Sys Rev Pharm 2020;11(11):254-263
A multifaceted review journal in the field of pharmacy

An Insight into Pyrazolo scaffold as anticancer

Mazin A.A. Najm [1], Khulood H. Oudah [1], Wassan Nori Mohammed Hassan [2] and Ali B. Roomi[3,4]

[1] Pharmaceutical Chemistry Department, College of Pharmacy, Al-Ayen University, Thi-Qar, Iraq
[2] Department of Obstetrics and Gynecology, College of Medicine, Mustansiriyah University, Iraq.
[3] Ministry of Education, Directorate of Education Thi-Qar, Iraq.
[4] College of Health and Medical Technology, Al-Ayen University, Iraq.
*Corresponding author: Dr. Ali B. Roomi, dr.ali_bader@alayen.edu.iq

ABSTRACT

Cancer is caused by the uncontrolled development of abnormal cells, a severe and life-threatening health problem globally. It is a collection of various diseases kept referring to as perhaps the deadliest after cardiovascular disease in terms of lives lost. Despite large and innovative effective innovations to cancer issues, there are still gaps in cancer treatment; it is predicted to be the leading cause of death in the new millennium. Today, pharmaceutical manufacturing costs billions of dollars to discover effective, safe, and reliable cancer drugs in particular pyrazole derivatives. Pyrazole is a heterocyclic heterogeneous ring containing five adjacent atoms of nitrogen C3H3N2H. Interestingly, these scaffolds are present in the pharmacokinetics of various therapeutic classes, such as pyrazole pyrimidines, Known as adenine biotic, which is essential for all aspects of cell survival. Pyrazolo[1,5-a] pyrimidine have been investigated for their inhibitory potential against a diverse array of protein kinase enzymes and with their part as an anticancer drug. This study primarily addresses the artificial and anticancer activity of various pyrazole scaffolds, in particular pyrazole pyrimidine scaffolds.

Keywords: Pyrazole activities, synthesis, pyrazolopyrimidine, and anticancer.

Correspondence:
Dr. Ali B. Roomi
4 College of Health and Medical Technology, Al-Ayen University, Iraq.
*Corresponding author: Dr. Ali B. Roomi email-address: dr.ali_bader@alayen.edu.iq

INTRODUCTION

Heterogeneous cycles are a vital and unique class of compounds; they constitute more than half of all recognized natural compounds and have a wide range of physical, chemical and biological interactions that seem to endure a broad range of interactions and stability.(1). Heterogeneous cycles are frequently available in nature and exert an important role in metabolism due to their unique structural units available in several natural commodities, as well as vitamins, hormones, antibiotics and alkalis similar to prescription medications, agrochemicals, dyes and many others (2). In addition to the existing compounds, a growing number of synthetic heterocyclic compounds containing physiological characteristics and deterministic drugs are already well recognized (3). These compounds provide scaffolding that pharmacies can arrange to produce newer efficient and competitive drugs amongst heterocyclic compounds. Heterogeneous nitrogen-containing cycles are the core structures of various natural dynamic compounds and provide potential usage in chemistry, biology and other sciences (4). These are building blocks of life due to their widespread presence in nature and the core parts of chemical reactions that occur across life. , besides; heterogeneous nitrogen-containing rings play a crucial role in the coordination of chemistry (5).

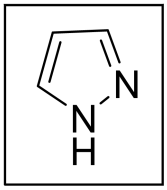


Figure 1: Structure of Pyrazole.

Pyrazole (Figure 1) is a heterogeneous aromatic system included in the azole class. It is a five-membered ring harvesting two nitrogen atoms and three carbon atoms tied together (6, 7). The nitrogen atom 1 (N1) is a "pyrrol type" referring to its undivided electrons' unique aromatic system. The nitrogen 2 (N2) atom is "pyridine type" because of its non-resonance electrons are not exchanged like residual pyridine.

Pyrazole reacts with acids and the base (8) due to the contrast between nitrogen atoms. Primary tautomerism is another significant primary feature of pyrazole. In non-replaceable pyrazole, three faucets can be visualized, while in single-substituted pyrazole, five pine nuclei can occur (Figure 2). Structures 1a, 2a and 2b are applicable because they maintain odors (9, 10).

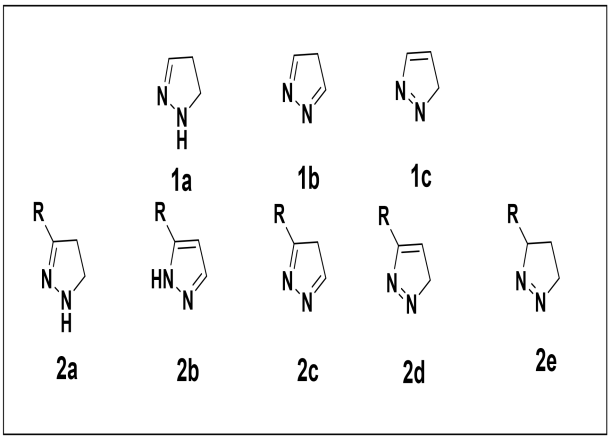


Figure 2: Tautomers of Pyrazole.

Pyrazole scaffold is a traditional nucleus of several pharmaceutical formulations and implies a broad variety of pharmacological activities (Figure 3). Anti-inflammatory drugs such as pheylbutazone 3 (11), antibacterial, antifungal and hypoglycemic (12), anti-hyperlipidemia (13), cyclooxygenase-2 inhibitors such as celecoxib 4 and anti-obesity drugs such as rimonabant 5 and Anti-obesity anticoagulant, antipsychotic, anti-depressant H2 agonist receptors such as Betazol 7 and anti-anxiety

products such as Zaleplon 8 and anti-cancer drugs such as CDK2 / CyclinA (14), but they are also an elegant starting point for the synthesis of pharmaceutical ingredients with specific activities and strong safety profiles (15). In the laboratory, various pyrazole compounds should be tested for their activity as a reproductive inhibitor and anti-tumor action in vivo, which contributes to promising drug targets.

