DOI: 10.1070/RCR4591

Synthesis and antitumour activity of 4-aminoquinazoline derivatives

Galina N. Lipunova,[a] Emiliya V. Nosova,[a, b] Valery N. Charushin,[a, b] Oleg N. Chupakhin [a, b]

[a] I.Ya.Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences ul. S.Kovalevskoi/Akademicheskaya 22/20, 620990 Ekaterinburg, Russian Federation
[b] Ural Federal University named after the first President of Russia B.N.Yeltsin ul. Mira 19, 620002 Ekaterinburg, Russian Federation

Pieces of data on the synthesis and antitumour activity of 4-aminoquinazolines are summarized and analyzed. Key methods for the synthesis of these compounds are considered, primarily cyclocondensation of carboxylic acid derivatives, as well as the oxidation of quinazolines and the cyclization of disubstituted thioureas. Improvements of synthetic schemes for erlotinib, gefitinib and lapatinib, which are the best-known pharmaceuticals based on compounds of the title class, are also considered. Synthetic strategies and biological activities for new 4-aminoquinazoline derivatives that are EGFR-tyrosine kinase inhibitors, multiactive compounds, and labelled compounds for use as positron emission tomography (PET) imaging agents are discussed.
The bibliography includes 263 references.

Contents

I. Introduction 759
II. Syntheses of 4-aminoquinazoline derivatives 761
III. Improvement of erlotinib, gefitinib and lapatinib synthetic schemes 766
IV. Synthesis of new antitumour 4-amino-quinazoline derivatives 769
V. Synthesis of labelled 4-anilinoquinazolines as positron emission tomography agents 786
VI. Conclusion 788

I. Introduction

Derivatives of the pyrimidine series have long established themselves as very important chemical structures; their role in biology and medicine is highlighted in detail in numerous monographs and textbooks on heterocyclic chemistry.[1–5] Widely known is the ability of hydroxy- and aminopyrimidines, especially very important DNA fragments (thymine, uracyl and cytosine), to interact with a variety of biological targets (amino acids, proteins and enzymes) thereby causing an effect on very important biological processes.[6, 7]

Pyrimidines play an important role in the chemotherapy of tumours and viral diseases. This role is not a unique property of monocyclic pyrimidines, such as fluorouracil, azidothymidine, ribavirin, acyclovir, and other antiviral agents, but rather is also intrinsic to bi- and tricyclic heterosystems, including benzo and aza analogues of pyrimidines, namely azoloazines, purines, aza and deaza purines, quinazolines, pteridines, and other heterocycles.[8–10]

In recent decades, quinazoline derivatives have attracted increasing attention of researchers involved in the search for biologically active compounds for use in tumour therapy.

G.N.Lipunova. Doctor of Chemical Sciences, Professor, Leading Researcher of the Laboratory of Coordination Compounds at the IOS UrB RAS. Telephone: +7(343)362–3065, e-mail: lipunova@ios.uran.ru
Current research interests: heterocyclic and organofluorine chemistry, formazans, biologically active compounds, photoluminescent materials.
E.V.Nosova. Doctor of Chemical Sciences, Senior Researcher of the Laboratory of Heterocyclic Compounds at the IOS UrB RAS, Assistant Professor of the Department of Organic and Biomolecular Chemistry at the Institute of Chemical Engineering, UrFU.
Telephone: +7(343) 375–4501, e-mail: emily74@rambler.ru
Current research interests: heterocyclic and organofluorine chemistry, chemistry of medicines, organic ligands.
V.N.Charushin. Academician, Director of the IOS UrB RAS, Professor of the Department of Organic and Biomolecular Chemistry at the Institute of Chemical Engineering, UrFU.
Telephone: +7 (343)374–1189, e-mail: charushin@ios.uran.ru
Current research interests: heterocyclic compounds, fluorinated compounds, medicinal chemistry.
O.N.Chupakhin. Academician, the Research Head of the IOS UrB RAS, Head of the Department of Organic and Biomolecular Chemistry at the Institute of Chemical Engineering, UrFU.
Telephone: +7(343)374–1189, e-mail: chupakhin@ios.uran.ru
Current research interests: synthetic organic chemistry, heterocyclic chemistry, supramolecular chemistry, organofluorine chemistry, chemistry of medicines.

Received 28 July 2015
Translation: O.P.Federova

© 2016 Russian Academy of Sciences and Turpion Ltd.

This is understandable, as more than 150 natural alkaloids contain quinazoline moieties. Synthetic analogues of these compounds exhibit antimalarial, anticonvulsant, anti-diabetic and other biological activities.[11]

Aminoquinazolines and their derivatives also have diverse physiological activities, including anti-inflammatory,[12,13] antibacterial[14] and antiviral[15,16] activities, but of greatest importance are their ability to inhibit enzymes (dihydrofolate reductase and tyrosine kinases)[17–20] and antitumour activity.[21–25] Aniline derivatives deserve special attention among the aminoquinazolines. Extensive chemical and biological studies of 4-arylaminoquinazoline derivatives were performed with variable substituents in the aniline moiety and benzene ring in the positions 6 and(or) 7; the influence of the nature of substituents in the position 2 of the pyrimidine ring was also studied.

Arylaminoquinazoline moieties are regarded to be an important pharmacophores, which are widely used in the design of a new class of cytostatic drugs, referred to as targeted or molecular-oriented drugs. Such the drugs include pharmaceuticals intended to affect certain intracellular molecular targets, which are crucial for tumour cell activity. For example, the major targets for a targeted therapy of gastrointestinal tumours are epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR).[26]

The best known first-generation products based on arylaminoquinazolines (Fig. 1) — gefitinib, erlotinib, lapatinib, and vandetanib — have become part of medical practice and have been successfully used to treat a variety of tumours, such as lung cancer, pancreatic cancer, breast cancer, *etc*.[27–32]

Gefitinib (known under the trade name Iressa) is a selective EGFR tyrosine kinase (EGFR-TK) inhibitor, whose expression is observed in many solid tumours. This agent retards growth of various human tumour cell lines, metastasis and angiogenesis, accelerates the apoptosis of tumour cells and enhances the efficiency of chemotherapy, radiation and hormone therapy.[33–35]

Erlotinib (the trade names are Tarceva) is an anticancer agent, an inhibitor of EGFR-TKs, which are responsible for the intracellular phosphorylation of epidermal growth factor whose expression is observed on the surfaces of both normal and tumour cells. Erlotinib is used in the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after a failure of one or more chemotherapy regimens, or (in combination with gemcitabine) in the treatment of locally advanced unresectable or metastatic pancreatic cancer.[36,37]

Lapatinib (the trade names are Tyverb, Tykerb) is an antitumour agent, a reversible inhibitor of various tyrosine kinase receptors. The results of trials[32,38,39] imply that lapatinib is efficient when used in monotherapy or combination therapy in patients with metastatic breast cancer. The combined use of lapatinib with capecitabine for the treatment of patients with ErbB2 (HER2)-positive breast cancer (HER2 stands for human epidermal growth factor receptor 2) significantly reduces the risk of disease progression and minimizes the incidence of metastasis.

Vandetanib (the trade name is Caprelsa or Zactima; the development name is AZD6474) is an antagonist of VEGFR and EGFR tyrosine kinases. Vandetanib also inhibits the activity of RET tyrosine kinase (an important growth promoter in certain types of thyroid cancers).[32,40]

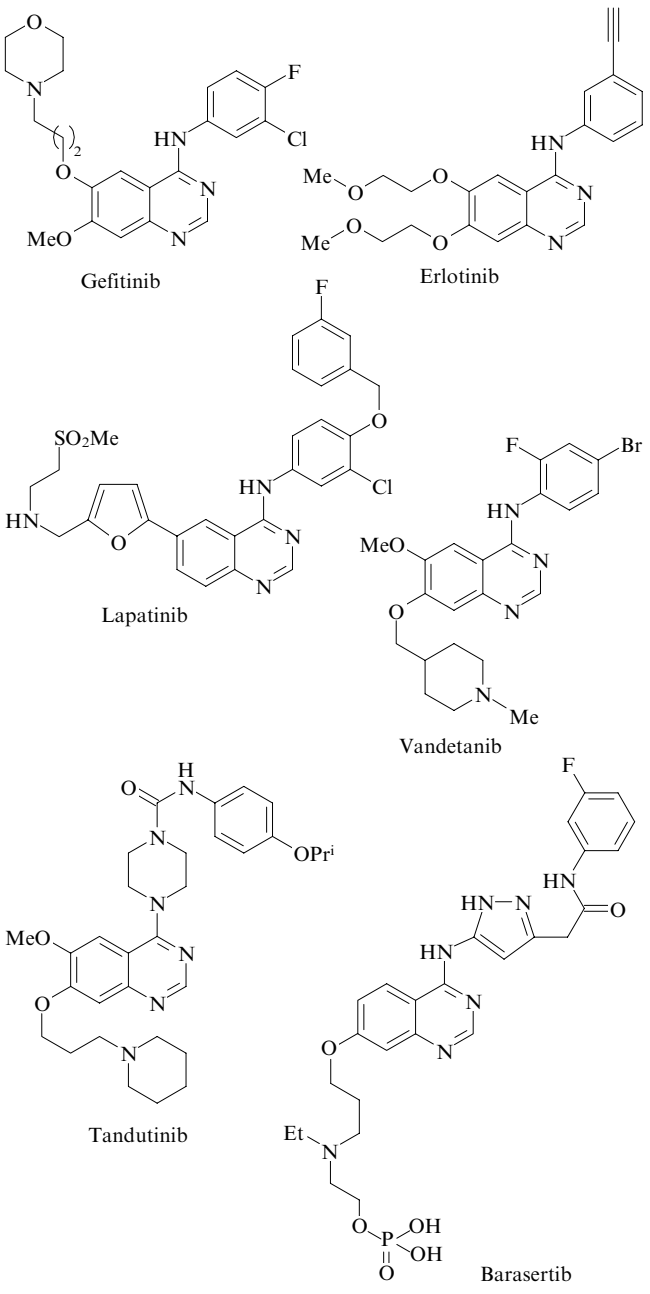


Figure 1. Structures of 4-aminoquinazoline-based antitumour agents.

Vandetanib is an oral tyrosine kinase inhibitor, developed by AstraZeneca for the treatment of thyroid cancer, non-small cell lung cancer and renal carcinoma. Vandetanib is suitable for the treatment of progressive medullary thyroid cancer in patients with unresectable advanced local or metastatic cancers. In April 2011, vandetanib was recommended in the United States for the treatment of unresectable medullary thyroid cancer and commercialized under the trade name Caprelsa.

High antitumour activities were also shown by some other 4-aminoquinazoline derivatives (see Fig. 1) that are now at various stages of preclinical or clinical studies (*e.g.* tandutinib and barasertib).[40] Tandutinib (MLN518/CT53518), a new FMS-like tyrosine kinase 3 (FLT3) recep-

tor inhibitor and a platelet-derived growth factor tyrosine kinase receptor (PDGF-R) inhibitor, is promising for the treatment of myeloid leukemia and myelodysplasia.[41 – 45] Barasertib (AZD1152), an aurora kinase inhibitor, is efficient against acute myeloid leukemia; it is now in phase II clinical trials for the treatment of melanoma and colorectal carcinoma.[46]

We should mention that more than half of the above-mentioned medicaments contain a fluorine atom in the aromatic moiety. Introduction of the fluorine atom is important not only for modifying the acid – base properties and lipophilicity of compounds, but also for endowing them with metabolic stability. The substitution of fluorine for hydrogen in an aromatic ring is a well-known efficient strategy to considerably slow down the oxidative stage of drug metabolism caused by cytochrome P450-dependent monooxygenase.[32]

The mechanism of action of this class of compounds is fundamentally different from that of the chemotherapeutics that violate the division of both the tumour and normal cells, causing severe side effects, namely anemia, neutropenia, faintness and others. Uncontrolled proliferation is an important feature of a tumour cell. An enhancement of the proliferative activity of a cell, specifically a tumour cell, is most frequently launched by an external signal. Growth factors, hormones and other biologically active substances activate the relevant receptors whose signals are transmitted to signal transduction proteins. The final recipients of signals are transcription factors, which are responsible for the activation of genes and subsequent production of the corresponding proteins involved in cell cycle regulation. Representatives of the EGFR family are key receptors that stimulate cell division. The examples of gefitinib, the first drug approved for clinical use, and erlotinib show that the activity of these compounds arises from their ability to bind competitively to the active sites of tyrosine kinase-C (TKC), where phosphorylation occurs, and thereby inhibit the phosphorylation of signal transduction proteins. Thus, signal transduction to transcription factors is interrupted at the TKC level.[27]

In recent years, much attention was paid to the binding modes of arylaminoquinazolines to EGFR-TKs, to recognize the key role of aminopyrimidine moieties in this process.[47 – 53] Docking of this binding was performed for 6-dithiolane carboxamide derivative **1** (Fig. 2).[47] The quinazoline N(1) atom was shown to interact, *via* hydrogen bonding, with the NH moiety of Met769 EGFR-TK; the hydrogen atom at the quinazoline C(2) atom interacts electrostatically with the carbonyl oxygen atom of the Gln767 enzyme; and the quinazoline N(3) atom is involved in hydrogen-bonding with the OH group of Thr766; further, hydrophobic interactions with Val702, Met742 and Leu764 favour the stabilization of the aniline moiety.

Despite the abundant documentation on the synthesis and biological properties of arylaminoquinazolines and structure – activity correlations in particular series of compounds of this class, there are only survey articles where synthesis and kinase activity data are summarized over short periods of time or where these data are merely included into a broader topical overview. Cruz-Lopez *et al.*,[54] for example, summarized the documents on substituted quinazolines as EGFR-TK inhibitors published over four years. The mini-review of Khan *et al.*[55] concerned with synthetic approaches and diverse applications of quinazoline derivatives has a small section where one can find the structures of some 4-(het)arylaminoquinazolines and concise information about their antitumour activities.

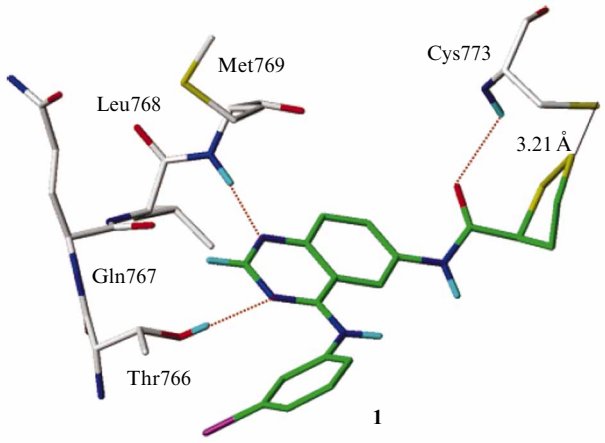


Figure 2. Results of docking [1,2]dithiolane-3-carboxylic acid [4-(3-bromophenylamino)quinazolin-6-yl]amide (**1**) in a low-energy conformation and EGFR-TK moiety.[47]

Our review is an attempt at summarizing data on the synthesis and antitumour activity of 4-aminoquinazolines and approaches to the preparation of the best-known drugs and new derivatives of this class.

II. Syntheses of 4-aminoquinazoline derivatives

To make up a pyrimidine moiety to an arene derivative is a traditional approach to the synthesis of quinazolines. Most popular is the cyclization of aniline derivatives.

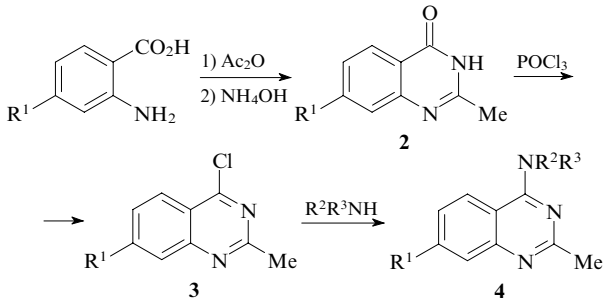
II.1. Cyclocondensation reactions

II.1.a. Cyclocondensations of anthranilic acid derivatives

The review of Nosova *et al.*[56] over fluorinated quinazolines and their oxa- and thia-analogues, dwells on cyclocondensation-involving syntheses of these compounds. Anthranilic acid and its derivatives (esters and nitriles) are most frequently used as precursor compounds.

A classical method to prepare 4-arylaminoquinazolines is the reaction of 4-chloroquinazolines with amines. Yakhontov *et al.*[57] refluxed anthranilic acid and 4-chloroanthranilic acid with acetic anhydride for 3 h to prepare the corresponding 2-methylbenzoxazinones, and then converted these, without isolation, into 2-methylquinazolin-4-ones **2** by refluxing for 1 h with aqueous ammonia (yields: 82% – 85%). The phosphorus(V) oxochloride treatment of

Scheme 1

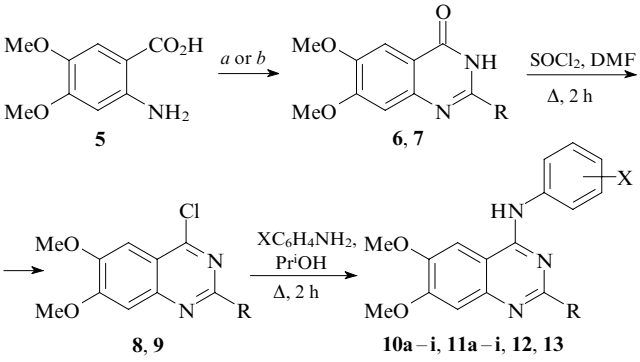


R^1 = H, Cl; NR^2R^3 = NEt_2, NHPh, NHBn, $NHCHMe(CH_2)_3NEt_2$

compounds **2** in the presence of *N,N*-dimethylaniline yielded chloro derivatives **3**; subsequent substitution of the chlorine atom in these derivatives in the reaction with amines resulted in 4-amino-2-methyl-quinazolines **4** in yields of 77%–96% (Scheme 1).

Rocco *et al.*[58] report a more efficient method for preparing both new and earlier described 4-anilino-6,7-dimethoxyquinazolines (Scheme 2).

Scheme 2



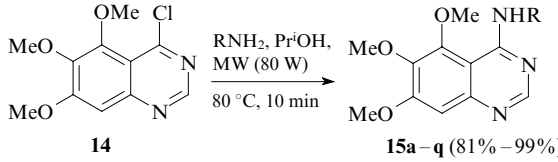
5 **6**, **7** **8**, **9** **10a–i**, **11a–i**, **12**, **13**

R = H (**6**, **8**, **10**, **11**), Me (**7**, **9**, **12**, **13**); isomers: *meta* (**10**), *para* (**11**); **10**, **11**: X = H (**a**), F (**b**), Cl (**c**), Br (**d**), I (**e**), OMe (**f**), Me (**g**), Ac (**h**), NO_2 (**i**); X = H (**12**), 3-Br (**13**); (*a*) for **6**: NH═$CHNH_2$·AcOH, 140 °C, 8 h; (*b*) for **7**: 1) Ac_2O, Δ, 4 h; 2) NH_4OH, rt, 4 h;

The cyclization of dimethoxyanthranilic acid **5** with formamidine acetate at 140 °C for 8 h (under conditions *a*) yielded quinazolinone **6** (R = H) in 76% yield. Compound **7** (R = Me) was prepared under conditions *b* through a benzoxazinone intermediate, as in the case of derivative **2**. 4-Chloroquinazolines **8** and **9** were isolated after compounds **6** and **7** were treated with thionyl chloride in the presence of a catalytic amount of DMF (79% and 90% yields, respectively). The nucleophilic substitution of the chlorine atom in compounds **8** and **9** induced by aniline derivatives upon refluxing in isopropanol for 2 h yielded target products **10a–i**, **11a–i**, **12** and **13** in 51%–93% yields.[58]

Liu *et al.*[59,60] describe the substitution of an aryl- or benzylamine moiety for the chlorine atom in trimethoxy-4-chloroquinazoline **14** under microwave exposure (MW) (Scheme 3). That the reaction was carried out in isopropanol at 80 °C not only made it possible to shorten the process time to 10 min (against 360 min in the classical method), but also provided a sesqui- to twofold gain in product yield.

Scheme 3



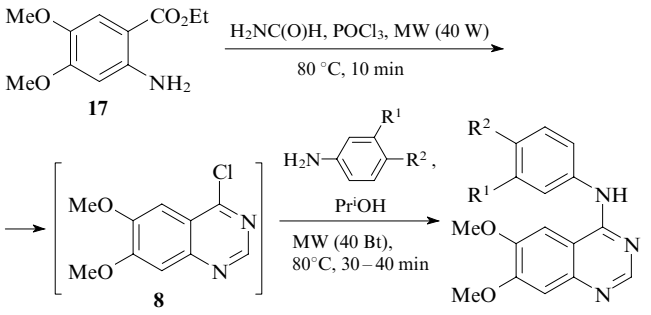
14 **15a–q** (81%–99%)

R = 4-BrC_6H_4 (**a**), 3-BrC_6H_4 (**b**), 3-ClC_6H_4 (**c**), 3-FC_6H_4 (**d**), 4-FC_6H_4 (**e**), 2-FC_6H_4 (**f**), 2-Cl-4-BrC_6H_3 (**g**), 3,4,5-$(MeO)_3C_6H_2$ (**h**), 4-$O_2NC_6H_4$ (**i**), 3-$O_2NC_6H_4$ (**j**), 2-$O_2NC_6H_4$ (**k**), 4-ClC_6H_4 (**l**), 4-HOC_6H_4 (**m**), Bn (**n**), (*R*)-PhCH(Me) (**o**), (*S*)-PhCH(Me) (**p**), 3-$FC_6H_4CH_2$ (**q**)

Similar conditions were later used to prepare a set of 4-arylamino-5,6,7-trimethoxyquinazolines **15a–q**.[61]

A one-pot microwave-assisted synthesis of 4-arylamino-quinazolines having one (**10c**,**g**, **11b**,**c**) and two (**16**) substituents in the aniline moiety was developed (Scheme 4).[62] A mixture of formamide with $POCl_3$ serves both to form the pyrimidine CN moiety from *o*-aminoester **17** and for subsequent chlorination, so 4-chloroquinazoline **8** is produced in one step. The treatment of 4-chloroquinazoline **8** with a solution of substituted aniline in isopropanol yields amino derivatives in high yields (87%–92%). This method has a number of advantages: reaction times reduced from 2 h or longer to several minutes, very mild conditions (irradiation power: 40 W), minimal amounts of the chlorinating agent and high yields and purity of target products.

Scheme 4



17 **8** **10c**,**g**, **11b**,**c**, **16**

R^2 = H: R^1 = Cl (**10c**), Me (**10g**); R^1 = H: R^2 = F (**11b**), Cl (**11c**); R^1 = Cl, R^2 = F (**16**)

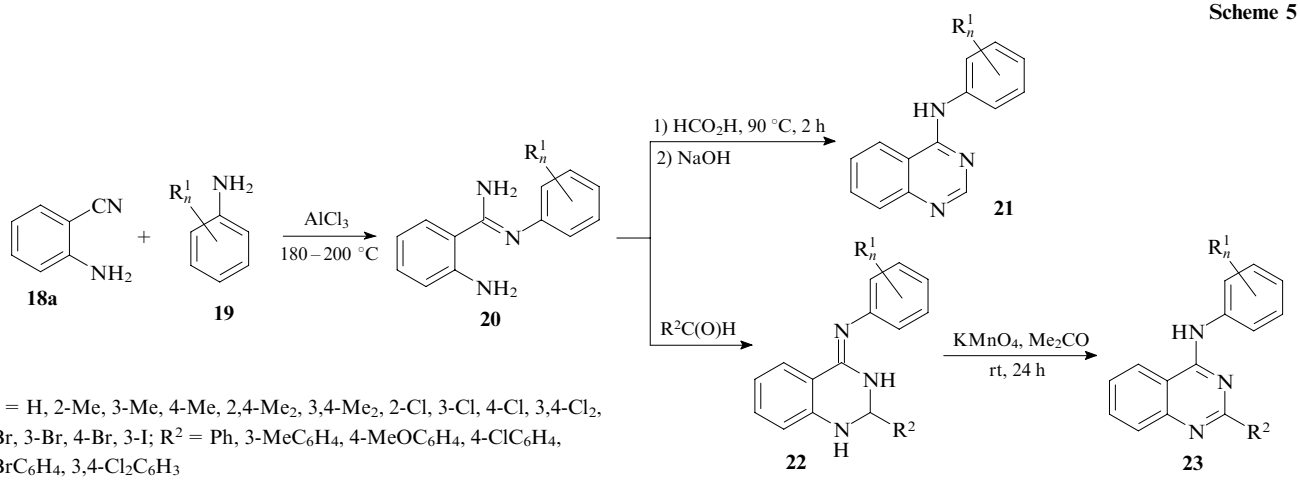
The precursors frequently used to produce 2-substituted 4-arylaminoquinazolines by ordinary substitution of an amine moiety for chlorine atom are commercially available 2-sulfanylquinazolin-4-ones or quinazoline-2,4-diones.[63]

Szczepankiewiez *et al.*[64,65] describe the synthesis of aminoquinazoline derivatives avoiding the preparation of chloro derivatives. The reaction of 2-aminobenzonitrile (**18a**) with substituted anilines **19** in the presence of aluminium chloride yields the corresponding 2-amino-*N*-arylbenzamidines **20**, which give rise to 4-arylaminoquinazolines **21** when heated with 85% formic acid (Scheme 5). Other carboxylic acids do not react with amidines under these conditions, so the authors concluded that the CHO group, which is formally present in formic acid (unlike in carboxylic acids), is able to form the quinazoline system.

Refluxing of amidines **20** with aromatic aldehydes in ethanol for 2.5 h yields 2-aryl-4-arylimino-1*H*-2,3-dihydroquinazolines **22**, which are oxidized by potassium permanganate in acetone to form arylaminoquinazolines **23**. The yields of products **23** (based on amidines) are 20% to 73% depending on the substituent R^1 (see Scheme 5).

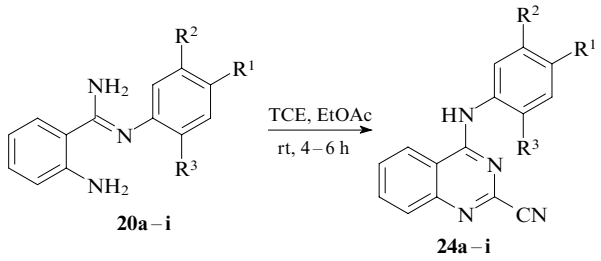
2-Amino-*N*-arylbenzamidines **20a–i** were made to react with tetracyanoethylene (TCE) in ethyl acetate at room temperature;[66] 4-arylaminoquinazoline-2-carbonitriles **24a–i** were prepared in yields of 41%–71% (Scheme 6). The treatment of 4-anilinoquinazoline-2-carbonitrile (**24a**) with sodium hydroxide in methanol for 4 days produced 4-anilino-2-methoxyquinazoline in 71% yield; refluxing with hydrochloric acid produced the corresponding 2-carboxamide derivative.[67]

Scheme 5



R^1_n = H, 2-Me, 3-Me, 4-Me, 2,4-Me_2, 3,4-Me_2, 2-Cl, 3-Cl, 4-Cl, 3,4-Cl_2, 2-Br, 3-Br, 4-Br, 3-I; R^2 = Ph, 3-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3,4-$Cl_2C_6H_3$

Scheme 6



R^1 = R^2 = H: R^3 = H (**a**), Me (**b**), Cl (**c**), Br (**d**), I (**e**), OMe (**f**);
R^1 = H: R^2 = R^3 = Me (**g**), Cl (**h**); R^1 = R^3 = H, R^2 = OMe (**i**)

The condensation of *N*-(2-cyanophenyl)amidines **25** with arylamines yielded 2-alkyl-4-arylaminoquinazolines **26a – g** (Scheme 7).[68] Amidines **25** were prepared *via* the thermal rearrangement of 5-morpholino-1-(2-cyanophenyl)-4,5-dihydrotriazoles **27**, which were formed by reacting 2-azidobenzonitrile (**28**) with aldehydes **29** and morpholine. The same initial compounds immediately yielded amidines **25** when reacted at high temperatures. Amidines **25** reacted with arylamines upon refluxing in propanoic acid or with arylamine hydrochlorides upon heating at 180 °C for 2 h (yields were 15% to 65% depending on the substituent and conditions).

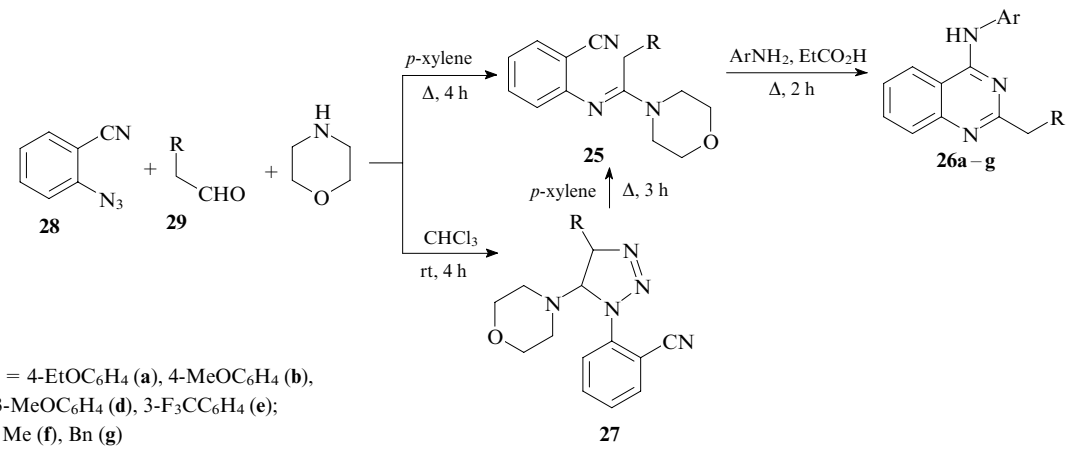
Yoon *et al.*[69] described a facile and efficient microwave-assisted method for preparing a large series of 4-aminoquinazolines **10d**, **30a – s** by the reaction of substituted *N*-(2-cyanophenyl)-*N′*,*N′*-dimethylformamidines **31** with aliphatic amines, substituted benzylamines and anilines (Scheme 8). Optimal parameters (temperature, solvent, process time) were found to produce target products in high yields (83% – 97%).

