JGTPS, 2015, Vol. 6(3): 2728 - 2744

ISSN- 2230-7346

Journal of Global Trends in Pharmaceutical Sciences

Journal home page: www.jgtps.com

PYRAZOLE SCAFFOLD: A PROMISING TOOL IN THE DEVELOPMENT OF ANTIPROLIFERATIVE AGENTS

Parameshwar. Ravula[1*],
Harinadha Babu. V[2],
Manichandrika. P[3],
Narendra Sharath Chandra JN[1],
Venkata Ramana Reddy M[1],
Srinivas.B[4]

[1]Department of Pharmaceutical Chemistry, Guru Nanak Institutions Technical Campus, School of Pharmacy, Hyderabad-501301, India.
[2]Medicinal Chemistry Division, G. Pulla Reddy College of Pharmacy, Osmania University, Hyderabad - 500028. India.

[3]Department of Pharmaceutical Chemistry, Bojjam Narsimulu Pharmacy College for Woman, Hyderabad-500028, India.

[4]Department of Humanities & Sciences, GNITC, Hyderabad-501301, India.

ABSTRACT

There have been remarkable development in the chemotherapy of cancer and thousands of researches are still developing novel drugs to combat cancer. In the recent years, pyrazole derivatives have been more attracted, because of their wide spectrum of pharmacological activities. Various structural variations in the pyrazole nucleus have been made to explore various biological activities. The present work aims to review current advances of an emerging 'new wave' of pyrazole scaffold as potent antiproliferative agents that may target a variety of receptors such as vascular endothelial growth factor (VEGF), tyrosine kinase, Aurora-A kinase, protein kinase inhibitor, polo-like kinase inhibitors, tumor growth factor (TGF), fibroblast growth factor (FGF), BRAF kinase, and cyclin dependent kinase (CDK), which are important for management of cancer.

Keywords: Pyrazoles, Vascular endothelial growth factor (VEGF), BRAF kinase, Cyclin dependent kinase (CDK).

INTRODUCTION

Cancer is a major chronic disease, social burden, and second leading cause of death worldwide. In recent years, small molecules are widely explored as biological agents and among them pyrazoles have attracted much attention, because of their unique structure. Some of the drugs, possessing pyrazole as basic nucleus, like lonazlac[1], celecoxib[2], deracoxib[3], Sildenafil[4] and atorivodine[5]. Pyrazole derivatives possess a wide range of biological activities such as antibacterial[6], antiglaucoma[7], antifungal[8], hypoglycaemic[9], antiviral[10], antiparasitic[11], and insecticidal[12]. Some of these derivatives also exhibit antioxidant[13], anti-inflammatory[14], antitumor[15], antiangiogenesis[16], antimalarial[17], sodium channel blocker[18], antihypertensive[19], antitubercular[20], and HIV-1 reverse transcriptase[21] activity.

Address for correspondence

Parameshwar. Ravula*
Department of Pharmaceutical Chemistry, Guru Nanak Institutions Technical Campus, School of Pharmacy, Hyderabad-501301.
E-mail: parmipharma@gmail.com

Structure of pyrazole

Pyrazole belongs to the class of five member heterocyclic diazole series[22], containing three carbon atoms and two nitrogen atoms in adjacent positions. Among the two nitrogen atoms; one is neutral and the other is basic in nature. These are aromatic molecules due to their planar conjugated ring structures with six delocalized π-electrons. The aromatic nature arises from the unshared pair of electrons on the –NH nitrogen and the four π electrons.

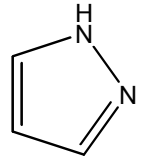
ANTI CANCER ACTIVITY

Pyrazoles against various cell lines

A. M. Farag et. al[23], by regioselective 1, 3-dipolar cycloaddition, prepared a new class of 3-[(E)-3-(dimethylamino)acryloyl]-1,5-diphenyl-1Hpyrazole-4-carbonitrile and antitumor screening utilizing 14 cell lines of breast and ovarian. Two of the synthesized derivatives **2a** and **2b** exhibited a significant anti-proliferative activity with IC_{50} values in nanomolar range.

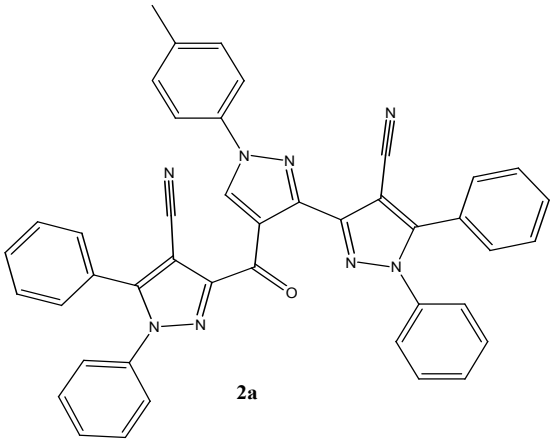
Properties

Molecular formula	C_3H_4N2
Molar mass	68.08 mol-1
Melting point	66-70°C
Boiling point	186-188°C
Basicity	11.5

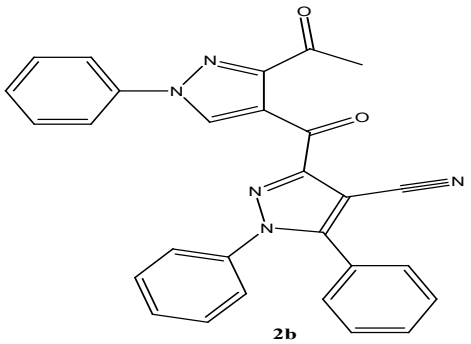


1*H*-pyrazole

1

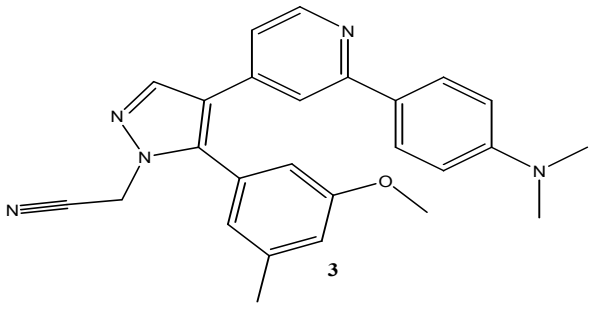


2a



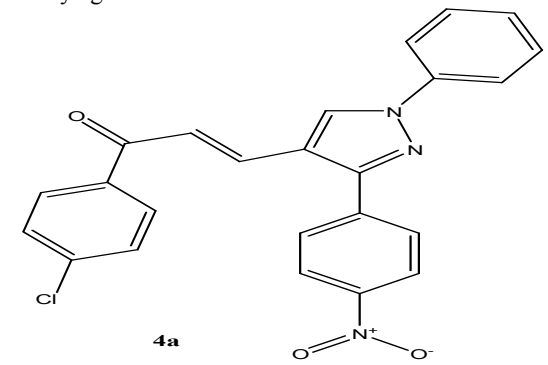
2b

I. M. El-Deeb et. al[24], synthesized a new series of 1H- and 2H-pyrazole derivatives, and tested for anticancer activity. 13 compounds in this series were tested over a panel of 60 cancer cell lines at a single dose concentration of 10 μM. At this concentration, six compounds have showed moderate to strong mean inhibitions. One of the synthesized compounds **3** showed remarkable anticancer activity.

