www.ijarp.com ISSN 2456-9992 Page: 01-10

International Journal Advanced Research Publications

Research Article

Volume: 02
Issue: 06

# TYROSINE KINASE INHIBITORS AS TARGETED ANTICANCER AGENTS: MECHANISMS AND THERAPEUTIC APPLICATIONS

**Dr. Padige Sri Varsha[1] Vislavath Rahul[2*]**

[1]Associate Professor, Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, Kompally(Po)Secunderabad-500100.

[2]PharmD Second Year, Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, Kompally(Po)Secunderabad-500100.

**Article Received: 24 April 2026, Article Revised: 14 May 2026, Published on: 04 June 2026**

***Corresponding Author: Vislavath Rahul**

PharmD Second Year, Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, Kompally(Po)Secunderabad-500100.

DOI: https://doi-doi.org/101555/ijarp.2231

**ABSTRACT:**

Cancer remains one of the leading causes of morbidity and mortality worldwide. Conventional treatment approaches such as chemotherapy and radiotherapy often affect both cancerous and healthy cells, resulting in significant adverse effects. The development of targeted therapies has transformed cancer treatment by selectively inhibiting molecular pathways involved in tumor growth and progression. Tyrosine kinase inhibitors (TKIs) represent an important class of targeted anticancer agents that block the activity of tyrosine kinases, enzymes involved in cell signaling, proliferation, differentiation, angiogenesis, and survival.

This review discusses the mechanisms of action of TKIs, their classification, therapeutic applications in various malignancies, advantages, limitations, and future perspectives in precision oncology.

**KEYWORDS:** Tyrosine kinase inhibitors, targeted therapy, cancer, receptor tyrosine kinase, molecular oncology, anticancer agents.

## INTRODUCTION

Advances in molecular biology have improved our understanding of cancer development and progression. Many cancers are driven by abnormalities in signaling pathways regulated by protein kinases. Tyrosine kinases play a crucial role in transmitting signals from the cell

surface to the nucleus, controlling cellular growth, survival, and differentiation. Dysregulation of these enzymes through mutations, overexpression, or chromosomal rearrangements can contribute to oncogenesis.

Tyrosine kinase inhibitors have emerged as a revolutionary treatment strategy by specifically targeting these abnormal signaling pathways. Unlike traditional chemotherapy, which affects rapidly dividing cells indiscriminately, TKIs selectively inhibit cancer-promoting molecules, thereby improving therapeutic outcomes and reducing toxicity.

**Tyrosine Kinases: Structure and Function**

Tyrosine kinases are enzymes that catalyze the transfer of phosphate groups from adenosine triphosphate (ATP) to tyrosine residues on substrate proteins. This phosphorylation process regulates intracellular signaling pathways involved in cell growth and survival.

**Tyrosine kinases are broadly classified into**

**1. Receptor Tyrosine Kinases (RTKs)**

These enzymes are located on the cell membrane and are activated by extracellular ligands such as growth factors. Examples include:

- Epidermal Growth Factor Receptor (EGFR)
- Human Epidermal Growth Factor Receptor 2 (HER2)
- Vascular Endothelial Growth Factor Receptor (VEGFR)
- Platelet-Derived Growth Factor Receptor (PDGFR)

**2. Non-Receptor Tyrosine Kinases**

These enzymes function within the cytoplasm and nucleus. Examples include:

- BCR-ABL kinase
- Src family kinases
- Janus kinases (JAKs)

Abnormal activation of these kinases contributes to uncontrolled cell proliferation and tumor progression**.**

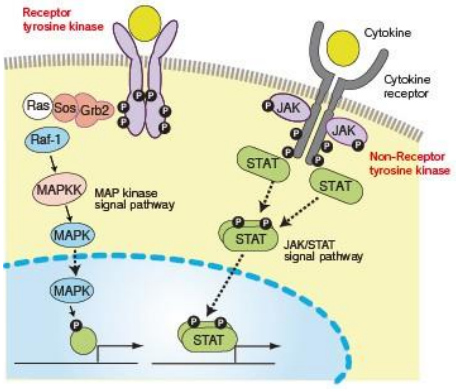


**Figure 1: Classification of tyrosine kinases into receptor tyrosine kinases (RTKs) and non- receptor tyrosine kinases involved in cancer progression.**

**Mechanism of Action of Tyrosine Kinase Inhibitors**

Tyrosine kinase inhibitors interfere with kinase-mediated signaling pathways by binding to the ATP-binding site or other regulatory regions of tyrosine kinases. This prevents phosphorylation and subsequent activation of downstream signaling cascades.