Later Foucourt *et al.*[11] improved this approach and implemented it to prepare 4-arylamino-6-nitroquinazolines **32a – l** (Scheme 9). The reaction of amidine **31a**, which was prepared by reacting 2-amino-5-nitrobenzonitrile (**18b**) with dimethylformamide dimethylacetal (DMF-DMA), was carried out in acetic acid under microwave exposure (800 W) at 118 °C

The reaction time depended on the nature and position of the substituent in the amine; it varied from 2 – 5 min (when electron-withdonating moieties were in the *meta*- and *para*-positions of the benzene ring) to 7 – 210 min (for electron-withdrawing groups, especially in the *ortho*-position).

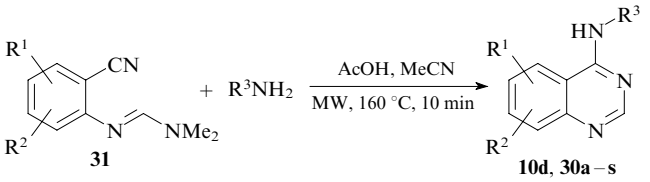
Reactions of 2-aminobenzonitriles **18a**,**c** with phenyl isocyanate (by refluxing in dry pyridine for 4 h or heating the reactants at 100 °C for 3 h) yield 2,2′-dithiobis(4-anilino-5-R-quinazolines) **33a**,**c** in 90% and 95% yield, respectively (Scheme 10). The occurrence of these reactions is due to the Dimroth rearrangement of intermediates **34a**,**c** to dihydroquinazolines **35a**,**c**.[70 – 72] The structure of disulfide

Scheme 7



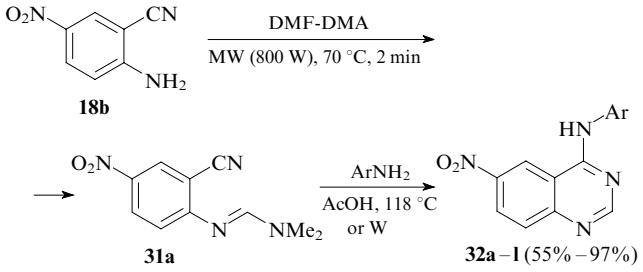
26: R = Et: Ar = 4-$EtOC_6H_4$ (**a**), 4-$MeOC_6H_4$ (**b**), 4-ClC_6H_4 (**c**), 3-$MeOC_6H_4$ (**d**), 3-$F_3CC_6H_4$ (**e**);
Ar = Ph: R = Me (**f**), Bn (**g**)

Scheme 8



Compound	R^1	R^2	R^3
10d	6-OMe	7-OMe	3-BrC_6H_4
30a	5-F	H	2-Me-4-$MeOC_6H_3$
30b	6-OMe	7-OMe	2-Me-4-$MeOC_6H_3$
30c	6-NO_2	H	2-Me-4-$MeOC_6H_3$
30d	6-Me	H	2-Me-4-$MeOC_6H_3$
30e	5-Me	H	2-Me-4-$MeOC_6H_3$
30f	5-F	H	2-$ClC_6H_4CH_2$
30g	6-OMe	7-OMe	2-$ClC_6H_4CH_2$
30h	6-NO_2	H	2-$ClC_6H_4CH_2$
30i	6-Me	H	2-$ClC_6H_4CH_2$
30j	5-Me	H	2-$ClC_6H_4CH_2$
30k	5-F	H	3-$F_3COC_6H_4CH_2$
30l	6-OMe	7-OMe	3-$F_3COC_6H_4CH_2$
30m	6-NO_2	H	3-$F_3COC_6H_4CH_2$
30n	6-Me	H	3-$F_3COC_6H_4CH_2$
30o	5-Me	H	3-$F_3COC_6H_4CH_2$
30p	5-F	H	$MeO(CH_2)_2$
30q	6-NO_2	H	$MeO(CH_2)_2$
30r	6-Me	H	$MeO(CH_2)_2$
30s	5-Me	H	$MeO(CH_2)_2$

Scheme 9



32: Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 3,5-$(MeO)_2C_6H_3$ (**d**), 3,4,5-$(MeO)_3C_6H_2$ (**e**), 4-FC_6H_4 (**f**), 3-NCC_6H_4 (**g**), 3-Cl-4-FC_6H_3 (**h**), 2-F-4-BrC_6H_3 (**i**), 2,3-$Cl_2C_6H_3$ (**j**), 2,3-$F_2C_6H_3$ (**k**), 2-$F_3CC_6H_4$ (**l**)

33c is supported by X-ray diffraction data (Fig. 3). According to these data, one quinazoline moiety is planar (the excursions of atoms from the root-mean-square plane are less than 0.035 Å), and the aniline substituent at the other moiety is rotated relative to the quinazoline plane (the angle between the root-mean-square planes passing through the ring atoms is 30.3°).

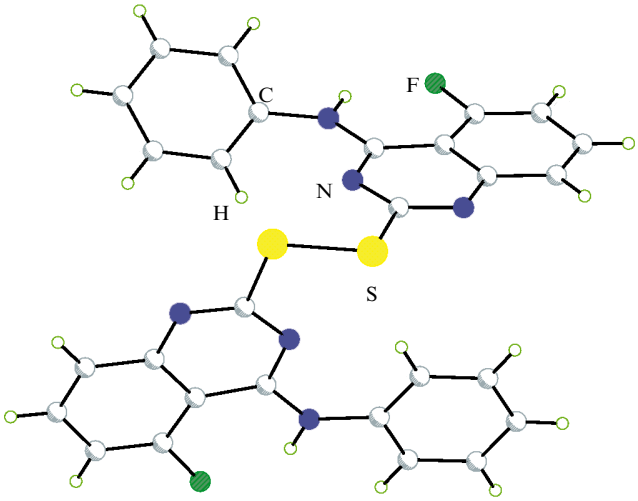
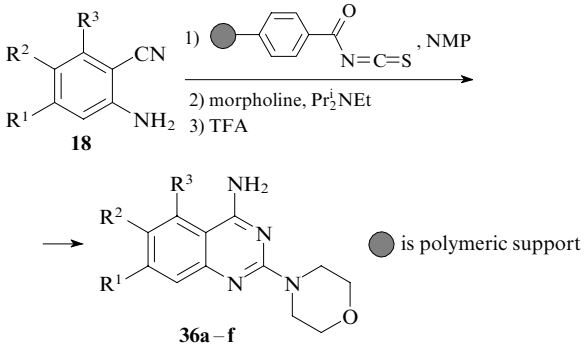


Figure 3. Structure of disulfide **33c** in a crystal as probed by X-ray diffraction.[71]

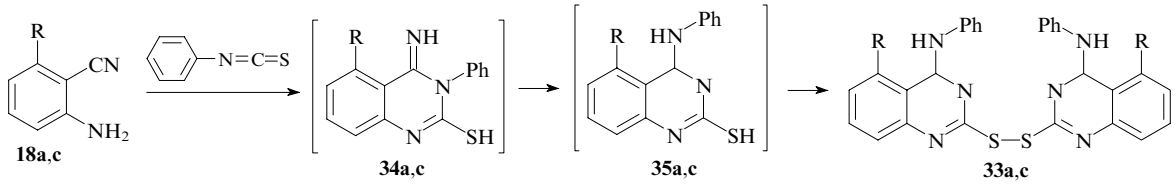
Wilson [73] reported on the solid-phase synthesis of a series of 2,4-diaminoquinazolines **36** (Scheme 11). The process comprises the reaction of 2-aminobenzonitriles **18** with immobilized acyl isocyanate in *N*-methylpyrrolidone (NMP) to produce a thiourea derivative. This derivative, when treated with morpholine, converts to the guanidine derivative that is capable of cyclizing to a substituted quinazoline. This method was used to produce compounds **36a–f** in 47%–67% yields and 87%–94% pure.

Scheme 11



36: $R^1 = R^2 = H$: R^3 = F (**a**), Me (**b**), Cl (**c**); $R^1 = R^2$ = OMe, R^3 = H (**d**); $R^2 = R^3 = H$: R^1 = Cl (**e**), Me (**f**);
TFA is trifluoroacetic acid

Scheme 10

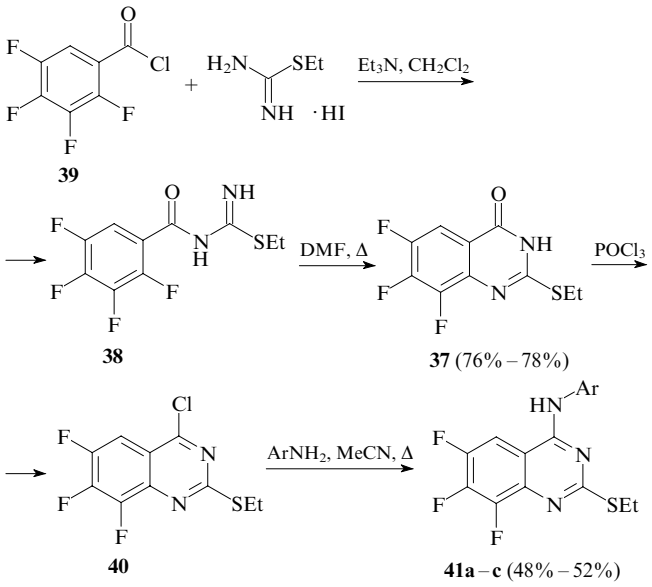


R = H (**a**), F (**c**)

II.1.b. Cyclocondensations of *o*-halobenzoic acid derivatives

Layeva *et al.*[74] developed an efficient synthetic strategy to prepare 6,7,8-trifluoro-2-ethylsulfanylquinazolin-4(3*H*)-one (**37**), involving the intramolecular cyclization of fluorine-containing *S*-ethyl-*N*-benzoylisothiourea **38**, which was prepared from tetrafluorobenzoic acid chloroanhydride (**39**) and *S*-ethyl-isothiourea (Scheme 12). The treatment of 6,7,8-trifluoro-2-ethylsulfanylquinazolin-4(3*H*)-one (**37**) by phosphorus(V) oxochloride with subsequent heating of the 4-chloro derivative **40** in acetonitrile with substituted anilines yields fluorinated 4-arylamino-2-ethylsulfanylquinazolines **41a – c**.

Scheme 12



39 **38** **37** (76% – 78%) **40** **41a – c** (48% – 52%)

41: Ar = Ph (**a**), 2-ClC$_6$H$_4$ (**b**), 3,4-F$_2$C$_6$H$_3$ (**c**)

II.2. Oxidation of quinazolines

The 4-arylaminoquinazoline preparation methods that use anthranilic acids have some drawbacks. The required acids are not necessarily commercially available, their synthesis meets some difficulty, and the overall yield of quinazolines usually does not exceed 30%.

Marzaro *et al.*[75] developed a new strategy for preparing quinazolin-4-ones where the formation of the pyrimidine ring was followed by oxidation (Scheme 13). The initial compounds used were 3,4-disubstituted anilines **42**. Marzaro *et al.* studied and optimized the conditions for converting acetanilides **43**. The advantages of this strategy include the availability of the precursor anilines, simple hardware and high yields of intermediates **44 – 46** in all stages (84% – 98%). The resulting overall yield of target 4-arylaminoquinazolines **47** was at the same level as in earlier described processes, or was even twofold to threefold higher. This method was used to produce known agents, namely erlotinib, gefitinib and vandetanib (see Fig. 1).

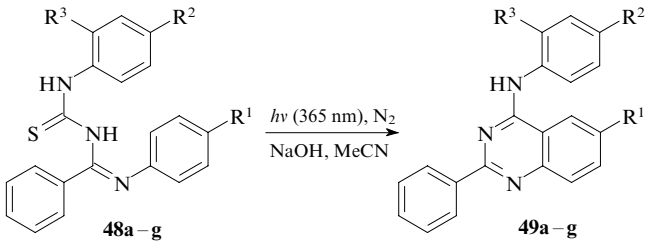
II.3. Cyclization of *N*,*N*′-disubstituted thioureas

The photocyclization of substituted arylthioureas to aminoquinazoline derivatives is documented.[76,77] Exposure of disubstituted thioureas **48a – g** to the light of a high-pressure mercury lamp (λ = 365 nm) in a mixture of acetonitrile and aqueous alkali at room temperature yielded, instead of expected 2-substituted benzothiazoles, 6-substituted 4-arylamino-2-phenylquinazolines **49a – g** in 39% – 49% yields (Scheme 14). The structure of compounds **49a – g** was proven by IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry; for compound **49a**, single-crystal X-ray diffraction was also employed.

II.4. Other methods

Cikotiene *et al.*[78,79] proposed a suitable method for preparing 4-arylamino-6-methoxycarbonyl-7-phenylquinazolines **50a – e**; this method consisted of annelating a benzene ring to the appropriate 6-ethynylpyrimidine-5-carbaldehyde derivatives **51a – e** (Scheme 15). The target products were obtained in 65% – 98% yields by reacting compounds **51** with the potassium salt of methyl sulfanyl acetate under

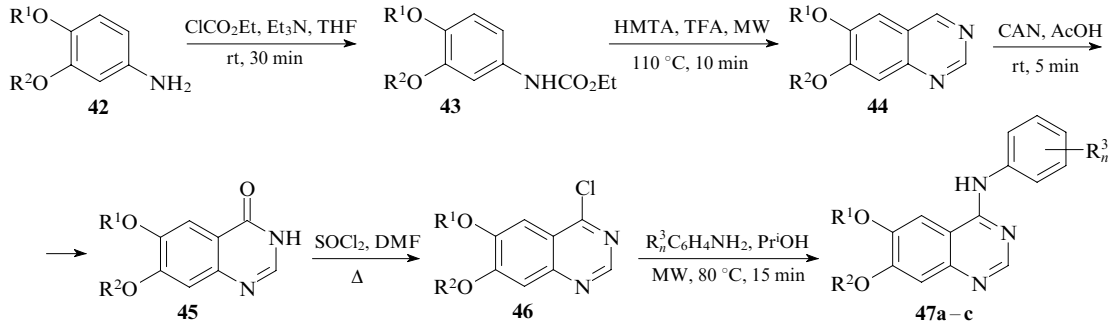
Scheme 14



48a – g **49a – g**

Compounds **48**, **49**	R^1	R^2	R^3
a	OMe	Cl	H
b	Me	H	Me
c	Me	Cl	H
d	H	Cl	H
e	Cl	Cl	H
f	Cl	H	Me
g	H	H	H

Scheme 13

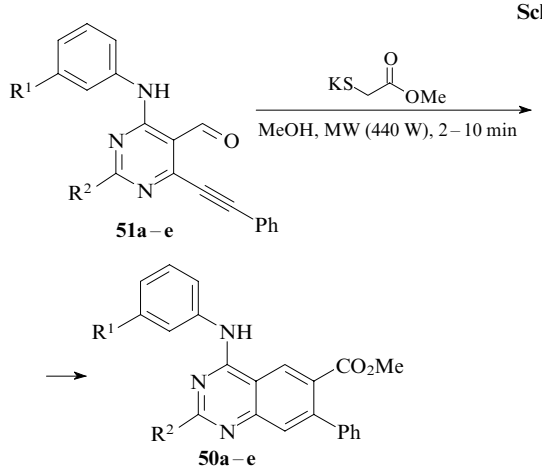


42 **43** **44** **45** **46** **47a – c**

R^1, R^2 = Alk; R^3_n = Hal, 3-CH≡C, *etc.*; HMTA is hexamethylenetetramine; CAN is cerium(IV) ammonium nitrate

microwave exposure. The derivatives that carried n-butyl in the position 7 instead of phenyl were prepared in the same manner.

Scheme 15



R^2 = SMe: R^1 = H (**a**), Br (**b**); R^2 = NHAll: R^1 = Br (**c**), CF_3 (**d**); R^1 = CF_3, R^2 = cyclo-[$N(CH_2CH_2)_2O$] (**e**)

III. Improvement of erlotinib, gefitinib and lapatinib synthetic schemes

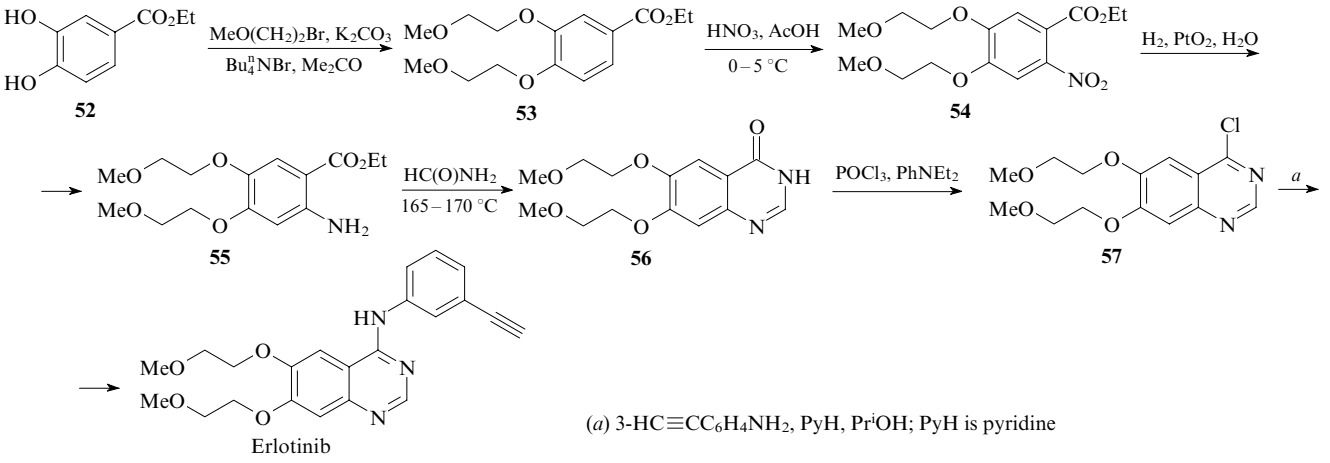
Although erlotinib, gefitinib and lapatinib are drugs that are already used in medical practice, chemists are constantly trying to improve the methods for their preparation with the goal of increasing the output and purity of the desired products, and reduce production costs.

Knesl *et al.*[45] modified erlotinib and gefitinib synthetic schemes. The conversion sequence starts with protecting hydroxy groups in protocatechuic acid ethyl ester (**52**); the stage of ethyl benzoate **53** nitration is followed by the reduction of nitro group in compound **54** and then by the heterocyclization of anthranilic acid derivative **55** (Scheme 16). The bottleneck of this scheme is the chlorination stage, where a side product [7-(2-methoxyethoxy)-4-chloro-6-(2-chloroethoxy)quinazoline] can be formed given an insufficient control of the ratio of ingredients, reaction temperature and reaction time, especially when thionyl chloride is the chlorinating agent. This side product readily reacts with ethynylaniline to yield 7-(2-methoxyethoxy)-6-(2-chloroethoxy)-4-(3-ethynylphenylamino)quinazoline, which is difficult to remove from erlotinib. Zhang and Zha [36] offered a method for purifying erlotinib: the nucleophilic substitution of the chlorine atom converts this impurity to 6-(2-piperazinylethoxy) derivative, which is easy to remove by recrystallization; the thus-purified erlotinib is >99.9% pure.

The chlorination of compounds **56** by phosphorus(V) oxochloride in the presence of diethylaniline enabled Knesl *et al.*[45] to increase the yield of chloride **57** to 89% and its purity to 96% (according to HPLC). The resulting total erlotinib yield was 56%.

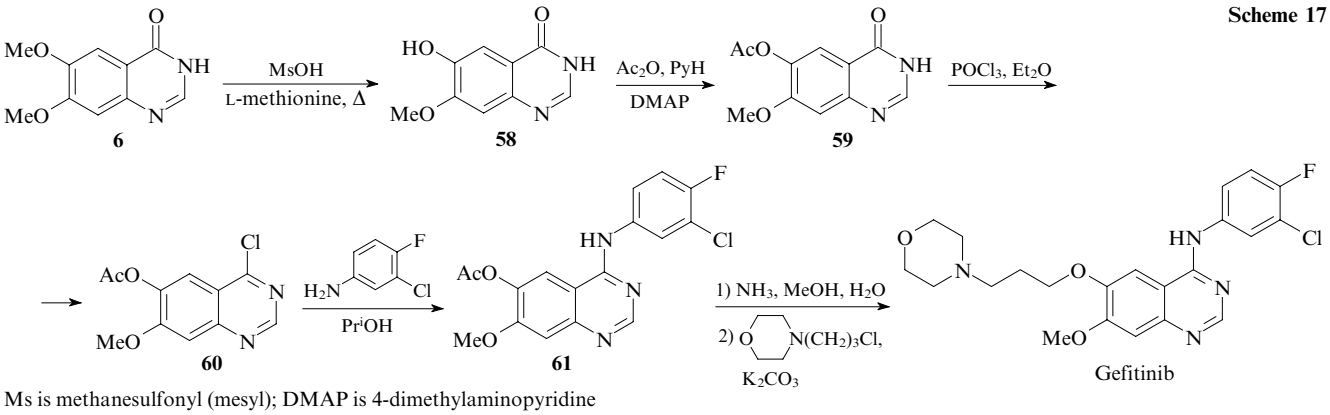
Improved synthetic schemes were also developed for gefitinib and tandutinib. The precursor was quinazolinone **6**, where, after the demethylating stage, the hydroxy group

Scheme 16



(*a*) 3-HC≡$CC_6H_4NH_2$, PyH, Pr^iOH; PyH is pyridine

Scheme 17

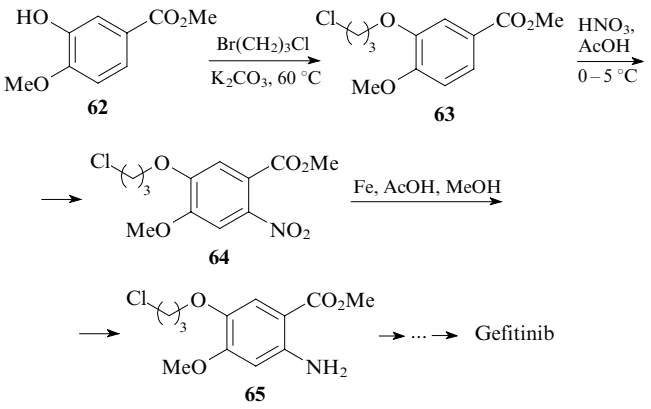


Ms is methanesulfonyl (mesyl); DMAP is 4-dimethylaminopyridine

in compound **58** was acylated by acetic anhydride (Scheme 17).[45, 80] The gefitinib synthesis process was improved at the step of chlorinating compounds **59** to chloride **60** and at the next step where aminoquinazoline **61** was produced, so the total gefitinib yield increased from 20% to 33%.

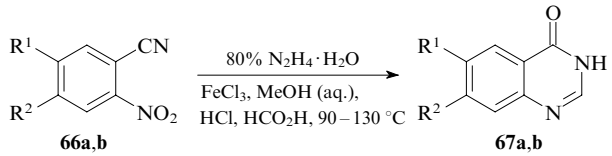
The drawbacks of Gibson's method [81] are high costs of quinazolinone **6** and low yields of product **58** (46%) at the regioselective demethylation step. These drawbacks were eliminated by Li *et al.*,[82] who used 3-hydroxy-4-methoxymethyl benzoate (**62**) as the precursor. As a result of alkylation of benzoate **62**, nitration of derivative **63** and reduction of compounds **64**, key intermediate **65** was formed in 77% yield (Scheme 18). Cyclization of intermediate **65**, chlorination and consecutive substitution of amine moieties for chlorine atoms gave rise to gefitinib. This scheme has fewer steps, yields a lower cost product due to the use of a lower cost precursor, and provides higher yields at all steps compared to the earlier employed strategies.

Scheme 18



Chandregowda *et al.*[83] described a new one-pot, highly efficient and economical process for the preparation of key intermediates in gefitinib and erlotinib syntheses, which can be commercialized to large-scale production. The process comprises the reductive formylation of 2-nitrobenzonitriles **66a**,**b** followed by *in situ* cyclization under mild conditions; the yields of quinazolin-4(3*H*)-ones **67a**,**b** are 86% and 81% (Scheme 19).

Scheme 19



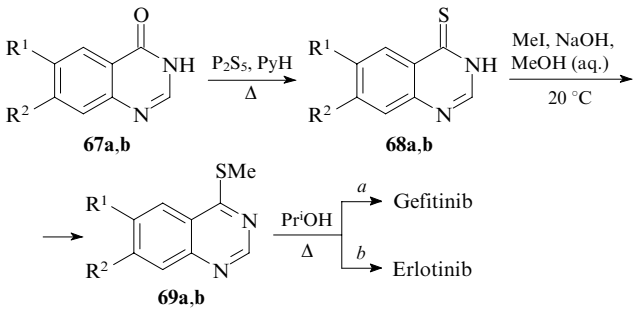
$R^1 = O(CH_2)_3[N(CH_2CH_2)_2O]$-cyclo, R^2 = OMe (**a**);
$R^1 = R^2 = O(CH_2)_2OMe$ (**b**)

The precursor benzonitriles **66a**,**b** are formed from the respective commercially available substituted aldehydes in high yields.

The same researchers altered the next step of gefitinib and erlotinib syntheses to exclude the use of chloro derivatives.[84] They prepared first thiones **68a**,**b** and then 4-methylsulfanyl derivatives **69a**,**b**, which are more stable than 4-chloroquinazolines (Scheme 20).

This scheme was used to prepare gefitinib from compound **67a** in 64% yield and erlotinib from its analogue **67b** in 73% yield; both products after recrystallization were 99% pure.

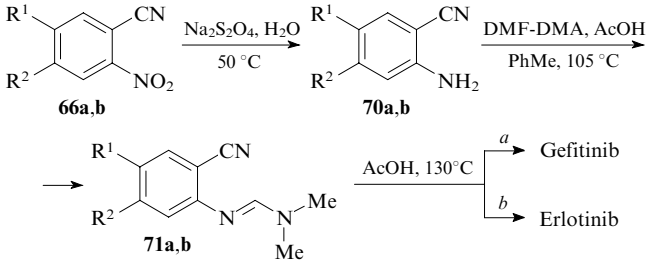
Scheme 20



$R^1 = O(CH_2)_3[N(CH_2CH_2)_2O]$-cyclo, R^2 = OMe (**a**); $R^1 = R^2 = O(CH_2)_2OMe$ (**b**); (*a*) 3-Cl-4-$FC_6H_3NH_2$, (*b*) 3-$HC{\equiv}CC_6H_4NH_2$

Chandregowda *et al.*[85] also described another approach to large-scale gefitinib and erlotinib syntheses. In order to reduce the number of steps and, accordingly, expenditures, the researchers claimed a one-pot synthesis of 4-anilinoquinazolines by reaction of formamidine derivatives with substituted anilines through Dimroth rearrangement. The nitro group in compounds **66a**,**b** was reduced by sodium dithionite in aqueous solution; aminobenzonitriles **70a**,**b** were treated with dimethylformamide dimethylacetal in toluene (Scheme 21). Formamidines **71a**,**b** as synthesized (without purification) were mixed with AcOH and the appropriate substituted aniline, and the mixture was heated at 130 °C. Gefitinib and erlotinib were obtained after recrystallization in 70% yield (based on compound **70**) and >99.5% and >99% pure, respectively.

Scheme 21



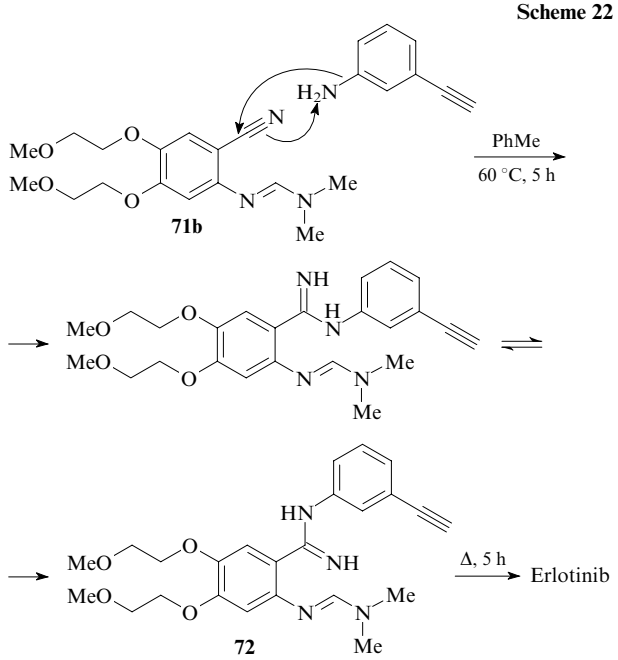
$R^1 = O(CH_2)_3[N(CH_2CH_2)_2O]$-cyclo, R^2 = OMe (**a**); $R^1 = R^2 = O(CH_2)_2OMe$ (**b**); (*a*) 3-Cl-4-$FC_6H_3NH_2$, (*b*) 3-$HC{\equiv}CC_6H_4NH_2$

An improved version of this strategy, exemplified by erlotinib synthesis, has been reported.[86] The authors described the protocatechuic acid conversion sequence comprised of eight steps, with a total product yield of 60%. The last two steps were carried out in a one-pot variant. 2-Aminobenzonitrile **70b** was treated with DMF–DMA in toluene and acetic acid to produce formamidine **71b**, the excess of reagent was removed, and 3-ethynylaniline and acetic acid were added. The reaction mixture was kept at 60 °C for 5 h, then the temperature was increased and refluxing was continued for another 5 h; erlotinib yield (based on compound **70b**) was 90%.

