglutamine aggregate burden agents
A quinazoline (Fig 150) that decreases polyglutamine aggregate burden in a cell-based assay was identified from a high-throughput screen of a chemical-compound library, provided by the NIH Molecular Libraries Small Molecule Repository (MLSMR). A structure and activity study yielded (Rinderspacher 2009) leads with submicromolar potency.

4.33. Analgesic and anti-inflammatory activity
(Kummerle 2009) synthesized a set of aza heterocycles (Fig 151) were designed as conformationally constrained N-acyl hydrazones and tested as analgesics.
Thioglycosides and C-glycosides have received considerable attention (Fig 152), because they are widely employed as biological inhibitors, inducers and ligands for affinity chromatography of carbohydrate processing enzymes and proteins. Moreover, they are promising candidates in synthetic carbohydrate chemistry as convenient and versatile glycosyl donors. Among these glycosyl donors are the thio glycosyl and N glycosyl heterocycles that are sufficiently stable under a variety of reaction conditions and have the ability to be readily converted into a variety of other functionalities.

(Rahman 2009), reported here, the synthesis of 2- thioxo-quinazolines which were used as a base to the synthesis of S-nucleoside, C-nucleoside analogs and their analgesic and anti-inflammatory activities were evaluated giving good results.

The pyrimido [4,5-b] quinolines and its oxidized form were prepared and used as key intermediates for the synthesis of pyrimido [6,1-b] quinazoline (El–Gazzar 2009).
Representative of the synthesized compounds was tested and evaluated for anti-
oxidant, anti-inflammatory and analgesic activities (Fig 153). Compounds showed the
highest inhibitory anti-oxidant activity either using erythrocyte hemolysis or ABTS
methods.

![Chemical structure](image)

Fig 153

A set of hybrid molecules were synthesized out of lipoic acid, diamines of different
lengths serving as spacers (Fig 154), and cholinesterase (ChE) inhibiting [2,1-b]
quinazolinimines. Depending on the length of the alkylene spacer the amide hybrids are
inhibitors of acetylcholinesterase (AChE) with inhibitory activities of 0.5–4.6 µM and
inhibitors of butyrylcholinesterase (BChE) with activities down to 5.7 nM, therefore
greatly exceeding the inhibitory activities of the parent quinazolinimines (Decker 2008)
by factors of up to 1000. Due to increasing activity at BChE with increasing length of the
alkylene spacer 100-fold selectivity toward BChE is reached with a hepta and octa
methylenespacer. Kinetic measurements reveal competitive and reversible inhibition of
both ChEs by the hybrids. Furthermore, cell viability and antioxidant activity (using the
ORAC-fluorescein assay) of several hybrids were evaluated, showing cytotoxicity at
concentrations from 3.7 to 10.2 µM and antioxidant properties are in the range of 0.4–0.8
Trolox equivalents (lipoic acid = 0.6).
A variety of novel 3-(benzyl)-2-substituted amino-quinazolin-4(3H) ones (Alagarsamy 2008) were synthesized by reacting the amino group of 3-benzyl-2-hydrazino quinazolin-4(3H)-one with a variety of aldehydes and ketones. The starting material, 3-benzyl-2-hydrazino quinazolin-4(3H)-one, was synthesized from benzyl amine. The compounds were investigated for analgesic, anti-inflammatory, and ulcerogenic index activities.

The compound 3-benzyl-2-[N'-(1-ethyl-propylidene)hydrazino]-3H-quinazolin-4-one (Fig 155) emerged as the most active compound of the series and is moderately more potent in its analgesic and anti-inflammatory activities when compared to the reference
standard diclofenac sodium. Interestingly the test compounds showed only mild ulcerogenic potential when compared to aspirin.

A variety of novel 3-phenyl-2-substituted-3H-quinazolin-4-ones (Alagarsamy 2007) were synthesized by reacting the amino group of 2-hydrazino-3-phenyl-3H-quinazolin-4-one with different aldehydes and ketones. The starting material 2-hydrazino-3-phenyl-3H-quinazolin-4-one was synthesized from aniline. The analgesic, anti-inflammatory and ulcerogenic index activities are performed for synthesized compounds. (Fig 156). While the test compounds exhibited significant activity, compound quinazolin-4-one exhibited moderate analgesic activity and showed more potent anti-inflammatory activity when compared to the reference standard diclofenac sodium. Interestingly, the test compounds showed only mild ulcerogenic side effect when compared to aspirin.