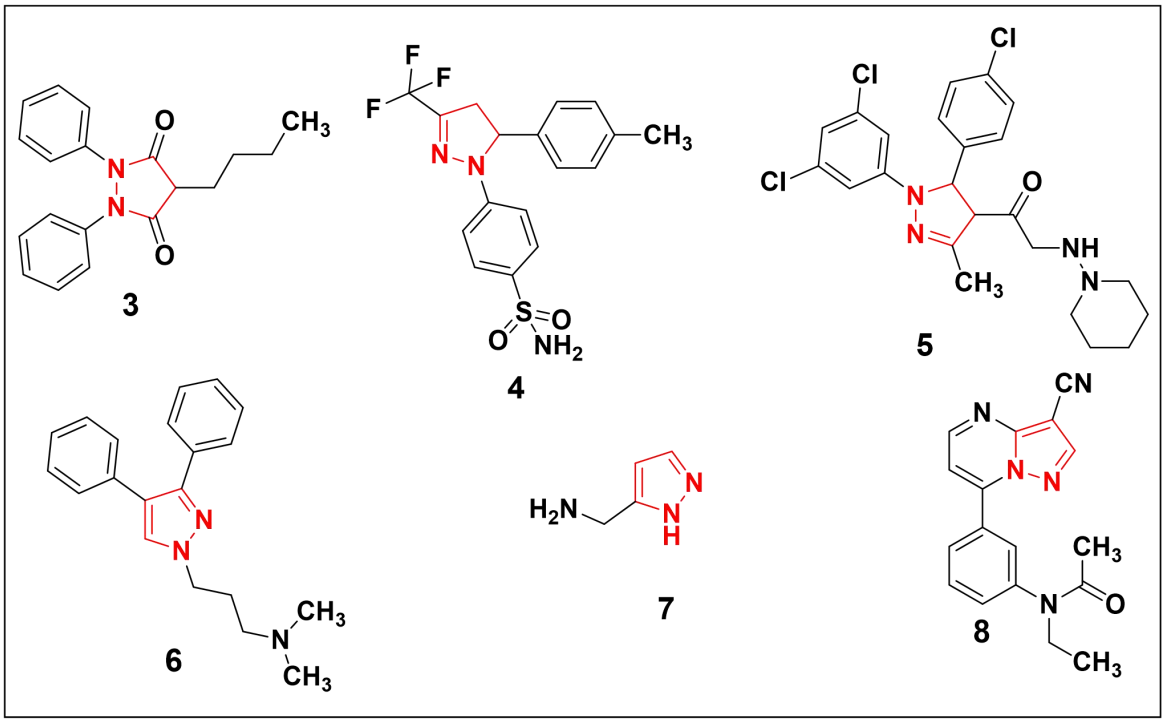


Figure 3: Drug molecules containing Pyrazole scaffold.

1. Synthetic strategies of pyrazole

Conventional pyrazole synthesis techniques include methodology based on either hydrazine condensation with 1,3-dicarbonyl or 1,3-dielectropiles, such as Knorr synthesis and [3 + 2] cycloadditions, and compounds that contain 1,3-dipoles and alkenes; For instance, the Pechmann aggregation (10, 16). Pyrazoles are found between two nitrogen molecules, also known as 1,2-diazole. Knorr provided the basis for the construction of the inverted base compound of pyrazole in 1883. Hydrazine condensation with 1,3-dicarbonyl compounds is the traditional pyrazole mixture technique (Figure 4).

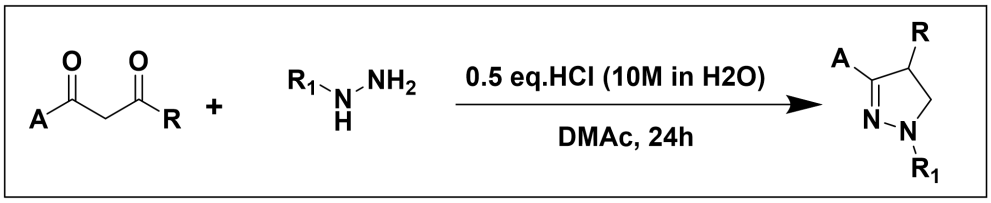
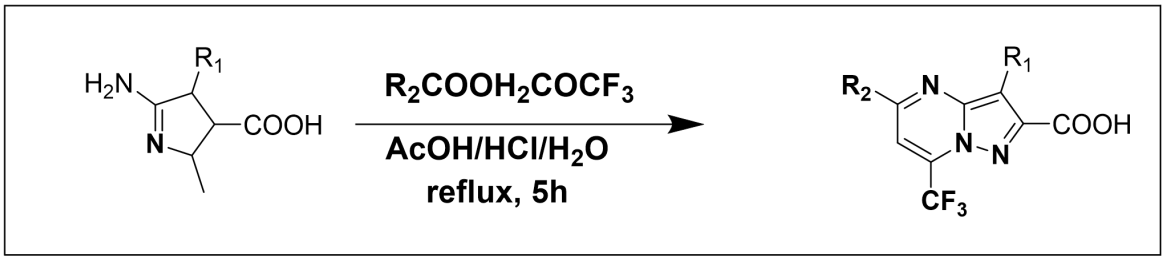


Figure 4: pyrazole syntheses in the classical technique.

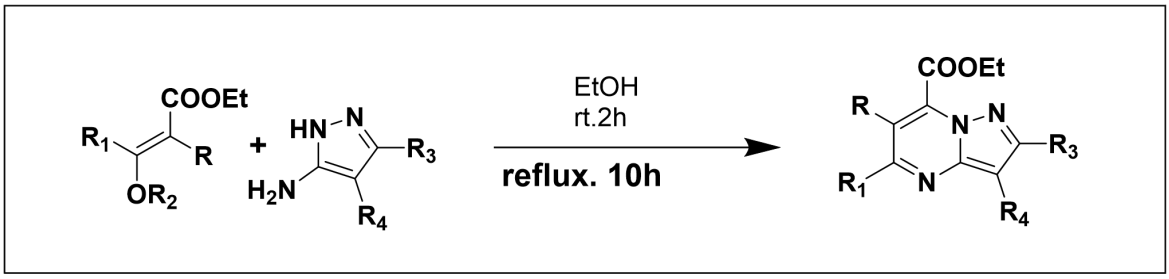
Latest developments in pyrazole synthesis have indeed been presented in the literature (17). In particular, Rollas obtained pyrazole reductase with a division of hydrazine hydrate for azo compounds [A] and [B] (Figure 5). Creation of new small pharmacological molecules based on pharmaceutically attractive scaffolds produced with thiazolidine(4-thiazolidinone) (17-19) and pyrazolopyrimidine, in particular pyrazollone [1,5-a]. Several of its derivatives are thought to have a broad range of biological effects, such as anti-cancer (20). Several synthetic methods have been proposed as follows for the production of pyrazolo [1,5-a] pyrimidines:

1. The condensation reaction (at reflux) of derivative I with the subsequent trifluoro-methyl a-deconate of 5h. (Scheme 1) (21).



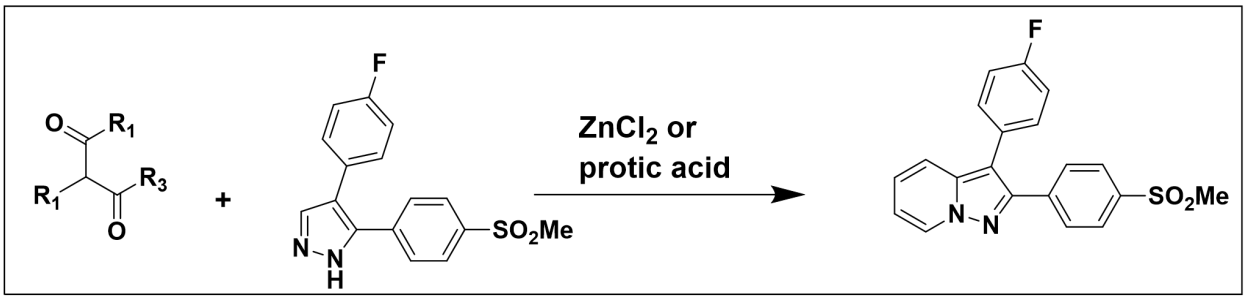
Scheme 1

2. In the second approach, the combination of compound I with β,γ unsaturated γ-alkoxy-α-keto esters in ethanol under reflux timed for 10 hours to yield corresponding derivatives along with an ester function at position 7 of the goal target compound (Scheme 2) (22).