Asgari *et al.*[86] also monitored the reaction between formamidine **71b** and 3-ethynylaniline first at room temperature and then at 125 °C. Only one intermediate (phenyl-

benzamidine **72**) was identified, isolated and characterized by NMR spectroscopy, IR spectroscopy and chromatography/mass spectrometry (Scheme 22). Refluxing of compounds **72** in acetic acid or in a toluene and acetic acid mixture resulted in erlotinib, so the authors inferred that the cyclization of formamidine **71** to a quinazoline derivative involves the formation of phenylbenzamidine **72** and not the Dimroth rearrangement.

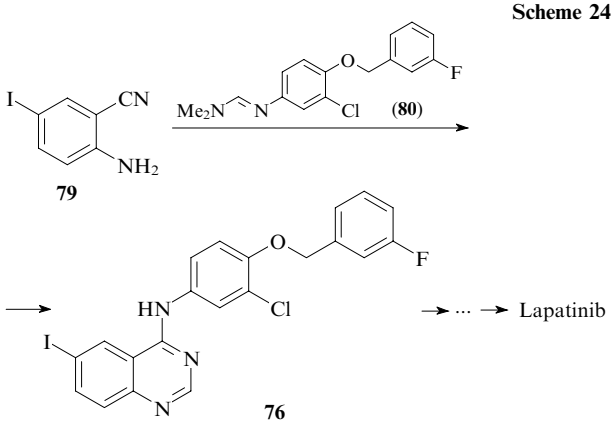
Scheme 22



There are several methods to prepare lapatinib where the precursor is 6-iodoquinazolin-4-one **73**.[87–90] For example, the chlorination of 6-iodoquinazolin-4-one and the substitution of the chlorine atom in compound **74** induced by aniline **75** gives rise to arylaminoquinazoline **76** (Scheme 23). The step of cross-coupling of iodide **76** with furanylboronic acids **77a**,**b** to form products **78** is palladium-catalyzed and contaminates the desired product with metal.

The drawbacks of this approach are the involvement of many steps, use of corrosive chemicals such as $POCl_3$ and $SOCl_2$, and low lapatinib yields (60% at the last step).

Scheme 24

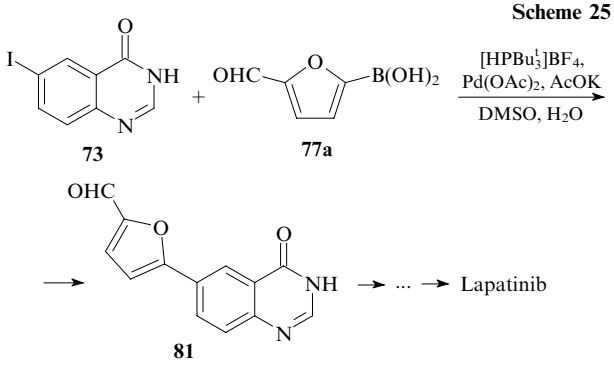


Subsequent patents[89,90] pertain to the purification and production of various salt forms of lapatinib.

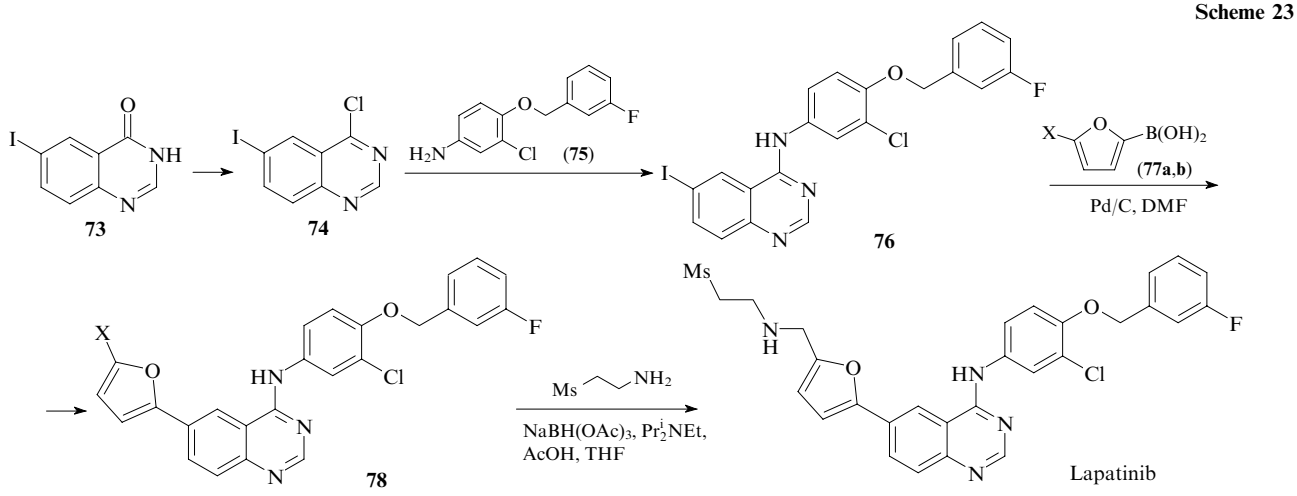
One more method for preparing lapatinib[91] uses cheaper materials and has no chlorination step. Intermediate **76** is prepared by the cyclocondensation of 2-amino-5-iodobenzonitrile (**79**) with imine **80**, which is prepared from compound **75** and dimethylformamide dimethylacetal (Scheme 24). This method is relatively facile and economical; lapatinib yield is 75% at the last step (purity is 90%; after the ultimate purification, 99.9%).

A process is described where the cross-coupling of commercially available compounds **73** and **77a** occurs in water–organic solutions in the presence of a base and a catalyst prepared from palladium acetate and a phospho-

Scheme 25

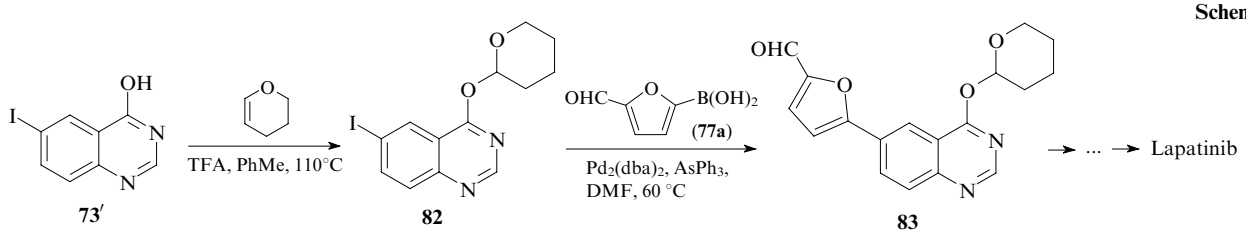


Scheme 23



77: X = CHO (**a**), $CH(OCH_2)_2$ (**b**)

Scheme 26



dba is dibenzylideneacetone

rus-containing ligand (Scheme 25).[88] Once the reaction is over, the inorganic salts and the catalyst are separated by filtration and centrifugation and compound **81** is recrystallized. The process requires only a catalytic amount of the phosphine ligand and palladium salt, which makes it possible to scale-up this reaction and then use compound **81** to produce lapatinib in 80% yield at the final step and 99.4% pure.

A similar strategy was patented.[92] The only difference consists in that the cross-coupling is preceded by protecting the hydroxy group of the tautomer of compound **73**, 6-iodoquinazolin-4-ol (**73′**), involving 3,4-dihydro-2*H*-pyran (Scheme 26). This results in new intermediates **82** and **83** for use in the preparation of lapatinib, which have high solubility in common organic solvents and make it possible to carry out subsequent reactions in highly concentrated solutions. The yield of lapatinib base at the last step is 96%; the ditosylate prepared from the lapatinib is 90.1% pure.

IV. Synthesis of new antitumour 4-amino-quinazoline derivatives

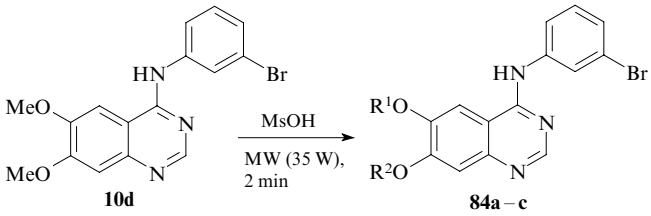
IV.1. First-generation tyrosine kinase inhibitors

New 4-arylaminoquinazoline derivatives can be prepared by introducing and modifying substituents in the quinazoline ring.

IV.1.a. Modifying alkoxy groups in the positions 6 and 7 of the quinazoline ring

Most research into the synthesis of new 4-arylaminoquinazoline derivatives involves varying substituents in the positions 6 and 7 of the heterocycle, particularly alkoxy groups. For example, an efficient method for the demethylation of 4-arylaminoquinazoline **10d** was developed (Scheme 27).[93]

Scheme 27



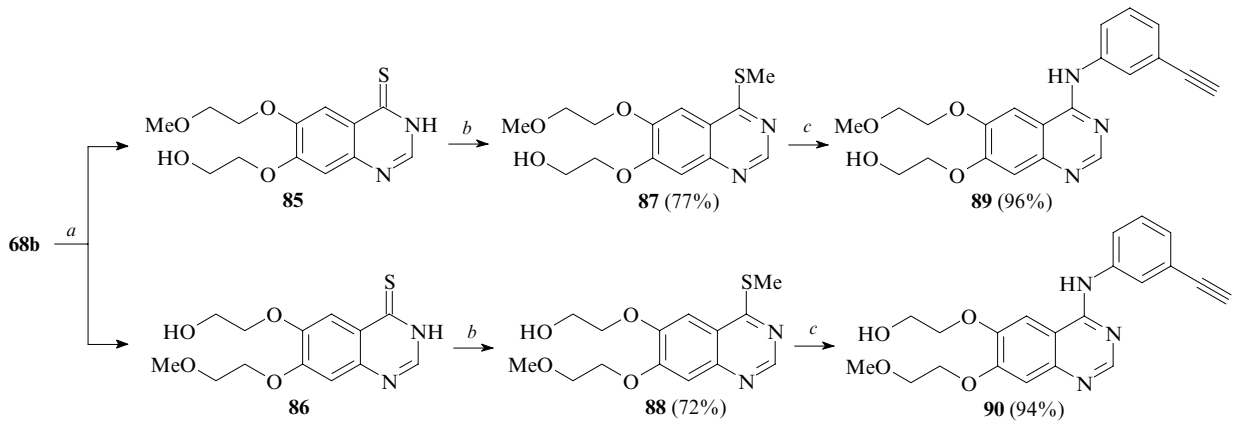
84: R^1 = H: R^2 = H (**a**), Me (**b**); R^1 = Me, R^2 = H (**c**)

A rapid conversion of quinazoline **10d** to demethylated compounds **84a – c** in high yields (> 82%) was achieved upon methanesulfonic acid treatment under microwave exposure. This method is of special interest for subsequent synthesis of ^{11}C-labelled alkoxy derivatives.

Two active erlotinib metabolites were prepared avoiding 4-chloroquinazolines.[94] Refluxing of quinazoline-4-thione **68a** with 38% HBr solution in isopropanol for 12 h resulted in a mixture of 7- and 6-hydroxy derivatives **85** and **86**, which were separated by column chromatography (Scheme 28). The subsequent methylation at the S atom and the replacement of methylsulfanyl group in compounds **87** and **88** by the action of 3-ethynylaniline yielded erlotinib metabolites **89** and **90** with purity better than 97.5%. The antitumour activity of these products was studied to show that they are more active than erlotinib against some types of tumours.

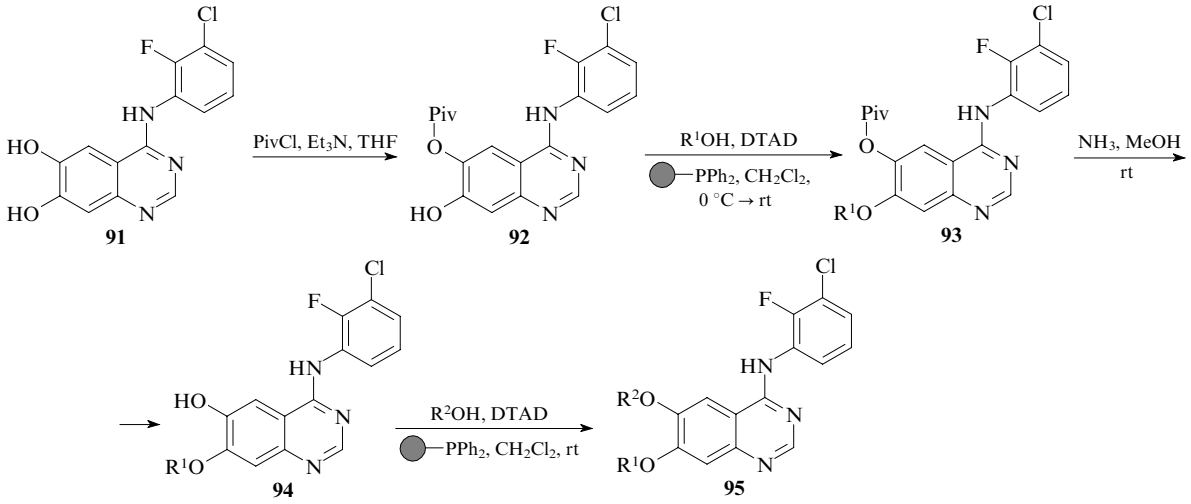
The introduction of various alkoxy groups into the quinoline system was addressed in many studies (see, *e.g.*,

Scheme 28



(*a*) 38% HBr, Pr^{i}OH, Δ, 12 h; (*b*) MeI, NaOH, MeOH (aq.), 20 °C; (*c*) 3-HC≡CC$_6$H$_4$NH$_2$, Pr^{i}OH, Δ

Scheme 29



91 **92** **93** **94** **95**

R^1, R^2 = Alk; Piv = C(O)Bu^t

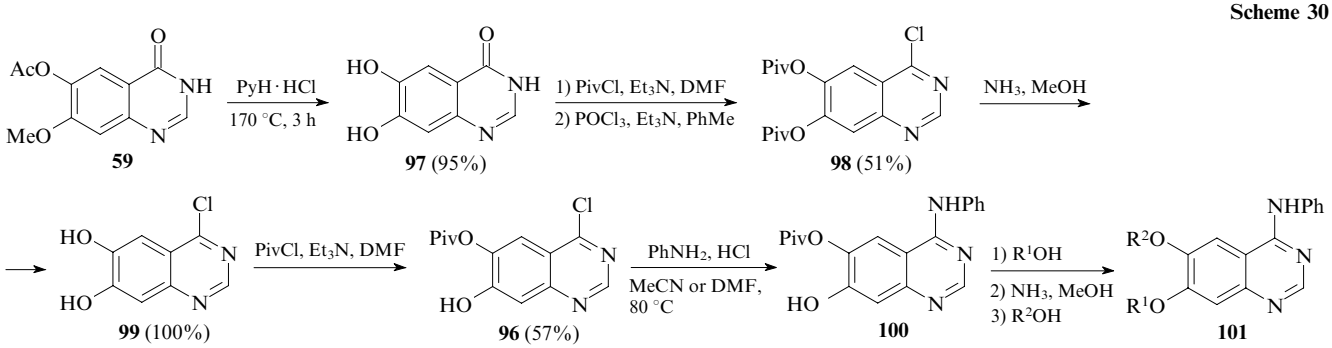
Ref. 95) and was successfully fulfilled by selectively alkylating 6,7-dihydroxy-4-arylaminoquinazoline **91** under Mitsunobu conditions.[96] Using the different acidities of phenol groups in compounds **91** (pK_a is 7.6 for 7-OH and 10.02 for 6-OH), the authors acylated the compound with pivaloyl chloride and isolated one regioisomer **92** (Scheme 29). This regioisomer was alkylated by an alcohol (R^1OH) in the presence of a polymer-bound triphenylphosphine, di-*tert*-butylazadicarboxylate (DTAD) in dichloromethane at 0 °C, followed by warming to room temperature. The deprotection of intermediate **93** and the alkylation of its 6-hydroxy derivative **94** with an alcohol (R^2OH) under the above-described conditions yielded desired dialkoxyarylaminoquinazolines **95** in 44% – 78% yields. This method served to prepare a large library of 6,7-dialkoxy-4-anilinoquinazolines.

Later, the same authors described a four-step method suitable for changing substituents in the quinazoline core of compounds **96**.[97] As the precursor, they used 6-acetoxy-7-methoxyquinazolone **59**, whose deprotection resulted in dihydroxy derivative **97** (Scheme 30). The subsequent protection of OH groups by the pivaloyl group and chlorination yielded chloroquinazoline **98**. The deprotection was followed by the regioselective acylation of compounds **99**. Thus, Harris *et al.*[97] obtained key intermediate **96** and then, by substituting the chlorine atom in the intermediate under the action of aniline followed by alkylation of compounds **100** under Mitsunobu conditions (see Scheme 29), they prepared a large series of gefitinib analogues **101** with alkoxy substituents in the positions 6 and 7.

The functionalization of alkoxy substituents in the position 6 or 7 of anilinoquinazolines is well documented. The 6-hydroxy group of compound **102a** was modified to prepare a series of gefitinib analogues **103** and **104** (Scheme 31).[98] A wide range of derivatives **103** was synthesized in two ways, *via* direct alkylation by ω-bromoalkylamines (see Scheme 31) or by introduction of a bromoalkyl (with dibromoethane or dibromopropane) followed by the substitution of the second bromine atom. In order to prepare 2-hydroxypropyl-containing compounds **104**, first an oxirane moiety was introduced into molecule **102a**, and then the three-membered ring in compound **105** was opened by an amine. Biological studies (*in vitro* and *in vivo*) showed that these 6-(aminoalkoxy) derivatives **103** and **104** are inhibitors of EGFR-TKs from carcinoma A431 cells.

Hennequin *et al.*[99] used 7-hydroxy derivative **106** to prepare a set of 4-anilinoquinazolines **107** and **108**, which contain an aminoalkoxy group in the position 7 (Scheme 32). Compounds **106** were made to react with amino alcohols under Mitsunobu conditions. Reactions with N-protected piperidines occur under similar conditions; subsequent removal of *tert*-butoxycarbonyl (Boc) protection yields compounds **108.** Enzymatic activity or tumour growth inhibition studies of compounds **107** and **108** showed that derivative **107** {R^1 = Br, R^2 = cyclo-[MeN$(CH_2CH_2)_2$CH]CH_2} has the highest activity.

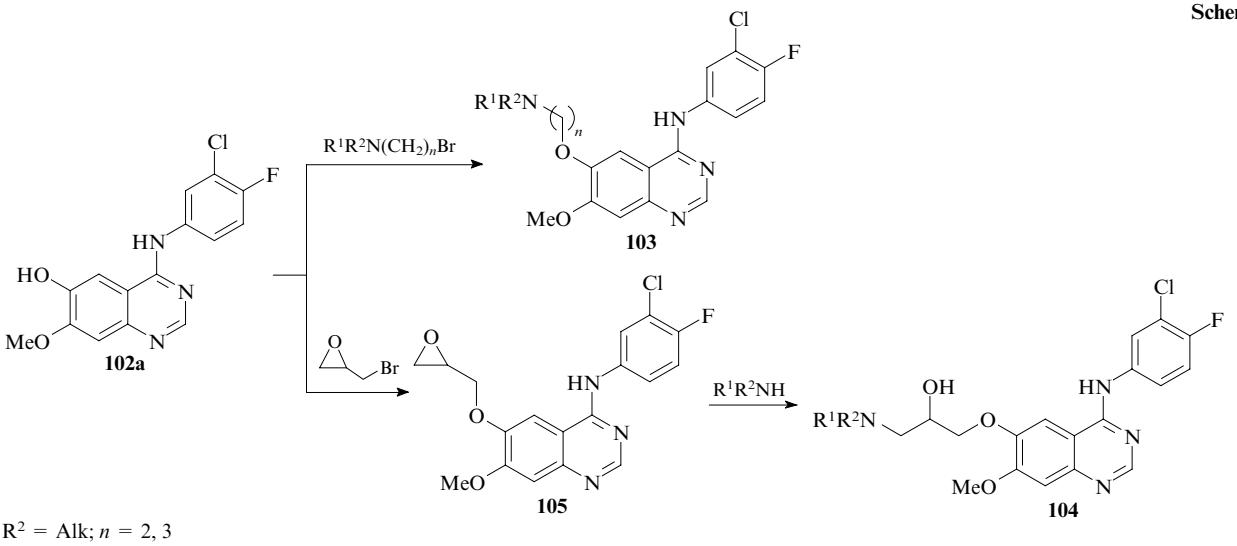
Scheme 30



59 **97** (95%) **98** (51%) **99** (100%) **96** (57%) **100** **101**

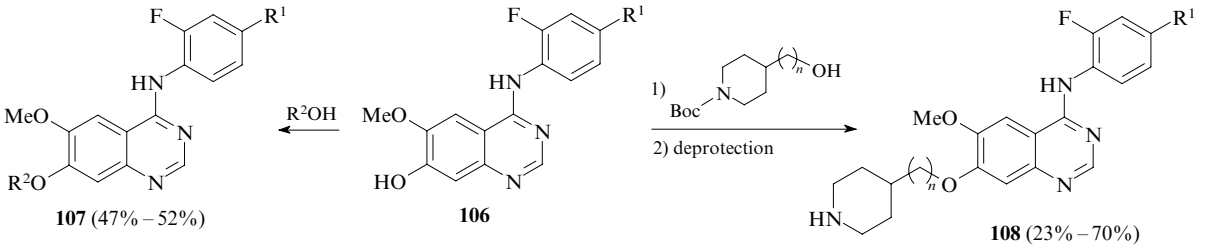
R^1, R^2 = Alk

Scheme 31



R^1, R^2 = Alk; n = 2, 3

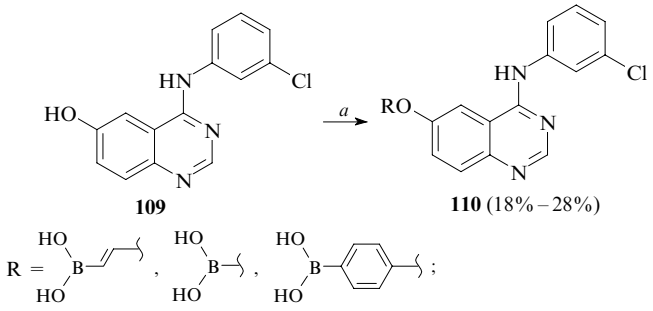
Scheme 32



R^1 = Br, Cl, Me, NC; R^2 = $Alk_2N(CH_2)_n$, *etc.*; n = 1, 2

The incorporation of boronic acid moieties into 6-hydroxyanilinoquinazoline **109** offered a way to create long-acting selective EGFR-tyrosine kinase receptor inhibitors (Scheme 33). Compounds **110** are presumably capable of binding a boron atom to the thiol group of Cys797 or the carboxy group of Asp800, in addition to hydrogen bonding.[100]

Scheme 33



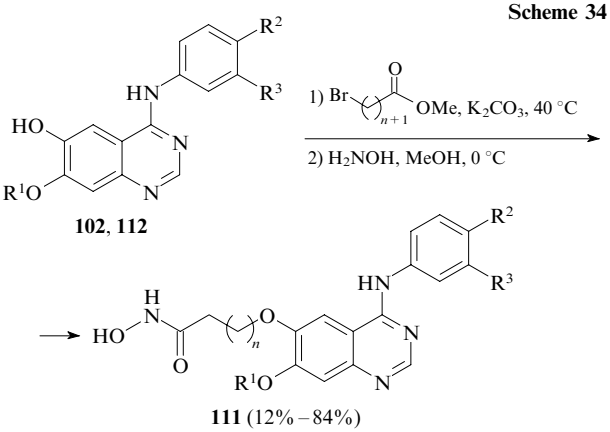
(*a*) 1) NaH, DMF; 2) RH; 3) KHF_2, MeOH, H_2O

New aminoquinazoline derivatives **111** were prepared, where 6-alkoxy groups contain hydroxamic acid moieties [well-known histone deacetylase (HDAC) inhibitors].[101] 6-Hydroxy derivatives **102** (R^3 = Cl) and **112** (R^3 = HC≡C) were alkylated by esters of ω-bromoalkylcarboxylic acids of various chain lengths; subsequent treatment with hydroxylamine yielded desired products **111** (Scheme 34).

Noteworthy, the yield of derivatives **111** depended on the oligomethylene chain length and the nature of substituents in the arylamine moiety.

These compounds were proven to be multiactive HDAC and tyrosine kinase (EGF receptor and HER2) inhibitors. Derivative **111** (n = 5, R^1 = Me, R^2 = H and R^3 = HC≡C) had the highest activity *in vivo* (exceeding erlotinib and lapatinib activities) and *in vivo*. The replacement of the oxygen atom in the 6-alkoxy group by another moiety (in compounds **113**) or introduction of hydroxamic acid moieties in the quinazoline position 7 and the replacement of N-phenyl by benzyl in the position 4 bring about a decline in inhibitory activity.

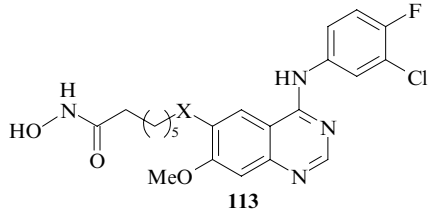
Scheme 34



n = 1 – 5; R^1 = Me, Et; R^2 = H, F; R^3 = Cl (**102**), HC≡C (**112**)

The ethynyl and allene moieties in the alkoxy group in the position 6 of anilinoquinazolines (compounds **114** and **115**) appreciably enhance EGFR-TK inhibitory activity.[102]

Structures 113



113

X = NHC(O), S, SO_2

Derivatives **114** were prepared from 4-anilino-6-hydroxyquinazolines **102** and haloalkylacetylenes in the presence of K_2CO_3 (Scheme 35). These compounds were converted to allene derivatives **115** when treated with paraformaldehyde and diisopropylamine in the presence of 2 equiv. CuBr in dioxane at 110 °C. Compounds **114** and **115** having long side chains (n = 3 – 6) showed long-acting inhibitory activity against tyrosine kinase EGF receptors.

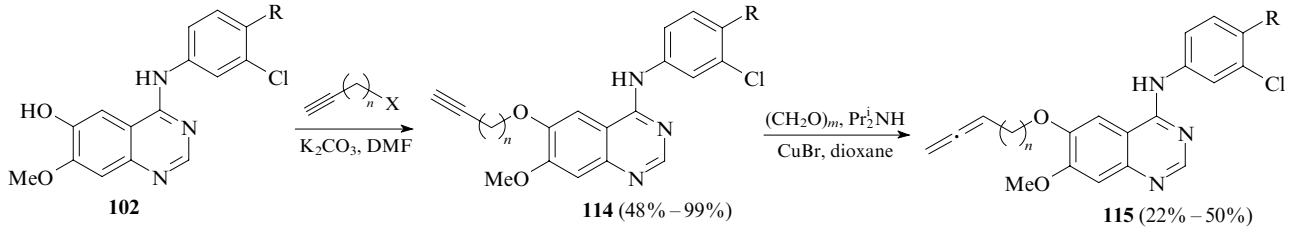
Pham *et al.*[103] used 4-anilino-7-hydroxyquinazoline **116** to prepare 7-propargyloxy derivative **117** and its analogue **118** with an oligoester chain (Scheme 36). The treatment of compounds **116** with propargyl bromide in the presence of K_2CO_3 affords product **117**, and its Mitsunobu reaction with alcohol **119** yields 7-(*ω*-*O*-propargyltetraethylene glycol) derivative **118**.

The coupling of dithiocarbamic acid moieties and 4-anilinoquinazolines was accomplished in the synthesis of compounds **120** (Scheme 37).[104] Chloro derivatives **121** were prepared from disubstituted benzoic acids **122a**,**b**. In biological studies, some representatives of compounds **120** were more active, than lapatinib, against three tumour cell lines.

Zhao *et al.*[105] described the synthesis of gefitinib analogues that contained azaspirocycle or azetidine moieties (Scheme 38). The substitution of an iodine atom for the chlorine atom in the alkyl chain of compounds **123**, followed by the alkylation of aza heterocycles, produced desired anilinoquinazolines **124a** – **g** in 14% – 82% yields, the yield depending on the amine. The EGF receptor inhibition activity and antitumour activity of these compounds were studied in two lung cancer cell lines to show that derivatives **124a**,**b**,**g** approached gefitinib in their activities; compound **124g** had the best solubility in water.

