

QUINAZOLINE COMPOUNDS FOR ANTITUMOR TREATMENT

G.I. Solyanik

R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology,
NAS of Ukraine, Kyiv 03022, Ukraine

Quinazolines are among the most useful heterocyclic compounds due to their diverse chemical reactivity and a wide range of biological activity. Despite a large number of publications devoted to quinazolines and their derivatives, information is presented predominantly regarding the features of the synthesis of these compounds and their structure. The studies of specific pharmacological activity and antitumor activity of these compounds are mainly limited to primary screening using enzyme systems and cell lines. In this mini review information concerning the potential targets for antitumor action of quinazoline compounds is summarized and discussed. **Key Words:** quinazolines, targets, antitumor action, antitumor treatment.

Quinazolines are among the most useful heterocyclic compounds due to their diverse chemical reactivity and a wide range of biological activity. Among the nitrogen-containing heterocyclic compounds, quinazolines are “building blocks” of more than 200 natural alkaloids isolated from plants, animals, and microorganisms [1]. Quinazoline derivatives exhibit antimalarial, antitumor, antimicrobial, antiviral, anti-inflammatory, antidepressant, anticonvulsant, diuretic, muscle relaxant activities and many others [2, 3].

The number of various compounds synthesized on the basis of quinazolines, and presented in the scientific literature is striking [4–7]. Most likely this is due to the relative simplicity of their synthesis and high expectations of their high pharmacological activity [8]. However, the majority of literary sources devoted to quinazolines and their derivatives provide only information on their synthesis and structure [9]. Studies of specific pharmacological activity are mainly limited to primary screening using enzyme systems and cell lines. This fully applies to studies of the antitumor activity of these compounds [10–12]. Information on *in vivo* studies involving experimental tumor models is scanty, and such data are mainly related to the compounds already registered for clinical use by pharmacological centers in various countries. One can only guess that *in vivo* studies of quinazoline compounds, which have shown good cytotoxic/cytostatic activity on cell lines, are conducted by the companies on a “non-disclosure” mode.

As has been shown by numerous studies, quinazolines and their derivatives can exhibit an antitumor effect via:

- inhibition of receptor tyrosine kinases (for example, epidermal growth factor receptor — EGFR) [13];
- inhibition of tubulins [14];
- induction of apoptosis [15, 16];

- inhibition of phosphatidylinositol-3-kinases (PI3K) [17];
- inhibition of ABC transporters to overcome the multidrug resistance of tumors [18, 19];
- inhibition of voltage-dependent sodium channels (antiangiogenic and analgesic effects) [20].

Of all the above-mentioned spectrum of targets for the antitumor action of quinazolines and their derivatives, inhibitors of receptor tyrosine kinases (RTK), mostly EGFR inhibitors have received the greatest development.

This specificity reflects, firstly, the current trend in oncology towards the creation of targeted anticancer drugs, and, secondly, the important role of RTK in vital activity of cells, including cancer cells [21, 22].

TYROSINE KINASES

In maintaining the life of higher organisms, the control of cell proliferation, differentiation and migration plays a key role. The normal course of these processes ensures the correct development and protective reactions of the body. The loss or weakening of their control can cause serious illnesses, including cancer. The appropriate regulation of cell proliferation, differentiation and cell motility is carried out through various mechanisms. One of them is the interaction of the cell with growth factors.

Growth factors are usually small polypeptides that stimulate or inhibit the main functions of cells. Growth factors act on their target cells, which are distinguished from other cells by the presence of specific receptors to the growth factor, exposed on the surface of cell membranes and characteristic of this particular cell type.

Surface receptors that perceive extracellular factors and “inform” the cell accordingly are “sensory organs” of cells. The specific interaction of external factors and membrane receptors initiates the process of signal transduction: the “impulse” that occurs on the cell membrane is amplified and transmitted into the cell along certain signal pathways. A cell response to a signal stimulus can have various manifestations: cell division (or, on the contrary, stopping of this process), differentiation, hormone secretion, etc.

Submitted: November 20, 2018.

Correspondence: E-mail: gsolyanik@gmail.com

Abbreviations used: EGFR – epidermal growth factor receptor; NSCLC – non-small cell lung cancer; PI3K – phosphatidylinositol-3-kinases; RTKs – receptor tyrosine kinases; TKIs – tyrosine kinase inhibitors; VDSCs – voltage-dependent sodium channels.