![Fig 156](image)

**Fig 156**

### 4.34. Anti-microbial activity

A number of organic compounds obtained by chemical synthesis as model compounds have useful antimicrobial activities. Quinazoline ring (Veerapandian 2009) is an aromatic benzopyrimidine system. In these study, the biological activity of synthesized quinazoline semicarbazone derivatives (Fig 157) were characterized by antimicrobial screening against several gram-positive, gram negative bacteria, and fungus. Antimicrobial screening for all the compounds exhibits characteristic microbial inhibition.
A series of novel Schiff bases (Panneerselvam 2009) were synthesized by condensation of 3-amino-6,8-dibromo-2-phenylquinazolin-4(3H)-ones with different aromatic aldehydes via cyclized intermediate 6,8-dibromo-2-phenyl benzoxazin-4-one. These compounds were screened for antibacterial (Fig 158) activities by paper disc diffusion technique. The minimum inhibitory concentrations (MICs) of the compounds were also determined by agar streak dilution method. Compounds 3-(3,4,5-trimethoxybenzylideneamino)-6,8-dibromo-2-phenylquinazolin-4(3H)-one was found to be the most potent antimicrobial activity.
The series of novel and new fused heterocyclic systems such as, triazolo[4,3-a]-quinazolin-7-ones, [1,2,4,5]-tetrazino[4,3-a]-quinazolin-8-ones (Tiwari 2007) have been screened for their antibacterial activity (Fig 159) against Gram-negative bacteria.

![Chemical structure](image)

Fig 159

The new quinazolone series has been designed, and synthesized by the (Tiwari 2007), The biological activities (antifungal, antibacterial as well as anti cancerous) of the evaluated compounds are discussed in this article (Fig 160).

In continuation of (Gaurav 2006) work on synthesis of bi heterocycles carrying the biodynamic heterocyclic systems, a series of new nalidixic acid derivatives having quinazolones moiety were synthesized to achieve enhanced biological activity and wide spectrum of activity. The current study also involves *in vitro* antimicrobial screening (using Agar dilution and Punch well diffusion method) of synthesized quinazolone derivatives (Fig 161) bearing nalidixic acid moiety on randomly collected microbial strains. The derivatives showed marked inhibitory activity against enteric pathogen like aeromonas hydrophila, a causative agent of diarrhoea in both children as well as adults.
A series of 3-hydroxy quinazoline-2,4-diones was synthesized by (Tran 2004) and evaluated for antibacterial activity. This series represents a novel addition to the DNA gyrase inhibitor class of antibacterials. Appropriate substitutions on to the core template yielded compounds with excellent potency against *E. coli* gyrase and significant *invitro* Gram-negative and Gram-positive antibacterial activity (Fig 162).

![Chemical structure of 3-hydroxy quinazoline-2,4-diones]

*Fig 160*

R = Phenyl, Styril, Phthalimido methyl

![Chemical structure of 3-hydroxy quinazoline-2,4-diones]

*Fig 161*
Novel quinazolines (Bedi 2004), having interesting antibacterial activity have been prepared, characterized and tested against a panel of susceptible and resistant Gram positive and Gram negative organisms (Fig 163).

A series of [1,3] thiazino thiazolo [2,3-b] quinazoline and pyrazolo thiazolo [2,3-b]quinazolines (Fig 164), synthesized by (Abdel–Gawad 2000). The antifungal activity was screened for the synthesized compounds.
New 2,3-diaryl-(2-aryl-3-N-arylamino) and 1,2-diaryl-1,2,3,4-tetrahydroquinazolin-4-ones (Sattarovao 2006) were obtained via reactions of arylamides and anthranilic acid phenylhydrazide or N-arylanthranilic acid amides with 5-bromo- or 5-nitrosalicylic aldehydes. One of these compounds was acetylated to a triacetyl derivative. The antimicrobial activity was evaluated for the synthesized compounds (Fig 165).

4.35. Anticonvulsant activity
A few novel 3-[5-(4-substituted) phenyl-1,3,4-oxadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones were synthesized by (Kashaw 2009) (Fig 166), and evaluated for anticonvulsant, neurotoxicity, sedative-hypnotic, and phenobarbitone-induced hypnosis potentiation test.
Several new 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea (Fig 167) were synthesized and screened for anticonvulsant, CNS depressant and sedative-hypnotic activity (Kashaw 2009) in the mice.