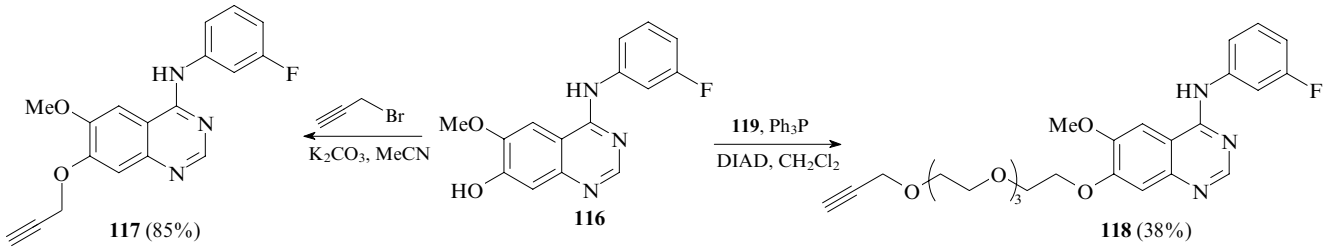
In continuation of studies by Ballard *et al.*[106] into the preparation of gefitinib analogues, Barlaam *et al.*[107] prepared new derivatives **125** – **127**, which differed from one another in the nature of the heterocyclic moiety in the side chain. EGF, HER2 and HER3 receptor inhibition values

Scheme 35



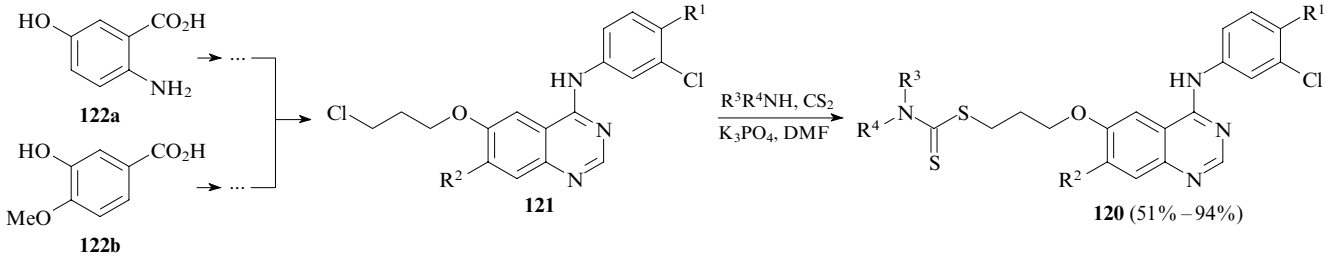
X = Br, I, Cl; R = H, F; n = 1 – 6

Scheme 36



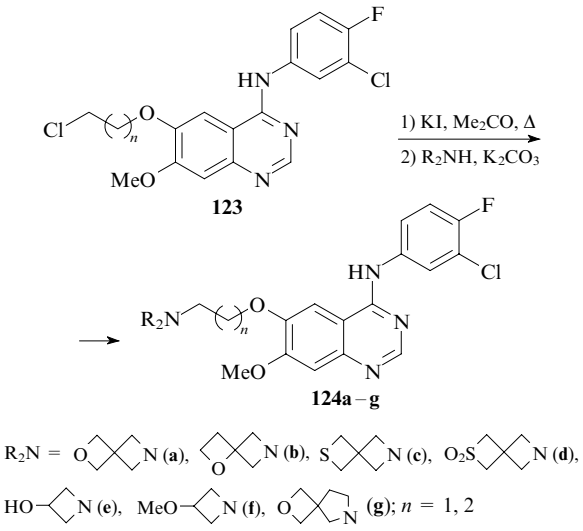
119 = $HC{\equiv}CCH_2O(CH_2CH_2O)_4H$; DIAD is diisopropylazodicarboxylate

Scheme 37



R^1 = H, F, 3-$FC_6H_4CH_2O$; R^2 = H, MeO; R^3R^4NH is piperazine, methylpiperazine, morpholine, thiomorpholine

Scheme 38



for these compounds were reported. Derivative **125b**, which contains a piperidineacetamide substituent, is the most active equipotential reversible inhibitor for those receptors and has good pharmacokinetic characteristics. Phase II clinical trials are now underway for this compound. The authors considered structure – activity correlations in the series of derivatives **125** using molecular modelling. The model comprised a piperidineacetamide substituent in three conformations (**A**, **B** and **C** in Fig. 4 *a*), but only one of them (conformation **B**), an analogue of the conformation observed by X-ray diffraction in the structure of compounds **125b** (Fig. 4 *b*), could explain the high activity of the compound.

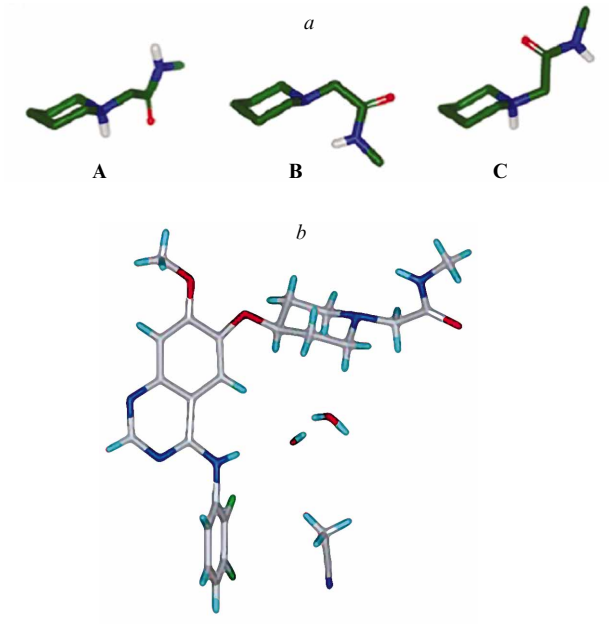
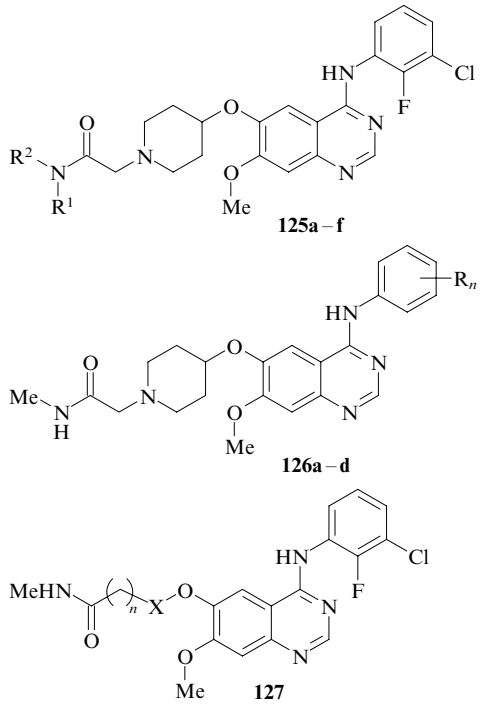


Figure 4. Three possible conformations of the piperidineacetamide moiety in compounds **125** (*a*) and the structure of molecule **125b** (in the form of a dihydrate and an acetonitrile solvate) in a crystal (*b*).[107]

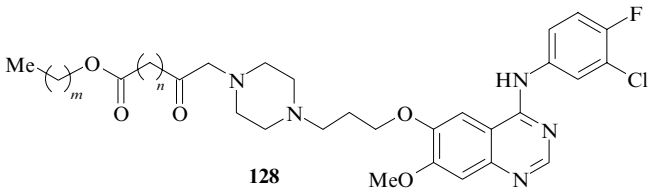
Yin *et al.*[108] prepared a series of new gefitinib analogues, compounds **128**, where the morpholine moiety was replaced by N-substituted piperazine groups having different numbers of methylene units in the spacer between two C(O) functions. Most of these compounds showed quite high activities against some tumour types, specifically lung carcinoma A-549.

Structures 125 – 127



125: NR^1R^2 = NH_2 (**a**), NHMe (**b**), NHEt (**c**), $NH(CH_2)_2OMe$ (**d**), $NHPr^i$ (**e**), NMe_2 (**f**); **126**: R_n = 3-Cl-4-F (**a**), 2-F-3-Cl-4-F (b), 3-Cl (**c**), 2-F-5-Cl (**d**); **127**: X is piperidine-1,4-diyl, piperidine-1,3-diyl, pirrolidine-1,3-diyl, azetidine-1,3-diyl; n = 1, 2

Structures 128

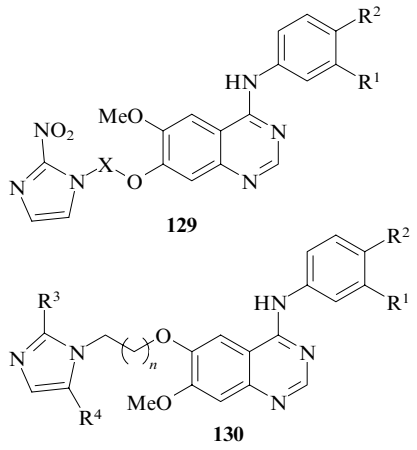


n = 3 – 7, m = 0; n = 2, m = 1 – 19

It is known that hypoxia is responsible for the radiation and chemotherapy resistance of most solid tumours, which poses a serious problem in the treatment of cancer.[109] New 4-anilinoquinazoline derivatives **129** were regarded to be potential EGFR inhibitors under normoxia and hypoxia. These compounds were prepared by introducting the 2-nitroimidazole moiety into 7-alkoxyquinazoline.[110] Compound **129** [X = $(CH_2)_5$, R^1 = HC≡C, R^2 = H] showed the highest potential; it had high inhibitory activity and noticeably inhibited A549 and HT-29 cell proliferation with submicromolar half-inhibition concentrations (IC_{50}) under normoxia and hypoxia; these values are several times lower than those for gefitinib or erlotinib.

In the next study, Cheng *et al.*[111] expanded the range of nitroimidazoles and introduced them into the 6-alkoxy substituent (compounds **130**). Most of the prepared com-

Structures 129, 130



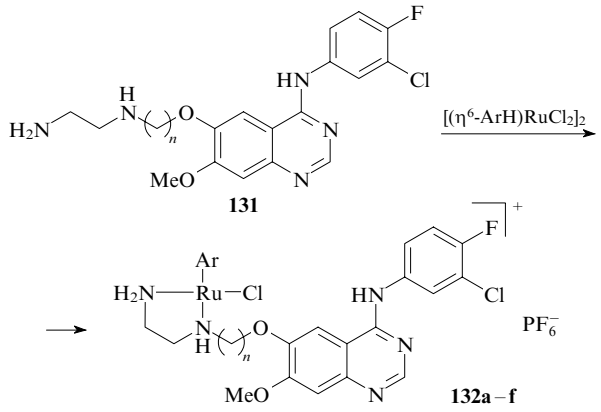
129

130

129: X = $(CH_2)_n$ (n = 3–6), $(CH_2)_2O(CH_2)_2$; R^1 = Cl, Br, HC≡C; R^2 = H, F, 3-$FC_6H_4CH_2O$;
130: n = 1–5; R^1 = Cl, Br, HC≡C; R^2 = H, F, 3-$FC_6H_4CH_2O$; R^3 = O_2N, Me; R^4 = H, O_2N

pounds had EGFR inhibitory activities comparable to that of gefitinib, and a moderate or high antiproliferative activity against HT-29 cells under normoxia and hypoxia. Derivative **130** (n = 3, R^1 = Cl, R^2 = F, R^3 = NO_2, R^4 = H) showed the highest activity; it was chosen to be studied further as an anticancer drug candidate. The results of trials imply that the introduction of an active moiety to an EGFR inhibitor would be helpful to overcome tumour hypoxia.

Scheme 39



131

132a–f

132: n = 2: Ar is phenyl (**a**), *p*-cymol (**b**), biphenyl (**c**); n = 3: Ar is phenyl (**d**), *p*-cymol (**e**), biphenyl (**f**)

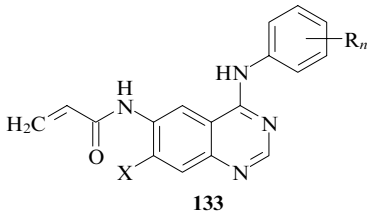
The generation of new hydrogen bonds enhances EGFR-TK inhibition provided that the ethylenediamine moiety exists in the 6-alkoxy substituent (compounds **131**).[112] Derivatives **132a–f** were prepared in 13%–36% yields by reacting anilinoquinazolines **131** with an aryl-containing dimeric ruthenium complex (Scheme 39). The structure of compounds **132b** was verified by X-ray diffraction.[113]

Compounds **132**, while holding the cytotoxicity of the organoruthenium complex, have a higher EGFR-TK inhibitory activity of anilinoquinazoline and a stronger ability to accelerate tumour cell apoptosis, specifically at early stages. The most valuable properties are observed for derivative **132d**, which exceeds, in activity, gefitinib and the complex $[(\eta^6\text{-}p\text{-cym})Ru(en)Cl]PF_6$ [*p*-cym stands for 4-isopropyltoluene (*p*-cymene) and en is ethylenediamine].

IV.1.b. Introduction of amide groups in the position 6 of the quinazoline ring

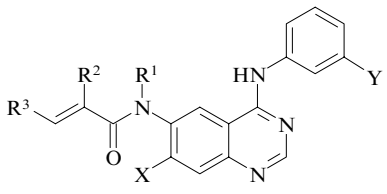
The synthesis and characterization of 4-anilinoquinazolines that bear amide groups in the position 6 of the heterocycle are well documented.[114–124]

Structures 133, 134



133

R_n = 3-Br, 3-Cl, 3-Me, 3-CF_3, 3-Br-4-F, 3-Cl-4-F, 4-OPh, 4-OBn, 4-CH_2NMe_2; X = H, OAlk, $O(CH_2)_3[N(CH_2CH_2)_2O]$-cyclo

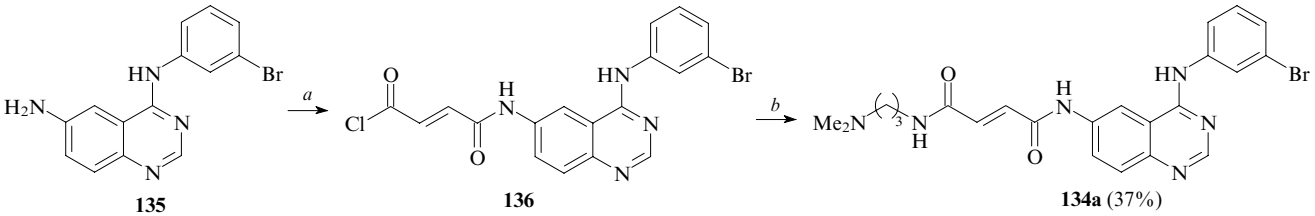


134

Y = Br, Cl; R^1 = H, $(CH_2)_3[N(CH_2CH_2)_2O]$-cyclo; R^2 = H, Me; R^3 = H, Me, CF_3, CH=CH_2, Ac, $CO_2(CH_2)_3NMe_2$, $C(O)NH(CH_2)_3NMe_2$, Ar

Series of anilinoquinazolines **133** and **134** were prepared with acrylamide and crotonamide moieties.[114,116,125–130] Scheme 40 illustrates the general synthetic strategy for these derivatives exemplified by quinazoline **134a**.[116] The initial compound used was 6-amino-4-[(3-bromophenyl)-amino]quinazoline (**135**), whose acylation with fumaryl

Scheme 40



135 **136** **134a** (37%)

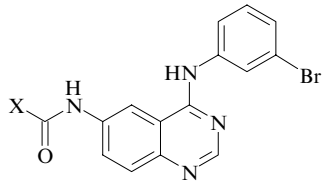
(*a*) ClC(O)CH=CHC(O)Cl, THF; (*b*) $Me_2N(CH_2)_3NH_2$, THF

chloride and subsequent substitution of the second chlorine atom under the action of *N*,*N*-dimethylpropane-1,3-diamine, without isolating intermediate **136**, leads to amido derivative **134a**.

According to biological studies, compounds **133** and **134** are irreversible EGFR-TK inhibitors; they show a considerable tumour growth reduction. It was studied how substituents in the quinazoline ring impact solubility in water and inhibitory activity. An ester or amide side chain in the position 3 of the acrylamide moiety in compounds **134** considerably increased solubility. The derivatives containing a morpholine moiety showed the highest inhibitory activity.

A group of compounds **137a**,**b** with a wide range of amide substituents in the quinazoline position 6 were prepared.[53, 131] The inhibitory activity of these compounds against EGFR and HER2 kinase autophosphorylation was studied to show that, along with improved water solubilities, the compounds had enhanced antitumour activities. Derivative **137b** (R = NMe_2) showed the highest activity.

Structures 137



137a,**b**

X = C≡CCH_2R (**137a**), CH=$CHCH_2$R (**137b**) (R = NMe_2, NEt_2, NPr^n_2, $NMePr^i$, NPr^i_2, NMeAll, cyclo-[$N(CH_2)_5$], cyclo-[$N(CH_2CH_2)_2O$], cyclo-[$N(CH_2CH_2)_2S$], cyclo-[$N(CH_2CH_2)_2NEt$], OMe, $O(CH_2)_2OMe$, OH)

Subsequently, Klutchko *et al.*[132] tested compounds **133** and **137a**,**b** as irreversible tyrosine kinase inhibitors, namely as ErbB1, ErbB2 and ErbB4 receptor inhibitors: their activities against ErbB1 receptors were about ten times those against ErbB2 and ErbB4.

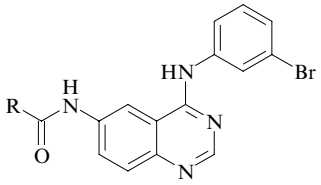
Studies of anilinoquinazolines **133**, **134** and **137** with amide groups and their analogues showed that they inhibited EGFR tyrosine kinases by irreversibly modifying the cysteine moiety (Cys773 in HER1 and Cys805 in HER2).[116, 133] This distinguishes these compounds from erlotinib and gefitinib, whose activity is due to modifying the Thr790 moiety, and moreover, the mutation T790M was observed to give rise to drug resistance. This observation attracted the attention of those skilled in the art; an approach was developed to overcome drug resistance due to the use of irreversible inhibitors like **133** and **137b**.[48] Compound **133** {X = $O(CH_2)_3[N(CH_2CH_2)_2O]$-cyclo; R_n = 3-Cl-4-F, development name: CI-1033} showed high activity and was selected for further clinical trials.[116]

Compounds **138**, where the amide group contains the 1,2-dithiolane ring of lipoic acid or its lower homologues, were proposed as multiactive anilinoquinazoline derivatives.[47] EGFR-TK inhibition studies did not show a considerable alteration of activity compared to amido-substituted derivatives **133**.

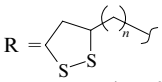
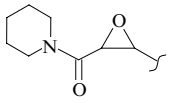
The introduction of anilinoquinazoline epoxyamide group (as three enantiomers: 2*R*,3*R*, 2*S*,3*S*, 2*R*,3*S*) or phenoxyacetamide group into the position 6 provided one more family of new EGFR inhibitors, which chemically modified the cysteine moiety (compounds **139** and **140**).[134] (2*R*,3*S*)-*N*-[4-(3-Bromoanilino)quinazolin-6-yl]-3-(piperidin-1-ylmethyl)-oxirane-2-carboxamide (**139**) inhibited EGFR autophosphorylation and induced apoptosis in gefitinib-resistant NCSLCH1975 cells at far lower concentrations than gefitinib did.

A series of new acryloylamido anilinoquinazoline derivatives **141a**–**c** were prepared, where the linker (X) and substituents in the position 7 and in the aniline moiety were varied.[135] The linkers used were azetidine, pyrrolidine or piperidine substituted at various positions. Compounds **141a**–**c** were trialed as HER-1/HER-2 inhibitors against two tumour cell lines: A-431 and SK-Br3. Derivatives where R_n^1 = 2-F or 2,4-F_2, R^2 = $O(CH_2)_2OMe$ and X = (*S*)-pyrrolidine-1,2-diyl showed excellent EGFR-TK inhibitory activities against T790M mutation, high selectivity and good pharmacokinetic profiles. Compounds **141a**–**c** were recommended for the treatment of solid tumours.

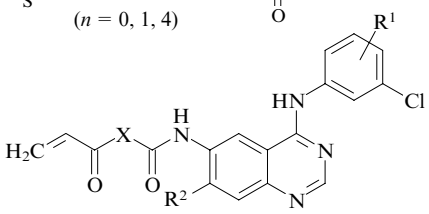
Structures 138 – 141



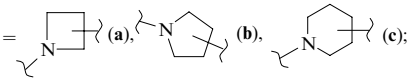
138–**140**

R =  (**138**),  (**139**), $ArOCH_2$ (**140**)

(*n* = 0, 1, 4)



141a–**c**

141: X =  (**a**), (**b**), (**c**);

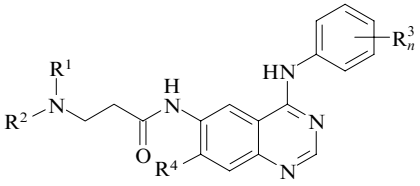
R^1 = 4-OCH_2Py, 2-F, 4-F, 2,4-F_2, 2-F-4-Br, 2-F-4-Cl;

R^2 = H, OMe, $O(CH_2)_2OMe$; isomers: 1,2 and 1,3 (for **141a**–**c**), 1,4 (for **141c**)

The acrylamide moiety of aminoquinazolines efficiently alkylates Cys797 in EGFR-TK, but its reactivity can cause metabolic deactivation or nonspecific reactions. There are some publications where this moiety was replaced by another.[136–138] Carmi *et al.*[136] prepared 4-anilinoquinazolines **142**, which contain 3-aminopropanimide group in the position 6. Some of these compounds, just as their acrylamide analogues, were efficient in inhibiting EGFR autophosphorylation in lung cancer cells A549. Moreover, these compounds inhibited the proliferation of gefitinib-resistant cells H1975 in low concentrations.

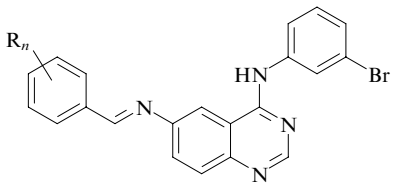
Later, the same researchers[139] studied the long-term effects (1 and 8 h after the inhibitor was removed from the culture medium) of both irreversible inhibitors **142** and reversible inhibitors, specifically gefitinib. They showed that the observed effect arose not only from the covalent interaction of the inhibitor with Cys797, but also from the

Structures 142 – 149



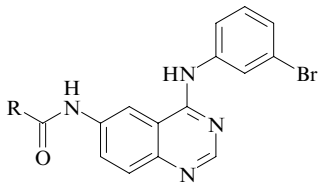
142

NR^1R^2 = NMe_2, cyclo-[$N(CH_2CH_2)_2O$], cyclo-[$N(CH_2CH_2)_2NMe$]; R^3_n = 3-Br, 3-Cl-4-F; R^4 = H, OEt



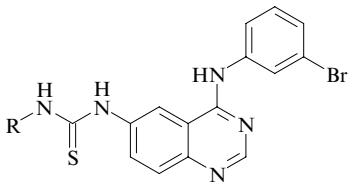
143

R_n = 4-OH, 2,4-$(OH)_2$, 3-NO_2, 4-NO_2, 2-OMe



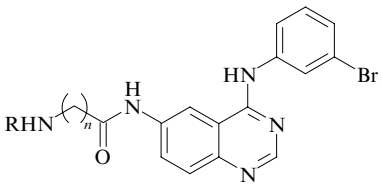
144

R = 4-$H_2NC_6H_4$, 4-NCC_6H_4, 4-$AcNHC_6H_4$, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,5-$(O_2N)_2C_6H_3$



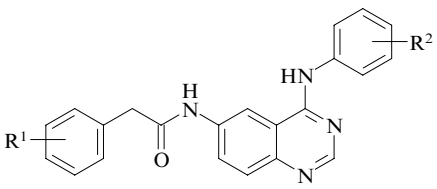
145

R = Bn, $(CH_2)_2[N(CH_2CH_2)_2O]$-cyclo



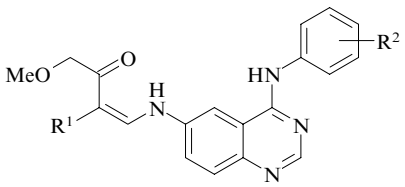
146

R = Bn, $(CH_2)_2[N(CH_2CH_2)_2O]$-cyclo, 4-(thiazol-2-ylsulfamoyl)phenyl; n = 1, 2



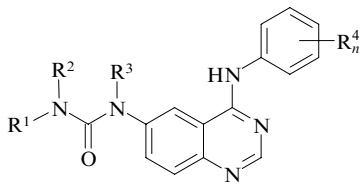
147

R^1 = H, 2-Br, 2-F, 2-Cl, 2-OMe, 2-NO_2, 3-Br, 3-Cl, 3-F, 4-Me; R^2 = H, 4-Br, 4-F, 5-OMe



148

R^1 = CO_2Et, CN; R^2 = 2-Cl, 2-Et, 3-Br, 3-OH, 3-C≡CH, 4-Cl, 4-OH



149

R^1 = H, $N(CH_2CH_2Cl)_2$, CH_2CH_2Cl; R^2 = H, N═O; R^3 = H, Me; R^4_n = 3-OH, 3-OMe, 3-Cl, 3-F, 3-Br, 4-Cl, 4-F, 4-Br, 2-F-3-Cl, 3-Cl-4-F, 3-Br-4-F

intracellular accumulation of noncovalent inhibitors through their active uptake by cells.

Hamed *et al.*[140] described a new group of anilinoquinazolines **143** – **146** where aryl or heterocyclic substituents are linked to the quinazoline through linkers such as imine, amide or thiourea moieties. Most of these compounds showed good inhibitory activities against EGFR-TK. Thiourea derivative **145** and amides **146** [R is 4-(thiazol-2-ylsulfamoyl)phenyl; n = 2] retained a considerable activity against clinical mutants $EGFR^{T790M/L858R}$, and compound **145** (R = Bn) was 24 times as active as gefitinib and retained high activity against gefitinib-resistant cells H1975.

4-Anilinoquinazoline derivatives **147**, which contain substituted phenylacetic acid amide moieties in the position 6, showed themselves as inhibitors of c-Src (a member of the Src tyrosine kinases family) in five tumour cell lines.[141] Most of them showed selectivity between cell line A549 and the other four lines, and compound **147** (R^1 = 3-Br, R^2 = 4-Br) had the highest cytotoxicity against all tested lines.

A set of new 4-anilinoquinazoline derivatives **148** and **149**, which contain enamine ester and urea moieties, is described.[142 – 145] Almost all of those compounds showed EGFR-TK inhibitory activity; six of them were trialed at the US National Cancer Institute (NCI) on 60 lines of nine tumour types. Compounds **149** where R^4_n = 4-Cl were most active against some non-small cell lung cancer, kidney cancer and brain cancer cell lines. Derivative **149** (R^1 = CH_2CH_2Cl, R^2 = N═O, R^3 = Me and R^4_n = 4-Cl), which combines nitrosourea and anilinoquinazoline moieties, inhibits both EGFR and ErbB2, and is considered to be a drug candidate for further research.

Introducing a mustard group into compounds **149** [R^1 = $N(CH_2CH_2Cl)_2$] enhanced antitumour activity; those compounds showed a 54% – 75% inhibition of breast carcinoma tumours MX-1 and prostate tumour PC-3 in animals (a xenographic model) with low toxicity.[144]

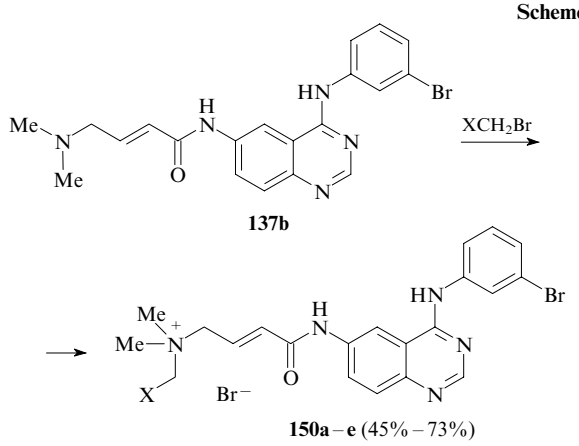
IV.2. Second-generation EGFR-tyrosine kinase inhibitors

IV.2.a. 4-Aminoquinazolines having amide groups in the position 6

An efficient route was developed to design prodrugs that would be efficient under hypoxia in order to improve the tumour selectivity in irreversible pan-ErbB multikinase inhibitors.[126, 146] This route comprises the quaternization of an aliphatic amine in the side chain of aminoquinazoline by known bioreductive bromomethylnitrohetaryl moieties. Using anilinoquinazoline derivative **137b** as the initial compound, Lu *et al.*[146] quaternized it in THF at room temperature to obtain ammonium salts **150a** – **e** (Scheme 41). The screening of these compounds in the presence of oxygen and in anoxic conditions showed that salt **150d** (SN 29966) exhibited the highest activity.[147] This salt was the first irreversible pan-ErbB inhibitor selective under hypoxia that had a noticeable activity against cell line A431 (in mice) and cell SKOV3 (in xenographic model). The effect of salt **150d** is due to its ability to undergo one-electron

reduction at a potential in the range of selective reduction of cellular reductases, efficient under hypoxia.

Scheme 41



150: X = 2-$O_2NC_6H_4$ (**a**), 4-$O_2NC_6H_4$ (**b**), 5-nitropyrrol-2-yl (**c**), 4-nitroimidazol-5-yl (**d**), 1-methyl-4-nitropyrazol-5-yl (**e**)

By the results of biological testing of anilinoquinazolines having amide groups in the position 6, afatinib, dacomitinib and canertinib [136, 148] (Fig. 5) were selected for preclinical and clinical trials. All of these drugs are second-generation irreversible EGFR inhibitors.

Afatinib, unlike erlotinib and gefitinib, covalently binds all members of the ErbB tyrosine kinase family, irreversibly inhibits their activities and, likely, blocks both partners in the ErbB receptor dimer; afatinib has a higher antitumour activity compared to the agents targeted at EGFR solely. In phase III clinical trials for the treatment of non-small cell lung cancer (NSCLC) and breast cancer, afatinib showed advantages over other signal transduction inhibitors. In 2013, afatinib was approved for the treatment of patients having EGFR-positive NSCLC.[149 – 153]

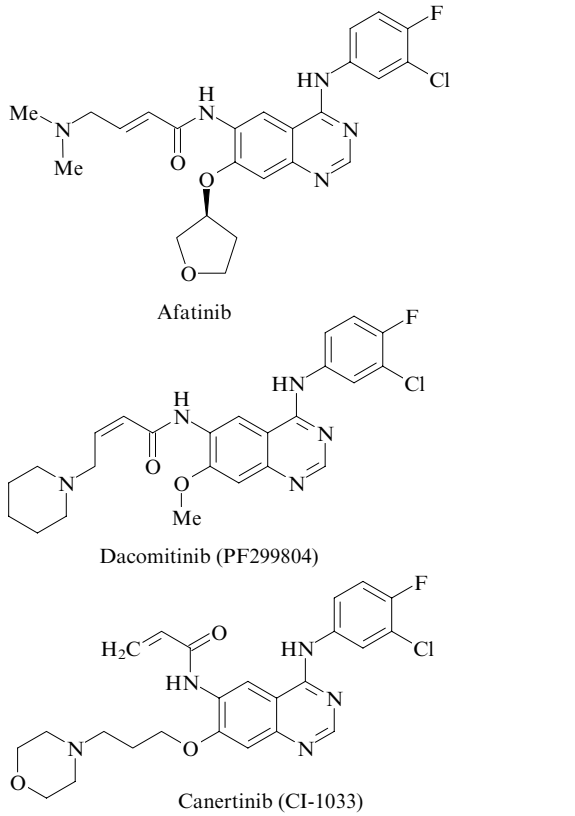
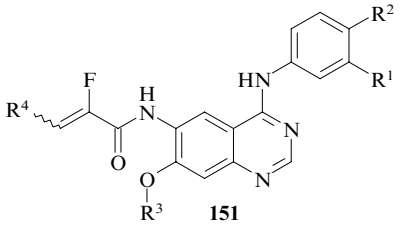


Figure 5. Structures of second-generation aminoquinazoline-based irreversible EGFR-tyrosine kinase inhibitors.