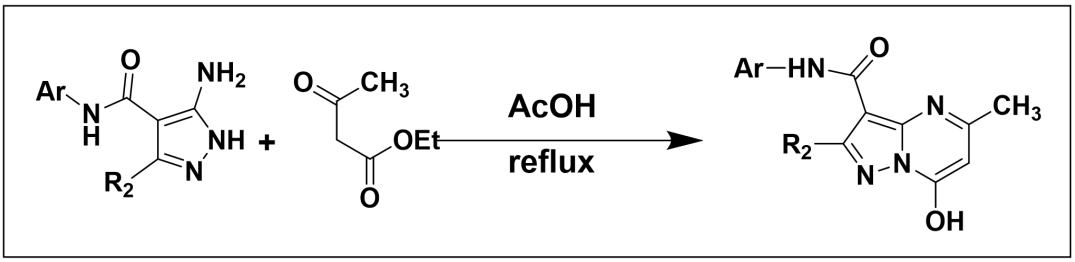
Scheme 2

3. Formulation of a diverse group of pyrazollo [1,5a] pyrimidines through condensing 4,5-unrefused pyrazole with 1.3-decarbonyl derivatives along with zinc chloride or acid (Scheme 3) (23)



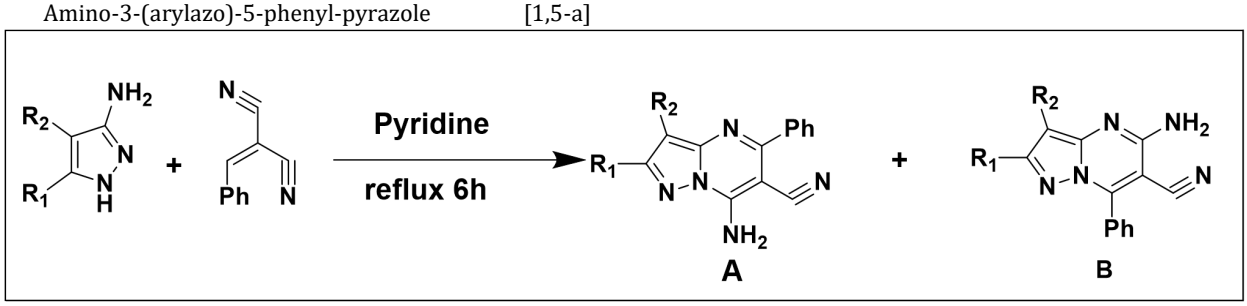
Scheme 3

4. The interaction of 5-amino-4-pyrazolecarboxamide with acetate in glacial acetic acid at reflux timed for 6 hours giving a 7-hydroxy-5-methyl-N- (aryl) pyrazolo [1, 5-a] pyrimidine (Scheme 4) (24).



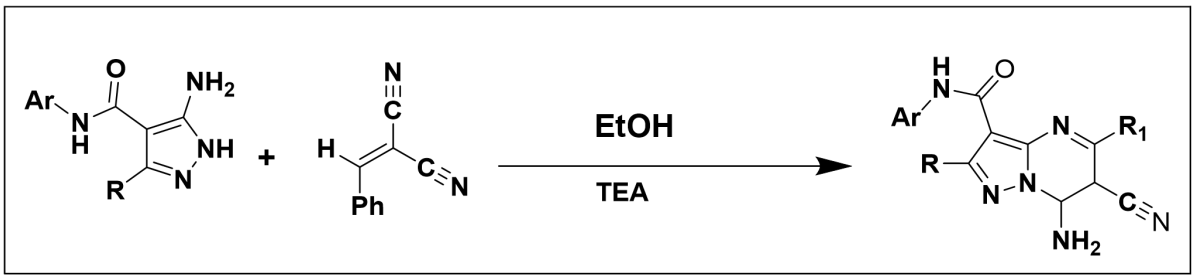
Scheme 4

5. Derivatives of I have been refluxed with benzylidenemalonitrile in pyridine for 6 h to 7-Amino-3-(arylazo)-5-phenyl-pyrazole [1,5-a] pyrimidine-6 carbonitrile which may be constructed as A or isomeric B (Scheme 5) (25).



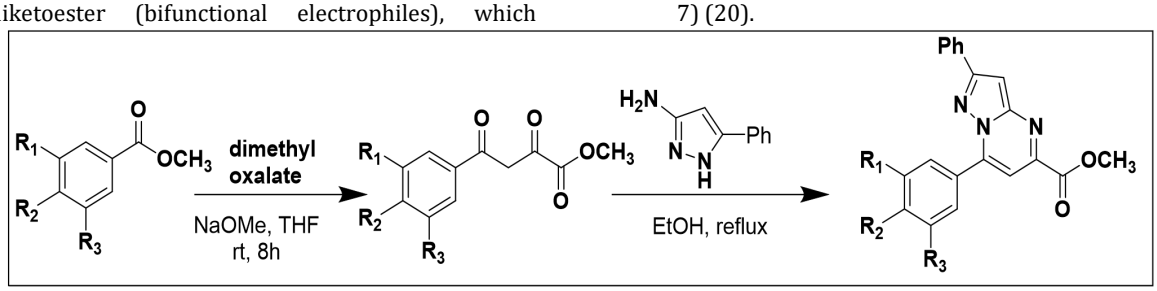
Scheme 5

6. A reaction was crafted between Benzylidene malononitrile and I derivatives under reflux timed for 6 h in ethanol in the presence of triethylamine to yield 7-amino-6-cyano-5-aryl-2-(arylamino)pyrazole[1,5-a]-pyrimidine-3-carboxamide (Scheme 6)(26).



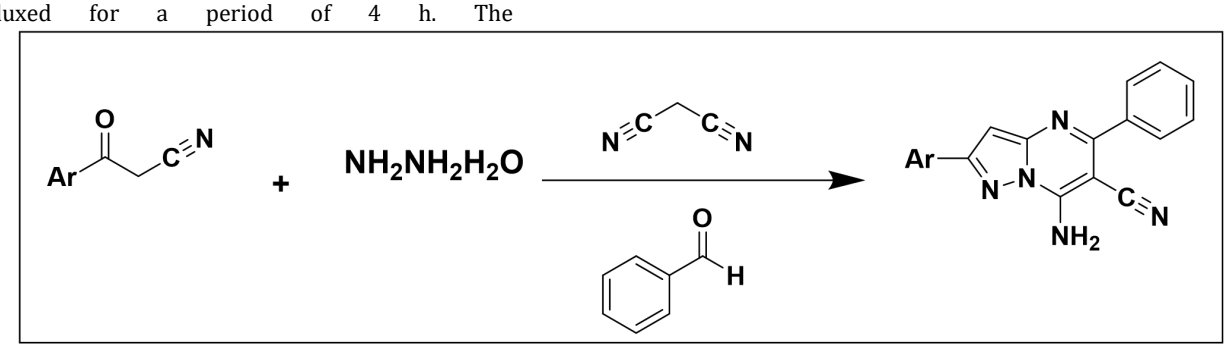
Scheme 6

7. A selection of substituted acetophenones was oxalated via dimethyl oxalate along with the presence of sodium methoxide and THF at room temperature of 8 h to create b-diketoester (bifunctional electrophiles), which is refluxed alongside 3-amino-5-phenyl-1Hpyrazole (bifunctional electrophiles) for 2 h in ethanol to produce cyclodehydrated methyl 2,7-diphenyl pyrazolo[1,5-a]pyrimidine-5-carboxylates (Scheme 7) (20).