4.36. Antihistaminic activity

A series of novel 1-substituted-4-(2-methylphenyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-ones (Alagarsamy 2008) were synthesized by the cyclization of 2-hydrazino-3-(2-methylphenyl)-3H-quinazolin-4-one with various one carbon donors. The starting material 2-hydrazino-3-(2-methylphenyl)-3H-quinazolin-4-one was synthesized from 2-methyl aniline by a novel innovative route (Fig 168). The compounds were tested for their in vivo $\text{H}_1$-antihistaminic activity on guinea pigs; all the tested compounds protected the animals from histamine-induced bronchospasm significantly.
A series of novel 1-substituted-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-ones (Alagarsamy 2007) were synthesized by the cyclization of 2-hydrazino-3-benzyl-3H-quinazolin-4-one with various one-carbon donors. The starting material 2-hydrazino-3-benzyl-3H-quinazolin-4-one was synthesized from benzyamine by a new innovative route. When tested for their \textit{in vivo} H\textsubscript{1}-antihistaminic activity on guinea pigs, all the test compounds protected the animals from histamine induced bronchospasm significantly.

The compound (Fig 169)1-methyl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one emerged as the most active compound of the series and it is more potent (percent protection 76%) when compared to the reference standard chlorpheniramine maleate (percent protection 71%).
4.37. CNS depressant activity

A series of novel 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones (Jatav 2008) were synthesized and evaluated for anticonvulsant, sedative-hypnotic and CNS depressant activities. After i.p. injection to mice at doses of 30, 100, and 300 mg/kg body weight 2-styrylquinazolin-4(3H)-one derivatives were examined in the maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice (Fig 170). The neurotoxicity was assessed using the rotorod method. Compounds only showed anticonvulsant activity and sedative-hypnotic activity via actophotometer screen. CNS depressant activity screened with the help of the forced swim pool method resulted into some potent compounds. From the experimental observation it can be concluded that synthesized compounds exhibited relatively better sedative-hypnotic and CNS depressant activities.

![Fig 170](image)

\[ R, R_1 = \text{C}_6\text{H}_5 \]

Closely related structural analogues of prazosin (Da Silva 2008) (Fig 171) have been synthesised and tested for inhibition and activation of Transport-P in order to identify the structural features of the prazosin molecule that appear to be necessary for activation of Transport-P.

4.38. Antiprion activity

Transmissible spongiform encepalopathies (TSEs) are thought to arise from aggregation of a protease resistant protein denoted PrPSc, which is a misfolded isoform of the normal cellular prion protein PrPC. Using virtual high-throughput screening (Cope
2006), have selected structures analogous to acridine, 2-methyquinoline and 2-phenylquinazoline (Fig 172) as potential therapeutic candidates for the treatment of TSEs.

![Fig 171](image1)

Fig 171

A = Furanyl, Thieryl
B = MeO
C = MeO
D = NH₂

![Fig 172](image2)

Fig 172

**4.39. Antimalarial activity**

Syntheses of new 6-ureido-4-anilinoquinazolines (Tusi 2009) have been accomplished and there *in vitro* antimalarial activities against chloroquine-sensitive *P. falciparum* have been examined (Fig 173). dose of 100 mg/kg 4days.

Synthesized antimalarial activity of a series of sulfonamide derivatives (2,4-diamino-6-quinazoline sulfonamides) was modeled topologically using Wiener (W), and Szeged (Sz)-indices (Agrawal 2001). The regression analysis of the data has shown that better
results are obtained in multi parametric regressions upon introduction of indicator parameters. Predicting ability of the models was tested by r2cv values. It was observed that models based on W index gave slightly better results than those in which Sz is involved (Fig 174).

4.40. Antiplasmodial activity
Identify a new safe antiplasmodial molecular scaffold, an original series of 2-trichloromethylquinazolines (Verhaeghe 2009), functionalized in position 4 by an alkyl- or aryl amino substituent, was synthesized from 4-chloro-2-trichloromethylquinazoline, via a cheap, fast and efficient solvent-free operating procedure. Several synthesized compounds exhibit a good profile with both a significant antiplasmodial activity on the W2 Plasmodium falciparum strain (IC$_{50}$ values: 0.4–2.2 IM) and a promising
toxicological behavior regarding human cells (HepG2/W2 selectivity indexes: 40–83), compared to the antimalarial drug compounds chloroquine and doxycycline. The \textit{in vitro} anti-toxoplasmonic and anti-leishmanial evaluations were conducted in parallel on the most active molecules, showing that these ones specifically display antiplasmodial properties (Fig 175).