Dacomitinib (PF299804) is a selective and irreversible inhibitor for human epidermal growth factor (HER) tyrosine kinase receptors; phase III cancer therapy clinical trials for it are now underway.[40]

However, these irreversible inhibitors can bind not only to target protein, so they are highly toxic. In order to reduce the risk of nonspecific covalent binding, Xia *et al.*[154] modified the afatinib structure by introducing a fluoro-substituted alkene moiety into the molecule (compounds **151**). The kinase-inhibitory and antiproliferative activity studies of these derivatives showed that they had high safety and improved pharmacokinetic properties. Compound **151** (*Z*-isomer; R^1 = Cl; R^2 = F; R^3 is tetrahydrofuran-3-yl and R^4 = NMe_2) was most efficient: it efficiently inhibited $EGFR^{WT}$, $EGFR^{T790M}$ and A431 and H1975 tumour cells. Since this pharmaceutical is more active and less toxic than afatinib, it seems promising for the treatment of NSCLC in drug-resistant patients.

Structures 151

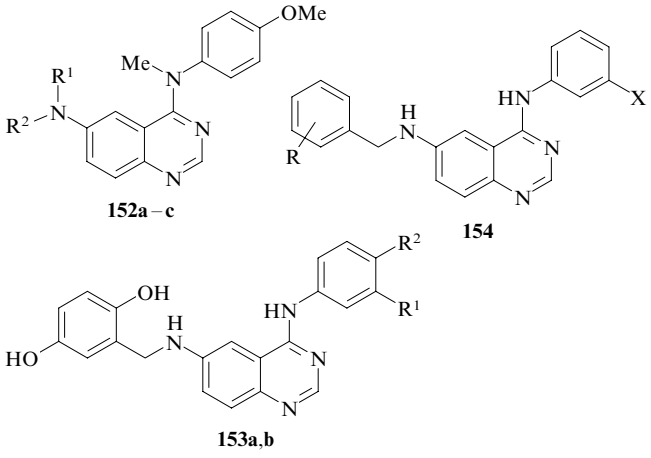


R^1 = Cl, Br; R^2 = H, F, 3-$FC_6H_4CH_2O$, cyclo-$C_3H_5CH_2O$, 2-methylpyridin-5-yloxy; R^3 = Me, Et, tetrahydrofuran-3-yl; R^4 = NMe_2, cyclo-[$N(CH_2CH_2)_2O$], cyclo-[$N(CH_2)_5$]

IV.2.b. Introducing amino groups in the position 6 or 7 of the quinazoline ring

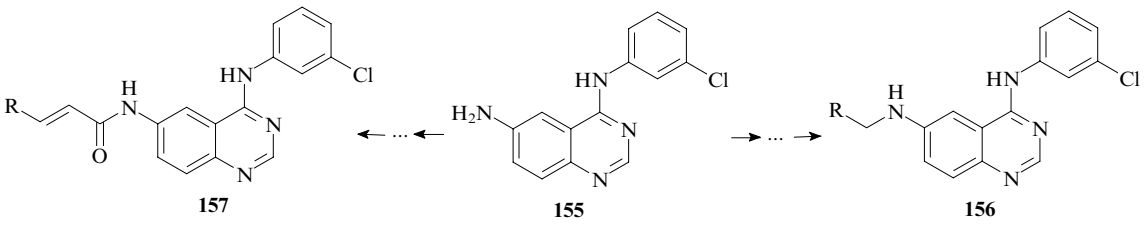
6-Amino derivatives of 4-anilinoquinazolines **152** – **154** were prepared and characterized as potential EGFR inhibitors

Structures 152 – 154



152: R^1 = R^2 = H (**a**), Me (**b**); R^1 = H, R^2 = Ac (**c**); **153**: R^1 = Br, R^2 = H (**a**); R^1 = Cl, R^2 = F (**b**); **154**: X = Br, Cl; R = 2-OH, 2-OMe, 2-Br, 2-Cl, 4-OH, 4-OMe, 4-Br, 4-Cl, 4-F

Scheme 42



157 **155** **156**

156, **157**: R = Bu^n, $(CH_2)_3SMe$, 3-Py, 6-bromopyridin-2-yl, 2-chloropyridin-2-yl, 6-methylpyridin-2-yl, quinazolin-2-yl, thiophen-2-yl, 5-bromothiophen-2-yl, 1*H*-indol-2-yl

by several research teams.[125, 155 – 159] Compounds **152a**,**c** showed relatively high activities in the apoptosis of lung cancer cell lines H1299 and T47D.[156]

4-Anilinoquinazolines **153**, which bear a 2,5-dihydroxybenzylamine moiety in the position 6, were active EGFR inhibitors and could inhibit cell growth in several types of tumours (leukemia, lung cancer, kidney cancer, ovarian cancer and brain cancer).[155] Albuschat *et al.*[155] noticed the ability of these compounds to be solvated by various solvent molecules, which was proved for compounds **153a** by X-ray diffraction.

A large group of 6-benzylamino 4-anilinoquinazoline derivatives **154** is described.[158] Those compounds had good antiproliferative activities and EGFR-TK inhibitory activities; compound **154** (X = Br, R = 4-OH) was most efficient.

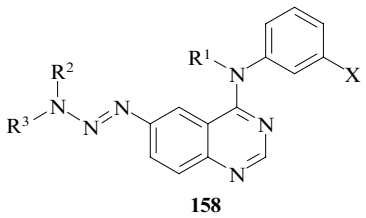
6-Amino-4-anilinoquinazoline **155** was used to prepare two series of derivatives, namely compounds **156** and **157** (Scheme 42), which appeared active EGFR-TK inhibitors and had a noticeable antiproliferative action to efficiently induce the apoptosis of A549 cells.[125]

IV.3. Compounds having a combination activity

There is a set of studies into the synthesis and characterization of combination molecules that contain a 4-anilinoquinazoline moiety and a triazene moiety.[160 – 167] Not only can those compounds inhibit EGFR-mediated signal transduction, but they also can release another EGFR-TK inhibitor and a cytotoxic DNA-alkylating agent upon hydrolysis under physiological conditions. 4-Anilinoquinazolines **158** with a mono- or dialkyltriazene moiety in the position 6 were prepared to elucidate the role of each pharmacophoric component.[161] These compounds were tested for EGFR-TK inhibition and antiproliferative activity. Those studies showed that each component of a combination molecule plays a very important role in the manifestation of antitumour activity. However, monoalkyltriazene derivatives **158** (R^2 = H) appeared to be insufficiently stable.

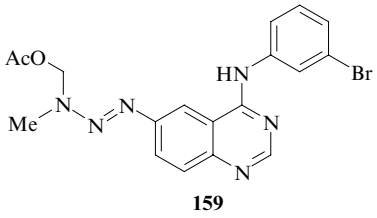
In order to improve the stability and EGFR-inhibitory activity of this series, Banerjee *et al.* prepared compound **159**, where the acetoxymethyltriazene group readily converts under hydrolytic conditions first to a hydroxymethyltriazene moiety and then to a monomethyltriazene moiety (the consecutive release strategy).[162] The half-life of quina-

Structures 158 – 163

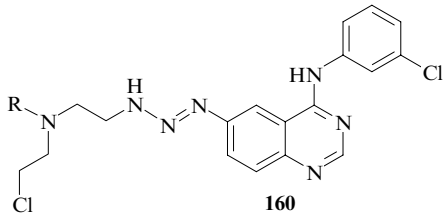


158

R^1, R^2 = H, Me; R^3 = Me, Bn, $(CH_2)_2OMe$, CH_2Py-2, $(CH_2)_2[N(CH_2CH_2)_2O]$-cyclo; X = H, Br, Cl, Me

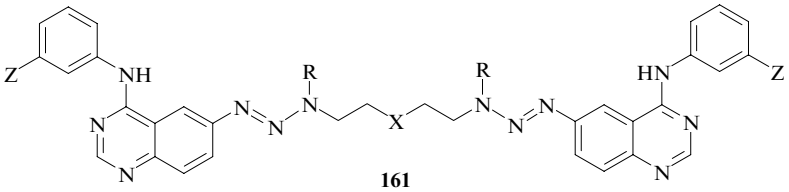


159



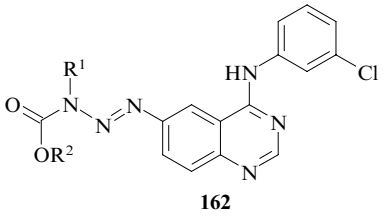
160

R = Me, Bn, 4-$MeOC_6H_4$, 4-ClC_6H_4



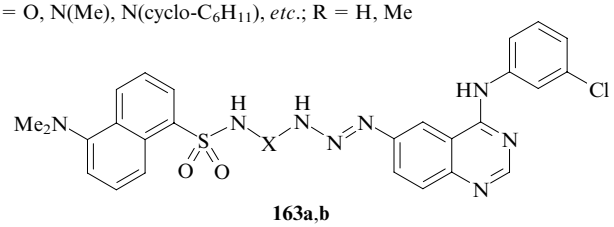
161

Z = Cl, Br, H, Me; X = O, N(Me), N(cyclo-C_6H_{11}), *etc.*; R = H, Me



162

R^1 = Me, $(CH_2)_2NMe_2$; R^2 = CH=CH_2, CH_2Cl, CH_2OAc, $C_6H_4NO_2$-4



163a,**b**

X = $(CH_2)_2$ (**a**), $(CH_2)_2N(Me)(CH_2)_2$ (**b**)

zoline **159** is 42 min; it was recommended for use as a prodrug to serve as a multiplet EGFR inhibitor and a methyldiazonium precursor.

Triazene – quinazoline combination molecules **160**, which can release an EGFR inhibitor and a bifunctional alkylator (alkylating agent), showed an increase in EGFR inhibitory activity as the basicity of the mustard moiety increased.[165] They selectively killed transfected EGFRs and were active against prostate cancer DU145. Derivative **160** (R = Me) irreversibly blocked EGFR phosphorylation and induced DNA cross-coupling.

A set of combination molecules **161** having antitumour activity were patented, where the bifunctional alkylator is linked to two anilinoquinazoline moieties.[164] Under physiological conditions, these compounds release two EGFR inhibitor molecules and a bifunctional alkylating agent.

Stable triazene-substituted combination molecules **162** have limited hydrolysis rates.[166] Importantly, the stability of compounds was attained without losing EGFR–DNA-targeting properties, for example, for compounds **162** (R^1 = Me, R^2 = Ac).

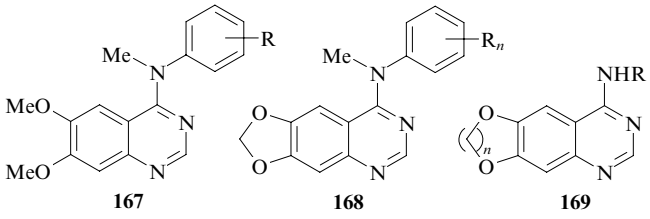
Larroque-Lombard *et al.*[167] described synthetic methods for triazenoquinazolines **163a**,**b**, which contain fluorescent labels and various spacers between the quinazoline moiety and the dansyl group. Compound **163b** having a long spacer is more stable and more cytotoxic than its analogue **163a**, and the antiproliferative effects of both are independent of the condition of P-glycoprotein of sarcoma cells MES-SA.

7-Amino-4-anilinoquinazolines **164**, potential EGFR inhibitors, were synthesized by aminating the quinazoline core (Scheme 43).[168] The initial compounds in that syntheses were 7-triflyloxy- (**165**) and 7-fluoroquinazolines (**166**). The reaction was performed in *N*-methylpyrrolidone at 135 °C with a fivefold excess of the amine for several hours. With triflates, the highest yields of **164** (44% – 85%) were with secondary amines, while for primary amines, yields were 10% – 14%. In the substitution of an amine moiety for the fluorine atom in compound **166**, the nature of amine had no noticeable effect on the yields of 7-amino derivative **164** (58% – 92%).

IV.3.a. Tricyclic aminoquinazoline derivatives

It was recently found that anilinoquinazoline and *N*-methylanilinoquinazoline moieties are candidate chemotypes for design of new DNA-targeted antitumour agents, where a decrease in conformational flexibility of a molecule by annelating the additional ring at the positions 6 and 7 provides for the specific conformation favourable for DNA intercalation.[169] Garofalo *et al.*[170] described a series of 4-anilino-6,7-dimethoxy- (**167**) and 6,7-methylenedioxyquinazolines (**168**) and studied their cytotoxic and intercalation activities. The anilinoquinazoline moiety was shown to be an efficient pharmacophore for DNA binding in the intercalation process.

Structures 167 – 169



167 **168** **169**

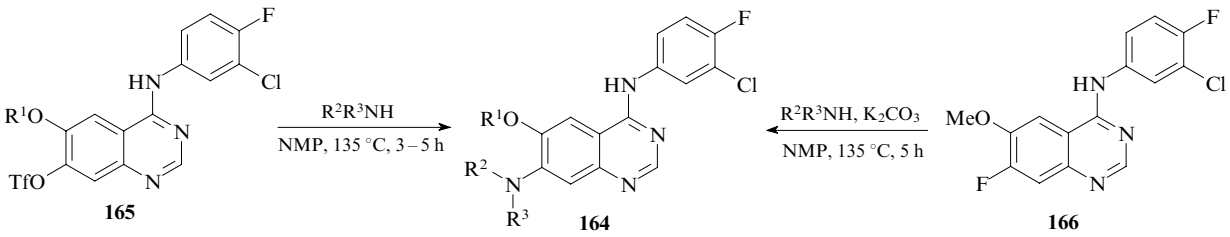
167: R = Cl, Br, F, Me, CF_3, NHC(O)NHAlk; isomers: *para*, *meta*; **168**: R_n = 3-Cl-4-F, 4-Br-2-F; **169**: R is Ar, 4-methyl-2-pyridyl, 6-methyl-2-pyridyl, biphenyl-3-yl; n = 1 – 3

Chilin *et al.*[171] and Conconi *et al.*[172] prepared derivatives **169** having rings of various sizes, each containing two oxygen atoms, and having (het)aryl substituents at the amino nitrogen atom in the position 4. The ring size is of extreme importance for biological activity: dioxane derivatives are most active in the context of antiproliferative properties. Compounds having dioxolane rings can inhibit tumour growth *in vivo*. Conconi *et al.*[172] showed that the biphenyl-3-ylamine moiety in the position 4 of quinazoline endows the compound with multityrosine kinase inhibitory activity. Specifically, derivative **169** (n = 2; R is biphenyl-3-yl) inhibits EGFR, EGFR-1, PDGFR*b*, Abl1 and Src kinase activity in submicromolar concentrations and is active against several types of tumours. Such compounds are considered to be tubulin polymerization inhibitors.[173]

Li *et al.*[174] introduced cyclic pyrocatechol ethers to the 6-amide (**170**, **171**) or 6-amino group (**172**) of quinazoline. Compounds **170** – **172** were studied as EGFR inhibitors; their cytotoxicity was studied against four tumour cell lines: A431, MCF-7, A549 and B16-F10. For most of them, the activity was commensurate to that of erlotinib; the size of the methylene linker between oxygen atoms was of importance in these derivatives: the most active compound was compound **172** (X = Br, n = 3).

A series of 4-anilinoquinazolines **173**, modified by crown ether moieties at the positions 6 and 7, is reported by Hu *et al.*[175] A sulfur or nitrogen atom can enter ring B, apart from oxygen atoms. A EGFR inhibitory activity study showed that the compounds having 12-membered ring B and bearing an X = Br, Cl or C≡CH substituent had most valuable properties. One such compound appeared to be selective toward Anl, Arg and other kinases, had a favourable pharmacokinetic profile in preclinical

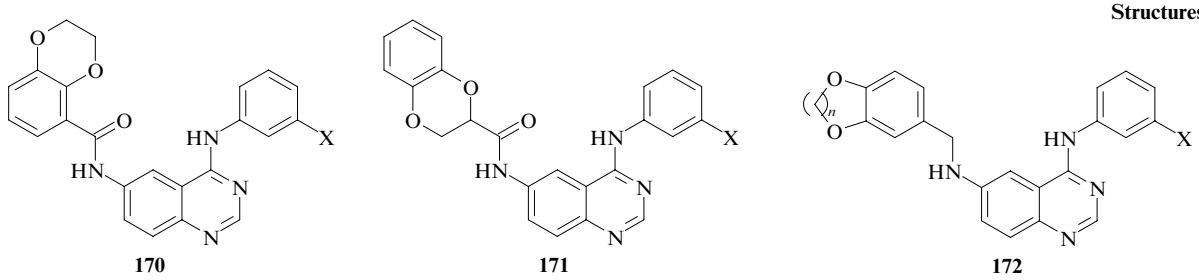
Scheme 43



165 **164** **166**

R^1 = Me, $(CH_2)_2[N(CH_2CH_2)_2O]$-cyclo; R^2, R^3 = H, Alk; Tf is trifluoromethylsulfonyl (triflyl)

Structures 170 – 172



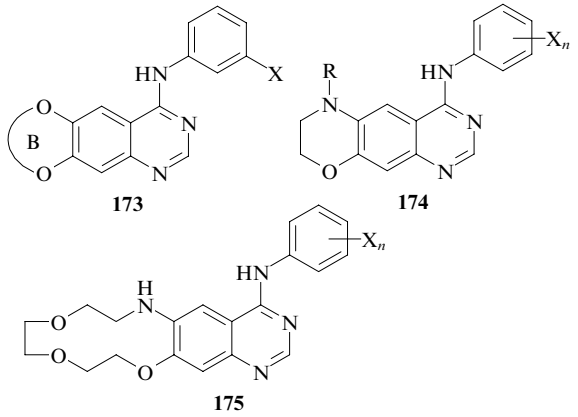
170 **171** **172**

X = Cl, Br; n = 1 – 4

trials and inhibited cell growth in a wide variety of solid tumours.

EGFR inhibitors **174** and **175** having restricted conformational flexibility were prepared.[176] They inhibited growth of both gefitinib-resistant cell lines (H1975) and gefitinib-responsive cell lines (A431), but were inefficient against EGFR-negative cells (A549, K562 and SW620). The substitution of an acryloyl group for the hydrogen atom in the morpholine moiety of derivatives **174** resulted in a fivefold gain in activity. The highest activity was observed in compound **174** [R = C(O)CH=CHCH$_2$NMe$_2$, X$_n$ = 4-F-3-Cl].

Structures 173 – 175



173 **174**

175

173: X = Br, Cl, C≡CH; B is (aza, thia)crown-ether moiety;
174: R = H, C(O)Et, C(O)CH=CHY (Y = H, Bn, CH$_2$NMe$_2$);
174, **175**: X$_n$ = Br, Cl, F, CF$_3$, *etc*.

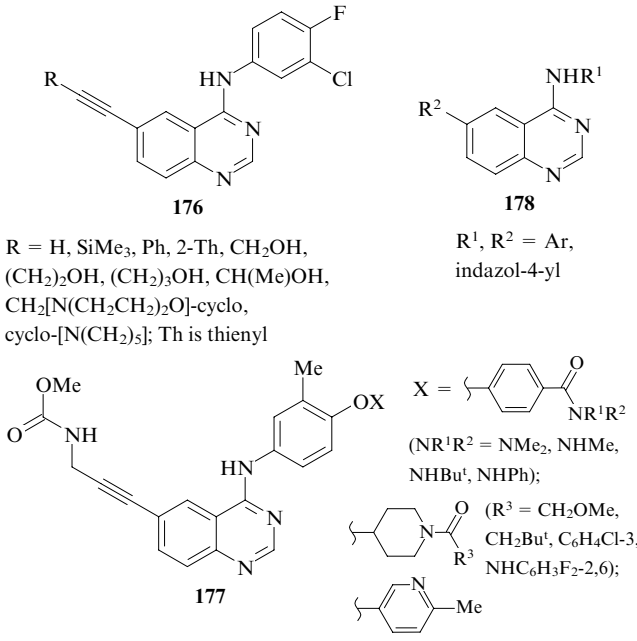
IV.3.b. Introducing alkyl, aryl or furanyl moieties into the position 6 of quinazoline

Another important way to modify the position 6 in 4-anilinoquinazolines is to introduce an alkynyl or aryl group to this position.[177 – 181] A series of 6-alkynyl-substituted anilinoquinazolines **176** was prepared by Sonogashira reaction from 6-brominated derivatives.[179] The *in vitro* EGFR inhibition activity tests of these compounds showed that derivative **176** (R = CH$_2$OH) was far superior to gefitinib.

The preparation of 6-alkynyl-substituted anilinoquinazolines **177** with pyridine, piperidine and benzamide substituents in the aniline moiety is described.[177, 180] These derivatives showed high selectivity as ErbB2(HER2) kinase inhibitors.

A large series of quinazolines **178**, which contain an aryl or indazole ring in the position 6 along with the aniline or aminoindazole moiety in the position 4, was patented.[181] Compounds **178** were tested *in vivo* for the inhibition of various protein kinases and for antiproliferative and antitumour activities.

Structures 176 – 178



176

R = H, SiMe$_3$, Ph, 2-Th, CH$_2$OH, (CH$_2$)$_2$OH, (CH$_2$)$_3$OH, CH(Me)OH, CH$_2$[N(CH$_2$CH$_2$)$_2$O]-cyclo, cyclo-[N(CH$_2$)$_5$]; Th is thienyl

178

R^1, R^2 = Ar, indazol-4-yl

177

X = C(O)NR^{1}R^2 (NR^{1}R^2 = NMe$_2$, NHMe, NHBu^t, NHPh);

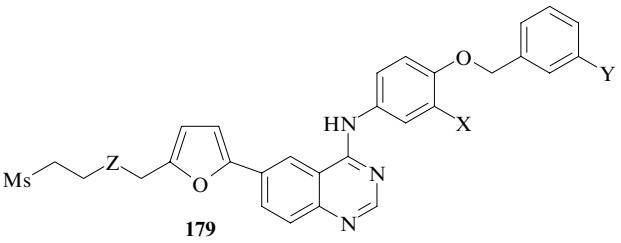
(R^3 = CH$_2$OMe, CH$_2$Bu^t, C$_6$H$_4$Cl-3, NHC$_6$H$_3$F$_2$-2,6);

There are studies directed to the preparation and characterization of 6-furanylquinazolines, which are analogues of lapatinib.[52, 182 – 188] Compounds of this type were capable of dual Erb-1/Erb-2 kinase inhibition owing to the bulky substituent in their aniline moiety. Petrov *et al*.[52] described a group of benzyloxyaniline 6-furanylquinazoline derivatives **179** with a variable substituent in the position 5 of the furan ring. Biological activity studies of compounds **179** showed that substituents in the furan ring only insignificantly affect inhibitory activity, but are of great importance for cellular selectivity. Compounds **179** with 4-(3-fluorobenzyloxy)-3-haloaniline moieties showed the best enzymatic and cellular selectivities. Derivative **179** with X = Cl, Y = F and Z = N[C(O)OCH$_2$OP(O)(OH)$_2$] was patented as a prodrug.[188]

Lapatinib analogue **180** with a branched side chain inhibits HER1/HER2 to a considerable extent, and shows *in vivo* activity commensurate to that of lapatinib and a good pharmacokinetic profile.[189]

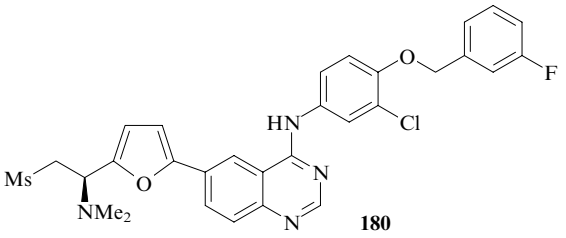
Hybrid analogues of lapatinib were synthesized where the furan ring contains moieties of known histone deacetylase inhibitors, in particular *N*-hydroxyacrylamide moiety (**181a – d**).[190, 191] Derivatives **181a**,**c** were most active; in biochemical tests they showed selectivity and ability to

Structures 179 – 182

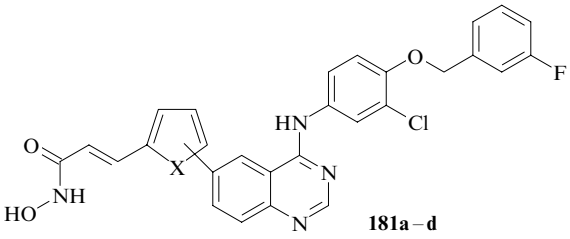


179

X = H, Cl, Br, OMe, CF_3; Y = H, F, Br, CF_3; Z = NH, N(Bn), $N(Pr^n)$, $NH(CH_2)_2$, $N(CH_2CN)$, $N[C(O)OCH_2OP(O)(OH)_2]$

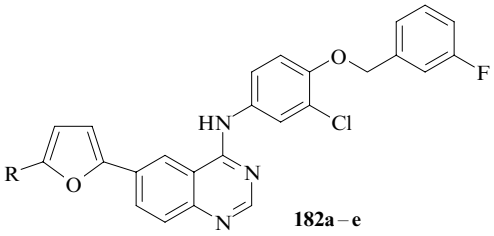


180



181a – d

X = O (2-isomer, **a**), S (2-isomer, **b**), CH=CH (*meta*-isomer, **c**; *para*-isomer, **d**)



182a – e

R = $NH(CH_2)_2SMe$ (**a**), $NH(CH_2)_2S(O)Me$ (**b**), $NHCH_2NHMs$ (**c**), $NH(CH_2)_2SO_2NH_2$ (**d**), $NH(CH_2)_2SO_2CH_2CF_3$ (**e**)

inhibit EGFR/HER2 and the enzymatic activity of HDAC. The authors assert that the combination of two moieties with different pharmacological properties in one molecule is responsible for a wider activity spectrum of these compounds and a lower incidence of drug resistance in patients.

A series of new lapatinib analogues **182a – e** is described in Refs 192 – 194. Comparison to lapatinib shows that compounds **182b**,**d** are more active against tumour cells BT-474 and NCl-N87.[192] Selatinib (**182b**) inhibits tumour growth *in vivo* to a considerable extent without causing a significant body weight loss: percent inhibition is 94.8% against NCl-N87 and 85.7% against SK-OV-3 (in a xenographic model). This derivative has a high solubility in water, which is responsible for its high bioavailability and good pharmacokinetic profile.

Noteworthy, compounds **182**, where R is a heterocyclic substituent (morpholine, piperazine or substituted piperazine), in most cases were less active than lapatinib.[192]

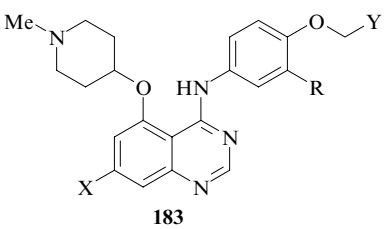
IV.3.c. Substitution in the position 5 of the quinazoline ring

The preparation and characterization of 5-substituted 4-anilinoquinazolines is documented.[51,195–201] Ballard *et al.*[195] prepared 5-hydroxy- and 5,7-dihydroxyquinazoline derivatives **183** with a modified aniline moiety, which were capable of selectively inhibit the Erb2 kinase receptor. Derivative **183** (X = H, R = Cl and Y = 2-Py) inhibited cell growth of tumour BT474C in mice (in a xenographic model).

5-Substituted anilinoquinazolines **184** showed high affinity and specificity to tyrosine kinases c-Src and Abl.[51] These compounds also showed high selectivity to non-receptor tyrosine kinases, excellent pharmacokinetics and activity *in vivo* with oral dosing. Compound **184** {X = O, R^1 = Cl, $R^2 = (CH_2)_2[N(CH_2CH_2)_2NMe]$-cyclo} inhibits tumour growth in Src-transfected 3T3-fibroblasts (in a xenographic model) and appreciably increases animal survival rates in a highly aggressive pancreatic cancer model. However, toxicological studies elucidated some drawbacks of this compound; Ballard *et al.*[196] held the opinion that those drawbacks arose from the basicity of the substituent in the position 5. A series of its analogues **185** were prepared with a modified substituent in the position 5. The hydroxyacylamine moiety (X) entering these compounds improved their properties: derivative **185**, which contains the pyrrolidine moiety, inhibited BT474C tumour growth in mice (in a xenographic model).

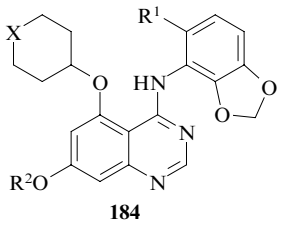
New erlotinib derivatives that contain one to four fluorine atoms in the quinazoline positions 5, 8 and 2 and in the aniline moiety were patented.[202] These compounds have high specificity and a higher protein EGFR binding ability than erlotinib has, and were recommended for use in the therapy of lung cancer and kidney cancer.