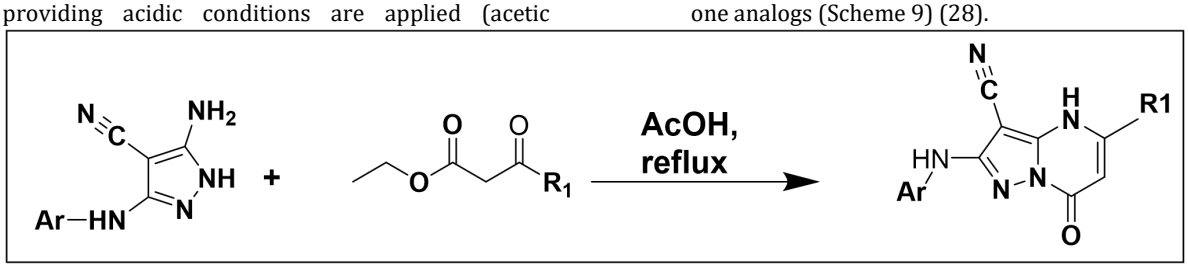
Scheme 7

8. A collection of oxoalkanitrile hydrazine hydrate, benzaldehyde and malononitrile were refluxed for a period of 4 h. The resulted product was solid and re-crystalled to give ethanol (Scheme 8) (27).



Scheme 8

9. Combing I derivatives with b-keto ester derivatives (ethyl acetoacetate derivatives) providing acidic conditions are applied (acetic acid) for 10 h along with stirring after which; reflux, to gain the 2-anilinopyrazolo [1, 5a] pyrimidine-7-one analogs (Scheme 9) (28).



Scheme 9

2. Anticancer activity of pyrazoles

Cancer is a major burden on public health and impacts almost all national and financial standards. It is the second leading cause of mortality globally, with 8.8 million deaths in 2015 and around 1 in 6 deaths in the world (29). According to the World health Organization (WHO), 15 million new cases of cancer are anticipated every year by 2020, unless specific preventive precautions are adopted thereafter (30). Efficient steps have been taken to seek modern therapies and to strengthen preventive and molecular diagnostic systems (31, 32). It will be impressive to search for new molecular target drugs and their rates can be recognized and established as new cancer drugs. Protein kinase, along with other things, is becoming an essential part of drug targets and the percentage of kinase inhibitors in clinical development is increasing rapidly (33). Cancer drugs have been developed from a chemically compound in previous centuries.

A huge number of interesting pyrazole derivatives have recently been explored. (34) Pyrazole variants possess anticancer activity owing to inhibition of different targets such as topoisomerase II (35-37), EGFR (38, 39), VEGF (40, 41), HDAC (42, 43), IGF-1R (44), AuroraA kinase (45), cMet (46), tubulin (47), mTOR (48), B-Raf (49, 50), ROS 1 (51), CDK

(52), PI3 K (53) JAK2 (54), ALK (55)). In this review, we will describe the different pyrazole structures, and their derivatives having anti-cancer activity.

3.1. Lck, Src, Kdr and Tie-2 inhibitors

The properties of pyrazolo as an anti-proliferative and proapoptopic agent have been investigated by Spreafico et al. (56) reporting that [3,4-d]pyrimidines are Src kinase inhibitors in human osteosarcoma cells. A conclusion was drawn; that pyrazolo[3,4d]pyrimidines were both necessary to stimulate the passage of modified cells and for reducing Src phosphorylation. PP2 (4-amino-5-(4-chlorophenyl)-7-(t-butyl)pyrazolo[3,4-d]pyrimidine) was alluded to as lead content due to the inhibitory activity of Src kinase. On the other hand, compound 9 was found to exert its effect through DNA damage by compound 10 acting by accelerating apoptosis (57) (Figure 5).

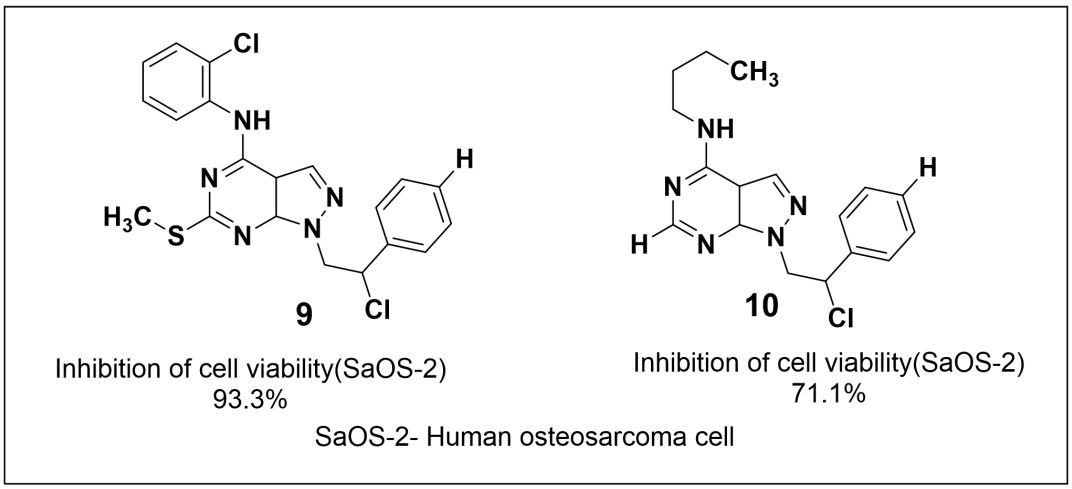


Figure 5: Reports of cell viability for potent inhibitors Lck, Src, Kdr and Tie-2.

Carraro et al. at 2006 declared that pyrazolo [3,4-d] pyrimidines are potent specialists with antiproliferative and proapoptotic active agents against A431 and 8701-BC cells in culture, implementing their action by limiting c-Src phosphorylation in the cell-free assay (58). (Figure 6) illustrating compounds **11**, **12** owing an inhibitory role on phosphorylation of Src on compression to the reference pp2

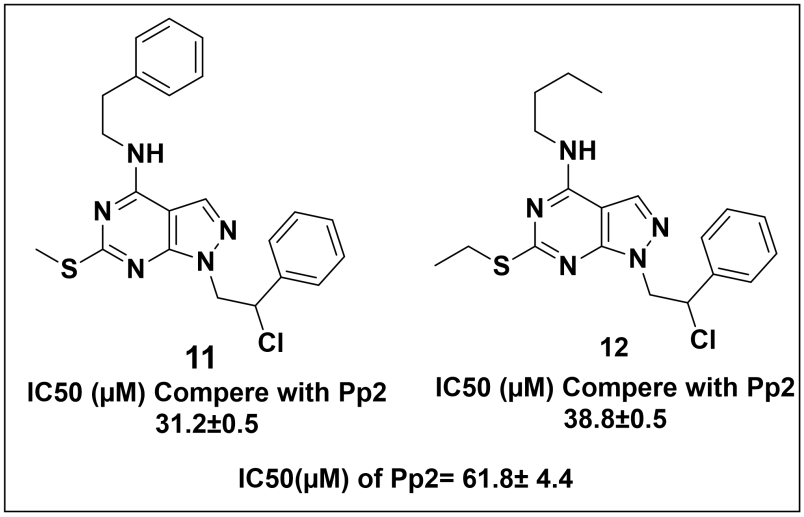


Figure 6: evaluating the effect of compounds 11 and 12 on A431and 8701-breast cancer cells.