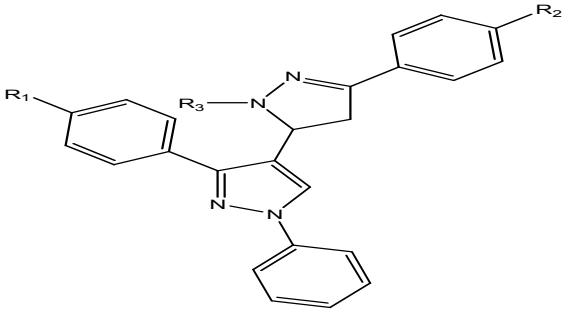


3

B. Insuasty et. al[25], developed a series of novel pyrazole derivatives, and scrutinized their antitumour potency against 60 human cancer cell lines. Two of the synthesized derivatives **4a** and **4b** showed remarkable activity mainly against leukemia (K-562 and SR), renal cancer (UO-31) and non-small cell lung cancer (HOP-92) cell lines, with the most important GI_{50} values ranging from 0.04 to 11.4 l μM.

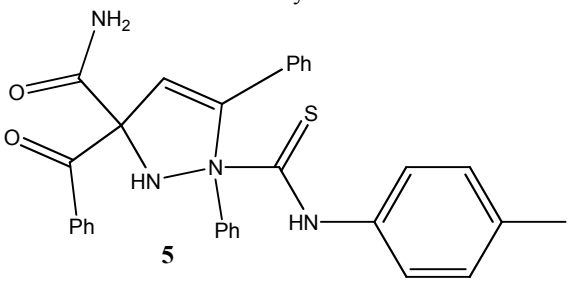


4a



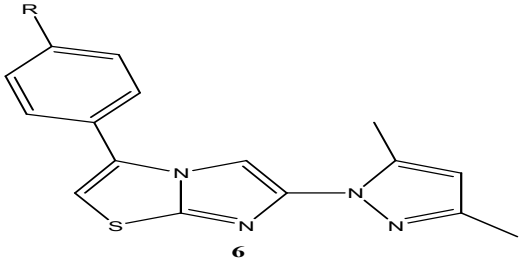
4b

I. Koca et. al[26], synthesized a new series of pyrazole containing acyl thiourea derivatives in good yield through one pot reaction of 4-benzoyl-1, 5-diphenyl-1H-pyrazole-3-carbonyl chloride with ammonium thiocyanate and evaluated them for their inhibitory potential against human colon, liver and leukemia cancer cell lines. These results showed that novel pyrazolyl acyl thiourea derivatives **5** could be utilized for cancer treatment.



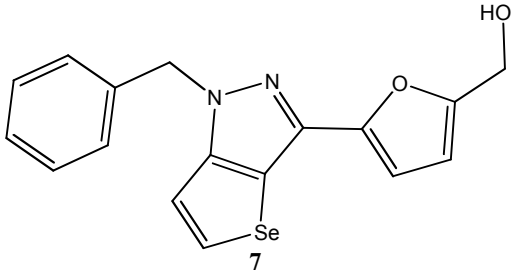
5

A. R. Ali et. al[27], synthesized a series of imidazo [2, 1-*b*] thiazoles bearing pyrazole moiety, and compounds were screened for anticancer activity at a single dose (10 μM). The *in vitro* anticancer evaluation revealed that compounds **6,** exhibited increased potency towards CNS SNB-75 and renal UO-31 cancer cell lines.



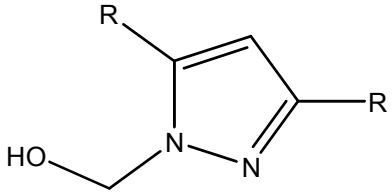
6

L. C. Chou et. al[28], prepared 1, 3-disubstituted selenolo [3,2-*c*]pyrazole derivatives and evaluated for their cytotoxicity against NCI-H226 non-small cell lung cancer and A-498 renal cancer cell lines. Among them, compound **7** was found to have the most potent anticancer activity.