The major mechanisms include:

**Inhibition of Cell Proliferation**

TKIs block signaling pathways such as PI3K/AKT and RAS/RAF/MEK/ERK, thereby suppressing tumor cell growth.

**Induction of Apoptosis**

Inhibition of survival pathways promotes programmed cell death in malignant cells.

**Anti-Angiogenic Activity**

Certain TKIs inhibit VEGFR-mediated angiogenesis, reducing blood supply to tumors and limiting their growth.

**Prevention of Metastasis**

By interfering with signaling pathways involved in cell migration and invasion, TKIs can reduce metastatic spread.

Growth Factor Binding

↓

Activation of Tyrosine Kinase Receptor

↓

Autophosphorylation of Tyrosine Residues

↓

Activation of Signaling Pathways (PI3K/AKT, RAS/RAF/MEK/ERK)

↓

Cell Proliferation, Survival & Angiogenesis

↓

TKI Administration

↓

Blockade of ATP Binding Site

↓

Inhibition of Phosphorylation

↓

Apoptosis + Reduced Tumor Growth

**Table 1: Classification of Tyrosine Kinase Inhibitors.**

| Class | Target | Examples | Indications |
|---|---|---|---|
| EGFR Inhibitors | EGFR | Gefitinib, Erlotinib, Osimertinib | NSCLC |
| BCR-ABL Inhibitors | BCR-ABL | Imatinib, Dasatinib, Nilotinib | CML |
| VEGFR Inhibitors | VEGFR | Sorafenib, Sunitinib, Pazopanib | RCC, HCC |
| ALK Inhibitors | ALK | Crizotinib, Alectinib, Lorlatinib | NSCLC |
| HER2 Inhibitors | HER2 | Lapatinib, Tucatinib | Breast Cancer |

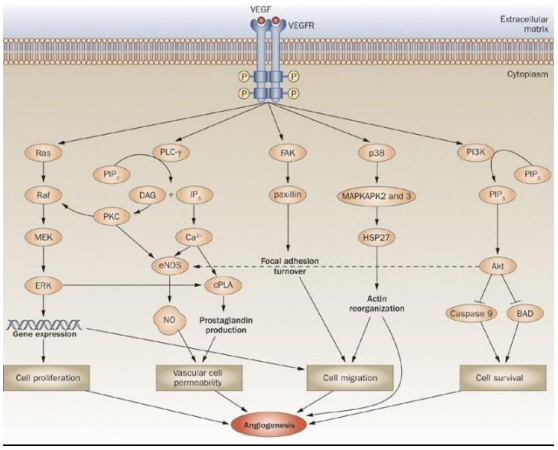


**Figure 2: Major molecular targets inhibited by currently approved tyrosine kinase inhibitors.**

**Table 2: FDA-Approved Tyrosine Kinase Inhibitors and Their Clinical Uses.**

| Drug | Target | Approved cancer type |
|---|---|---|
| Imatinib | BCR-ABL, KIT | CML, GIST |
| Gefitinib | EGFR | NSCLC |
| Erlotinib | EGFR | NSCLC, Pancreatic Cancer |
| Osimertinib | EGFR T790M | NSCLC |
| Sorafenib | VEGFR, RAF | Hepatocellular Carcinoma |
| Sunitinib | VEGFR, PDGFR | Renal Cell Carcinoma |
| Crizotinib | ALK | NSCLC |

**Development of Drug Resistance to TKIs**

Initial TKI Treatment

↓

Effective Tumor Response

↓

Prolonged Drug Exposure

↓

Secondary Mutations or Alternative Pathway Activation

↓

Reduced Drug Sensitivity

↓

Disease Progression

↓

Next-Generation TKIs / Combination Therapy

**Table 3: Advantages and Limitations of Tyrosine Kinase Inhibitors.**

| Advantages | Limitations |
|---|---|
| Target-specific action | Development of resistance |
| Oral administration | High treatment cost |
| Better patient compliance | Long-term adverse effects |
| Reduced toxicity | Need for molecular testing |
| Improved survival outcomes | Limited efficacy in some tumors |

**Therapeutic Applications**

**Chronic Myeloid Leukemia (CML)**

The introduction of imatinib significantly improved the prognosis of patients with CML by targeting the BCR-ABL fusion protein. It remains a landmark example of successful targeted therapy.