3.2. Abl inhibitors

It's Manetti et al. In 2008, formulated pyrazolo[3,4-d]pyrimidines as Abl inhibitors and antiproliferatives, with an advantage over human leukemia cell line (59). Molecular modeling literature has expressed the influence of the substation of different substituents, such as halogen and the ATP restricting hydrophobic region, which implies a decisive action to give Abl affinity. Compound **13** (Figure 7) expressing K562 characteristics as Abl Inhibitors and antiproliferative agents plays its role in Human leukemia cell lines.

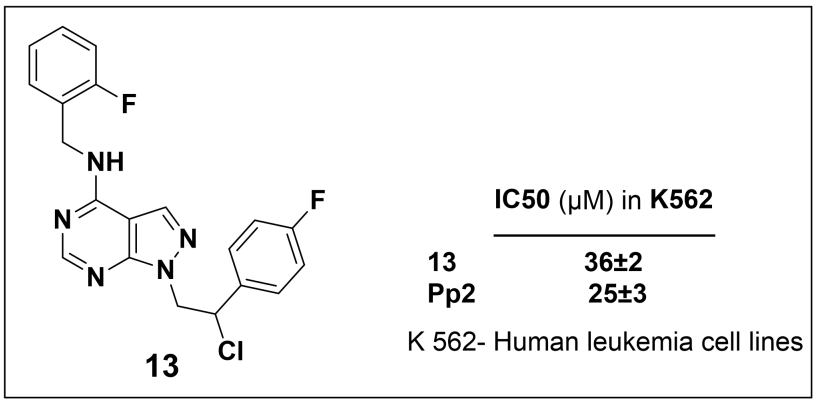


Figure 7: K562 values as Abl Inhibitors and antiproliferative agent 13.

Radi et al. introduce pyrazolo[3,4-d]pyrimidines possessing an inhibitory role in hypoxic human leukemia cells and elaborated on the in vitro ADME characteristics and metabolic activities. These compounds as **14** were cautionary followed by restriction means of Bcr-Abl kinase action, enlarged caspase-3 action, and increased cleavage of poly-ADP-ribose-polymerase (60) (Figure 8).

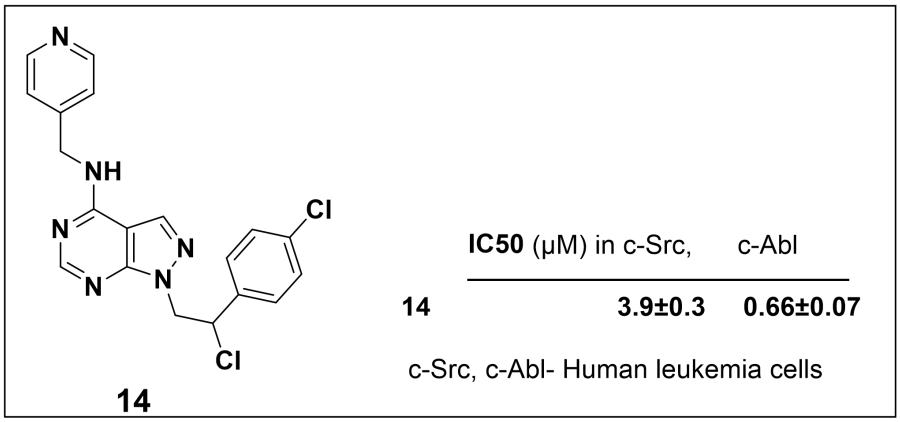


Figure 8: Action of pyrazolo[3,4-d]pyrimidines as inhibitor to Bcr-Abl kinase.

3.3. Activated Cdc42Hs-associated kinase 1 inhibitors

The recognition and optimization of N3,N6-diaryl1H-pyrazolo[3,4-d]pyrimidine-3,6-diamines as a genuine course of enacted Cdc42Hs-associated kinase 1 inhibitors was made by, Kopecky et al in 2008. In silico information suggested that the substances possessing hydrogen holding with Thr205 own tall power as compound **15** (Figure 9) (61).

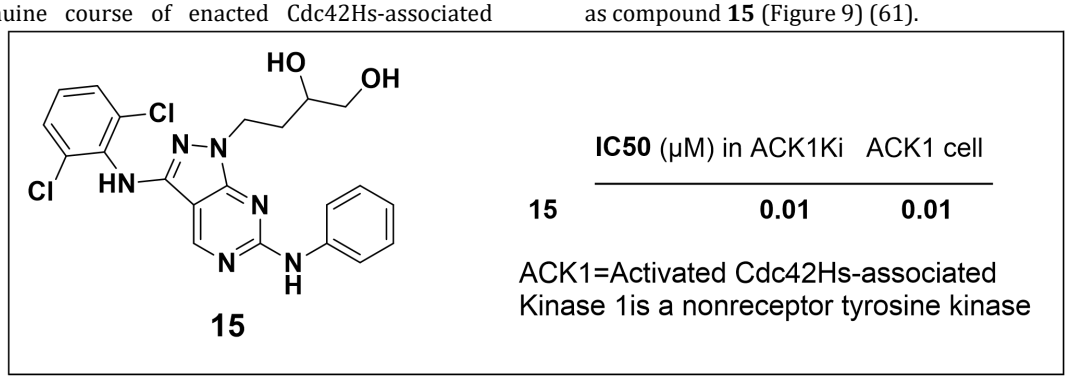


Figure 9: Compound 15 having activity on Cdc42Hs-associated kinase 1 inhibitors.

3.4. Generation of reactive oxygen species

In 2011, Hassan et al. announced that pyrazolo[3,4-d]pyrimidines treated in vitro own cytotoxic properties toward breast adenocarcinoma. The explanation for this finding was; an advanced generation of the free radical; hydrogen peroxide and others exerting oxidative stress. The insight of pyrazole input of pyrazolo[3,4-d]pyrimidines was less. Being present sulfonic gather between pyrazolo[3,4-d]pyrimidine and 4-chlorophenyl moiety **16** (Figure 10), anticancer activity was improved (62).

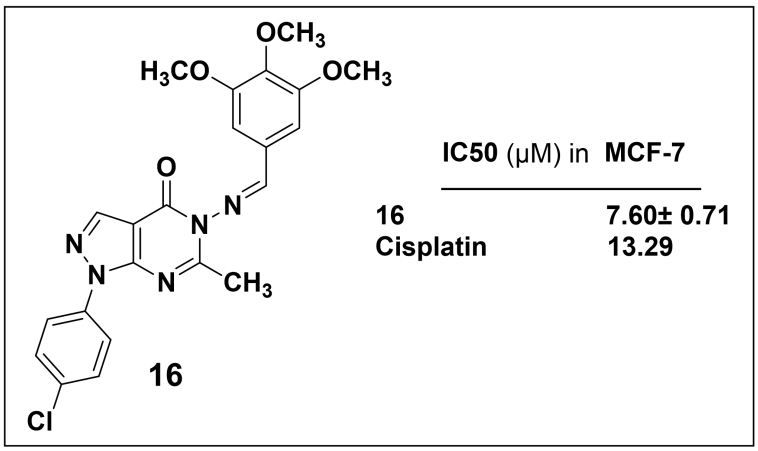


Figure 10: Pyrazolo[3,4-d]pyrimidines having in vitro cytotoxic activity and effect on MCF-7 treated cells.