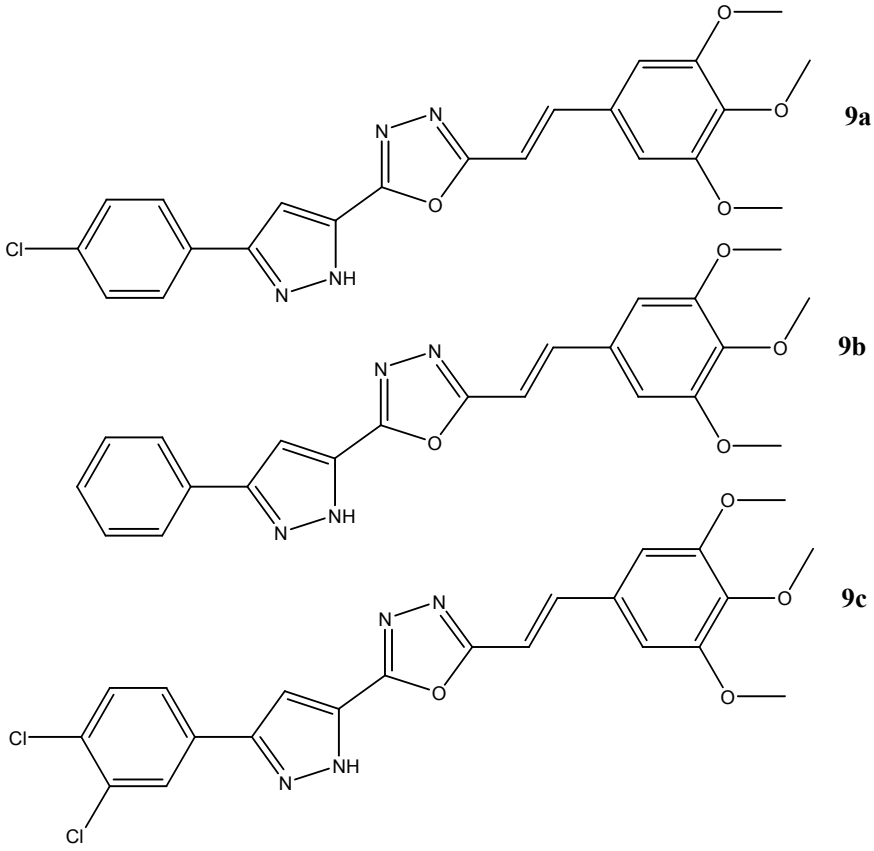
7

F. Abrigach et. al[29], carried out the evaluation of novel active molecules from a synthetic library of 14 nitrogen compounds. All these compounds exert antiproliferative activity against breast, and colorectal cancer cell lines with varying IC_{50}. The most active compound **8** showed an IC_{50} values equal to 8.5µg/ml in both MDA-MB 231(breast cancer) and LOVO (colorectal cancer) cell lines.



8

A. Kamal et. al[30], reported a new series of pyrazole-oxadiazole conjugates and evaluated for antiproliferative activity against various human cancer cell lines. Three of these compounds **9a**, **9b** and **9c** reported potent antiproliferative activity and disrupt microtubule network, when analyzed by cell cycle assay. When Molecular docking was carried out, compounds were observed bound at the colchicine site of tubulin, resulting inhibition of microtubule.

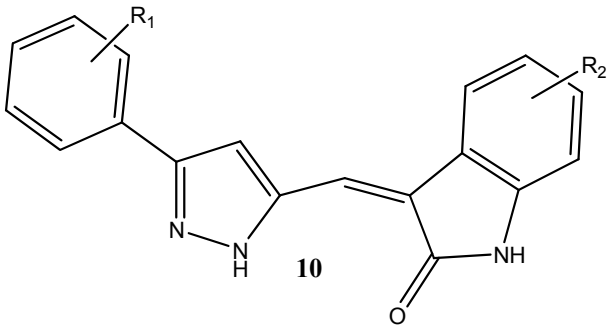


9a

9b

9c

A. Kamal et. al[31], synthesized a series of twenty one compounds with pyrazole and oxindole conjugates by Knoevenagel condensation, and investigated for their antiproliferative activity against different human cancer cell lines. Some of the synthesized compounds **10** manifested significant cytotoxicity and inhibited tubulin assembly.



10

R. S. Gouhar et. al[32], developed a novel derivatives of substituted pyrazole ring incorporated to or fused with other heterocyclic ring. Anticancer evaluation represented that, the derivatives **11a** and **11b** showed potential activity against MCF-7, HCTH-6, and HePG-2 carcinoma cell lines.

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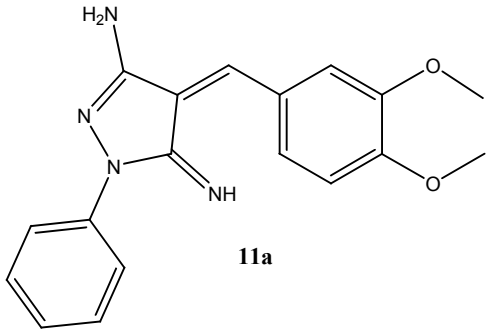
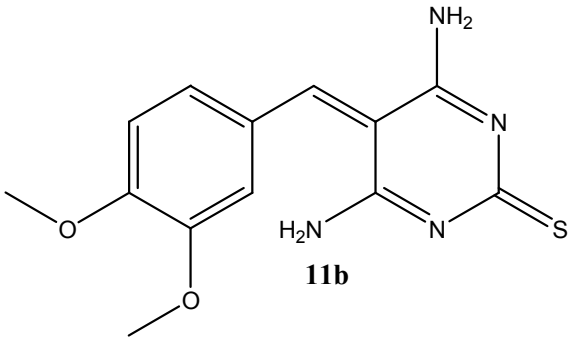
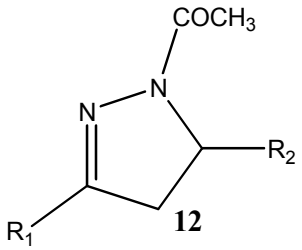


11a



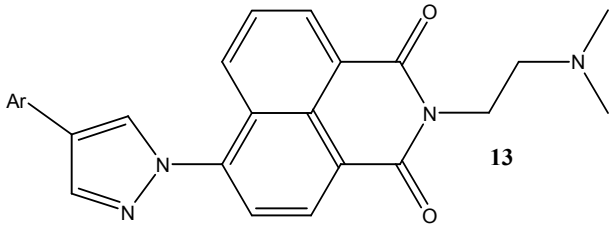
11b

J. M. Alex et. al[33], synthesized a series of 17 analogs of 1-acetyl-4, 5-dihydro (1H) pyrazoles **12** and evaluated for their antiproliferative potential against breast cancer (MCF- 7 and T- 47D) and lung cancer (H-460 and A-549) cell lines. Most of the compounds were exhibited significant antiproliferative activity against MCF-7 cells. The investigated compounds were found to lower the intracellular reactive oxygen species in the H2DCFDA assay and also caused mitochondria-dependent cell death in the MCF-7 cell line, indicating a plausible mechanism of their anticancer effect.



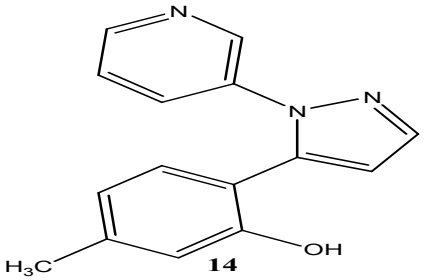
12

A novel series of 4-pyrazolyl-1, 8-naphthalimide derivatives prepared by S. Li et. al[34], were evaluated for anticancer activity *in vitro*, most of the compounds were found to be more toxic against human mammary cancer cells (MCF-7) than human cervical carcinoma cells (Hela). Two of the synthesized compounds exhibited a promising cytotoxic and antiproliferative activity. The DNA-binding properties of **13** were investigated by UV-Visible fluorescence, Circular Dichroism (CD) spectroscopic methods, and thermal denaturation. The results indicated that, compound **13** as the DNA-intercalating agent exhibited middle binding affinity with CT-DNA.