Structures 183 – 185



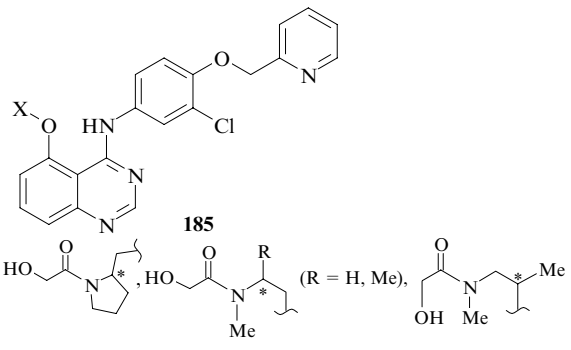
183

X = H, OMe; R = H, Cl; Y = 2-Py, pyrazin-3-yl, thiazol-4-yl



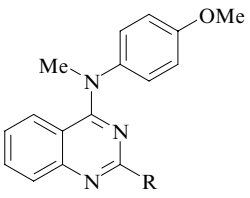
184

X = O, NMe; R^1 = H, Cl; $R^2 = (CH_2)_2[N(CH_2)_4]$-cyclo, $(CH_2)_2[N(CH_2)_5]$-cyclo, $(CH_2)_2[N(CH_2CH_2)_2NMe]$-cyclo



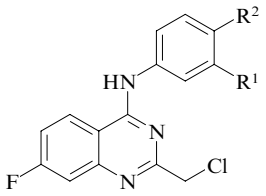
185

Structures 186 – 189



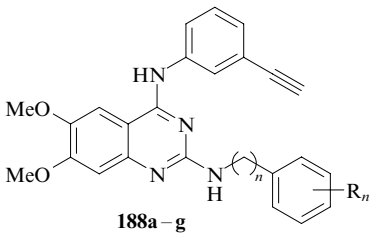
186a – f

R = Cl (**a**), OMe (**b**), NMe_2 (**c**), $NHNH_2$ (**d**), NHMe (**e**), Me (**f**)



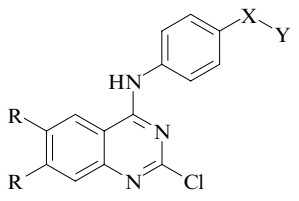
187a,b

R^1 = Cl, R^2 = F (**a**); R^1 = Br, R^2 = H (**b**)



188a – g

n = 0: R_n = 3-CF_3-4-Cl (**a**), 4-OPh (**b**), 3-Cl (**c**), 2-F-5-Me (**d**), 3-OC_6H_4CN-4 (**e**), 4-OC_6H_4CN-4 (**f**); *n* = 1, R_n = H (**g**)



189

R = OMe, R – R = OCH_2O; X = SO_2, C(O); Y = OH, NH_2, NHMe, NMe_2, NHAc, Me, NH(thiazol-2-yl)

IV.3.d. Substitution in the position 2 of the quinazoline ring

The effect of the nature of substituent in the position 2 on the antitumour activity of anilinoquinazolines was studied.[203–211] Most attention was paid to quinazoline derivatives **186a – f**, which are not substituted in the positions 6 and 7. Sirisoma *et al.*[203] showed that the methyl group at the aniline nitrogen atom is significant for apoptosis-initiating activity, and substituents in the position 6(7) reduce this activity. Compound **186a** has high activity in launching apoptosis and inhibits T47D and HCT-116 tumour cell growth and proliferation. Later, Sirisoma *et al.*[205] studied how the nature of substituent R in derivatives **186a – f** influences the ability to launch cell apoptosis in three types of tumours: T47D, HCT-116 and SNU-398. Compound **186f** has the highest activity; it also has an excellent permeability through the brain – blood barrier and is highly efficient against breast cancer MX-1 and other experimental tumours in mice.

Anilinoquinazolines **187a,b**, which contain a chloromethyl group in the position 2 and a fluorine atom in the position 7, were tested for antiproliferative activity on three types of tumours (HepG2, MDA-MB-468 and HCT-116) and were far more active than gefitinib in those tests.[206]

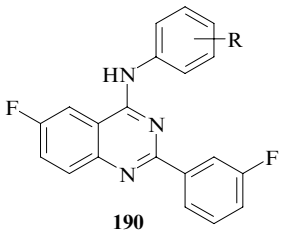
The erlotinib derivatives prepared by Chen *et al.*,[209] where the aniline moiety (**188a – f**) or benzylamine moiety was (**188g**) in the position 2, were tested for the inhibition of protein phosphatase CIP2A of tumour cells and for biological activity against hepatocellular carcinoma (HCC). Compounds **188b,g** showed the greatest antiproliferative effect and were the best in inhibition. Subsequent studies proved a correlation between the cell death and CIP2A inhibition.

2-Chloroanilinoquinazolines **189**, where the aniline moiety contains a spacer (X) and a hydrogen-bond donor (acceptor) (Y), are described as inhibitors of two receptors: EGFR and vascular endothelial growth factor receptor (VEGFR-2).[211] Derivative **189** [$R^1 = R^2$ = OMe, X = C(O) and Y = NH_2] showed the highest inhibitory activity. The results of inhibition evaluation showed the importance of the donor character of substituent Y for the interaction with amino acid moieties Glu and Asp at the EGFR and VEGFR-2 binding sites.

Hour *et al.*[212] noticed the important role of fluorine atoms in substituents of anilinoquinazolines **190** for enhancing the activity and selectivity of these compounds as antitumour agents. Compound **190** (R = 3-OMe) induces the death of apoptotic cells, depending on the presence of mitochondrial receptors, in osteosarcoma U-2 OS.

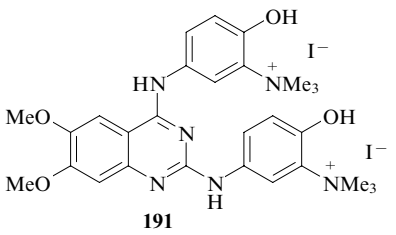
Quinazoline derivative **191**, which contains diaminophenol moieties with charged ammonium groups in the positions 2 and 4, showed good inhibitory activity against DNA transcription.[213]

Structures 190, 191



190

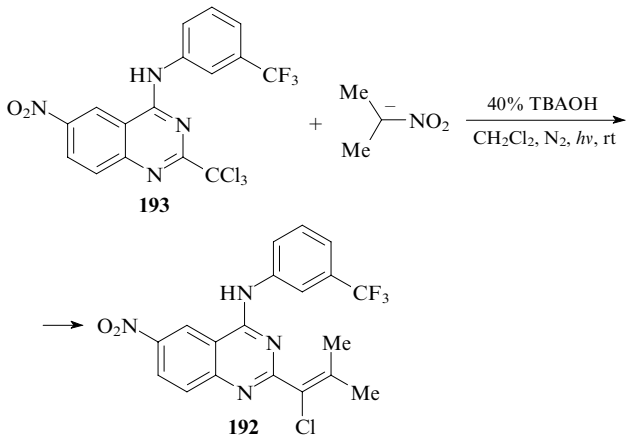
R = H, 2(3,4)-OMe, 2(3,4)-F, 2(3,4)-Cl, 2(3,4)-Br, 2(3,4)-OH, 2(3,4)-NH_2, 2(3,4)-CF_3



191

4-Anilinoquinazoline **192** with a chlorovinyl substituent in the position 2 was prepared using one-electron transfer reactions (Scheme 44).[214] 2-(Trichloromethyl)quinazoline **193** served as the initial compound for consecutive substitution and elimination reactions ($S_{RN}1$-$E_{RC}1$). It was made to react with nitropropane in phase-transfer catalysis conditions under an inert atmosphere at room temperature. Compound **193** was added to a fivefold excess of a prior-prepared mixture of nitropropane and 40% tetra-n-butyl-

Scheme 44



193

192

ammonium hydroxide (TBAOH) and exposed for 4 h; product **192** was obtained in 45% yield.

IV.3.e. Modifying the aniline moiety

The nature of substituents in the aniline moiety considerably affects the biological properties of anilinoquinazolines. It was as early as in 1999 that Hennequin *et al.*[215] showed, in a large group of 6,7-dialkoxy derivatized 4-anilinoquinazolines, that the greatest enhancement of inhibitory activity is provided by such substituents as a halogen atom and a methyl group, preferably in the position 4 of aniline, hydrogen and fluorine atoms in the position 2, and a hydroxy group in the position 3.

Introducing arsenic acid moiety in the aniline position 2 or 4 gave rise to a considerable anti-leukemic activity in derivatives **194** against NALM-6 and MOLT-3 tumour cell lines.[216]

Compounds **195**, where the aniline moiety bears a 2-arylethenesulfonylmethyl substituent, were active *in vitro* against HT-29 adenocarcinoma, and the derivative with a fluorine atom in the position 4 showed activity *in vivo*, too.[217] Compounds **196** with a sulfamide group showed sufficiently high activities against breast sarcomas (MCF-7).[218]

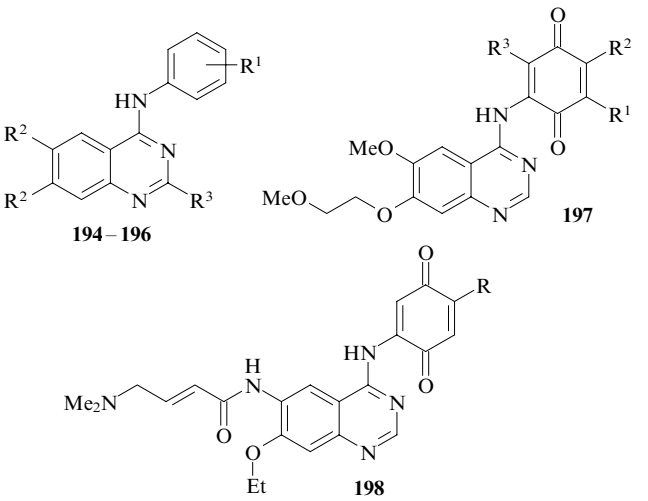
Two groups of quinazolines **197** and **198**, which contained an aminobenzoquinone moiety in the position 4, prepared by oxidation of the appropriate *p*-dimethoxyaryl substituent, were synthesized and characterized.[50, 219, 220] Compounds **197** perform as irreversible VEGFR-2 inhibitors; they covalently interact with Cys-1045. Unlike them, derivatives **198** each have two autonomous reaction sites and can function as dual irreversible EGFR and VEGFR-2 inhibitors. Each reactive site in these compounds interacts with a cysteine moiety, the 6-(dimethylamino) crotonamide acceptor group acts on Cys-773 in EGFR and the 4-amino[1,4]benzoquinone group acts on Cys-1045 in VEGFR-2.

Entering of amide groups and arylboronic acid moieties into the aniline moiety, as in the position 6 of quinazoline (see above), positively affects biological activity.[221 – 223] Derivatives **199a** are described as dual inhibitors (against EGFR and VEGFR-2);[211] for compounds **199b**, selective inhibition was observed, *para*-isomers being more active.[223] The series of 4-anilinoquinazolines **200** prepared by Rao *et al.*[222] was tested for antitumour activity against cell lines A-549 and MCF-7. Most of those compounds were highly active against MCF-7.

Hybrid 4-anilinoquinazolines **201**, which contain pyrazolourea moieties (in the *meta*- or *para*-position), are described.[224, 225] Compounds **201** are presented as new type II inhibitors; they inhibit tyrosine kinase cSrc at low (nanomolar) concentrations, and can overcome cSrc-T338M mutations and tyrosine kinase mutations KIT-T6701 and Abl-T3151. Derivative **201** where $R^1 = R^2 = Me$ blocks tumour cell proliferation by directly inhibiting tyrosine kinase cSrc and infringing the generation of focal adhesion kinases. Other representatives also exert a strong antiproliferative effect in solid tumour cells and are candidates for future studies.

One more group of hybrid molecules (**202** and **203**) has anilinoquinazoline and asymmetrical diarylurea pharmacophores in the structure.[226, 227] Derivatives **202** showed a selective VEGFR-2 kinase inhibition; compound **202** where $R^1 = R^2 = H$ and $R^3 = 3\text{-}FC_6H_4$ showed, along with good kinase selectivity, an antiproliferative effect and activity *in vivo* against murine HepG2 tumour (in a xenographic model).[226]

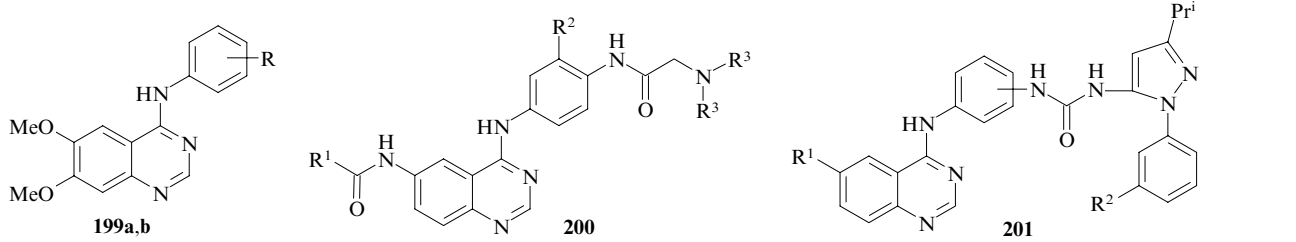
Structures 194 – 198



194 – 196 **197** **198**

194: R^1 = 2-As(O)(OH)$_2$, 4-As(O)(OH)$_2$, 4-N=NC$_6$H$_4$As(O)(OH); R^2 = H, OMe; R^3 = H, CCl_3; **195**: R^1 = 4-CH_2SO_2CH=$CHC_6H_{5-n}X_n$ (X_n = H, 4-F, 4-Br, 4-CN, 4-Cl, 3,4-Cl_2, 2,4-Cl_2, 2,4-F_2, 4-OH, 2-F-4-CF_3); R^2 = H, OMe; R^3 = H; **196**: R^1 = 4-SO_2NHHet (Het is thiazol-2-yl, 5-methylisoxazol-3-yl); R^2 = OMe; R^3 = Cl; **197**: R^1 = H, Cl, Br, OMe; R^2 = H, Cl, Br, OMe, SMe; R^3 = H, Cl, Br, SMe, SPy-2; **198:** R = OMe, OBn, $OCH_2C_6H_4F$-3, $OCH_2C_6H_3F_2$-3,4, $OCH_2C_6H_4Cl$-3, $OCH_2C_6H_4Me$-3, $OCH_2C_6H_4OMe$-3, OCH_2Py-2, OCH_2Th-2, $OCH(CH_2F)_2$

Structures 199 – 201



199a,**b** **200** **201**

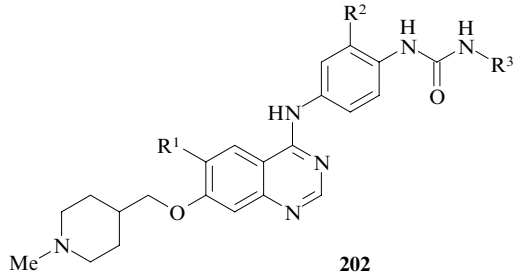
R = C(O)NH$_2$ (**a**), B(OH)$_2$ (**b**); isomers: *meta*, *para*

R^1 = Et, Pr^i, OBu^i, $OCH_2C_6H_{11}$-cyclo; R^2 = H, Cl; R^3 = Et, Pr^n

R^1 = H, Me, NH_2, NHC(O)Et, NHC(O)$(CH_2)_3NMe_2$, NHC(O)$(CH_2)_2$[N$(CH_2CH_2)_2$NMe]-cyclo, NHC(O)$(CH_2)_2$[N$(CH_2CH_2)_2$O]-cyclo; R^2 = Me, NO_2, NH_2; isomers: *meta*, *para*

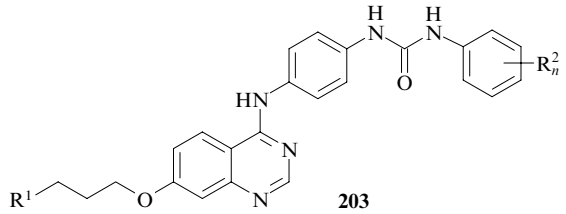
Compounds **203** were described as multikinase inhibitors, which showed sufficiently high activities in biochemical assays against the gene product BRAF, VEGFR-2 and EGFR.[227] One of these derivatives was found to interact with the DFG-out conformation of BRAF and VEGFR-2, which served the authors to infer that compounds **203** can be type II kinase inhibitors.

Structures 202, 203

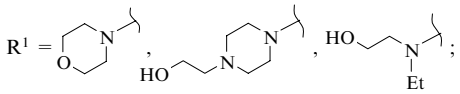


202

R^1 = H, MeO; R^2 = H, F, Cl; R^3 = Et, cyclo-C_3H_5, cyclo-C_6H_{11}, 3-FC_6H_4, 2-F-4-BrC_6H_3, 4-Me-3-BrC_6H_3, 3,4-$F_2C_6H_3$, 3-CF_3-4-ClC_6H_3



203

R^1 = 

R^2_n = 3-Cl-4-F, 3-CF_3-4-Cl

Introduction of a polar group, such as a hydroxamic group, into the aniline moiety (in the *para*- or *meta*-position) of erlotinib or gefitinib, gave compounds **204**, new dual HDAC inhibitors.[228] Inhibitory activity studies *in vitro* showed that compounds **204** were more active hybrid inhibitors for HDAC /HER2 than for HDAC/EGFR.

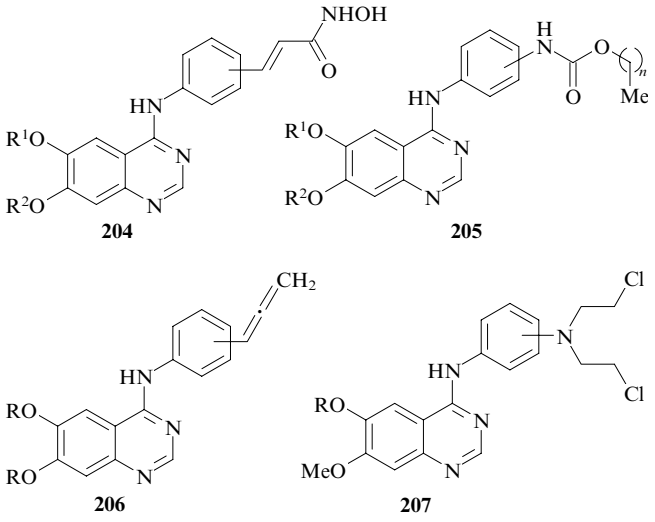
Quinazoline derivatives **205** having a carbamate group in the aniline moiety constitute a new series of efficient dual tyrosine kinase EGFR/VEGFR-2 inhibitors with IC_{50} values in the submicromolar range.[229]

Anilinoquinazolines **206**, where the aniline moiety bears an allene substituent in the *meta*- or *para*-position, were prepared from the appropriate 4-(iodoanilino) quinazolines *via* Sonogashira cross-coupling followed by palladium-catalyzed hydride transfer.[230] Compound **206a** (R = Me, *meta*-isomer) showed an ability to inhibit cell growth in several types of tumours at the level of erlotinib.

A series of quinazoline derivatives **207** with a mustard substituent in the *ortho*-, *meta*- and *para*-positions of the aniline moiety were synthesized.[61,231] Cytotoxicity studies on five tumour cell lines showed a high tumour growth inhibiting ability of derivative **207** {R = $(CH_2)_2[N(CH_2CH_2)_2O]$-cyclo; *meta*-isomer}; this derivative inhibited cellular cycle in S- and G_2/M phases and induced apoptosis.

The replacement of the aniline moiety by amino benzodioxol yielded quinazoline derivatives **208**, which showed high affinity and high specificity as c-Src tyrosine kinase inhibitors.[232]

Structures 204 – 207



204 **205**

206 **207**

204: $R^1 = R^2 = (CH_2)_2OMe$; $R^1 = (CH_2)_3[N(CH_2CH_2)_2O]$-cyclo, R^2 = Me; **205**: n = 0 – 3; $R^2 = (CH_2)_2NEt_2$: R^1 = Me, Bu^n; R^2 = Me: $R^1 = (CH_2)_2NEt_2$, $(CH_2)_2[N(CH_2)_5]$-cyclo; **206**: R = Me, $(CH_2)_2OMe$; **207**: R = H, Ac, $(CH_2)_2[N(CH_2CH_2)_2O]$-cyclo; isomers: *ortho* (**207**), *meta* and *para* (**204** – **207**)

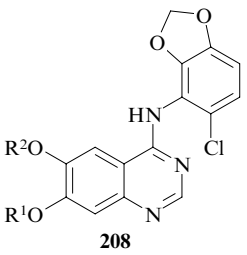
The results of biological studies of 5,6,7-trialkoxyquinazolines **209**, where the position 4 is substituted with piperazine,[233] showed tumour cell proliferation inhibitory activity in most of these compounds and a wide activity spectrum in some of them. 5,6,7-Triethoxy derivatives are more active than the respective methoxy analogues. The activities against PC3, MGC803, A375 and A549 cells in compounds **209** (R^1 = Et, R^2 = 3-$MeOC_6H_4$) are far higher than in gefitinib.

Quinazoline derivatives **210**, which contain aminobenzimidazole moieties in the position 4, were tested as dual tyrosine kinase receptor inhibitors for c-Met and VEGFR-2.[234] Derivative **210** (R = 4-F) showed the highest activity; it also showed antitumour activity against MCF-7 and Hep-G2 and was chosen for further studies.

Regioisomeric hybrids of quinazoline and benzimidazole were prepared, namely (3-allyl-2-methyl-3*H*-benzimidazol-5-yl)amines (**211a** – **d**) and (1-allyl-2-methyl-1*H*-benzimidazol-5-yl)-(2-NR_2-quinazolin-4-yl)amines (**212a**,**b**), and tested for antitumour activity against 60 tumour cell lines.[235] The structure of compounds **211a** – **d** and **212a**,**b** was determined relying on ^{1}H and ^{13}C NMR spectroscopy, including 2D experiments using nuclear Overhauser effect (NOE), and verified by X-ray diffraction data for compound **212a**. Derivative **211b** was the most efficient agent against leukemia, melanoma, kidney cancer, bowel cancer and pancreatic cancer; its activity exceeded that of the known drug 5-fluorouracyl.

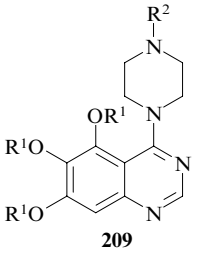
Cai *et al.*[236] prepared a group of 4-(benzothiazol-2-ylamino)quinazoline derivatives **213**, which contain a substituted propoxy group in the position 7 and a substituted phenylamide moiety in the benzene ring of benzothiazole. The cytotoxic activity of compounds **213** was studied against six tumour cell lines, but the authors compared their results with those for the pyrimidine analogue (dasatinib), rather than with quinazoline-based therapeutics.

Structures 208 – 213



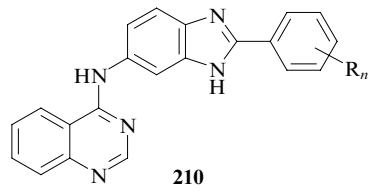
208

208: R^1 = Me, $(CH_2)_2[N(CH_2)_5]$-cyclo; R^2 = Me, $(CH_2)_2[N(CH_2CH_2)_2O]$-cyclo, 6-cyanopyridin-4-yl



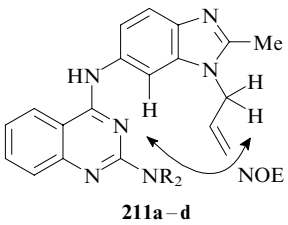
209

R^1 = Me, Et; R^2 = SO_2Ph, $SO_2C_6H_4CF_3$-2, $SO_2C_6H_4CF_3$-4, $SO_2C_6H_4Me$-4, $SO_2C_6H_4OMe$-4, C_6H_4F-4, $C_6H_4NO_2$-4, C_6H_4OMe-3, C_6H_4(2-Py)-4, Bn, $CH_2C_6H_4Cl$-4



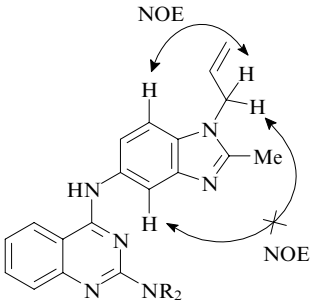
210

R_n = H, 2-OH, 2(3,4)-F, 2(3,4)-Me, 2(3,4)-OMe, 4-Et, 2(3,4)-Cl, 2(3,4)-CF_3, 2-Br-5-F, 2,6-Cl_2, 3,4-Cl_2, 3,5-Cl_2



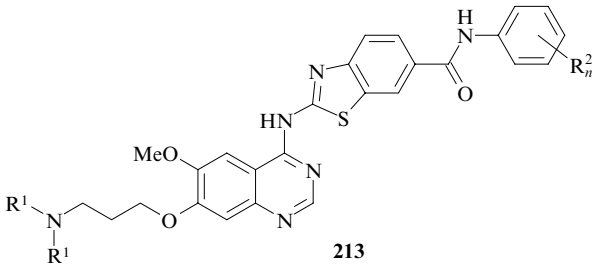
211a – d

R – R = $(CH_2)_2O(CH_2)_2$ (**a**), $(CH_2)_4$ (**b**), $(CH_2)_5$ (**c**), $(CH_2)_2NMe(CH_2)_2$ (**d**)



212a,b

R – R = $(CH_2)_2O(CH_2)_2$ (**a**), $(CH_2)_4$ (**b**)



213

$R^1 – R^1$ = $(CH_2)_2O(CH_2)_2$, $(CH_2)_4$, $(CH_2)_5$; R^2_n = 2-Cl-6-Me, 2,6-Me_2, 2,4,6-Me_3

IV.3.f. Metal derivatives of 4-arylaminoquinazolines

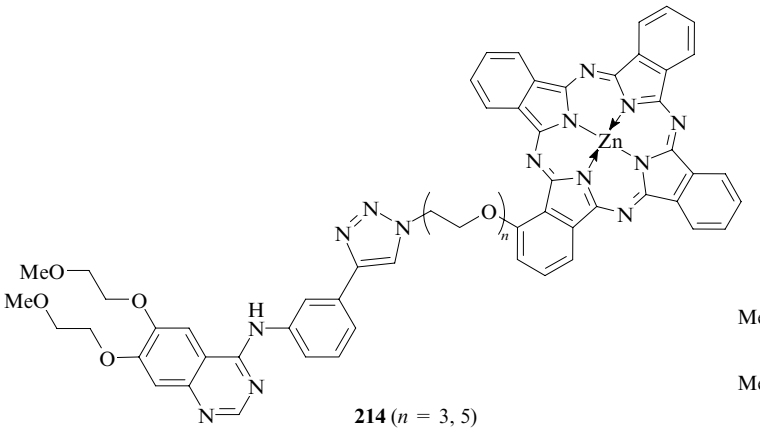
Conjugates **214** are a combination of the antitumour agent erlotinib and a zinc phthalocyanine complex linked by an oligoethylene glycol chain.[237] Compounds **214** have photodynamic activity against tumour cells HepG2 and specific affinity to tumour tissues (experiments in mice). The results of studies imply the promise of conjugates **214** for use in the photodynamic therapy of tumours.

Amin *et al.*[238] prepared 6,7-dimethoxyquinazoline derivatives **215a – c**, where the position 4 contains the ferrocene moiety (Fc), which is bioisosteric to an aryl substituent. The structure of compounds **215a**,**c** was verified by X-ray diffraction. Biological studies showed that these complexes are EGFR inhibitors with micro- or submicromolar values of IC_{50}, which is appreciably higher than in the respective prior-art organic items. However, complexes **215** are of importance as a tool to study kinases.

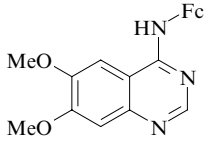
Studies[239, 240] are concerned with the design of fluorescent labels for signal transduction and ligand – receptor interactions. Shreder *et al.*[239] prepared quinazoline derivative **216**, which contains an azide group in aniline, a tetraethylene glycol linker and a 5(6)-carboxytetramethylrhodamine (TAMRA) moiety as a fluorescent label. Those studies showed that this compound is a photoactive probe for EGFR.

Quinazoline derivative **217**, which contains a tetrafluorophenylazide group and a biotin label in the alkoxy moiety, was studied as one more photoactive probe.[240] Compound **217** showed itself as a VEGFR-2 inhibitor, which inhibited VEGF-induced proliferation in human umbilical vein endothelial cells (HUVEC).

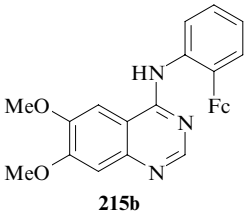
Structures 214, 215



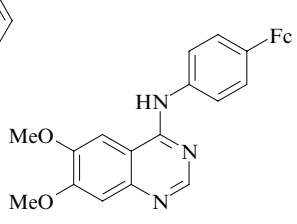
214 (*n* = 3, 5)



215a

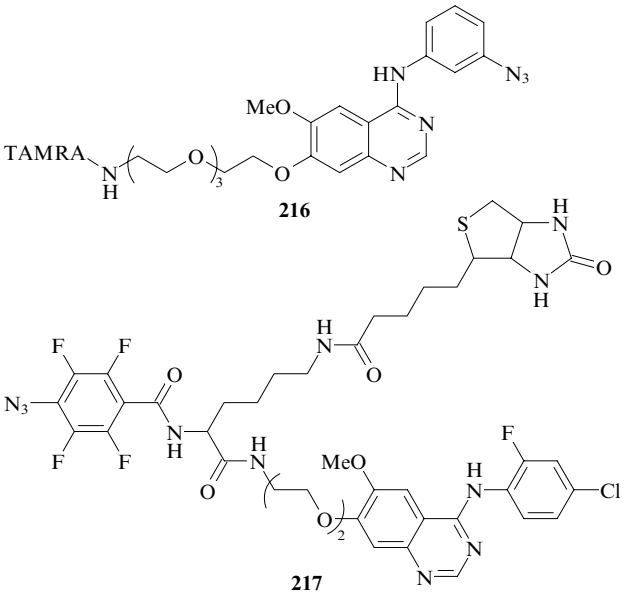


215b



215c

Structures 216, 217



V. Synthesis of labelled 4-anilinoquinazolines as positron emission tomography agents

There are a number of recent publications concerned with the preparation and applications of biomarkers for positron emission tomography (PET), labelled anilinoquinazoline-based pharmaceuticals for PET imaging of tumours. The positron-emitting nuclides most frequently used for this class of compounds are short-lived radioisotopes [^{11}C; half-life: ($t_{1/2}$) = 20.4 min; ^{18}F, $t_{1/2}$ = 110 min] or long-lived radioisotopes (^{124}I, $t_{1/2}$ = 4.2 days; ^{125}I, $t_{1/2}$ = 59.4 days). Anilinoquinazoline derivatives functionalized with a labelled methyl group ($^{11}CH_3$) are described.[241–244] Compounds **218**–**220** were prepared by the alkylation of hydroxy group in the position 6(7) or piperidine using $^{11}CH_3OTf$. [^{11}C]-Labelled gefitinib (**218**) was prepared in 30%–40% radiochemical yields as a new PET agent for detecting EGFR in tumours.[243] Labelled vandetanib (**219**) and its chlorinated analogue (**220**) were prepared in 40%–50% radiochemical yields and used for PET imaging of VEGFR in tumour.[244]

In another chlorinated analogue of vandetanib, compound **221**, the $^{11}CH_3$ group was introduced by alkylating the amide group in piperidine ring by means of $^{11}CH_3OTf$ under basic conditions.[245] Derivative **221** was prepared in 40%–50% radiochemical yields and described as a new PET agent for tomographic imaging of EGFR, HER2 and HER3 in animals and humans.

