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From molecule to medicine: introducing emerging strategies to synthesize potent anticancer purine scaffolds

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Cancer remains a major global health concern, necessitating the continuous development of novel anticancer agents with enhanced efficacy and reduced side effects. Purine derivatives are privileged bioactive scaffolds that play a crucial role in drug discovery due to their presence in essential biomolecules such as DNA, RNA, ATP, and coenzymes. This review highlights the synthesis, structure–activity relationships (SARs), and anticancer evaluations of various purine hybrids, including aryl piperazine, triazole-hybrid piperidine/pyrrolidine, and diazenyl-containing purines, from 2020 to 2024. Hybrid molecules incorporating chalcones, thiazoles, thiazolidinones, xanthine, and bis-purine linkers have expanded the therapeutic landscape of purine-based anticancer agents. Comparative analyses of IC_{50} values reveal that piperazine-containing purine derivatives exhibit potent activity against Huh7, HCT116, and MCF7 cancer cells, while trisubstituted triazole analogs display selective cytotoxicity against A549, IMR-32, HCT-15, and THP-1 cell lines. Moreover, bis-purine derivatives and chalcone–xanthine hybrids exhibit broad-spectrum anticancer potential against A549, HeLa, CFPAC-1, and SW620 cells. Theobromine- and adamantane-based purine scaffolds have emerged as promising anticancer agents, with potent activity against MCF7 and HepG2 cells as well as the VEGFR-2 protein. Comparative SAR studies highlight the role of different heterocyclic substitutions in optimizing anticancer efficacy, offering valuable insights for medicinal chemists in the pursuit of more effective and safer cancer treatments.

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1 Introduction

Cancer is one of the leading causes of death worldwide.[1] The majority of cancer patients experience a low quality of life due to the negative outcomes linked to the disease.[2] Chemotherapy is one of the best ways to stop the growth of tumors and eradicate them.[3] However, thrombocytopenia, anemia, nausea, and vomiting are common side effects experienced by many chemotherapy patients.[4] Research continues in the hope of discovering new anticancer drugs with enhanced efficacy and a high degree of safety for normal host cells, despite several studies documenting the possible chemotherapeutic effects of novel molecules. To cure cancer, many heterocyclic drugs containing purine nuclei have been synthesized and are considered the top potent biological drugs (Fig. 1). Recently, a team of scientists understood the frequency of nitrogen-based heterocycles among FDA-approved lead compounds and found that 60% of medication molecules contain these heterocycles.[5] Emil Fischer—the 1902 Nobel winner in chemistry—named the fused imidazo[4,5-d]pyrimidine purine in 1884 and synthesized it in 1898.[6] Cancer refers to over 120 distinct diseases characterized by the uncontrolled and rapid proliferation of abnormal cells. These cells can spread to other organs and ultimately lead to death, if left unchecked.[7] In the past years, purines with functionality at one or more of the seven peripheral atoms that comprise their bicyclic structure were easily produced from monocyclic precursors using well-known pathways.[8] Purine scaffolds are synthesized by *N*-acylation of diaminopyrimidines,[9] *N*-amination and *N*-alkylation,[10] S_NAr reaction, the Vorbrüggen reaction, metal-catalyzed cross-coupling reaction, the Mitsunobu reaction and many other well-known reactions.[6] The substituted derivatives synthesized by these reactions showed vast biological activities.[11] *N*-Heterocyclic compounds have a wide range of remarkable biological characteristics. Aromatic heterocyclic molecules with nitrogenous bases known as purines, along with their derivative nucleobases [adenine (A) and guanine (B), purine (C), and xanthine (D)], are vital in biological chemistry (Fig. 2). The metabolism of all living things depends on purine bases. DNA, RNA, ATP, nicotinamide adenine dinucleotide (NAD) coenzyme, and alkaloids are substances that contain purine moieties.[8] To develop effective drugs with a wide range of biological activities, the synthesis and analysis of purine moieties has sparked interest. Numerous

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purine derivatives that have been demonstrated to function as antimetabolites have been created as anticancer medications.[12] Consequently, different bio-isosteres with altered activity have been discovered as a consequence of modifications to the *N*-heterocyclic purine and different substitutions.[13]

Among many other pharmaceutical candidates, the Food and Drug Administration (FDA) has frequently approved this privileged scaffold. This moiety is becoming increasingly popular in a range of illnesses because of its simplicity in parallelization and possibilities for chemical space testing. The major purine nucleus hybridized with different substitutions plays a very important key role in enhancing the activities of compounds. These purine-based scaffolds may act as antimalarials,[14] anti-fungals,[15] anti-tuberculosis agents,[16] anti-kinetoplastid agents,[17] as well as anti-cancer,[18] anti-viral,[19] anti-diabetic,[20] anti-leishmanial[21] and anti-depressant[22] compounds. Many drugs approved by the FDA contain a purine moiety as the core nucleus and act as strong anti-cancer drugs, such as CDK inhibitor, leukaemia inhibitor, *etc.* (Fig. 3). Clofarabine (**E**) is an effective drug that relapsed lymphoblastic leukaemia. It is considered as a next generation deoxyadenosine analogue that has higher efficacy and less toxicity in body.[23,24] Roscovitine (**F**) acts as an CDK inhibitor in cancer therapy.[25] Purinethol (**G**) is a chemotherapeutic drug that is effective against leukemia (blood disorder).[26] Fludarabine (**H**) is a commercially available anti-cancer drug that can form palladium and platinum complexes to enhance the anti-cancer activity of fludarabine. It may act as a frontline therapy for CLL cells.[27] Leustatine (**I**) is an anti-cancer drug against hairy cell leukemia. It acts as a rare lymphoproliferative malignoma.[28] Tabloid (**J**) is a candidate to cure myelogenous leukemia.[29] Nelarabin (**K**) is the most potent chemotherapeutic drug that may diminish the acute T-cell leukemia containing purine moiety in its structure.[30] Olomoucine (**L**) is a kinase inhibitor that specifically affects CDK. It is a strong CDK inhibitor that is 10-fold more effective then roscovitine (**F**).[31]