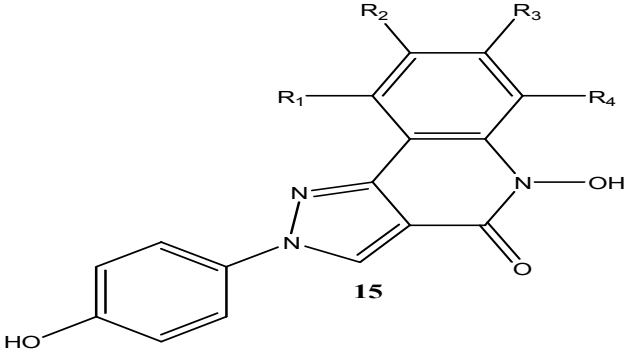
13

A. Balbi et. al[35], prepared thirty six novel substituted pyrazole derivatives and studied their antiproliferative potency in human lung carcinoma A549, human ovarian adenocarcinoma A2780, and murine P388 leukemia cell lines. Four of these compounds showed good antiproliferative and apoptotic inducing activity when analyzed by western blot assay. One amongst those four compounds, **14**, arrested a phase of cell cycle and inhibited polyploidy cell formation. When the tubular polymerization assay, immune fluorescence staining and docking analysis were carried out, some derivatives were observed bound to α and β tubulins, resulting in the distortion of microtubules.



14

M. S. Christodoulou et. al[36], synthesized a series of novel trisubstituted pyrazole derivatives and screened for antiproliferative activity against of human breast (MCF-7) and cervical (Hela) carcinoma cells. The antiangiogenic activity of these compounds was evaluated by using chicken chorioallantoic membrane (CAM) assay. Compounds containing the fused pyrazolo [4, 3-*c*] quinoline **15** motifs emerged as potent anti-angiogenic compounds.



15

Evaluation of a novel class of 3-(1*H*-indole-3-yl)-1*H*-pyrazole-5-carbohydrazide derivatives **16** for their cytotoxic effect against 4 human cancer cell lines by MTT method., was accomplished by D. Zhang et. al[37]. Some of them exhibited more potent antiproliferative activity against HepG-2, BGC823, and BT474 cell lines.

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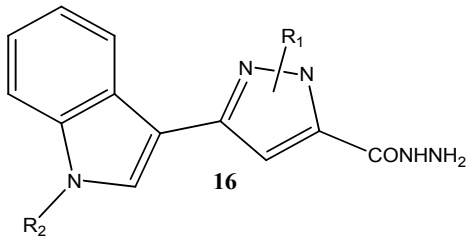
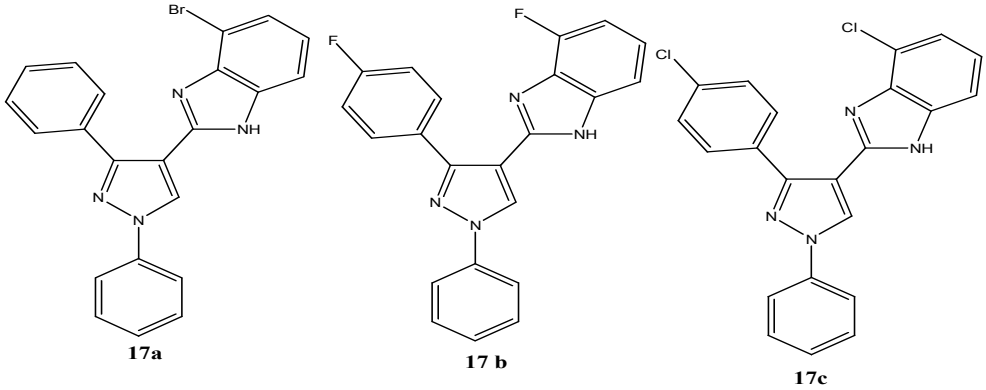


16

T. S Reddy et. al[38], synthesized a series of forty different pyrazole containing benzimidazole hybrids and evaluated for their potential antiproliferative activity against three human tumor cell lines-lungs (A549), breast (MCF-7), and cervical (HeLa). Some of the compounds, specifically **17a**, **17b**, and **17c** exhibited potent growth inhibition against all the cell lines tested, with IC_{50} values in the range of 0.83–1.81 μM.



17a **17 b** **17c**

A. R. Ali et. al[39], prepared a novel series of imidazo[2,1-*b*]thiazoles bearing pyrazole moiety, and eleven compounds were screened for anticancer activity at a single dose (10 μM) towards CNS SNB-75 and renal UO-31 cancer cell lines. Few of the synthesized compounds **18a** and **18b** were found to be potent anticancer activity.

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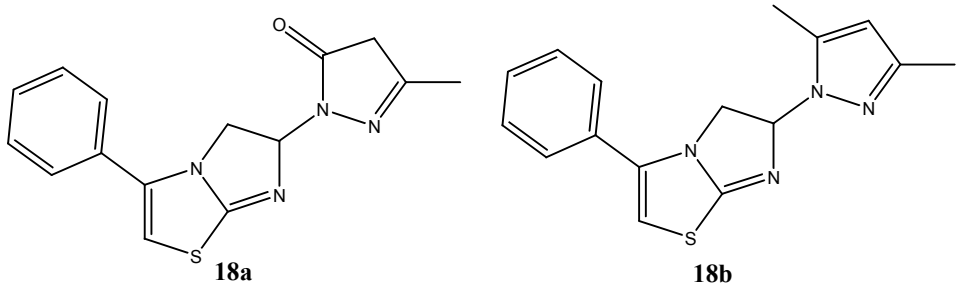
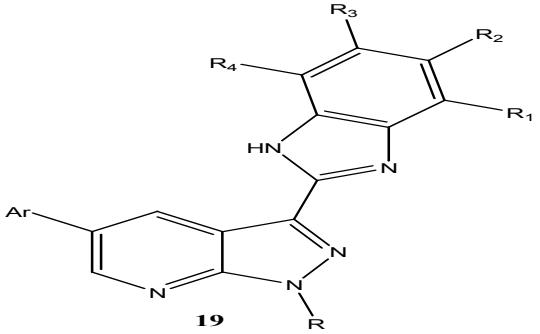