3.5. p38 α Kinase inhibitors

In 2011, 3-amino-pyrazolo[3,4-d] pyrimidines were designed and established as p38a kinase inhibitors by, Soth et al. he unravel the enzymatic measure that amide usefulness exerts a mellow effect on strength keeping in mind the fact; that it is the official location while amine moiety appeared to distinguish tall due to its close official to the dynamic location. Sulfonamide arrangement was reported to be impermeable to cells (63). Compound **17** was recognized as strong selective a p38a kinase inhibitor (Figure 11).

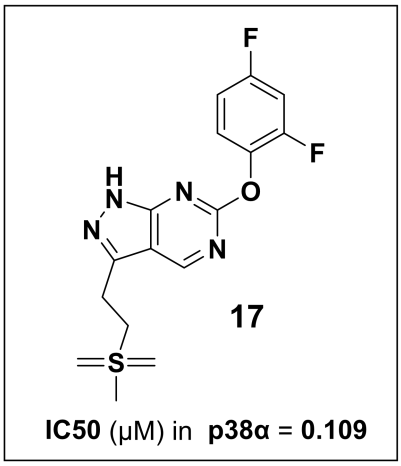


Figure 11: Action of pyrazolo[3,4-d]pyrimidines as p38a kinase inhibitors.

3.6. Aurora kinases and CDK1 inhibitors

1,6 disubstituted-1H-pyrazolo[3,4-d]pyrimidines were generated and SAR explain in 2012 by Brazidec et al. as an inhibitor of both Aurora kinases and CDK1. Driven by the desire of creating a strong biochemical and controlled clogP value, they speculated that R1 is crucial for activity as it interacts with the binding site of CDK1. Compound 18 mode of action is illustrated in (Figure 12) (64).

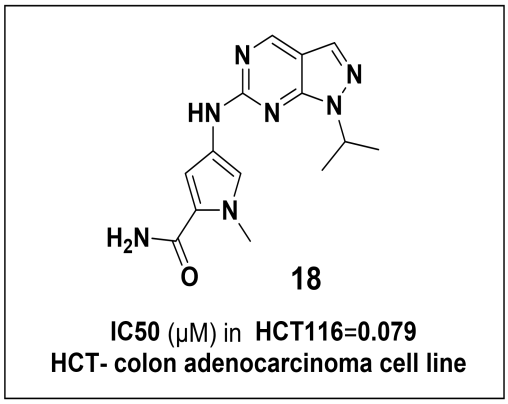


Figure 12: Pyrazolo[3,4-d]pyrimidines have cell cycle arrest at G2/M phase and activity on HCT116.

3.7. 7Akt/p70S6K inhibitors

The action of pyrazolopyrimidines as a dual inhibitor to Akt/p70S6K was described by Rice et al in 2012. Conversion of the highly potent and selective compound 19 into dual inhibitors of Akt/p70S6K was the scope; this is illustrated in (Figure 13) (65).

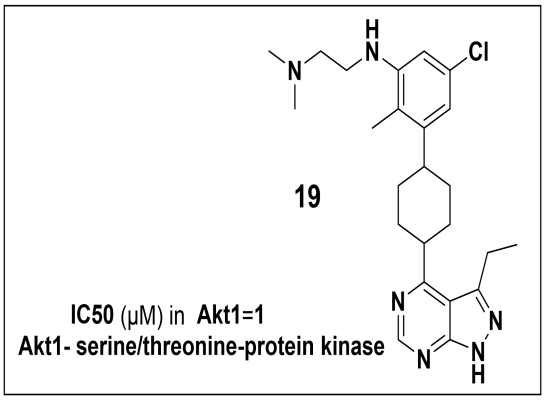


Figure 13: The anticancer action of Compound 19 as Akt/p70S6K inhibitors.

3.8. CK 1 inhibitors

The novel role of N6-phenyl-1H-pyrazolo[3,4-d]pyrimidine-3,6-diamine derivatives as an inhibitor to CK1 was made clear by Yang et al in 2012. Compound **20** stands out as having the strongest activity in the CK1 (Figure 14) (66).

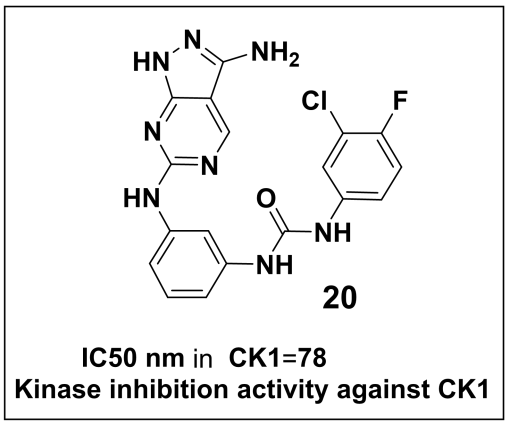


Figure 14: Pyrazolo[3,4-d]pyrimidine as CK1 inhibitors.