![Chemical structure](image)

\textbf{Fig 175}

A series of original 4-aryl-substituted 2-trichloromethylquinazoline (Verhaeghe 2008), derivatives was synthesized using a microwave assisted Suzuki-Miyaura cross-coupling approach. Anti-plasmodial activity was evaluated on both chloroquine resistant and sensitive \textit{Plasmodium falciparum} strains, and the selectivity indexes for THP1 and HepG2 human cells were also calculated, revealing their antiplasmodial potential (Fig 176).

Bioassay-guided purification from the seeds of \textit{Peganum harmala} led to the isolation of harmine, harmaline, vasicinone, and deoxyvasicinone. Harmine and harmaline showed a moderate \textit{in vitro} anti-plasmodial activity against \textit{Plasmodium falciparum} (Astulla 2008). Quinazoline alkaloid (Fig 177), vasicinone, showed a vasorelaxant activity against phenylephrine-induced contraction of isolated rat aorta.
4.41. Antihypertensive activity

A series of 3-benzyl-2-substituted-3H-[1,2,4]triazolo[5,1-b]quinazolin-9-ones (Alagarsamy 2007) have been synthesized by the cyclocondensation of 3-amino-2-benzylamino-3H-quinazolin-4-one with a variety of one-carbon donors. The starting material 3-amino-2-benzylamino-3H-quinazolin-4-one was synthesized from methyl anthranilate by a novel innovative route. The compounds were evaluated for their in vivo antihypertensive activity using spontaneously hypertensive rats (SHR) (Fig 178).
4.42. Antileishmanial activity

4- (Substituted-benzylidine)-2- substituted -5,6-dihydrobenzo \([H]\) quinazoline and 4- (substituted benzylidine)-2-substituted-3, 4, 5, 6-tetrahydrobenzo[ \(H\)] quinazoline have been synthesized from 2-(substituted-benzylidine)tetalone and several substituted guanidine sulfates by (Agarwal 2009) (Fig 179). These compounds were tested for their \textit{in vitro} antileishmanial activity. The compounds show promising antileishmanial activity against \textit{Leishmania donovani}.

Protozoic infections caused by genus Leishmania pose an enormous public health threat in developing countries, compounded by the toxicity and resistance to current therapies. Under the aegis of our ongoing program on drug discovery and development on antileishmanial agents from plants, (Khaliq 2009), carried out bioassay guided fractionation on \textit{Peganumharma} la seeds which resulted in the isolation of as an antileishmanial agent. The compounds exhibited \textit{invitro} activity against both extracellular promastigotes as well as intracellular amastigotes residing within murine macrophages in \textit{Leishmania donovani} (Fig 180).
Several indolo [2,1-b]quinazoline-6,12-dione (Bhattacharjee 2002) derivatives exhibited remarkable activity, when tested against \textit{in vitro} Leishmania donovani amastigotes. The \textit{in vitro} toxicity studies indicate that the compounds are fairly well tolerated in both macrophage and neuronal lines. An analysis based on qualitative and quantitative structure–activity relationship studies between \textit{in vitro} antileishmanial activity and molecular electronic structure of indolo[2,1-b]quinazoline-6,12-dione is presented here by using a combination of semi-empirical AM1 quantum chemical, cyclic voltammetry and a pharmacophore generation (CATALYST) methods (Fig 181). A modest to good correlation is observed between activity and a few calculated molecular properties such as molecular density, octanol–water partition coefficient, molecular orbital energies, and redox potentials. Electron transfer seems to be a plausible path in the mechanism of action of the compounds.
Synthesized a new class of 4-(hetero) aryl-2-piperazino quinazolines (Kumar 2009) were synthesized and assessed for in vitro activity against extracellular promastigotes and intracellular amastigotes of Leishmania donovani (Fig 182).

4.43. Antihyperglycemic activity
A series of 2-sec-amino-3H-quinazolin-4-ones and 4-sec-amino-2-chloro quinazolines (Ram 2003) have been synthesized by nucleophilic substitution reaction of 2-chloro-4(3H)-quinazolones and 2,4-dichloroquinazolines with amines respectively. Most of the synthesized compounds were evaluated for antihyperglycemic activity. Compound displayed significant reduction in blood glucose level instreptozotocin and sucrose loaded rat models (Fig 183).
4.44. Antileukemic activity
A series of organicarsonic acid compounds has been synthesized and evaluated against human B-lineage (NALM-6) and T-lineage (MOLT-3) acute lymphoblastic leukemia (ALL) cell lines. The lead compounds 2-trichloromethyl-4-[4-(4-phenylazo) phenyl arsenic acid] amino quinazoline (PingLiu 2003) exhibited potent leukemic activity at low micromolar concentrations (Fig 184).