18a **18b**

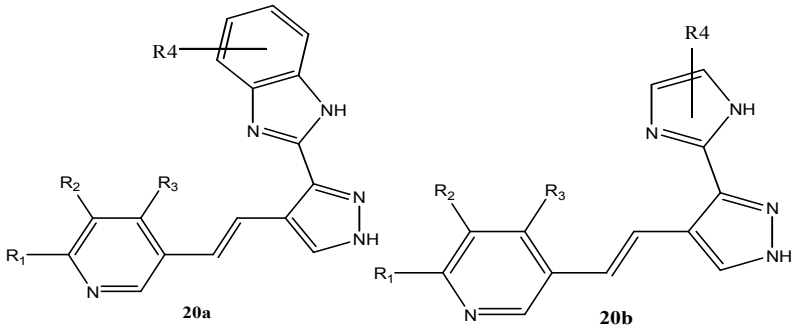
Pyrazoles as CDK inhibitor

R. Lin et. al[40], synthesized a novel series of 3, 5-disubstituted-pyrazolo [3, 4-b] pyridine as significant cyclin-dependent kinase (CDK) inhibitors. The prepared compounds were evaluated in an *in vivo* tumor xenograft model. The derivatives **19** showed selective CDK inhibitory activity and showed inhibition *in vitro* cellular proliferation in human tumor cells.

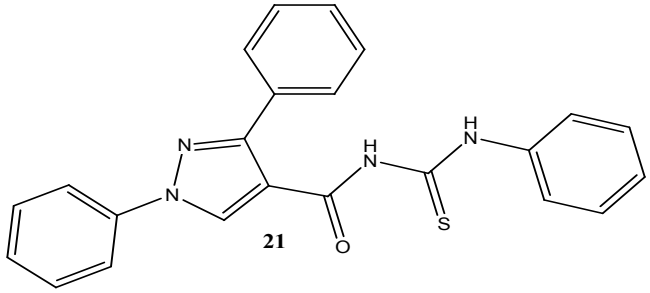


19

R. Lin et. al[41], prepared a novel series of 3, 4-disubstituted pyrazole analogues, 3-(benzimidazol-2-yl)-4-[2-(pyridin-3-yl)-vinyl]-pyrazoles **20a** and 3-(imidazol-2-yl)-4-[2-(pyridin-3-yl)-vinyl]-pyrazoles **20b** as novel cyclin-dependent kinase (CDK) inhibitors. Some compounds showed potent and selective CDK inhibitory activity and inhibited *in vitro* cellular proliferation in various human tumor cells.

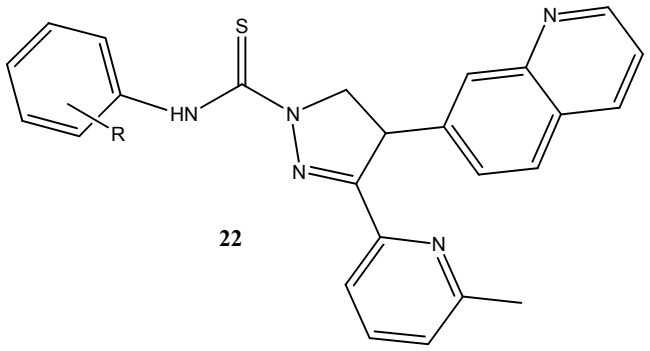


J. Sun et. al[42], discovered a number of cyclin dependent kinase inhibitors containing the pyrazole structure exhibited high inhibitory activity against broad-range CDKs and corresponding anti-proliferative activity. Compound **21** demonstrated the most potent inhibitory activity.

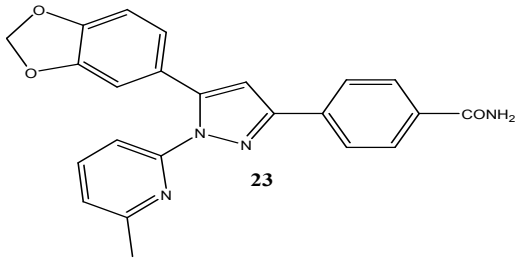


Pyrazoles as TGF inhibitor

P. M. Dewang et. al[43], synthesized a series of 2-pyridyl-substituted pyrazoles and evaluated for their transforming growth factor-β (TGF) inhibitory activity in cell-based luciferase assay. Among them, 3-(3-(6-methylpyridin-2-yl)-4-(quinolin-6-yl)-1*H*-pyrazole-1-carbothioamido) benzamide **22** showed 96% inhibition at 0.1 μM in luciferase assay using HaCaT cells transiently transfected with p3TP-luc reporter construct.

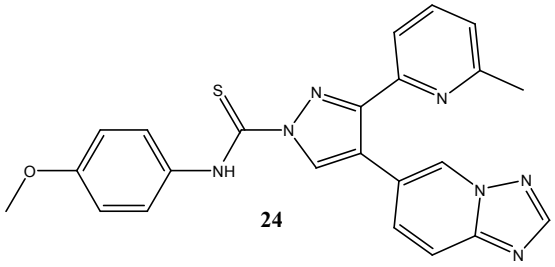


X. Li et. al[44], prepared a series of 1, 3, 5-trisubstituted pyrazoles, and evaluated for their ALK5 inhibitory activity in a ALK4/5/7 autophosphorylation and cytotoxicity performing TGF-b-Smad2, and MTT assay. Among the tested compounds, compound **23** showed relatively potent ALK-5 inhibition and inhibiting the transforming growth factor b (TGF-b) type 1 receptor.



23

C. H. Jin et. al[45], synthesized a series of 1-substituted-3-(6-methylpyridin-2-yl)-4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)pyrazoles, and evaluated for their ALK5 inhibitory activity in a cell-based luciferase reporter assay. One of the synthesized pyrazole derivatives **24** inhibited ALK5 phosphorylation and showed 94% inhibition at 100 nM in a luciferase reporter assay using HaCaT cells.