REFERENCE

1. Eftekhari-Sis B, Zirak M, Akbari AJCr. Arylglyoxals in synthesis of heterocyclic compounds. 2013;113(5):2958-3043.
2. Ju Y, Varma RSJTJooc. Aqueous N-heterocyclization of primary amines and hydrazines with dihalides: microwave-assisted syntheses of N-azacycloalkanes, isoindole, pyrazole, pyrazolidine, and phthalazine derivatives. 2006;71(1):135-41.
3. Zárate-Zárate D, Aguilar R, Hernández-Benitez RI, Labarrios EM, Delgado F, Tamariz JJT. Synthesis of α-ketols by functionalization of captodative alkenes and divergent preparation of heterocycles and natural products. 2015;71(38):6961-78.
4. Li X, He L, Chen H, Wu W, Jiang HJTJooc. Copper-Catalyzed Aerobic C (sp2)–H Functionalization for C–N Bond Formation: Synthesis of Pyrazoles and Indazoles. 2013;78(8):3636-46.
5. Khalil SMJJoCC. Synthesis, spectroscopic and magnetic studies on metal complexes of 5-methyl-3-(2-hydroxyphenyl) pyrazole. 2003;56(12):1013-24.
6. Li M, Zhao B-XJEjomc. Progress of the synthesis of condensed pyrazole derivatives (from 2010 to mid-2013). 2014;85:311-40.
7. Kumar H, Saini D, Jain S, Jain NJEjomc. Pyrazole scaffold: a remarkable tool in the development of anticancer agents. 2013;70:248-58.
8. Godoy Netto AVd, Frem RCG, Mauro AEJQN. A química supramolecular de complexos pirazólicos. 2008;31(5):1208-17.
9. Jarboe C, Behr L, Fusco RJIPNY. Pyrazoles, Pyrazolines, pyrazolidines, Indazoles, and Condensed Rings. 1979:p117-8.
10. Worley JDJJoCE. Heterocyclic chemistry, (Gilchrist, TL). 1993;70(3):A89.
11. Elguero J, Goya P, Jagerovic N, Silva A. In Targets in Heterocyclic Systems, Vol. 6, edited by OA Attanasi & D. Spinelli. Rome: Springer; 2002.
12. Viale M, Anzaldi M, Aiello C, Fenoglio C, Albicini F, Emionite L, et al. Evaluation of the anti-proliferative activity of three new pyrazole compounds in sensitive and resistant tumor cell lines. 2013;65(3):717-23.
13. Meng L, Lorsbach BA, Sparks TC, Fettinger JC, Kurth MJJJocc. Parallel synthesis of bis-heterocyclic isoxazolylmethyl-and isoxazolinylmethylpyrazoles. 2010;12(1):129-36.
14. Regan J, Breitfelder S, Cirillo P, Gilmore T, Graham AG, Hickey E, et al. Pyrazole urea-based inhibitors of p38 MAP kinase: from lead compound to clinical candidate. 2002;45(14):2994-3008.
15. Michaelides M. PCT Int Appl WO 2010065825. 2010.
16. v. Pechmann HJBddcG. Pyrazol aus acetylen und diazomethan. 1898;31(3):2950-1.
17. Lesyk R, Zimenkovsky BJCOC. 4-Thiazolidones: centenarian history, current status and perspectives for modern organic and medicinal chemistry. 2004;8(16):1547-77.
18. Knorr L, Laubmann HJBddcG. Ueber das verhalten der pyrazole und pyrazoline. 1888;21(1):1205-12.
19. Jain AK, Vaidya A, Ravichandran V, Kashaw SK, Agrawal RKJB, chemistry m. Recent developments and biological activities of thiazolidinone derivatives: A review. 2012;20(11):3378-95.
20. Kamal A, Tamboli JR, Nayak VL, Adil S, Vishnuvardhan M, Ramakrishna SJB, et al. Synthesis of pyrazolo [1, 5-a] pyrimidine linked aminobenzothiazole conjugates as potential anticancer agents. 2013;23(11):3208-15.
21. Dalinger IL, Vatsadse IA, Shevelev SA, Ivachtchenko AVJJocc. Liquid-phase synthesis of combinatorial libraries based on 7-trifluoromethyl-substituted pyrazolo [1, 5-a] pyrimidine scaffold. 2005;7(2):236-45.
22. Ishizawar R, Parsons SJJCc. c-Src and cooperating partners in human cancer. 2004;6(3):209-14.
23. Ajani OO, Isaac JT, Owoeye TF, Akinsiku AAJIJoBC. Exploration of the chemistry and biological properties of pyrimidine as a privilege pharmacophore in therapeutics. 2015;9(4):148-77.
24. Hassan AS, Hafez TS, Osman SAM, Ali MMJTJoC. Synthesis and in vitro cytotoxic activity of novel pyrazolo [1, 5-$ a $] pyrimidines and related Schiff bases. 2015;39(5):1102-13.
25. Anwar HF, Fleita DH, Kolshorn H, Meier H, Elnagdi MHJA. 2H-Pyrazol-3-ylamines as precursors for the synthesis of polyfunctionally substituted pyrazolo [1, 5-a] pyrimidines. 2006;15:133-41.
26. Hassan AS, Hafez TS, Osman SAJSp. Synthesis, characterization, and cytotoxicity of some new 5-aminopyrazole and pyrazolo [1, 5-a] pyrimidine derivatives. 2015;83(1):27-39.
27. Al-Matar HM, Khalil KD, Adam AY, Elnagdi MHJM. Green one pot solvent-free synthesis of pyrano [2, 3-c]-pyrazoles and pyrazolo [1, 5-a] pyrimidines. 2010;15(9):6619-29.
28. Mukaiyama H, Nishimura T, Shiohara H, Kobayashi S, Komatsu Y, Kikuchi S, et al. Discovery of novel 2-anilinopyrazolo [1, 5-a] pyrimidine derivatives as c-Src kinase

inhibitors for the treatment of acute ischemic stroke. 2007;55(6):881-9.
29. Yan X, Zhang C, Liang T, Yang F, Wang H, Wu F, et al. A PTEN-COL17A1 fusion gene and its novel regulatory role in Collagen XVII expression and GBM malignance. 2017;8(49):85794.
30. Belpomme D, Irigaray P, Sasco A, Newby J, Howard V, Clapp R, et al. The growing incidence of cancer: role of lifestyle and screening detection. 2007;30(5):1037-49.
31. Chen Y-L, Lin S-Z, Chang J-Y, Cheng Y-L, Tsai N-M, Chen S-P, et al. In vitro and in vivo studies of a novel potential anticancer agent of isochaihulactone on human lung cancer A549 cells. 2006;72(3):308-19.
32. Nakhjiri M, Safavi M, Alipour E, Emami S, Atash AF, Jafari-Zavareh M, et al. Asymmetrical 2, 6-bis (benzylidene) cyclohexanones: Synthesis, cytotoxic activity and QSAR study. 2012;50:113-23.
33. Cohen PJNrDd. Protein kinases—the major drug targets of the twenty-first century? 2002;1(4):309-15.
34. Fustero S, Sánchez-Roselló M, Barrio P, Simon-Fuentes AJCr. From 2000 to mid-2010: a fruitful decade for the synthesis of pyrazoles. 2011;111(11):6984-7034.
35. Baviskar AT, Banerjee UC, Gupta M, Singh R, Kumar S, Gupta MK, et al. Synthesis of imine-pyrazolopyrimidinones and their mechanistic interventions on anticancer activity. 2013;21(18):5782-93.
36. Legentil L, Benel L, Bertrand V, Lesur B, Delfourne EJJomc. Synthesis and antitumor characterization of pyrazolic analogues of the marine pyrroloquinoline alkaloids: wakayin and tsitsikammamines. 2006;49(10):2979-88.
37. Baviskar AT, Madaan C, Preet R, Mohapatra P, Jain V, Agarwal A, et al. N-fused imidazoles as novel anticancer agents that inhibit catalytic activity of topoisomerase IIα and induce apoptosis in G1/S phase. 2011;54(14):5013-30.
38. Tao X-X, Duan Y-T, Chen L-W, Tang D-J, Yang M-R, Wang P-F, et al. Design, synthesis and biological evaluation of pyrazolyl-nitroimidazole derivatives as potential EGFR/HER-2 kinase inhibitors. 2016;26(2):677-83.
39. Ducray R, Ballard P, Barlaam BC, Hickinson MD, Kettle JG, Ogilvie DJ, et al. Novel 3-alkoxy-1H-pyrazolo [3, 4-d] pyrimidines as EGFR and erbB2 receptor tyrosine kinase inhibitors. 2008;18(3):959-62.
40. Miyamoto N, Sakai N, Hirayama T, Miwa K, Oguro Y, Oki H, et al. Discovery of N-[5-({2-[(cyclopropylcarbonyl) amino] imidazo [1, 2-b] pyridazin-6-yl} oxy)-2-methylphenyl]-1, 3-dimethyl-1H-pyrazole-5-carboxamide (TAK-593), a highly potent VEGFR2 kinase inhibitor. 2013;21(8):2333-45.
41. Harris PA, Boloor A, Cheung M, Kumar R, Crosby RM, Davis-Ward RG, et al. Discovery of 5-[[4-[(2, 3-dimethyl-2 H-indazol-6-yl) methylamino]-2-pyrimidinyl] amino]-2-methyl-benzenesulfonamide (Pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor. 2008;51(15):4632-40.
42. Wen J, Bao Y, Niu Q, Yang J, Fan Y, Li J, et al. Identification of N-(6-mercaptohexyl)-3-(4-pyridyl)-1H-pyrazole-5-carboxamide and its disulfide prodrug as potent histone deacetylase inhibitors with in vitro and in vivo anti-tumor efficacy. 2016;109:350-9.
43. Yao Y, Liao C, Li Z, Wang Z, Sun Q, Liu C, et al. Design, synthesis, and biological evaluation of 1, 3-disubstituted-pyrazole derivatives as new class I and IIb histone deacetylase inhibitors. 2014;86:639-52.
44. Aware V, Gaikwad N, Chavan S, Manohar S, Bose J, Khanna S, et al. Cyclopentyl-pyrimidine based analogues as novel and potent IGF-1R inhibitor. 2015;92:246-56.
45. Bavetsias V, Faisal A, Crumpler S, Brown N, Kosmopoulou M, Joshi A, et al. Aurora isoform selectivity: design and synthesis of imidazo [4, 5-b] pyridine derivatives as highly selective inhibitors of Aurora-A kinase in cells. 2013;56(22):9122-35.
46. Cheng H, Nair SK, Murray BW, Almaden C, Bailey S, Baxi S, et al. Discovery of 1-{(3 R, 4 R)-3-[({5-Chloro-2-[(1-methyl-1 H-pyrazol-4-yl) amino]-7 H-pyrrolo [2, 3-d] pyrimidin-4-yl} oxy) methyl]-4-methoxypyrrolidin-1-yl} prop-2-en-1-one (PF-06459988), a Potent, WT Sparing, Irreversible Inhibitor of T790M-Containing EGFR Mutants. 2016;59(5):2005-24.
47. Kamal A, Shaik AB, Jain N, Kishor C, Nagabhushana A, Supriya B, et al. Design and synthesis of pyrazole–oxindole conjugates targeting tubulin polymerization as new anticancer agents. 2015;92:501-13.
48. Reddy GL, Guru SK, Srinivas M, Pathania AS, Mahajan P, Nargotra A, et al. Synthesis of 5-substituted-1H-pyrazolo [4, 3-d] pyrimidin-7 (6H)-one analogs and their biological evaluation as anticancer agents: mTOR inhibitors. 2014;80:201-8.
49. Wang S-F, Zhu Y-L, Zhu P-T, Makawana JA, Zhang Y-L, Zhao M-Y, et al. Design, synthesis and biological evaluation of novel 5-phenyl-1H-pyrazole derivatives as potential BRAFV600E inhibitors. 2014;22(21):6201-8.
50. Zhao M-Y, Yin Y, Yu X-W, Sangani CB, Wang S-F, Lu A-M, et al. Synthesis, biological evaluation and 3D-QSAR study of novel 4, 5-dihydro-1H-pyrazole thiazole derivatives as BRAFV600E inhibitors. 2015;23(1):46-54.
51. Park BS, Al-Sanea MM, Abdelazem AZ, Park HM, Roh EJ, Park H-M, et al. Structure-based optimization and biological evaluation of trisubstituted pyrazole as a core structure of potent ROS1 kinase inhibitors. 2014;22(15):3871-8.
52. Heffron TP, Wei B, Olivero A, Staben ST, Tsui V, Do S, et al. Rational design of phosphoinositide 3-kinase α inhibitors that exhibit selectivity over the phosphoinositide 3-kinase β isoform. 2011;54(22):7815-33.
53. Hart AC, Schroeder GM, Wan H, Grebinski J, Inghrim J, Kempson J, et al. Structure-based design of selective janus kinase 2 Imidazo [4, 5-d] pyrrolo [2, 3-b] pyridine Inhibitors. 2015;6(8):845-9.