Among the main participants in the chain of signal transduction in cells are various types of kinases (tyrosine kinases), an important function of which is the transfer of the phosphate group from ATP (usually competitive) to amino acid residues of other proteins. Phosphorylation of target proteins leads to an instantaneous change in their conformation and properties. The balance between phosphorylation and dephosphorylation determines the transduction of intracellular signals.

Despite the fact that protein phosphorylation by tyrosine residues is a rarer event compared to serine or threonine phosphorylation, it has been established that tyrosine phosphorylation plays a key role in many cellular processes, such as proliferation, differentiation and migration [23].

There are two types of tyrosine kinases and tyrosine phosphatases: receptor and cytoplasmic [24–26]:

- RTKs are associated with receptors of almost all growth factors (epidermal growth factor, insulin-like growth factor, platelet growth factor, vascular growth factor, etc. [27]) and are involved in transmembrane signaling;
- intracellular (cytoplasmic) tyrosine kinases are involved in cell signaling processes, including the transfer of information to the nucleus.

All RTKs have a similar structure — they consist of a ligand-binding extracellular region, a hydrophobic transmembrane domain, and an intracellular (cytoplasmic) region. The latter, along with the catalytic tyrosine kinase domain, contains regulatory domains.

Recently, a special group of receptors transducing information involving tyrosine kinase has been identified among RTKs. These receptors do not have their own catalytic tyrosine kinase domain, but when activated they bind to cytoplasmic tyrosine kinases and form a signaling complex.

In a normal cell, kinases provide “awareness” and sensitivity of the cell to the action of the body’s regulatory systems (its “obedience”). Such “obedience” includes an adequate cell response to a signal to divide or to stop division, a signal to differentiation or apoptosis, a signal to move or not to move.

In contrast to normal cell, cancer cell is characterized by functional “deafness”, which ensures its independence from signals from tissues and other functional systems of the body. Such functional deafness of cancer cell is often provided by a disruption in the functioning of kinases (due to the numerous mutations of the genes encoding these proteins). Almost all nosological forms of malignant neoplasms are characterized by the presence of numerous mutations of the genes encoding kinases. Mutated RTKs can generate an intracellular proliferation signal in the absence of a ligand (growth factor). Other mutant growth factor receptors can block the differentiation of certain cell types [28]. It is important to note that kinase-independent programs can be activated in cancer cells, providing a high proliferative activity of these cells, which eliminates the cell response to the inhibitory effect of certain growth factors.

TYROSINE KINASE INHIBITORS

The important role that tyrosine kinases play in the biology of tumor cells has led to an intensive search for and creation of targeted antitumor drugs capable of inhibiting the activity of tyrosine kinases, both normal and mutant (tyrosine kinase inhibitors — TKIs). Table shows some of TKIs and their clinical status.

It is noteworthy that the main targets of the quinazoline-based TKIs are RTKs, among which EGFR prevails. The first generation of EGFR inhibitors, to which belong gefitinib and erlotinib, is characterized by a reversible mechanism of action. Their relatively high efficacy has been shown in multicenter clinical studies in the treatment of patients with non-small cell lung cancer (NSCLC) with EGFR mutations [29–31]. Based on these studies, gefitinib and erlotinib are recommended as the first line therapy for NSCLC patients with EGFR mutations [32–35].

Afatinib belongs to the class of irreversible inhibitors of mutant EGFR (the second generation of inhibitors) [36, 37]. The last two randomized blocks of clinical studies of this drug showed its high efficacy against NSCLC, and it was included in the treatment standards as the first line therapy for this localization [38].

Table. Antitumor activity of TKIs

Inhibitor	Tyrosine kinase target	Localization	Clinical status
Imatinib mesylate	BCR-ABL c-KIT PDGFR	Chronic myeloid leukemia; gastrointestinal stromal tumors	Approved
Gefitinib	ErbB1 (EGFR)	Lung cancer	Approved
Erlotinib	ErbB1 (EGFR)	Lung cancer	Approved
Afatinib	ErbB1 (EGFR)	Lung cancer	Approved
Lapatinib	ErbB1 (EGFR)	Breast cancer	Approved
Vandetanib	VEGFR	Metastatic medullar thyroid cancer	Approved
Rociletinib	ErbB1 (EGFR)	Lung cancer	Phase I/II
Canertinib	EGFR (nonselective)	Breast cancer	Phase I/II
Semaxinib (SU5416)	VEGFR-2 c-KIT, FLT-3	Acute myeloid leukemia	Phase I/II
Vatalanib	VEGFR-1 VEGF-2	Colorectal cancer; prostate and renal cancer	Phase I/II
Sunitinib malate	VEGFR PDGFR, c-KIT, FLT-3	Gastrointestinal stromal tumors; renal cancer	Phase II/III
Sorafenib	B-Raf VEGFR-2	Renal cancer; malignant melanoma	Phase II/III
Leflunomide	PDGFR	Prostate cancer	Phase II/III

Note: Inhibitors based on quinazoline compounds are highlighted in bold. CML – chronic myeloid leukemia; GIST – gastrointestinal stromal tumors.