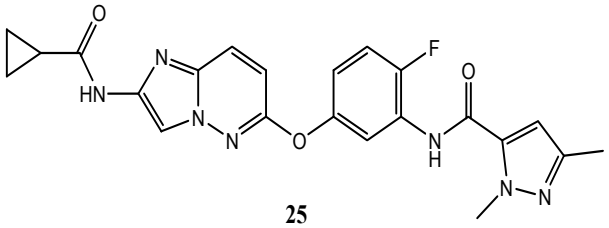
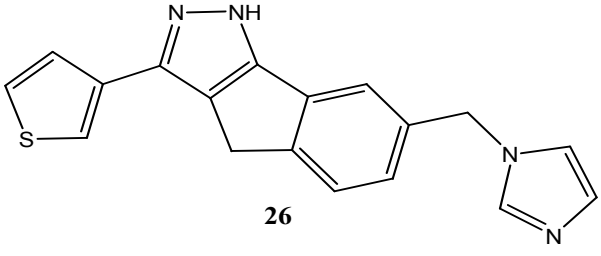


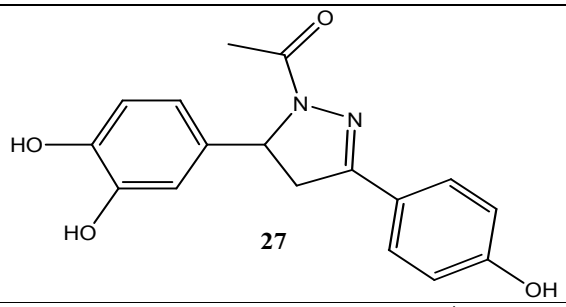
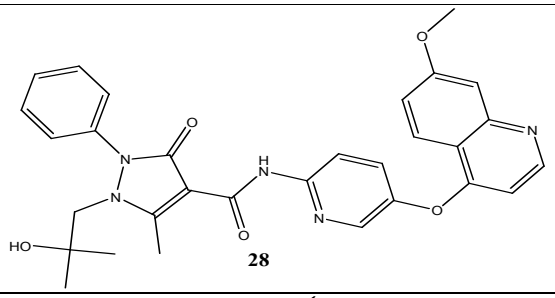
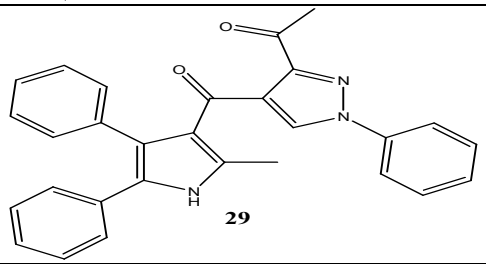
24

Pyrazoles as VEGF inhibitor

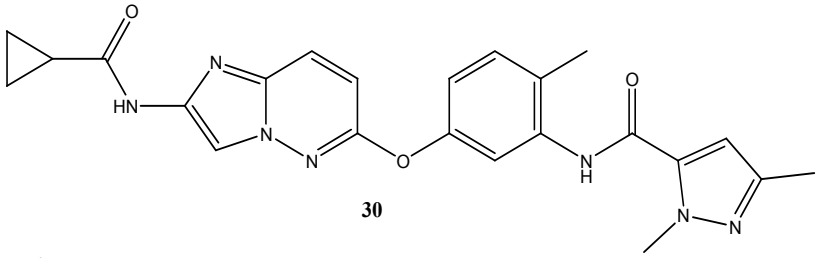
Vascular endothelial growth factor (VEGF) and their receptor play important role in tumor angiogenesis, and the inhibition of its signaling pathway is considered an effective option and drugabble target for the treatment of cancer. The most researchers in this field have targeted VEGF classes of receptors for designing novel antiproliferative agents. From the extensive literature survey, it was found that several pyrazole derivatives were synthesized, and evaluated for VEGF receptor kinase inhibitory activity, which has been displayed in the **Table 1**.

Table.1 List of potent VEGF receptor kinase inhibitor

no	Work reported by	Structure of potent molecule	Inhibition of	Ref
1	Y. Oguro et. al 2013	 **25**	VEGF-2 receptor kinase	46
2	J. Dinges et. al 2006	 **26**	VEGF-2 receptor kinase	47

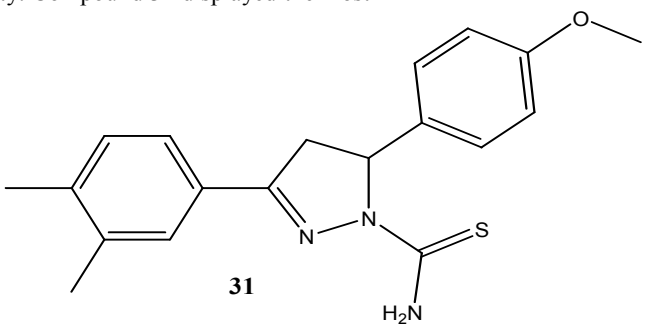
3	Z. Zhou et. al 2013	 **27**	VEGF-2 receptor kinase	48
4	L. Longbin et.al 2008	 **28**	VEGF-2 receptor kinase	49
5	T. M. A. Eldebss et.al 2015	 **29**	VEGF-2 receptor kinase	50

N. Miyamoto et. al[51], prepared a novel series of pyrazole derivatives, and evaluated for VEGFR-kinase inhibitory activity. The synthesized compound **30** was exhibited highly potent VEGF receptor 2 kinase activity with an IC_{50} value of 0.95 nM and strongly suppressed proliferation of VEGF-stimulated human umbilical vein endothelial cells with IC_{50} of 0.30 nM.



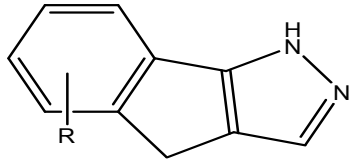
30

P. C. Lv et. al[52], discovered a novel series of pyrazole derivatives for potential EGFR kinase inhibitors. Some of them exhibited significant EGFR inhibitory activity. Compound 31 displayed the most potent EGFR inhibitory activity with IC_{50} of 0.07 μM and showed significant antiproliferative activity against MCF-7 with IC_{50} of 0.08 μM.



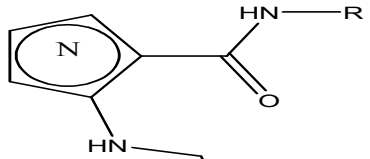
31

H. Zhang et. al[53], carried out molecular docking and 3D-QSAR molecular modeling studies on the designed 140 compounds of 1,4- dihydroindeno[1,2-c]pyrazole series **32**. The designed derivatives were docked into vascular endothelial growth factor receptor tyrosine kinases (VEGFR-2) using Auto-Dock software. Structure activity correlation of designed compounds was performed using 3D-QSAR, CoMFA, and CoMSIA models. The obtained results strongly suggest that, the developed 3D-QSAR models and the obtained VEGFR-2 inhibitor binding structures are reasonable for the prediction of the activity of new inhibitors.