**Non-Small Cell Lung Cancer (NSCLC)**

EGFR-targeted TKIs such as gefitinib, erlotinib, and osimertinib have demonstrated remarkable efficacy in patients harboring EGFR mutations.

**Renal Cell Carcinoma**

VEGFR inhibitors including sunitinib and pazopanib are widely used to inhibit tumor angiogenesis and disease progression.

**Breast Cancer**

HER2-positive breast cancer patients benefit from HER2-targeted TKIs such as lapatinib and tucatinib, particularly in advanced disease settings.

**Gastrointestinal Stromal Tumors (GIST)**

Imatinib has shown substantial clinical benefits in GIST patients with KIT or PDGFRA mutations.

**Hepatocellular Carcinoma**

Sorafenib and lenvatinib have become important treatment options for advanced liver cancer by targeting multiple kinase pathways.

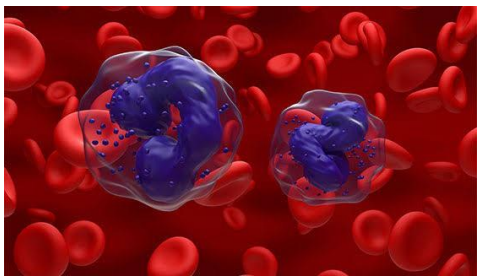

**Figure 3: Major cancer types successfully treated using tyrosine kinase inhibitors.**

**Targeted Therapy for Cancer**

**Table 4: Major cancer types successfully treated using tyrosine kinase inhibitors.**

## RESULTS

### Advantages of Tyrosine Kinase Inhibitor

- High target specificity
- Improved therapeutic efficacy
- Reduced systemic toxicity compared to conventional chemotherapy ● Oral administration enhances patient convenience
- Potential for personalized treatment based on molecular profiling ● Improved progression-free survival in several cancers

## LIMITATIONS AND CHALLENGES

### Drug Resistance

Resistance remains a significant challenge and may occur through:

- Secondary mutations in target kinases
- Activation of alternative signaling pathways ● Gene amplification
- Tumor heterogeneity

### Adverse Effects

Although generally better tolerated than chemotherapy, TKIs may cause:

- Skin rash ● Diarrhea
- Fatigue
- Hypertension ● Hepatotoxicity ● Cardiotoxicity

### High Treatment Cost

The long-term use of targeted therapies can impose substantial economic burdens on healthcare systems and patients.

### Future Perspectives

The future of TKI therapy is closely linked to precision medicine. Advances in genomic profiling and biomarker identification are enabling more accurate patient selection and treatment optimization. Combination therapies involving TKIs, immunotherapies, and monoclonal antibodies are being investigated to overcome resistance and improve outcomes. The development of next-generation inhibitors with greater selectivity and reduced toxicity is expected to further enhance cancer management.

## CONCLUSION

Tyrosine kinase inhibitors have revolutionized cancer treatment by providing a targeted and effective approach to managing various malignancies. Their ability to selectively inhibit dysregulated signaling pathways has improved survival outcomes and quality of life for many patients. Despite challenges such as resistance and adverse effects, ongoing research continues to expand their therapeutic potential. As precision oncology evolves, TKIs are expected to remain a cornerstone of personalized cancer therapy.