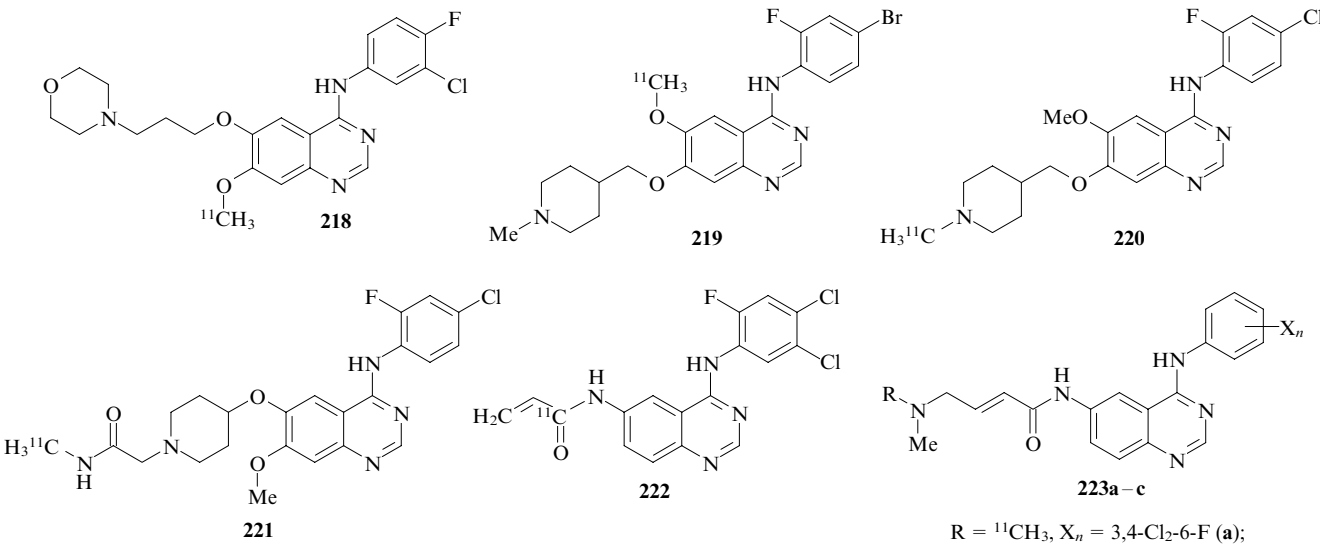
Some other ^{11}C-labelled anilinoquinazoline derivatives contain amide groups in the position 6.[246–248] Irreversible [^{11}C]-EGFR-TK inhibitor **222**, described as a PET imaging biomarker, showed rapid metabolism *in vivo* for the reason of the high reactivity of acrylamide group, with low levels of indicator piling-up in the tumour.[246]

In order to eliminate those drawbacks, Mishani *et al.*[247] prepared derivatives **223a**–**c**. Radioisotope ^{11}C was introduced into compound **223a** as a methyl group by alkylating the HNMe substituent of the precursor. Compound **223a** appeared to be more stable than its analogue **222**, had high selectivity and high EGFR-inhibitory ability (no radioactive metabolism was observed in blood for 60 min). The authors concluded that derivative **223a** is most suitable for use as a biomarker for imaging tumours.

Using various vinyl iodides **224** as reagents in the palladium-catalyzed carbonylation of 6-amino-4-anilinoquinazolines **225** with [^{11}C]-carbon monoxide as nucleophiles (Scheme 45), Aberg and Langstrom[248] performed the combinatorial synthesis of a library of ^{11}C-carbonyl-labelled acrylamides **226** as potential biomarkers of EGFR expression. Compounds **226** were ^{11}C-labelled in the carbonyl group and obtained with 24%–61% radiochemical yields and low isotope dilutions, which is favourable for biological experiments. Aberg and Langstrom[248] do not report biological assay data.

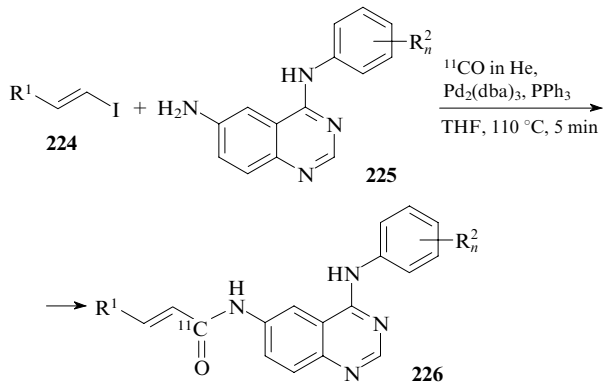
Isotope ^{18}F is a more frequently used radioactive label than other isotopes owing to its favourable half-life time. For example, ^{18}F-labelled analogues of gefitinib (**227b**) and lapatinib (**228**) were described as PET radiopharmaceu-

Structures 218 – 223



R = $^{11}CH_3$, X_n = 3,4-Cl_2-6-F (**a**);
R = Me: X_n = 3-Br (**b**), 3-I (**c**)

Scheme 45



R^1 = H, $CH_2[N(CH_2)_5]$-cyclo, $CH_2[N(CH_2CH_2)_2O]$-cyclo, $CH_2[N(CH_2CH_2)_2S]$-cyclo; R^2_n = 3-Br, 3-Cl-4-F, 3-Cl-4-($OCH_2C_6H_4F$-3)

tics.[249,250] Derivatives **227a – c** were prepared by reaction of 4-chloroquinazoline with 3-chloro-4-[^{18}F]fluoroaniline in isopropanol in 25% – 40% radiochemical yields. In compound **228**, the radioisotope entered with *m*-[^{18}F]fluorobenzyl bromide, which was used to substitute for the hydroxy hydrogen atom in the aniline moiety of Boc-substituted lapatinib precursor.[250] Radioisotope ^{18}F was also introduced into anilinoquinazoline derivatives **229a**,**b** as [^{18}F]fluoroanilines.[251,252]

However, ^{18}F-labelled anilinoquinazolines **227 – 229** have some drawbacks, which are low uptakes by tumour, low solubilities and low stabilities *in vivo*.[253] In order to enhance biological activity, Chen *et al.*[254] prepared ^{18}F-labelled anilinoquinazolines **230**, which were modified by a ^{18}F-containing 2-fluoroethoxy moiety. Biodistribution experiments to track compounds **230** in mice with tumour S180 showed that the derivatives were piled up in the tumour and rapidly excreted from muscles and blood. Derivative **230c** was found to have the best physiological characteristics, comparable with, or even exceeding, those of fluorodeoxyglucose ([^{18}F]-FDG), a PET radiopharmaceutical known in clinical diagnostics. So, the tumour : muscle uptake ratio reached 7.70 in 60 min post injection, the tumour : blood uptake ratio reached 6.61 in 120 min and tumour : brain uptake ratio reached 41.11 in 120 min. This compound is promising for use as a PET agent for imaging tumours.

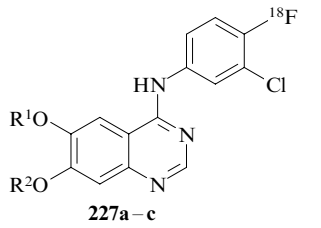
Iodine-isotope-labelled anilinoquinazolines are presented in Refs. [255 – 257]. The radioisotope was introduced in the aniline moiety by substituting ^{125}I for the trimethylstannyl group by means of Na^{125}I (for compounds **231a**,**b** [255]), or substituting ^{124}I for the tributylstannyl group using Na^{124}I (in compounds **232a – c** [256]) . Derivatives **232b**,**c** have higher EGFR-inhibitory activities and show more promise as PET agents compared to the other compounds of this series.

Into the amide moiety of aminoquinazoline **233,** the iodine isotope was introduced by substituting ^{125}I for the bromine atom with 48% radiochemical yield and > 98% radiochemical purity.[257] The *in vitro* study of derivative **233** showed its radiochemical stability in physiological saline at 6 and 37°C up to day 4 and in fresh human serum at 37 °C up to four hours of incubation. Fernandes *et al.*[257] concluded that this compound is a candidate for use in single-photon emission computer tomography (SPECT) of breast cancer.

Dissoki *et al.*[258] prepared anilinoquinazoline derivatives **234 – 236**, modified with polyethylene glycol moieties and labelled with ^{11}C, ^{124}I and ^{18}F. These compounds showed lower lipophilicities and higher solubilities in water compared to their unlabelled analogues. In addition, they had high EGFR-inhibitory activities with the irreversible binding effect; they were stable in blood samples for 1 – 2 h and are now regarded as promising PET bioprobes.

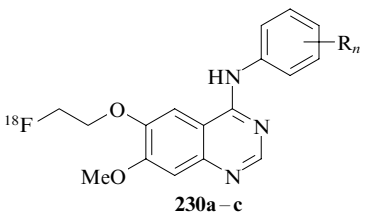
The properties of the metastable isotope ^{99m}Tc ($t_{1/2}$ = 65.9 h), which are almost ideal for SPECT applications, and its availability compared to PET isotopes

Structures 227 – 233



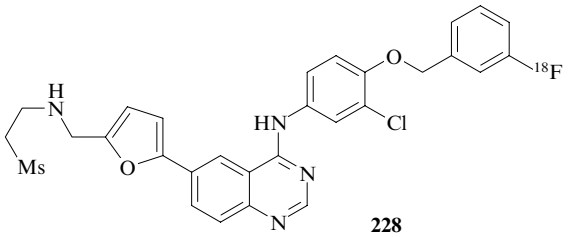
227a – c

$R^1 = R^2 = (CH_2)_2OMe$ (**a**);
$R^1 = (CH_2)_3[N(CH_2CH_2)_2O]$-cyclo,
R^2 = Me (**b**); R^1 = Me,
$R^2 = CH_2[N(CH_2CH_2)_2NMe]$-cyclo (**c**)

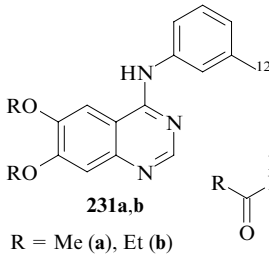


230a – c

R_n = 3-Cl-4-F (**a**),
3-C≡CH (**b**), 3-Br (**c**)

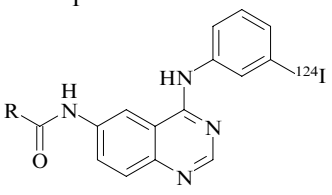


228



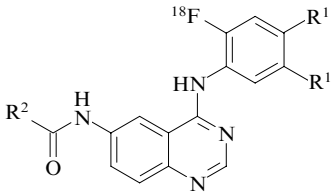
231a,**b**

R = Me (**a**), Et (**b**)



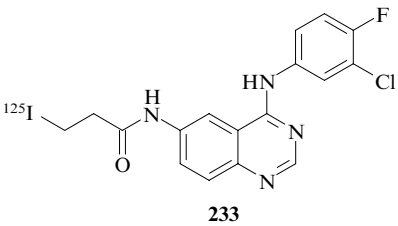
232a – c

R = CH_2OMe (**a**), CH_2Cl (**b**),
$CH{=}CHCH_2NMe_2$ (**c**)



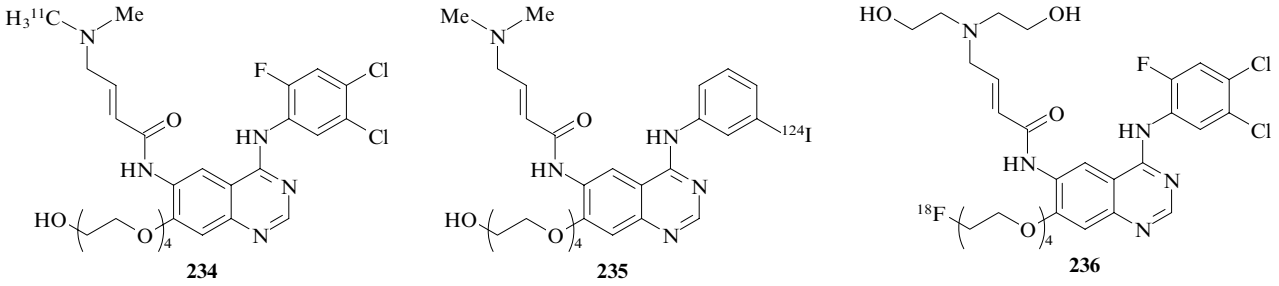
229a,**b**

R^1 = Cl, $R^2 = CH{=}CHCH_2NMe_2$ (**a**),
R^1 = H, $R^2 = CH{=}CH_2$ (**b**)



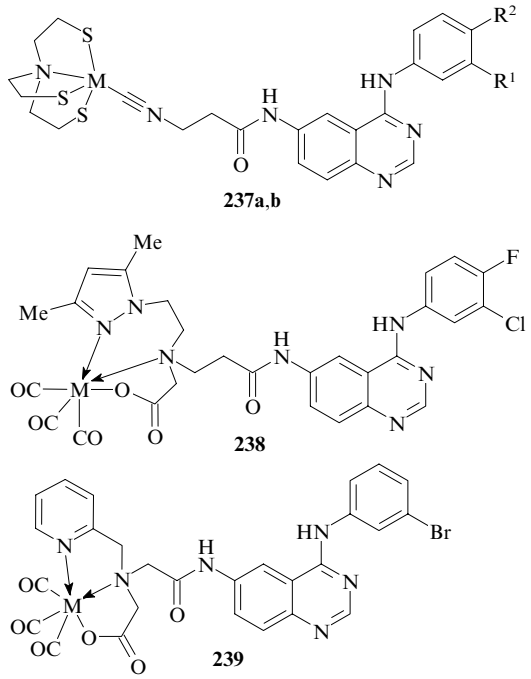
233

Structures 234 – 236



234 **235** **236**

Structures 237 – 239



237a,**b** **238** **239**

237 – 239: M = ^{99m}Tc; **237**: R^1 = Cl, R^2 = F (**a**); R^1 = Br, R^2 = H (**b**)

stipulated the preparation of ^{99m}Tc-labelled anilinoquinazolines. Fernandes *et al.*[259] presented two strategies for ^{99m}Tc-labelling to use a mixed-ligand '4 + 1' system [Tc(NS_3)(CNR)], where R is the aminoquinazoline moiety, and tricarbonyl cation $[Tc(CO)_3]^+$. In the former (in compounds **237a**,**b**), technetium is stabilized by the monodentate isocyanide group of quinazoline moiety (CNR) and the tris(2-sulfanylethyl)amine (NS_3 tetradentate trigonal ligand). In the latter (in compounds **238** and **239**), the technetium cation is bonded to N_2O-tridentate quinazoline ligands, which differ from each other by the nature of heterocycle in the coordination sphere (pyrazole or pyridine, respectively). The anilinoquinazoline ligands of complexes **237 – 239** showed considerable EGFR-autophosphorylation activity in *in vitro* experiments and inhibited tumour cell growth in A431. Their rhenium complexes retained pharmacological properties, so the authors continued their studies into the synthesis of ^{99m}Tc-containing compounds for the early detection of EGFR-positive tumours.

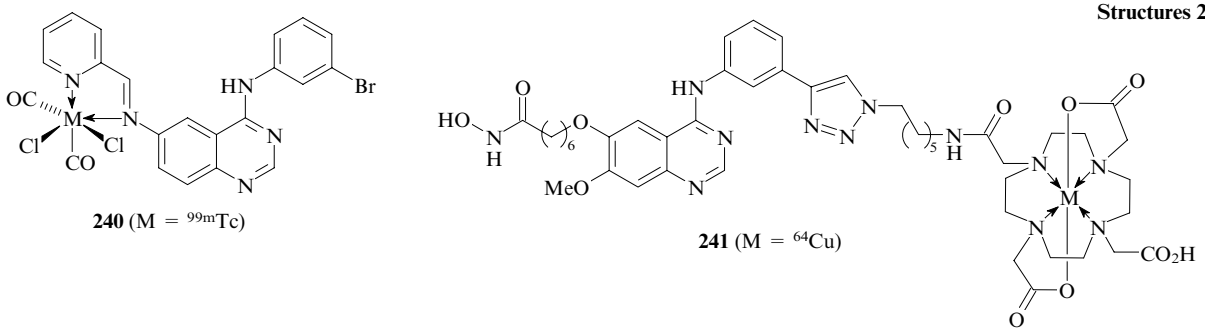
The next communication[260] describes the preparation and characterization of ^{99m}Tc complex **240** with the N,N-bidentate anilinoquinazoline ligand as a biomarker for imaging EGFR. The biodistribution of the complex was studied in healthy mice and showed rather rapid removal from blood and soft tissues in the first 15 min post injection, mostly through the hepatobiliary system.

Meng *et al.*[261] synthesized the first complex **241** based on a ^{64}Cu-labelled anilinoquinazoline ligand ($t_{1/2}$ = 12.7 h) as a PET biomarker for non-invasive imaging of expression of histone deacetylases *in vivo*. Studies on enzymes showed that this complex had high inhibitory activity against HDAC, like the uncomplexed ligand, and the specific binding of compound **241** to HDAC was proven. Biodistribution data imply that the complex has a high tumour : background ratio for breast cancer MDA-MB-231 with high HDAC expression (in a xenographic model). The results of that study show the potential of compounds **241** for use in monitoring the treatment efficacy for this type of tumour.

VI. Conclusion

The above analysis of literature data shows that, in recent years, there has been an increased interest in 4-anilinoquinazolines as promising antitumour agents; new therapeutics based on compounds of this class appear continuously. Our

Structures 240, 241



240 (M = ^{99m}Tc) **241** (M = ^{64}Cu)

survey focuses on the main strategies to prepare 4-(het)arylaminoquinazolines, either through substitution for the chlorine atom in the quinazoline moiety, or in the absence of this stage. We compiled data on the improvement of synthetic schemes for the best-known first-generation pharmaceuticals of that series of compounds. Another focus of our survey is on the preparation of new anilinoquinazoline derivatives that have antitumour activity. We highlight that most research efforts are directed to modifying substituents in the positions 6 and 7 of the quinazoline ring. For example, second-generation pharmaceuticals were designed by the replacement of alkoxy groups by amide ones. Approaches to the design of hybrid molecules by means of introducing ureas, mustard, triazene and phthalocyanine groups or dioxo rings into quinazoline moieties were developed to result in multiactive drugs. Modifying of substituents in the positions 5 and 2 of quinazoline and in the aniline moiety gave rise to multikinase inhibitors.

Promising areas of research are into the design of fluorescent probes for studying the mechanism of action of pharmaceuticals and the preparation of labelled anilinoquinazolines for use as PET imaging agents in management of tumours. The inspection of related literature shows that structural alteration of anilinoquinazolines offers a means for preparing both reversible and irreversible inhibitors for various tyrosine kinase families.

Noteworthy, many 4-anilinoquinazolin derivatives have more activities in addition to antitumour activity, specifically antiviral activity. For example, close analogues of gefitinib are active against pox viruses.[262] Fluorinated 4-anilino-2-ethylsulfanylquinazolines show high activity against the smallpox virus and are of interest for future research.[263]

This survey was prepared with financial support from the Russian Science Foundation (Project No. 15-13-00077, Sections I – III) and the Government Assignment of the Ministry for Education and Science of the Russian Federation (Project No. 2458, Sections IV – VI).

References

1. V N Charushin, V L Rusinov, O N Chupakhin, in *Comprehensive Heterocyclic Chemistry III* Vol. 9 (Ed. A R Katritzky) (Oxford: Elsevier, 2008) p. 95
2. A F Pozharsky, A T Soldatenkov, A R Katritzky *Heterocycles in Life and Society* (Chichester: Wiley, 1997)
3. V G Granik *Osnovy Meditsinskoi Khimii* (Foundations of Medicinal Chemistry) (Moscow: Vuzovskaya Kniga, 2001)
4. J A Joule, K Mills *Heterocyclic Chemistry* (New York: Wiley-Blackwell, 2010)
5. D J Brown, R F Evans, W B Cowden, M D Fenn Wiley *The Pyrimidines* (New York: Wiley, 1994)
6. I M Lagoja *Chem. Biodivers.* **2** 1 (2005)
7. D M Vasudevan, S Speekumari, K Vaidyanathan *Textbook of Biochemistry for Medical Students* (6th Ed.) (New Delhi, India: Jaypee Brothers Medical Publishers, 2011)
8. J L Marshall, in *Colorectal Cancer* (Ed. L B Saltz) (Totowa, NS: Humama Press, 2002)
9. V S Mokrushin, G A Vavilov *Osnovy Khimii i Tekhnologii Bioorganicheskikh i Sinteticheskikh Lekarstvennykh Veshchestv* (Foundations of Chemistry and Technology of Biological and Synthetic Drug Compounds) (St Petersburg: Prospekt Nauki, 2009)
10. O A Mel'nikova, A Yu Petrov, E N Ulomskii, M Yu Kinev, V A Zyryanov *Sovremennye Podkhody k Sozdaniyu Protivovirusnykh Sredstv* (Modern Approaches to the Development of Antiviral Agents) (Ekaterinburg: Ural State Medical University, 2014)
11. A Foucourt, C Dubouilh-Benard, E Chosson, C Buquet, M Iannelli, B Leblond, F Marsais, T Besson *Tetrahedron* **66** 4495 (2010)
12. Q Chao, L Deng, H Shih, L M Leoni, D Genini, D A Carson, H B Cottam *J. Med. Chem.* **42** 3860 (1999)
13. R A Smits, M Adami, E P Istyastono, O P Zuiderveld, C M E van Dam, F J J de Kanter, A Jongejan, G Coruzzi, R Leurs, I J P de Esch *J. Med. Chem.* **53** 2390 (2010)
14. P P Kung, M D Casper, K L Cook, L Wilson-Lingardo, L M Risen, T A Vickers, R Ranken, L B Blyn, J R Wyatt, D Cook, D J Ecker *J. Med. Chem.* **42** 4705 (1999)
15. M Nasr, J C Drach, S H Smith, C Shipman, J H Burckhalter *J. Med. Chem.* **31** 1347 (1998)
16. Patent WO 2008009078 (2008)
17. A J Bridges, H Zhou, D R Cody, G W Rewcastle, A McMichael, H D H Showalter, D W Fry, A J Kraker, W A Denny *J. Med. Chem.* **39** 267 (1996)
18. M R Myers, N N Setzer, A P Spada, A L Zulli, C J Hsu, A Zilberstein, S E Johnson, L E Hook, M V Jacoski *Bioorg. Med. Chem. Lett.* **7** 417 (1997)
19. A Garofalo, L Goossens, A Lemoine, A Farce, Y Arlot, P Depreux *J. Enzyme Inhib. Med. Chem.* **25** 158 (2010)
20. T Furuta, T Sakai, T Senga, T Osawa, K Kubo, T Shimizu, R Suzuki, T Yoshino, M Endo, A Miwa *J. Med. Chem.* **49** 2186 (2006)
21. P Blume-Jensen, T Hunter *Nature (London)* **411** 355 (2001)
22. J Mendelsohn, J Baselga *Oncogene* **19** 6550 (2000)
23. A Vijaychand, S N Manjula, E N Bharath, B Divya *Int. J. Pharm. Biosci.* **2** 780 (2011)
24. M Font, A Gonzalez, J A Palop, C Sanmartin *Eur. J. Med. Chem.* **46** 3887 (2011)
25. F Liu, D B Lovejou, A A Hassani, Y He, J M Herold, X Chen, C M Yates, S V Frye, P J Brown, J Huang, M Vedadi, C H Arrowsmith, J Jin *J. Med. Chem.* **54** 6139 (2011)
26. J Mendelson, H Baselga *J. Clin. Oncol.* **21** 2787 (2003)
27. S A Tyulyandin, D A Nosov *Sovrem. Onkologiya* **7** (4) 176 (2005)
28. H J Broxterman, N H Georgopapadakou *Drug Resist. Updates* **7** 79 (2004)
29. J G Paez, P A Jinne, J C Lee, S Tracy, H Greulich, S Gabriel, P Herman, F J Kaye, N Lindeman, T J Boggon, K Naoki, H Sasaki, Y Fuji, M J Eck, W R Sellers, B E Johnson, M Meyerson *Science* **304** 1497 (2004)
30. M Tiseo, M Loprevite, A Ardizzoni *Anti-Cancer Agents Med. Chem.* **4** 139 (2004)
31. M A Morgan, L A Parsels, L E Kollar *Clin. Cancer Res.* **14** 5142 (2008)
32. J Wang, M Sónchez-Roselld, J L Acena, C del Pozo, A E Sorochinsky, S Fustero, V A Soloshonok, H Liu *Chem. Rev.* **114** 2432 (2014)
33. C Leitner, R von Moos, M Mark, M Früh, R Cathomas *Cancer Treat. Commun.* **2** 4 (2014)
34. X Chen, W Li, X Hu, Y Geng, R Wang, Y Yin, Y Shu *Biomed. Pharmacother.* **65** 542 (2011)
35. M Muhsin, J Graham, P Kirkpatrick *Nat. Rev. Drug Discov.* **2** 515 (2003)
36. G Zhang, L Zha *Res. Chem. Intermed.* **39** 2303 (2013)
37. F Yamasaki, D Zhang, C Bartholomeusz, T Sudo, G Hortobagyi, K Kurisu, N T Ueno *J. Mol. Cancer Ther.* **6** 2168 (2007)