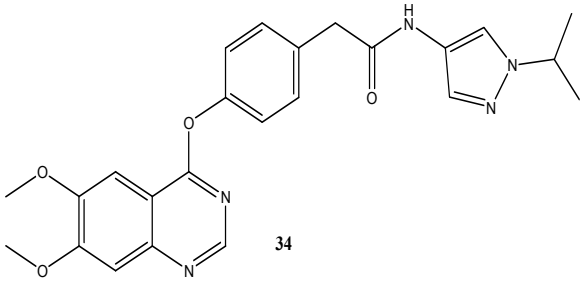
32

A. S. Kiselyov et. al[54], developed a series of novel potent ortho-substituted azole derivatives, active against VEGFR-1 and VEGFR-2 kinases. The most specific molecule **33** displayed >10-fold selectivity for VEGFR-2 over VEGFR-1.



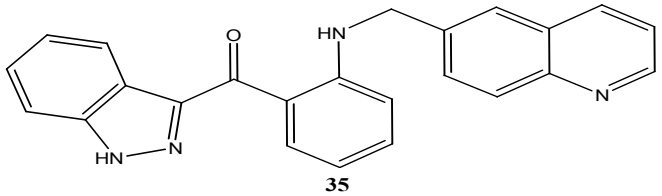
33

P. A. Ple et. al[55], described a new series of quinazoline ethers bearing pyrazole moiety and tested all the synthesized compounds against VEGFR-2 and PDGFR tyrosine kinases. *In vitro*, pharmacokinetics and *in vivo* evaluations led to the selection of compound **34**.



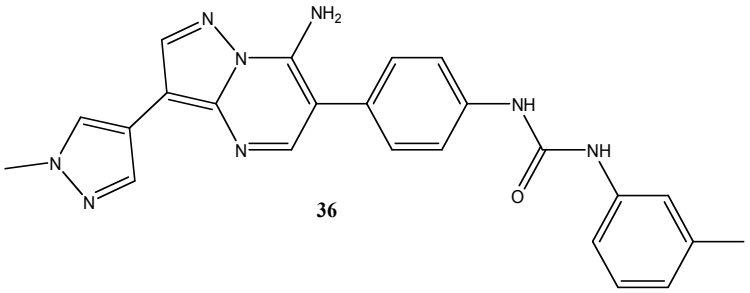
34

E. L. P. Chekle et. al[56], synthesized a novel series of potent heteroaryl-ketone derivatives active against VEGFR-2 kinase. One of the compounds **35** displayed acceptable exposure levels, when administered orally to mice.



35

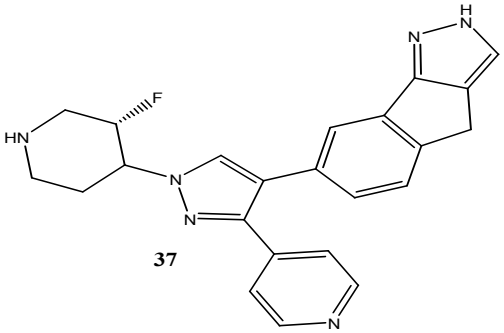
R.R. Frey et. al[57], discovered a novel series of 7-Aminopyrazolo [1,5-a]pyrimidine urea. From the Investigation of structure activity relationships of the pyrazolo[1,5-a]pyrimidine nucleus led to a series of 6-(4-N,N'-diphenyl) ureas, that potently inhibited vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) kinase. Among the synthesized, compound **36**, was found to be potent inhibitors of kinase insert domain- receptor tyrosine kinase.



36

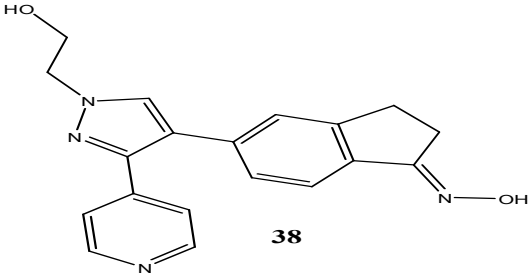
Pyrazoles as BRAF inhibitor

BRAF is an oncogene, which causes the activation of number of kinase enzymes, leading to signaling transduction and phosphorylation, thereby resulting proliferation, cell movement (migration), the process by which cells mature to carry out specific functions (differentiation), and the self-destruction of cells (apoptosis). Designing the molecules, that target B-raf gene, may be an attractive target for anticancer in future. From the literature survey, several pyrazole derivatives were reported as BRAF inhibitor, which has been given in the **Table 2**. B. J. Newhouse et. Al [58] synthesized a novel series of non-oxime pyrazoles and shown excellent enzyme activity. One of the synthesized compounds **37** was found to be as a selective and potent B-Raf inhibitor.



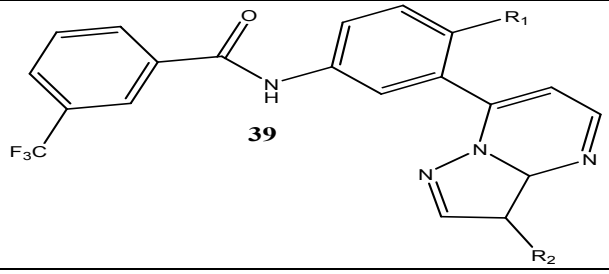
37

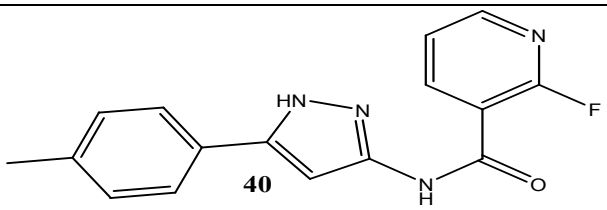
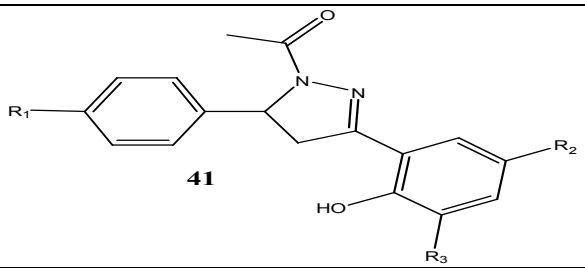
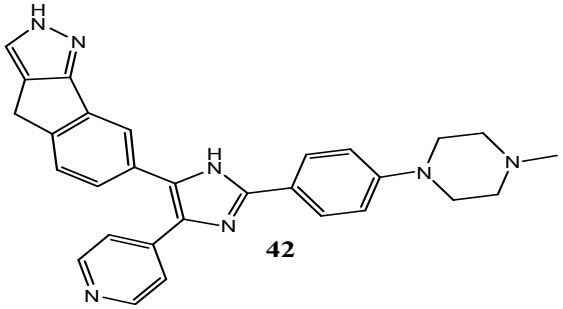
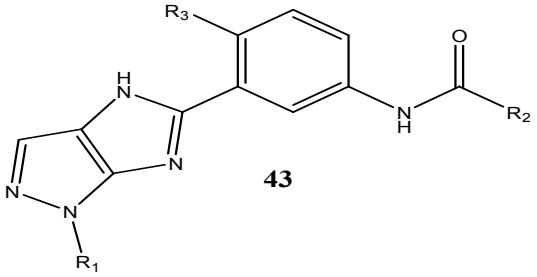
J. D. Hansen et. al[59], described a novel pyrazole-based class of ATP competitive B-Raf inhibitors. These inhibitors showed both striking B-Raf selectivity and excellent cellular potency. Among the synthesized compounds, a compound **38** was found to be good preclinical *in vivo* activity against tumor xenograft models.