4.45. Antimycobacterial activity
Series of 3-phenyl-6,8-dichloro-2\(H\)-1,3-benzoxazine-2,4(3\(H\))-dithiones, 3-arylquinazoline-2,4(1\(H\),3\(H\))-diones and 3-arylquinazoline-2,4(1\(H\),3\(H\))-dithiones (Gregor 2001) were synthesized, and the antimycobacterial activities of the derivatives evaluated in vitro. The compounds were active against *Mycobacterium tuberculosis* and conditionally pathogenic mycobacteria (*Mycobacterium kansasii* and *Mycobacterium aium*). The
replacement of oxygen by sulfur in 3-phenyl-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-diones and 3-arylquinazoline-2,4(1H,3H)-diones gave rise to an increase of antimycobacterial activity (Fig 185).

\[
\text{Fig 185}
\]

4-Quinazolinol was prepared by (Kunes 2000). The hydroxy group was converted into the thiol function by treatment with phosphorus sulfide, and the subsequent alkylation of the thiol group was carried out with alkyl halides under the conditions of phase-transfer catalysis.

\[
\text{Fig 186}
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Antimycobacterial activity of the synthesized compounds exhibited significant activity against the strains of *Mycobacterium tuberculosis*, *Mycobacterium aium*, *Mycobacterium fortuitum*, *Mycobacterium kansasii* and *Mycobacterium intracellulare*. 4-(SButylthio) quinazoline (Fig 186) was even more active than isoniazide against atypical strains of mycobacteria.
The synthesized and evaluated the anti-inflammatory activity of a series of 4-quinazolinone derivatives (Santagati 1999). Two approaches were used to yield the synthesized compounds. A first group of quinazolinone derivatives was obtained by the appropriate substituted anthranilates. A second group of quinazolinone compounds was prepared through the benzoxazin-4-ones intermediate. The pharmacological results reveal that the synthesized derivatives exhibit a significant anti-inflammatory effect in an experimental ocular inflammation model (Fig 187).

![Chemical Structure](image)

\[ R_1 = \text{H, Cl} \]
\[ R_2 = \text{H, Me} \]

Fig 187
5. SAR OF QUINAZOLINE

Structure activity relationship studies according to literature survey

- Structure–activity relationship studies indicated that different substitutions on the quinazoline nucleus exerted varied biological activity. The electronic nature of the substituent groups at fourth, sixth and seventh positions in quinazoline nucleus led to significant variation in anti-cancer activity. The substituted aniline and alkoxy groups enhanced the anticancer activity.

- The alkyl and aryl substitutions at 2nd and 4th position led promising analgesic and antipyretics activity.

- 4th, 6th and 7th positions are substituted with keto, substituted amine and halogen leads anti-hypertensive activity.

- Alkyl group at 2nd position, substituted alkyl and aryl group at 3rd position and keto group at 4th position led hypnotics and sedatives action.

- 2nd, 3rd and 5th position substitutions of quinazoline ring increase diuretic activity and substitutions such as substituted alkyl, aryl and halogen.

- The positions 2nd, 3rd, 4th, 6th and 7th are substituted with alkyl, aryl, substituted amides, substituted aniline and substituted alkoxy group led promising enzyme and receptor inhibitory activity.
6. CONCLUSIONS

The article has outlined the chemistry and biological activities of the quinazoline scaffold. The synthetic methods are indicating the simple, maneuverable and versatile, which offer the medicinal chemist a complete range of novel derivatives. Given the advances in synthetic methodology and technology in recent years and the continued interest in the quinazoline skeleton in medicinal chemistry and drug development, the development of efficient and reliable methods for the construction of these molecules will ensure that this is an active and important area of research in heterocyclic chemistry. The high degree of protection against seizures can be positive signs for further investigation of quinazoline derivatives as anticonvulsants. The activity of quinazoline as antitubercular compounds in multi-drug resistant tuberculosis and their potent anthelmintic activity are promising. The broad spectrum microbiological activity of this synthesized compound could lead to a new series of antimicrobials. The quinazoline derivatives have demonstrated significant antiviral and anticancer activities. The enzymes and receptor agonist or antagonist action of these derivatives furthers their biological importance. Thus quinazoline scaffold is not only synthetically important but also possesses a wide range of promising biological activities. Further investigations of this scaffold in future could give some more encouraging results.
7. REFERENCES


Chapter II


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