38. P B Larsen, I Kümler, D L Nielsen *Cancer Treat. Rev.* **39** 720 (2013)
39. H Bonnefoi, K Zaman, M Debled, M Fiche, M Fournier, M Nobahar, J Y Pierga, K M Koch, J Bartlett, A Zimmer, S Marreaud, J Bogaerts, D Cameron *Eur. J. Cancer* **49** 281 (2013)
40. S Kumar, G Mishra, P Singh, K K Jha, R L Khosa, S K Gupta *Der Chemica Sinica* **2** (4) 36 (2011)
41. A S Corbin, I J Griswold, P La Rosée, K W Yee, M C Heinrich, C L Reimer *Blood* **104** 3754 (2004)
42. Y Cheng, K Paz *IDrugs* **11** (1) 46 (2008)
43. D J De Angelo, R M Stone, M L Heaney, S D Nimer, R L Paquette, R B Klisovic *Blood* **108** 3674 (2006)
44. X Q Zhao, C L Dai, S Ohnuma, Y J Liang, W Deng, J J Chen, M S Zeng, S V Ambudkar, Z S Chen, L W Fu *Eur. J. Pharm. Sci.* **49** 441 (2013)
45. P Knesl, D Roseling, U Jordis *Molecules* **11** 286 (2006)
46. C M Hattinger, M Posello, S Terrari, P Picci, M Serra *Exp. Opin. Emerg. Drugs* **15** 615 (2010)
47. A Antonello, A Tarozzi, F Morroni, A Cavalli, M Rosini, P Hrelia, M L Bolognesi, C Melchiorre *J. Med. Chem.* **49** 6642 (2006)
48. A Michalczyk, S Kluter, H B Rode, J R Simard, C Grutter, M Rabiller, D Rauh *Bioorg. Med. Chem.* **16** 3482 (2008)
49. J J Laskin, A B Sandler *Cancer Treat. Rev.* **30** 1 (2004)
50. A Wissner, H L Fraser, C L Ingalls, R G Dushin, M B Floyd, K Cheung, T Nittoli, M Ravi, X Tan, F Loganzo *Bioorg. Med. Chem.* **15** 3635 (2007)
51. L F Hennequin, J Allen, J Breed, J Curwen, M Fennell, T P Green, C Lambert-van der Brempt, R Morgentin, R Norman, A Olivier, L Otterbein, P A Ple, N Warin, G Costello *J. Med. Chem.* **49** 6465 (2006)
52. K G Petrov, Y M Zhang, M Carter, G S Cockerill, S Dickerson, C A Gauthier, Y Guo, R A Mook, D W Rusnak, A L Walker, E R Wood, K E Lackey *Bioorg. Med. Chem. Lett.* **16** 4686 (2006)
53. H R Tsou, N Mamuya, B D Johnson, M F Reich, B C Gruber, F Ye, R Nilakantan, R Shen, C Discafani, R DeBlanc, R Davis, F E Koehn, L M Greenberger, Y F Wang, A Wissner *J. Med. Chem.* **44** 2719 (2001)
54. O Cruz-Lopez, A Conejo-Garcia, M C Nunez, M Kimatrai, M E Garcia-Rubino, F Morales, V Gomez-Perez, J M Campos *Curr. Med. Chem.* **18** 943 (2011)
55. I Khan, A Ibrar, N Abbas, A Saeed *Eur. J. Med. Chem.* **76** 193 (2014)
56. E V Nosova, G N Lipunova, V N Charushin *Russ. Chem. Rev.* **78** 387 (2009)
57. L N Yakhontov, G P Zhikhareva, E V Pronina, G N Pershin, S S Liberman, E N Padeiskaya, T N Zykova, T A Gus'kova, E A Berlyand *Khim.-Farm. Zh.* **9** (11) 12 (1975)
58. S A Rocco, J E Barbarini, R Rittner *Synthesis* 429 (2004)
59. G Liu, L Sun, C Liu, C Ji, Q Wen, S Ma *J. Heterocycl. Chem.* **45** 759 (2008)
60. G Liu, D Y Hu, L H Jin, B A Song, S Yang, P S Liu, P S Bhadury, Y Ma, H Luo, X Zhou *Bioorg. Med. Chem.* **15** 6608 (2007)
61. Y Zhang, L Jin, H Xiang, J Wu, P Wang, D Hu, W Xue, S Yang *Eur. J. Med. Chem.* **66** 335 (2013)
62. K S Jain, M K Kathiravan, J B Bariwal, P K Chaskar, S S Tompe, N Arya *Synth. Commun.* **43** 719 (2013)
63. E Moreno, D Plano, I Lamberto, M Font, I Encío, J A Palop, C Sanmartín *Eur. J. Med. Chem.* **47** 283 (2012)
64. W Szczepankiewiez, J Suwinski *Tetrahedron Lett.* **39** 1785 (1998)
65. W Szczepankiewiez, J Suwinski, R Bujok *Tetrahedron* **56** 9343 (2000)
66. K M El-Shaieb, H Hopf, P G Jones *Z. Naturforsch., B* **64** 858 (2009)
67. S I Mirallai, M J Manos, P A Koutentis *J. Org. Chem.* **78** 9906 (2013)
68. E Erba, D Sporchia *J. Chem. Soc., Perkin Trans 1* 3021 (1997)
69. D S Yoon, Y Han, T M Stark, J C Haber, B T Gregg, S B Stanovich *Org. Lett.* **6** 4775 (2004)
70. P K Atanassov, A Linden, H Heimgartner *Helv. Chim. Acta* **87** 1873 (2004)
71. E V Nosova, A A Layeva, T V Trashakhova, A V Golovchenko, G N Lipunova, P A Slepukhin, V N Charushin *Zh. Org. Khim.* **45** 916 (2009)
72. A A Layeva, E V Nosova, G N Lipunova, T V Trashakhova, V N Charushin *Russ. Chem. Bull., Int. Ed.* **56** 1821 (2007) [*Izv. Akad. Nauk, Ser. Khim.* 1758 (2007)]
73. L J Wilson *Org. Lett.* **3** 585 (2001)
74. A A Layeva, E V Nosova, G N Lipunova, T V Trashakhova, V N Charushin *J. Fluorine Chem.* **128** 748 (2007)
75. G Marzaro, A Guiotto, G Pastorini, A Chilin *Tetrahedron* **66** 962 (2010)
76. Z Y Xing, Q Zhao, Y Fu, F Ye *Chem. Heterocycl. Compd.* **47** 607 (2011) [*Khim. Geterotsikl. Soedin.* 727 (2011)]
77. Z Y Xing, Y Fu, F Ye *J. Heterocycl. Chem.* **49** 1210 (2012)
78. I Cikotiene, R Buksnaitiene, R Sazinas *Tetrahedron* **67** 706 (2011)
79. I Cikotiene, M Morkunas *Synlett* 284 (2009)
80. Patent WO 9633980 (1996)
81. Patent US 5770599 (1998)
82. M D Li, Y G Zheng, M Ji *Molecules* **12** 673 (2007)
83. V Chandregowda, G V Rao, G C Reddy *Heterocycles* **71** 39 (2007)
84. V Chandregowda, G V Rao, G C Reddy *Synth. Commun.* **37** 3409 (2007)
85. V Chandregowda, G V Rao, G C Reddy *Org. Process Res. Dev.* **22** 813 (2007)
86. D Asgari, A Aghanejad, J S Mojarrad *Bull. Korean Chem. Soc.* **32** 909 (2011)
87. Patent US 6727256 (2004)
88. Patent WO 2011116634 (2011)
89. Patent WO 2012083440 (2012)
90. Patent WO 2013080218 (2013)
91. Patent US 2011263852 (2011)
92. Patent EP 2468745 (2012)
93. A Fredriksson, S Stone-Elander *J. Label. Compd. Radiopharm.* **45** 529 (2002)
94. H Li, M Li, Z Li, L Li, S Bi, C Deng, R Chen, T Zhou, W Lu *Chin. J. Chem.* **29** 1709 (2011)
95. V Chandregowda, A K Kush, G C Reddy *Eur. J. Med. Chem.* **44** 3046 (2009)
96. C S Harris, L F Hennequin, J G Kettle, O A Willerval *Tetrahedron Lett.* **46** 7715 (2005)
97. C S Harris, L F Hennequin, O A Willerval *Tetrahedron Lett.* **50** 1600 (2009)
98. A J Barker, K H Gibson, W Grundy, A A Godfrey, J J Barlow, M P Healy, J R Woodburn, S E Ashton, B J Curry, L Scarlett, L Henthorn, L Richards *Bioorg. Med. Chem. Lett.* **11** 1911 (2001)
99. L F Hennequin, E S E Stokes, A P Thomas, C Johnstone, P A Ple, D J Ogilvie, M Dukes, S R Wedge, J Kendrew, J O Curwen *J. Med. Chem.* **45** 1300 (2002)
100. H S Ban, T Usui, W Nabeyama, H Morita, K Fukuzawa, H Nakamura *Org. Biomol. Chem.* **7** 4415 (2009)
101. X Cai, H X Zhai, J Wang, J Forrester, H Qu, L Yin, C J Lai, R Bao, C Qian *J. Med. Chem.* **53** 2000 (2010)
102. H S Ban, Y Tanaka, W Nabeyama, M Hatori, H Nakamura *Bioorg. Med. Chem.* **18** 870 (2010)
103. H T Pham, R N Hanson, S L Olmsted, A Kozhushnyan, A Visentin, P J Weglinsky, C Massero, K Bailey *Tetrahedron Lett.* **52** 1053 (2011)
104. R D Li, X Zhang, Q Y Li, Z M Ge, R T Li *Bioorg. Med. Chem. Lett.* **21** 3637 (2011)

105. F Zhao, Z Lin, F Wang, X Zhao, X Dong *Bioorg. Med. Chem. Lett.* **23** 5385 (2013)
106. P Ballard, R H Bradbury, C S Harris, L F A Hennequin, D M Hickinson, J G Kettle, J Kendrew, T Klinowska, D Ogilvie, S E Pearson, E J Williams, I Wilson *Bioorg. Med. Chem. Lett.* **16** 4908 (2006)
107. B Barlaam, J Anderton, P Ballard, R H Bradbury, L F A Hennequin, D M Hickinson, J G Kettle, G Kirk, T Klinowska, C L Brempt, C Trigwell, J Vincent, D Ogilvie *ACS Med. Chem. Lett.* **4** 742 (2013)
108. K H Yin, Y H Hsieh, R S Sulake, S P Wang, J I Chao, C Chen *Bioorg. Med. Chem. Lett.* **24** 5247 (2014)
109. W R Wilson, M P Hay *Nat. Rev. Cancer* **11** 393 (2011)
110. W Cheng, Y Yuan, N Qiu, P Peng, R Sheng, Y Hu *Bioorg. Med. Chem.* **22** 6796 (2014)
111. W Cheng, S Zhu, X Ma, N Qiu, P Peng, R Sheng, Y Hu *Eur. J. Med. Chem.* **89** 826 (2015)
112. S Lu, W Zheng, L Ji, Q Luo, X Hao, X Li, F Wang *Eur. J. Med. Chem.* **61** 84 (2013)
113. W Zheng, Q Luo, Y Lin, Y Zhao, X W Yu, S Lu, L Ji, X Li, L Yang, F Wang *Chem. Commun.* **49** 10224 (2013)
114. J B Smaill, B D Palmer, G W Rewcastle, W A Denny, D J McNamara, E M Dobrusin, A J Bridges, H Zhou, H D H Showalter, R T Winters, W R Leopold, D W Fry, J M Nelson, V Slintak, W L Elliot, B J Roberts, P W Vincent, S J Patmore *J. Med. Chem.* **42** 1803 (1999)
115. J B Smaill, G W Rewcastle, J A Loo, K D Greis, O H Chan, E L Reyner, E Lipka, H D H Showalter, P W Vincent, W L Elliot, W A Denny *J. Med. Chem.* **43** 1380 (2000)
116. J B Smaill, H D H Showalter, H Zhou, A J Bridges, D J McNamara, D W Fry, J M Nelson, V Sherwood, P W Vincent, B J Roberts, W L Elliot, W A Denny *J. Med. Chem.* **44** 429 (2001)
117. Patent US 2003225079 (2003)
118. Patent US 2005250761 (2005)
119. Patent US 2008300248 (2008)
120. Patent US 2009105247 (2009)
121. Patent WO 2010076764 (2010)
122. Patent WO 2012000182 (2012)
123. Patent WO 2012030160 (2012)
124. D D Li, P C Lv, H Zhang, H J Zhang, Y P Hou, K Liu, Y H Ye, H L Zhu *Bioorg. Med. Chem.* **19** 5012 (2011)
125. Y Y Xu, S N Li, G J Yu, Q H Hu, H Q Li *Bioorg. Med. Chem.* **21** 6084 (2013)
126. Patent WO 2010104406 (2010)
127. Patent EP 2612860 (2013)
128. Patent WO 2013053206 (2013)
129. Patent WO 2013166952 (2013)
130. Patent WO 2013173254 (2013)
131. A Wissner, E Overbeek, M F Reich, B D Johnson, N Mamuya, E C Rosfjord, C Discafani, R Davis, X Shi, S K Rabindran, B C Gruber, F Ye, W A Hallett, R Nilakantan, R Shen, Y F Wang, L M Greenberger, H R Tsou *J. Med. Chem.* **46** 49 (2003)
132. S R Klutchko, H Zhou, R T Winters, T P Tran, A J Bridges, I W Althaus, D M Amato, W L Elliot, P A Ellis, M A Meade, B J Roberts, D W Fry, A J Gonzales, P J Harvey, J M Nelson, V Sherwood, H K Han, G Pace, J B Smaill, W A Denny, H D H Showalter *J. Med. Chem.* **49** 1475 (2006)
133. S Campos, O Hamid, M V Seiden, A Oza, M Plante, R K Potkul, P F Lenehan, E P Kaldjian, M L Varterasian, C Jordan, C Charbonneau *J. Clin. Oncol.* **23** 5597 (2005)
134. C Carmi, A Cavazzoni, S Vezzosi, F Bordi, F Vacondio, C Silva, S Rivara, A Lodola, R R Alfieri, S L Monica, M Galetti, A Ardizzoni, P G Petronini, M Mor *J. Med. Chem.* **53** 2038 (2010)
135. M Y Cha, K O Lee, J W Kim, C G Lee, J Y Song, Y H Kim, G S Lee, S B Park, M S Kim *J. Med. Chem.* **52** 6880 (2009)
136. C Carmi, E Galvani, F Vacondio, S Rivara, A Lodola, S Russo, S Aiello, F Bordi, G Costantino, A Cavazzoni, R R Alfieri, A Ardizzoni, P G Petronini, M Mor *J. Med. Chem.* **55** 2251 (2012)
137. Patent US 2012283280 (2012)
138. Patent WO 2012125913 (2012)
139. F Vacondio, C Carmi, E Galvani, M Bassi, C Silva, A Lodola, S Rivara, A Cavazzoni, R R Alfieri, P G Petronini, M Mor *Bioorg. Med. Chem. Lett.* **23** 5290 (2013)
140. M M Hamed, D A Abou El Ella, A B Keeton, G A Piazza, A H Abadi, R W Hartmann, M Engel *ChemMedChem* **8** 1495 (2013)
141. J R Li, D D Li, F Fang, Q R Du, L Lin, J Sun, Y Quin, H L Zhu *Org. Biomol. Chem.* **11** 8375 (2013)
142. S Mowafy, N A Farag, K A M Abouzid *Eur. J. Med. Chem.* **61** 132 (2013)
143. Patent US 2010009958 (2010)
144. B Marvania, P C Lee, R Chaniyara, H Dong, S Suman, R Kakadtya, T C Chou, T C Lee, A Shah, T L Su *Bioorg. Med. Chem.* **19** 1987 (2011)
145. J Domarkas, F Dudouit, C Williams, Q Qiyu, R Banerjee, F Brahimi, B J Jean-Claude *J. Med. Chem.* **49** 3544 (2006)
146. G L Lu, A Ashoorzadeh, R F Anderson, A V Patterson *Tetrahedron* **69** 9130 (2013)
147. A V Patterson, J K Jaiswal, S P Valentine, M R Abbattista, W van Leeuwen, M A Puryer, A S Thompson, A Hsu, S Y Mehta, A Pruijn, G Lu, F Donate, W A Denny, W R Wilson, J B Smaill *Mol. Cancer Ther.* **8** (Suppl.) B76 (2009)
148. W J Slichenmyer, W L Elliott, D W Fry *Semin. Oncol.* **28** 80 (2001)
149. D Li, L Ambrogio, T Shimamura, S Kubo, M Takahashi, L R Chirieac *Oncogene* **27** 4702 (2008)
150. N Ioannou, A G Dalgleish, A M Seddon, D Mackintosh, U Guertler, F Solca, H Modjtahedi *Br. J. Cancer* **105** 1554 (2011)
151. Patent WO 2012121764 (2012)
152. Patent WO 2013052157 (2013)
153. N Katakami, S Atagi, K Goto, T Hida, T Horai, A Inoue, Y Ichinose, K Koboyashi, K Takeda, K Kiura, K Nishio, Y Seki, R Ebisawa, M Shahidi, N Yamamoto *J. Clin. Oncol.* **31** 3335 (2013)
154. G Xia, W Chen, J Zhang, J Shao, Y Zhang, W Huang, L Zhang, W Qi, X Sun, B Li, Z Xiang, C Ma, J Xu, H Deng, Y Li, P Li, H Miao, J Han, Y Liu, J Shen, Y Yu *J. Med. Chem.* **57** 9889 (2014)
155. R Albuschat, W Lowe, M Weber, P Luger, V Jendrossek *Eur. J. Med. Chem.* **39** 1001 (2004)
156. N Sirisoma, A Pervin, H Zhang, S Jiang, A Willardsen, M B Anderson, G Mather, C M Pleiman, S Kasibhatla, B Tseng, J Drewe, S X Cai *Bioorg. Med. Chem. Lett.* **20** 2330 (2010)
157. Patent WO 2008141843 (2008)
158. H Q Li, D D Li, X Lu, Y Y Xu, H L Zhu *Bioorg. Med. Chem.* **20** 317 (2012)
159. Patent WO 2013142875 (2013)
160. S Matheson, J P McNamee, B J Jean-Claude *J. Pharm. Exp. Ther.* **296** 832 (2001)
161. Z Rachid, F Brahimi, A Katsoulas, N Teoh, B J Jean-Claude *J. Med. Chem.* **46** 4313 (2003)
162. R Banerjee, Z Rachid, J McNamee, B J Jean-Claude *J. Med. Chem.* **46** 5546 (2003)
163. Z Rachid, F Brahimi, J Domarkas, B J Jean-Claude *Bioorg. Med. Chem. Lett.* **15** 1135 (2005)
164. Patent US 2006003970 (2006)

165. Z Rachid, F Brahimi, Q Qiu, C Williams, J M Hartley, J A Hartley, B J Jean-Claude *J. Med. Chem.* **50** 2605 (2007)
166. Z Rachid, M MacPhee, C Williams, M Todorova, B J Jean-Claude *Bioorg. Med. Chem. Lett.* **19** 5505 (2009)
167. A L Larroque-Lombard, M Todorova, N Golabi, C Williams, B J Jean-Claude *J. Med. Chem.* **53** 2104 (2010)
168. C S Harris, J G Kettle, E J Williams *Tetrahedron Lett.* **46** 7381 (2005)
169. J F Goossens, E Bouey-Bencteux, R Houssin, J P Henichart, P Colson, C Houssier, W Laine, B Baldeyrou, C Bailly *Biochemistry* **40** 4663 (2001)
170. A Garofalo, L Goossens, B Baldeyrou, A Lemoine, S Ravez, P Six, M-X David-Cordonnier, J-P Bonte, P Depreux, A Lansiaux, J-F Goossens *J. Med. Chem.* **53** 8089 (2010)
171. A Chilin, M T Conconi, G Marzaro, A Guiotto, L Urbani, F Tonus, P Parnigotto *J. Med. Chem.* **53** 1862 (2010)
172. M T Conconi, G Marzaro, L Urbani, I Zanusso, R Di Liddo, I Castagliuolo, P Brun, F Tonus, A Ferrarese, A Guiotto, A Chilin *Eur. J. Med. Chem.* **67** 373 (2013)
173. G Marzaro, A Coluccia, A Ferrarese, P Brun, I Castagliuolo, M T Conconi, G L Regina, R Bai, R Silvestri, E Hanel, A Chilin *J. Med. Chem.* **57** 4598 (2014)
174. D D Li, F Fang, J R Li, Q R Du, J Sun, H B Gong, H L Zhu *Bioorg. Med. Chem. Lett.* **22** 5870 (2012)
175. S Hu, G Xie, D X Zhang, C Davis, W Long, Y Hu, F Wang, X Kang, F Tan, L Ding, Y Wang *Bioorg. Med. Chem. Lett.* **22** 6301 (2012)
176. J Wu, W Chen, G Xia, J Zhang, J Shao, B Tan, C Zhang, W Yu, Q Weng, H Liu, M Hu, H Deng, Y Hao, J Shen, Y Yu *ACS Med. Chem. Lett.* **4** 974 (2013)
177. S K Bhattacharya, E D Cox, J C Kath, A M Mathiowetz, J Morris, J D Moyer, L R Pustilnik, K Rafidi, D T Richter, C Su, M D Wessel *Biochem. Biophys. Res. Commun.* **307** 267 (2003)
178. Patent WO 2004046101 (2004)
179. L T Liu, T T Yuan, H H Liu, S F Chen, Y T Wu *Bioorg. Med. Chem. Lett.* **17** 6373 (2007)
180. B Lippa, G S Kauffman, T Kwan, J Chen, W Hungerford, S Bhattacharya, X Zhao, C Williams, J Xiao, L Pustilnik, C Su, J D Moyer, L Ma, M Campbell, S Steyn *Bioorg. Med. Chem. Lett.* **17** 3081 (2007)
181. Patent US 2013165458 (2013)
182. G S Cockerill, C Stubberfield, J Stables, M Carter, S Guntrip, K Smith, S McKeown, R Shaw, P Tapley, L Thomson, K Affleck, A Jowett, D Hayes, M Wilson, P Wollard, D Spalding *Bioorg. Med. Chem. Lett.* **11** 1401 (2001)
183. Patent US 20050143401 (2005)
184. Patent US 6933299 (2005)
185. Patent WO 2005120512 (2005)
186. Patent WO 2006066267 (2006)
187. Patent US 2008051422 (2008)
188. Patent WO 2010005585 (2010)
189. A Lyu, L Fang, S Gou *Eur. J. Med. Chem.* **87** 631 (2014)
190. S Mahboobi, A Sellmer, M Winkler, E Eichhorn, H Pongratz, T Ciossek, T Baer, T Maier, T Beckers *J. Med. Chem.* **53** 8546 (2010)
191. Patent WO 2009063054 (2009)
192. L Zhang, C Fan, Z Guo, Y Li, S Zhao, S Yang, Y Yang, J Zhu, D Lin *Eur. J. Med. Chem.* **69** 833 (2013)
193. Patent EP 2484678 (2012)
194. Patent WO 2011084796 (2011)
195. P Ballard, R H Bradbury, L F A Hennequin, D M Hickinson, P D Johnson, J G Kettle, T Klinowska, R Morgentin, D J Ogilvie, A Olivier *Bioorg. Med. Chem. Lett.* **15** 4226 (2005)
196. P Ballard, B C Barlaam, R H Bradbury, A Dishington, L F A Hennequin, D M Hickinson, I M Hollingsworth, J G Kettle, T Klinowska, D J Ogilvie, S E Pearson, J S Scott, A Suleman, R Whittaker, E J Williams, R Wood, L Wright *Bioorg. Med. Chem. Lett.* **17** 6326 (2007)
197. Patent WO 2004096226 (2004)
198. Patent WO 2004093880 (2004)
199. Patent WO 2005026152 (2005)
200. Patent WO 2005051923 (2005)
201. Patent WO 2005118572 (2005)
202. Patent US 20130012528 (2013)
203. N Sirisoma, S Kasibhatla, A Pervin, H Zhang, S Jiang, J A Willardsen, M B Anderson, V Baichwal, G G Mather, K Jessing, R Hussain, K Hoang, C M Pleiman, B Tseng, J Drewe, S X Cai *J. Med. Chem.* **51** 4771 (2008)
204. Patent WO 2006074147 (2006)
205. N Sirisoma, A Pervin, H Zhang, S Jiang, J A Willardsen, M B Anderson, G G Mather, C M Pleiman, S Kasibhatla, B Tseng, J Drewe, S X Cai *J. Med. Chem.* **52** 2341 (2009)
206. H Z Li, H Y He, Y Y Han, X Gu, L He, Q R Qi, Y L Zhao, L Yang *Molecules* **15** 9473 (2010)
207. Patent WO 2010006115 (2010)
208. Patent US 20100068197 (2010)
209. K F Chen, K C Pao, J C Su, Y C Chou, C Y Liu, H J Chen, J W Huang, I K Kim, C W Shiau *Bioorg. Med. Chem.* **20** 6144 (2012)
210. J W Lockman, Y Klimova, M B Anderson, J A Willardsen *Synth. Commun.* **42** 1715 (2012)
211. M L de Castro Barbosa, L M Lima, R Tesch, C M R Sant'Anna, F Totzke, M H G Kubbutat, C Schachtele, S A Laufer, E J Barreiro *Eur. J. Med. Chem.* **71** 1 (2014)
212. M J Hour, J S Yang, T L Chen, K T Chen, S C Kuo, J G Chung, C C Lu, C Y Chen, Y H Chuang *Eur. J. Med. Chem.* **46** 2709 (2011)
213. L Zhang, L Ren, M Bai, L Weng, J Huang, L Wu, M Deng, X Zhou *Bioorg. Med. Chem.* **15** 6920 (2007)
214. M Maillard-Boyer, C Castera-Ducros, P Verhaeghe, F Sifredi, P Rathelot, P Vanelle *Molecules* **15** 2719 (2010)
215. L F Hennequin, A P Thomas, C Johnstone, E S E Stokes, P A Ple, J M Lohmann, D J Ogilvie, M Dukes, S R Wedge, J O Curwen, J Kendrew, C L van der Brempt *J. Med. Chem.* **42** 5369 (1999)
216. X P Liu, R K Narla, F M Uckun *Bioorg. Med. Chem. Lett.* **13** 581 (2003)
217. V D Sharma, K V A Seshu, V C Sekhar, S Madan, B Vishnu, P A Babu, C V Krishna, J Sreenu, V R Krishna, A Venkateswarlu, S Rajagopal, R Ajaykumar, T S Kumar *Bioorg. Med. Chem. Lett.* **14** 67 (2004)
218. K Abouzid, S Shouman *Bioorg. Med. Chem.* **16** 7543 (2008)
219. A Wissner, M B Floyd, B D Johnson, H L Fraser, C Ingalls, T Nittoli, R G Dushin, C Discafani, R Nilakantan, J Marini, M Ravi, K Cheung, X Tan, S Musto, T Annable, M M Siegel, F Loganzo *J. Med. Chem.* **48** 7560 (2005)
220. Patent WO 2005115145 (2005)
221. Patent WO 2007071963 (2007)
222. G W Rao, G J Xu, J Wang, X L Jiang, H B Li *ChemMedChem* **8** 928 (2013)
223. H Nakamura, R Horikoshi, T Usui, H S Ban *Med. Chem. Commun.* **1** 282 (2010)
224. M Getlik, C Grutter, J R Simard, M Rabiller, H B Rode, A Robubi, D Rauh *J. Med. Chem.* **52** 3915 (2009)
225. A Richters, J Ketzer, M Getlik, C Grutter, R Schneider, J M Heuckmann, S Heynck, M L Sos, A Gupta, A Unger, C Schultz-Fademrecht, R K Thomas, S Bauer, D Rauh *J. Med. Chem.* **56** 5757 (2013)

226. B Yu, L D Tang, Y L Li, S H Song, X L Ji, M S Lin, C F Wu *Bioorg. Med. Chem. Lett.* **22** 110 (2012)
227. Q Zhang, Y Diao, F Wang, Y Fu, F Tang, Q You, H Zhou *Med. Chem. Commun.* **4** 979 (2013)
228. X Zhang, M Su, Y Chen, J Li, W Lu *Molecules* **18** 6491 (2013)
229. A Garofalo, L Goossens, A Lemoine, S Ravez, P Six, M Howsam, A Farce, P Depreux *Med. Chem. Commun.* **2** 65 (2011)
230. H Nakamura, S Onagi *Tetrahedron Lett.* **47** 2539 (2006)
231. S Li, X Wang, Y He, M Zhao, Y Chen, J Xu, M Feng, J Chang, H Ning, C Qi *Eur. J. Med. Chem.* **67** 293 (2013)
232. P A Ple, T P Green, L F Hennequin, J C Curwen, M Fennell, J Allen, C L van der Brempt, G Costello *J. Med. Chem.* **47** 871 (2004)
233. Y Zhang, Y J Huang, H M Xiang, P Y Wang, W Xue, B A Song, S Yang *Eur. J. Med. Chem.* **78** 23 (2014)
234. L Shi, T T Wu, Z Wang, J Y Xue, Y G Xu *Bioorg. Med. Chem.* **22** 4735 (2014)
235. A Sharma, V Luxami, K Paul *Bioorg. Med. Chem. Lett.* **23** 3288 (2013)
236. J Cai, M Sun, X Wu, J Chen, P Wang, X Zong, M Ji *Eur. J. Med. Chem.* **63** 702 (2013)
237. F L Zhang, Q Huang, K Zheng, J Li, J Y Liu, J P Xue *Chem. Commun.* **49** 9570 (2013)
238. J Amin, I Chuckowree, G J Tizzard, S J Coles, M Wang, J P Bingham, J A Hartley, J Spencer *Organometallics* **32** 509 (2013)
239. K R Shreder, M S Wong, T Nomanbhoy, P S Leventhal, S R Fuller *Org. Lett.* **6** 3715 (2004)
240. S Y Han, S S Park, W G Lee, Y K Min, B T Kim *Bioorg. Med. Chem. Lett.* **16** 129 (2006)
241. P Johnström, A Fredriksson, J O Thorell, S Stone-Elander *J. Label. Compd. Radiopharm.* **41** 623 (1998)
242. S L Matheson, S Mzengeza, B J Jean-Claude *J. Label. Compd. Radiopharm.* **46** 729 (2003)
243. J Q Wang, M Gao, K D Miller, G W Sledge, Q H Zheng *Bioorg. Med. Chem. Lett.* **16** 4102 (2006)
244. M Gao, C M Lola, M Wang, K D Miller, G W Sledge, Q H Zheng *Bioorg. Med. Chem. Lett.* **21** 3222 (2011)
245. M Wang, M Gao, Q H Zheng *Bioorg. Med. Chem. Lett.* **24** 4455 (2014)
246. G Ortu, I Ben-David, Y Rozen, N M T Freedman, R Chisin, A Levitzki, E Mishani *Int. J. Cancer* **101** 360 (2002)
247. E Mishani, G Abourbeh, O Jacobson, S Dissoki, R Ben-Daniel, Y Rozen, M Shaul, A Levitzki *J. Med. Chem.* **48** 5337 (2005)
248. O Aberg, B Langstrom *J. Label. Compd. Radiopharm.* **55** 477 (2012)
249. Y Seimbille, M E Phelps, J Czernin, D H S Silverman *J. Label. Compd. Radiopharm.* **48** 829 (2005)
250. F Basuli, H Wu, C Li, Z D Shi, A Sulima, G L Griffiths *J. Label. Compd. Radiopharm.* **54** 633 (2011)
251. N Vasdev, P N Dorff, A R Gibbs, E Nandanan, L M Reid, J P O'Neil, H F VanBrocklin *J. Label. Compd. Radiopharm.* **48** 109 (2005)
252. S Dissoki, D Laky, E Mishani *J. Label. Compd. Radiopharm.* **49** 533 (2006)
253. A Pal, J A Balatoni, U Muhopadhyay, K Ogawa, C Gonzalez-Lepera, A Shavrin, A Volgin, W Tong, M M Alauddin, J G Gelovani *Mol. Imag. Biol.* **13** 853 (2011)
254. Y Chen, M Feng, S Li, J Xu, H Ning, Y He, X Wang, R Ding, C Qi *Bioorg. Med. Chem. Lett.* **22** 4745 (2012)
255. J K Lim, K Negash, S M Hanrahan, H F VanBrocklin *J. Label. Compd. Radiopharm.* **43** 1183 (2000)
256. M Shaul, G Abourbeh, O Jacobson, Y Rozen, D Laky, A Levitzki, E Mishani *Bioorg. Med. Chem.* **12** 3421 (2004)
257. C Fernandes, C Oliveira, L Gano, A Bourkoula, I Pirmettis, I Santos *Bioorg. Med. Chem.* **15** 3974 (2007)
258. S Dissoki, R Eshet, H Billauer, E Mishani *J. Label. Compd. Radiopharm.* **52** 41 (2009)
259. C Fernandes, I C Santos, I Santos, H J Pietzsch, J U Kunstler, W Kraus, A Rey, N Margaritis, A Bourkoula, A Chiotellis, M Paravaton-Petsotas, I Pirmettis *Dalton Trans.* 3215 (2008)
260. A Bourkoula, M Paravaton-Petsotas, A Papadopoulos, I Santos, H J Pietzsch, E Livaniou, M Prlecanou, M Papadopoulos *Eur. J. Med. Chem.* **44** 4021 (2009)
261. Q Meng, F Li, S Jiang, Z Li *ACS Med. Chem. Lett.* **4** 858 (2013)
262. H Yang, S K Kim, P A Reche *J. Clin. Invest.* **115** 379 (2005)
263. G N Lipunova, E V Nosova, A A Laeva, V N Charushin *Farm. Chem. J.* **45** 709 (2011) [*Khim.-Farm. Zh.* **45** (12) 7 (2011)]