## REFERENCES


1. Cohen P. Protein kinases—the major drug targets of the twenty-first century. Nat Rev Drug Discov. 2002;1(4):309–315.
2. Roskoski R Jr. Properties of FDA-approved small molecule protein kinase inhibitors. Pharmacol Res. 2019;144:19–50.
3. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR- ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344(14):1031–1037.
4. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 2010;141(7):1117–1134.
5. Zhang J, Yang PL, Gray NS. Targeting cancer with small molecule kinase inhibitors. Nat Rev Cancer. 2009;9(1):28–39.
6. Manning G, Whyte DB, Martinez R, et al. The protein kinase complement of the human genome. Science. 2002;298(5600):1912–1934.
7. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med. 2005;353(2):172–187.
8. Hunter T. Tyrosine phosphorylation: thirty years and counting. Curr Opin Cell Biol. 2009;21(2):140–146.
9. Baselga J. Targeting tyrosine kinases in cancer: the second wave. Science. 2006;312(5777):1175–1178.
10. Arteaga CL. Overview of epidermal growth factor receptor biology and its role as a therapeutic target in human neoplasia. Semin Oncol. 2002;29(5):3–9.
11. Ségaliny AI, Tellez-Gabriel M, Heymann MF, et al. Receptor tyrosine kinases: characterization, mechanism of action and therapeutic interests for bone cancers. J Bone Oncol. 2015;4(1):1–12.
12. Gschwind A, Fischer OM, Ullrich A. The discovery of receptor tyrosine kinases. Nat Rev

Cancer. 2004;4(5):361–370.

13. Hojjat-Farsangi M. Small-molecule inhibitors of the receptor tyrosine kinases: promising tools for targeted cancer therapies. Int J Mol Sci. 2014;15(8):13768–13801.
14. Roskoski R Jr. Classification of small molecule protein kinase inhibitors based upon the structures of their drug-enzyme complexes. Pharmacol Res. 2016;103:26–48.
15. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007;7(3):169–181.
16. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947–957.
17. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced NSCLC. N Engl J Med. 2018;378(2):113–125.
18. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK- positive lung cancer. N Engl J Med. 2013;368(25):2385–2394.
19. Camidge DR, Peters S, Mok T, et al. Alectinib versus crizotinib in untreated ALK-positive NSCLC. N Engl J Med. 2018;379(20):2027–2039.
20. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002;347(7):472–480.
21. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumors. J Clin Oncol. 2003;21(23):4342– 4349.
22. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115–124.
23. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125–134.
24. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–390.
25. Burstein HJ, Sun Y, Dirix LY, et al. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor. J Clin Oncol. 2010;28(8):1301–1307.
26. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020;382(7):597–609.
27. Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. Nat Rev Cancer. 2010;10(11):760–774.
28. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. Nat Rev Cancer. 2013;13(10):714–726.

29. Gottesman MM. Mechanisms of cancer drug resistance. Annu Rev Med. 2002;53:615–627.
30. Redaelli S, Piazza R, Rostagno R, et al. Activity of tyrosine kinase inhibitors in cancer therapy. Cancer Lett. 2012;320(1):1–10.
31. Blume-Jensen P, Hunter T. Oncogenic kinase signalling. Nature. 2001;411(6835):355–365.
32. Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther. 2005;315(3):971–979.
33. Bhullar KS, Lagarón NO, McGowan EM, et al. Kinase-targeted cancer therapies: progress, challenges and future directions. Mol Cancer. 2018;17(1):48.
34. Roskoski R Jr. Targeting oncogenic protein kinases in cancer therapy. Pharmacol Res. 2015;100:1–23.
35. Wu P, Nielsen TE, Clausen MH. FDA-approved small-molecule kinase inhibitors. Trends Pharmacol Sci. 2015;36(7):422–439.
36. Ferguson FM, Gray NS. Kinase inhibitors: the road ahead. Nat Rev Drug Discov. 2018;17(5):353–377.
37. Chislock EM, Ring C, Pendergast AM. Abl kinases are required for vascular leak during inflammation. Cell Commun Signal. 2013;11:21.
38. Dancey J, Sausville EA. Issues and progress with protein kinase inhibitors for cancer treatment. Nat Rev Drug Discov. 2003;2(4):296–313.
39. Shawver LK, Slamon D, Ullrich A. Smart drugs: tyrosine kinase inhibitors in cancer therapy. Cancer Cell. 2002;1(2):117–123.
40. Fabbro D, Cowan-Jacob SW, Möbitz H, Martiny-Baron G. Targeting cancer with small-molecule kinase inhibitors. Cancer Res. 2015;75(7):1158–1163.