However, despite such striking successes, the antitumor effect of gefitinib and erlotinib lasts about a year, and then most patients show an expressed disease progression due to the development of tumor resistance to the action of these targeted drugs. There are several mechanisms for the development of resistance to first-generation TKIs [39]. In about half of the cases, resistance is due to the emergence of an additional mutation in the tyrosine kinase domain of the receptor, which disrupts their binding to active sites. In another 35–40% of cases, resistance is due to the activation of additional signaling pathways in cancer cell. Unfortunately, second-generation TKIs, such as afatinib, have not been effective enough in the case of development of resistance to first-generation inhibitors. Third-generation TKIs such as rociletinib were synthesized to induce an antitumor effect in the presence of the Del19, L858R and T790M mutations and are now in Phase I–II of clinical trials [40].

The third generation of kinase inhibitors with a new molecular target includes vandetanib, which inhibits the kinase of the vascular endothelial growth factor receptor. This receptor is actively involved in tumor angiogenesis and its inhibition causes antiangiogenic and, as a result, antimetastatic effect. This is reflected in the results of both preclinical and clinical studies. This drug has proven to be effective in treating metastatic forms of medullary thyroid cancer and has been approved for the treatment of patients with this localization [41].

The search for and creation of new quinazoline-based antitumor compounds, which are able to effectively and selectively inhibit the EGFR, is being actively pursued [42]. The synthesis of quinazoline compounds capable of acting simultaneously on several molecular targets that affect the survival of malignant cells is also promising. For example, there are studied compounds that simultaneously inhibit (i) EGFR and tubulin polymerization in cancer cells [43] or (ii) EGFR and PI3K [44].

OTHER POTENTIAL TARGETS FOR ANTITUMOR ACTION OF QUINAZOLINE COMPOUNDS

The ability of some quinazolines and their derivatives to inhibit tubulins undoubtedly deserves special attention [45]. It is known that tubulin is the main structural protein of microtubules, which play an important role in cell division and cell motility. Tubulin is a target for such effective anticancer drugs widely used in oncological practice as vincristine, vinblastine, taxol, docetaxel and paclitaxel. By binding to tubulin, these agents prevent the formation of microtubules involved in the mitotic spindle. Tubulin-inhibiting agents also provide an antimetastatic effect by inhibiting cell motility and invasiveness.

The ability of quinazolines to inhibit voltage-dependent sodium channels (VDSCs) can also provide the antimetastatic effect [20]. It is known that VDSCs have a significant effect on cell proliferation, adhesion, mo-

tility, etc. [46]. VDSCs are expressed not only in nerve and muscle cells, but also in many non-excitabile cell systems, including endothelial cells and cancer cells. The important role played by VDSCs in cell activity, as well as the high expression of these channels in metastatically active cells, give reason to consider them as a promising molecular target for antitumor, antiangiogenic and antimetastatic therapy [47]. It is also important to emphasize that inhibition of VDSCs underlies the analgesic effect, a very important property for the creation of antitumor drugs.

CONCLUSION

The pharmacological properties of quinazolines substantially depend on their structure. The limiting factor is undoubtedly the poor solubility of many quinazoline compounds. High chemical reactivity can also complicate the study of their specific antitumor or antimetastatic activity. Despite that, quinazolines represent promising “chemical construction set” for creating anticancer drugs with a wide arsenal of targets for therapeutic intervention.