54. Tu C-H, Lin W-H, Peng Y-H, Hsu T, Wu J-S, Chang C-Y, et al. Pyrazolylamine derivatives reveal the conformational switching between type I and type II binding modes of Anaplastic Lymphoma Kinase (ALK). 2016;59(8):3906-19.
55. Frank AO, Feldkamp MD, Kennedy JP, Waterson AG, Pelz NF, Patrone JD, et al. Discovery of a potent inhibitor of replication protein a protein–protein interactions using a fragment-linking approach. 2013;56(22):9242-50.
56. Spreafico A, Schenone S, Serchi T, Orlandini M, Angelucci A, Magrini D, et al. Antiproliferative and proapoptotic activities of new pyrazolo [3, 4-d] pyrimidine derivative Src kinase inhibitors in human osteosarcoma cells. 2008;22(5):1560-71.
57. Chauhan M, Kumar R. Medicinal attributes of pyrazolo[3,4-d]pyrimidines: a review. Bioorg Med Chem. 2013;21(18):5657-68.
58. Carraro F, Naldini A, Pucci A, Locatelli GA, Maga G, Schenone S, et al. Pyrazolo [3, 4-d] pyrimidines as potent antiproliferative and proapoptotic agents toward A431 and 8701-BC cells in culture via inhibition of c-Src phosphorylation. 2006;49(5):1549-61.
59. Manetti F, Brullo C, Magnani M, Mosci F, Chelli B, Crespan E, et al. Structure-based optimization of pyrazolo [3, 4-d] pyrimidines as Abl inhibitors and antiproliferative agents toward human leukemia cell lines. 2008;51(5):1252-9.
60. Radi M, Dreassi E, Brullo C, Crespan E, Tintori C, Bernardo V, et al. Design, synthesis, biological activity, and ADME properties of pyrazolo [3, 4-d] pyrimidines active in hypoxic human leukemia cells: a lead optimization study. 2011;54(8):2610-26.
61. Kopecky DJ, Hao X, Chen Y, Fu J, Jiao X, Jaen JC, et al. Identification and optimization of N3, N6-diaryl-1H-pyrazolo [3, 4-d] pyrimidine-3, 6-diamines as a novel class of ACK1 inhibitors. 2008;18(24):6352-6.
62. Hassan GS, Kadry HH, Abou-Seri SM, Ali MM, Mahmoud AEE-DJB, chemistry m. Synthesis and in vitro cytotoxic activity of novel pyrazolo [3, 4-d] pyrimidines and related pyrazole hydrazones toward breast adenocarcinoma MCF-7 cell line. 2011;19(22):6808-17.
63. Soth M, Abbot S, Abubakari A, Arora N, Arzeno H, Billedeau R, et al. 3-Amino-pyrazolo [3, 4-d] pyrimidines as p38α kinase inhibitors: design and development to a highly selective lead. 2011;21(11):3452-6.
64. Le Brazidec J-Y, Pasis A, Tam B, Boykin C, Black C, Wang D, et al. Synthesis, SAR and biological evaluation of 1, 6-disubstituted-1H-pyrazolo [3, 4-d] pyrimidines as dual inhibitors of Aurora kinases and CDK1. 2012;22(5):2070-4.
65. Zhang B, Peng Q, Guo D, Wang JJOL. NHC-Catalyzed Radical Trifluoromethylation Enabled by Togni Reagent. 2020.
66. Yang L-L, Li G-B, Yan H-X, Sun Q-Z, Ma S, Ji P, et al. Discovery of N6-phenyl-1H-pyrazolo [3, 4-d] pyrimidine-3, 6-diamine derivatives as novel CK1 inhibitors using common-feature pharmacophore model based virtual screening and hit-to-lead optimization. 2012;56:30-8.