38

Table.2 List of potent BRAF kinase inhibitor

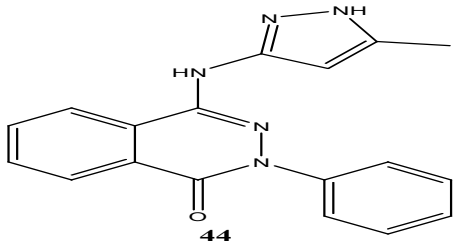
S.no.	Work reported by	Structure of potent molecule	Inhibition of	Ref
1	D. M. Berger et.al 2009	 **39**	BRAF kinase	60

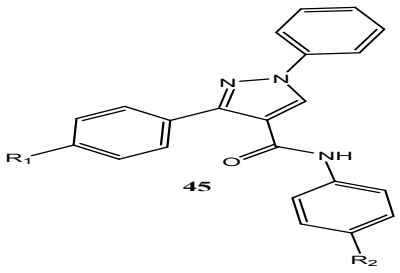
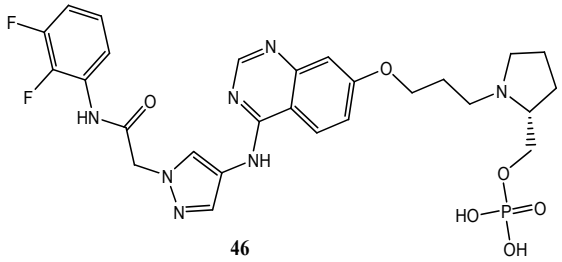
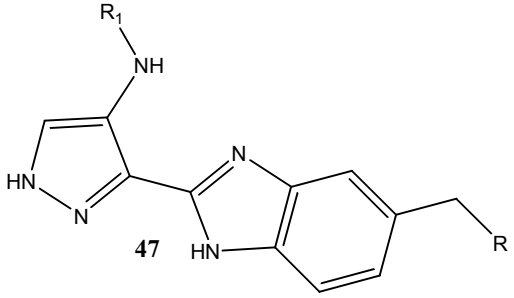
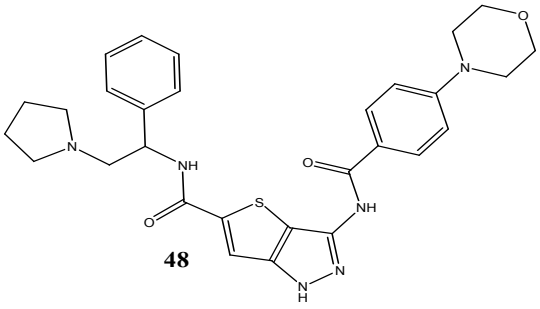
2	S. F. Wang et.al 2014	 **40**	BRAF kinase	61
3	J. J. Liu et.al 2012	 **41**	BRAF kinase	62
4	D.N. Duvaz et.al 2010	 **42**	BRAF kinase	63
5	H. Yu et.al 2010	 **43**	BRAF kinase	64

Pyrazoles as Aurora-A kinase inhibitor

Aurora A kinase is an enzyme. It is implicated with important process of mitosis and meiosis during the G2 phase to M phase transition in the cell cycle, leading to cell proliferation. Inhibiting the Aurora A kinase enzyme activity may help in antiproliferation, which may lead to the cure of cancer. From the literature survey, research groups have been reported pyrazole derivatives as aurora-A kinase inhibitor, which has been displayed in the **Table 3.**

Table.3 List of potent aurora-A kinase inhibitor

S. no	Work reported by	Structure of potent molecule	Inhibition of	Ref
1	M. E. Prime et. al 2011	 **44**	Aurora-A kinase	65

2	X. Li et.al 2012	 **45**	Aurora-A kinase	66
3	K. M. Foote et. al 2008	 **46**	Aurora-A kinase	67
4	Y. Zheng et.al 2013	 **47**	Aurora-A kinase	68
5	S. Bindi et.al 2010	 **48**	Aurora-A kinase	69

CONCLUSION

Pyrazole is a unique structure, and associated with several biological activities. The present article has described the structure of pyrazole scaffold. The pyrazole derivative has beneficial effects on proliferation which interacts with various heterocyclic nucleus. Anticancer activity of derivatives of pyrazoles such as pyridyl pyrazoles, pyrazole-oxadizole, pyrazole-oxaindole, acetyldihydro pyrazoles, pyrazolyl-1, 8-naphthalimide, and indole-pyrazoles has been described. Role of docking studies, 3D-QSAR, and molecular modeling have been discussed for the development of novel antiproliferative agents. From the extensive research survey, pyrazole derivatives have been found to inhibit family of kinase enzymes i.e. cyclin dependent kinase (CDK), Aurora kinase A, tyrosine kinase, and various growth factors like vascular endothelial growth factor (VEGF), tumor growth factor (TGF-b) and BRAF gene. Further investigation of this scaffold may lead to development of the new anticancer agents.

Acknowledgments

We would like to acknowledge the University grants commission for financial support under research grants MRP-6254/15 (SERO/UGC) and also thank full to GNITC, School of pharmacy, Hyderabad, for the facilities provided for this review article.

Declaration of interest

The authors report no conflict of interest.

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How to cite this article:

Parameshwar. Ravula*, Harinadha Babu. V, Manichandrika. P,Narendra Sharath Chandra JN, Venkata Ramana Reddy M, Srinivas.B, pyrazole scaffold: a promising tool in the development of antiproliferative agents, 6 (3): 2628 – 2744 (2015)