REFERENCES

1. Long S, Resende DISP, Kijjoa A, *et al.* Antitumor activity of quinazolinone alkaloids inspired by marine natural products. *Mar Drugs* 2018; **16**: e261.
2. Asif M. Chemical characteristics, synthetic methods, and biological potential of quinazoline and quinazolinone derivatives. *Int J Med Chem* 2014; **2014**: 395637.
3. Srivastava S, Srivastava S. Biological activity of quinazoline: a review. *Int J Pharma Sci Res* 2015; **6**: 1206–13.
4. Rakesh KP, Darshini N, Shubhavathi T, Mallesha N. Biological applications of quinazolinone analogues: A review. *Org Med Chem IJ* 2017; **2**: 555585.
5. Abbott JR, Patel PA, Howes JE, *et al.* Discovery of quinazolines that activate SOS1-mediated nucleotide exchange on RAS. *ACS Med Chem Lett* 2018; **9**: 941–6.
6. Chen J, Sang Z, Jiang Y, *et al.* Design, synthesis, and biological evaluation of quinazoline derivatives as dual HDAC1 and HDAC6 inhibitors for the treatment of cancer. *Chem Biol Drug Des* 2018. doi: 10.1111/cbdd.13405.
7. Hameed A, Al-Rashida M, Uroos M, *et al.* Quinazoline and quinazolinone as important medicinal scaffolds: a comparative patent review (2011–2016). *Expert Opin Ther Pat* 2018; **28**: 281–97.
8. Conconi MT, Marzaro G, Urbani L, *et al.* Quinazoline-based multi-tyrosine kinase inhibitors: synthesis, modeling, antitumor and antiangiogenic properties. *Eur J Med Chem* 2013; **67**: 373–83.
9. Alam MJ, Alam O, Naim MJ, *et al.* Recent investigations on quinazoline scaffold. *Int J Advanced Res* 2015; **3**: 1656–64.
10. Abdel Gawad NM, Georgey HH, Youssef RM, *et al.* Synthesis and antitumor activity of some 2, 3-disubstituted quinazolin-4(3H)-ones and 4, 6-disubstituted-1, 2, 3, 4-tetrahydroquinazolin-2H-ones. *Eur J Med Chem* 2010; **45**: 6058–67.
11. He J, Wang X, Zhao X, *et al.* Synthesis and antitumor activity of novel quinazoline derivatives containing thiosemicarbazide moiety. *Eur J Med Chem* 2012; **54**: 925–30.
12. Marvania B, Lee PC, Chaniyara R, *et al.* Design, synthesis and antitumor evaluation of phenyl N-mustard-quinazoline conjugates. *Bioorg Med Chem* 2011; **19**: 1987–98.
13. Alqasoumi SI, Al-Taweel AM, Alafeefy AM, *et al.* Discovering some novel tetrahydroquinoline derivatives bearing the biologically active sulfonamide moiety as a new

class of antitumor agents. *Eur J Med Chem* 2010; **45**: 1849–53.

14. Chinigo GM, Paige M, Grindrod S, et al. Asymmetric synthesis of 2,3-dihydro-2-arylquinazolin-4-ones: methodology and application to a potent fluorescent tubulin inhibitor with anticancer activity. *J Med Chem* 2008; **51**: 4620–31.

15. Sirisoma N, Pervin A, Zhang H, et al. Discovery of N-methyl-4-(4-methoxyanilino)quinazolines as potent apoptosis inducers. Structure-activity relationship of the quinazoline ring. *Bioorg Med Chem Lett* 2010; **20**: 2330–4.

16. Al-Obeed O, Vaali-Mohammed MA, Eldehna WM, et al. Novel quinazoline-based sulfonamide derivative (3D) induces apoptosis in colorectal cancer by inhibiting JAK2-STAT3 pathway. *Onco Targets Ther* 2018; **11**: 3313–22.

17. Peng W, Tu ZC, Long ZJ, et al. Discovery of 2-(2-aminopyrimidin-5-yl)-4-morpholino-N-(pyridin-3-yl)quinazolin-7-amines as novel PI3K/mTOR inhibitors and anticancer agents. *Eur J Med Chem* 2016; **108**: 644–54.

18. Krapf MK, Gallus J, Spindler A, et al. Synthesis and biological evaluation of quinazoline derivatives — A SAR study of novel inhibitors of ABCG2. *Eur J Med Chem* 2018; **161**: 506–25.

19. Krapf MK, Gallus J, Wiese M. Synthesis and biological investigation of 2,4-substituted quinazolines as highly potent inhibitors of breast cancer resistance protein (ABCG2). *Eur J Med Chem* 2017; **139**: 587–611.

20. Alafeefy AM, Kadi AA, Al-Deeb OA, et al. Synthesis, analgesic and anti-inflammatory evaluation of some novel quinazoline derivatives. *Eur J Med Chem* 2010; **45**: 4947–52.

21. Marzaro G, Guiotto A, Chilin A. Quinazoline derivatives as potential anticancer agents: a patent review (2007–2010). *Expert Opin Ther Pat* 2012; **22**: 223–52.

22. Ravez S, Castillo-Aguilera O, Depreux P, et al. Quinazoline derivatives as anticancer drugs: a patent review (2011–present). *Expert Opin Ther Pat* 2015; **25**: 789–804.

23. Glenney JR. Tyrosine-phosphorylated proteins: mediators of signal transduction from the tyrosine kinases. *Biochim Biophys Acta* 1992; **1134**: 113–27.

24. Karin M, Hunter T. Transcriptional control by protein phosphorylation: signal transmission from the cell surface to the nucleus. *Curr Biol* 1995; **5**: 747–57.

25. Schlaepfer DD, Hunter T. Signal transduction from the extracellular matrix — a role for the focal adhesion protein-tyrosine kinase FAK. *Cell Struct Funct* 1996; **21**: 445–50.

26. Tonks NK, Neel BG. From form to function: signaling by protein tyrosine phosphatases. *Cell* 1996; **87**: 365–8.

27. Cadena DL, Gill GN. Receptor tyrosine kinases. *FASEB J* 1992; **6**: 2332–7.

28. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009; **361**: 958–67.

29. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350**: 2129–39.

30. Song Z, Zhang Y. Efficacy of gefitinib or erlotinib in patients with squamous cell lung cancer. *Arch Med Sci* 2015; **1**: 164–8.

31. Asami K, Atagi S. Comparing the efficacy of gefitinib, erlotinib, and afatinib in non-small cell lung cancer with acti-

vating epidermal growth factor receptor (EGFR) mutations. *Austin J of Lung Cancer Res* 2016; **1**: 1–6.

32. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010; **362**: 2380–8.

33. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; **12**: 735–42.

34. Faehling M, Achenbach J, Staib P, et al. Erlotinib in routine clinical practice for first-line maintenance therapy in patients with advanced non-small cell lung cancer (NSCLC). *J Cancer Res Clin Oncol* 2018; **144**: 1375–83.

35. Zhang W, Wei Y, Yu D, et al. Gefitinib provides similar effectiveness and improved safety than erlotinib for advanced non-small cell lung cancer: A meta-analysis. *Medicine (Baltimore)* 2018; **97**: e0460.

36. Marquez-Medina D, Popat S. Afatinib: a second-generation EGF receptor and ErbB tyrosine kinase inhibitor for the treatment of advanced non-small-cell lung cancer. *Future Oncol* 2015; **11**: 2525–40.

37. Joshi M, Rizvi SM, Belani CP. Afatinib for the treatment of metastatic non-small cell lung cancer. *Cancer Manag Res* 2015; **7**: 75–82.

38. Sharma N, Graziano S. Overview of the LUX-Lung clinical trial program of afatinib for non-small cell lung cancer. *Cancer Treat Rev* 2018; **69**: 143–51.

39. Yoshimura A, Uchino J, Tanimura K, et al. An observational study of the epidermal growth factor receptor-tyrosine kinase inhibitor resistance mechanism in epidermal growth factor receptor gene mutation-positive non-small cell lung cancer. *Medicine (Baltimore)* 2018; **97**: e12660.

40. Sequist LV, Soria J-C, Goldman JW, et al. Rociletinib in EGFR-Mutated Non-Small-Cell Lung Cancer. *N Engl J Med* 2015; **372**: 1700–9.

41. Fallahi P, Ferrari SM, Baldini E, et al. The safety and efficacy of vandetanib in the treatment of progressive medullary thyroid cancer. *Expert Rev Anticancer Ther* 2016; **16**: 1109–18.

42. Hou W, Ren Y, Zhang Z, et al. Novel quinazoline derivatives bearing various 6-benzamide moieties as highly selective and potent EGFR inhibitors. *Bioorg Med Chem* 2018; **26**: 1740–50.

43. Zayed MF, Rateb HS, Ahmed S, et al. Quinazolinone-amino acid hybrids as dual inhibitors of EGFR kinase and tubulin polymerization. *Molecules* 2018; **23**: e1699.

44. Ding HW, Deng CL, Li DD, et al. Design, synthesis and biological evaluation of novel 4-aminoquinazolines as dual target inhibitors of EGFR-PI3K α . *Eur J Med Chem* 2018; **146**: 460–70.

45. Li W, Yin Y, Shuai W, et al. Discovery of novel quinazolines as potential anti-tubulin agents occupying three zones of colchicine domain. *Bioorg Chem* 2018; **83**: 380–90.

46. Nilius B, Droogmans G. A role for K⁺ channels in cell proliferation. *News Physiol Sci* 1994; **9**: 105–10.

47. Fraser S, Grimes J, Djamgo M. Effects of voltage-gated ion channel modulators on rat prostatic cancer cell proliferation: Comparison of strongly and weakly metastatic cell lines. *Prostate* 2000; **44**: 61–76.