The purine ring is a unique structure that exhibits several therapeutic qualities in different cancer types. Purines are imidazole motifs joined with pyrimidines that provide a wide range of chemical modification options. Primarily, a variety of purine derivative libraries are produced by the seven reactive centers of the purine ring.[32] This review describes the synthesis of purine-based hybrids with potential anticancer activity, highlighting various synthetic methodologies. It provides valuable insights for both synthetic and medicinal chemists in designing small-molecule drugs with enhanced anticancer efficacy. By addressing challenges such as drug resistance, minimizing side effects, and improving therapeutic outcomes, this study contributes to the ongoing development of more effective cancer treatments.

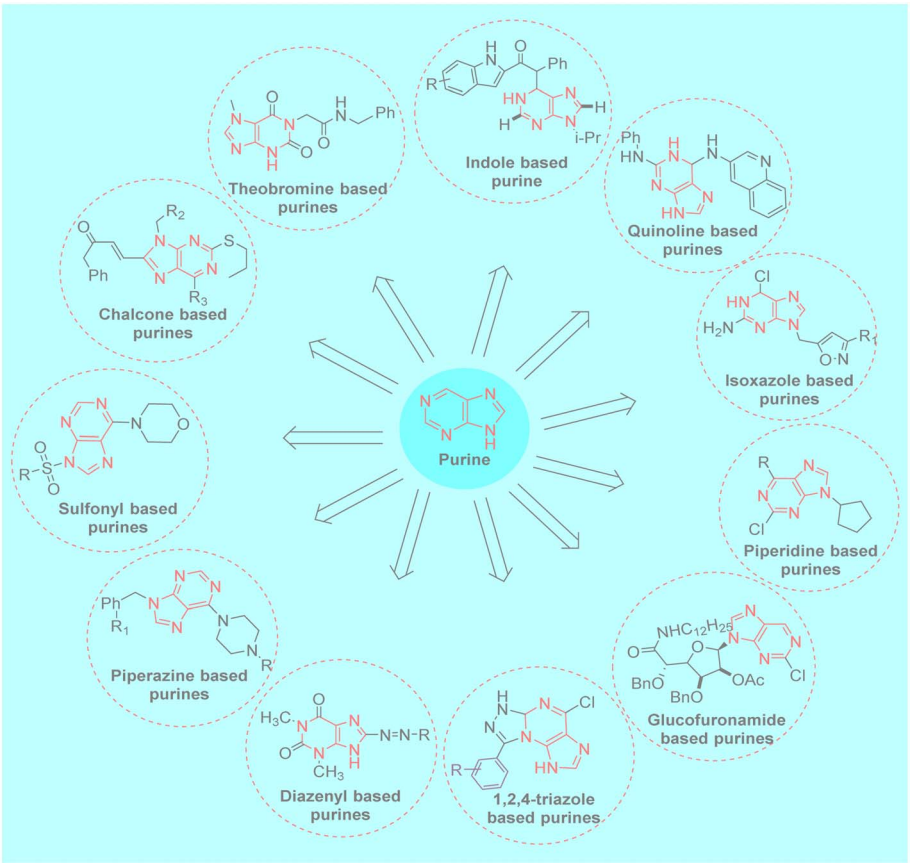


Fig. 1 Graphical abstract.

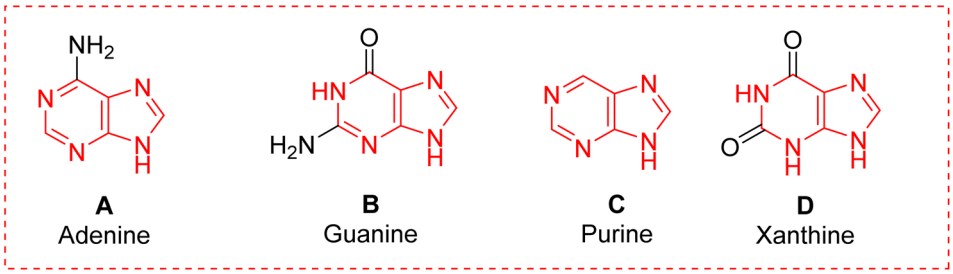


Fig. 2 General structure of adenine, guanine, purine and xanthine.

2 Synthetic routes

2.1 Hybrid purine-based derivatives

2.1.1 Linker-containing hybrids. B. Popov *et al.* reported the design to synthesize novel bis-purine and pyrimidine scaffolds.[33] Their studies revealed that two purine monomers were attached through a linker. The linker enhanced the antiproliferative activity. The novelty in their work was the use of ultrasound radiation as a source of energy which made the reaction proceeds rapidly and shortened the reaction time. The synthesis was initiated with the *N*-alkylation of 4-aminopurine (**1**) with 1,2-dibromoethane in the presence of K_2CO_3 as base, and DMF as the solvent at room temperature for 24 h to afford 2-bromoethyl-6-chloropurine (**2**). In the next step, the reaction of (**2**) with sodium azide afforded diazidio derivatives (**3**), which was further reacted with bis alkyne in the presence of

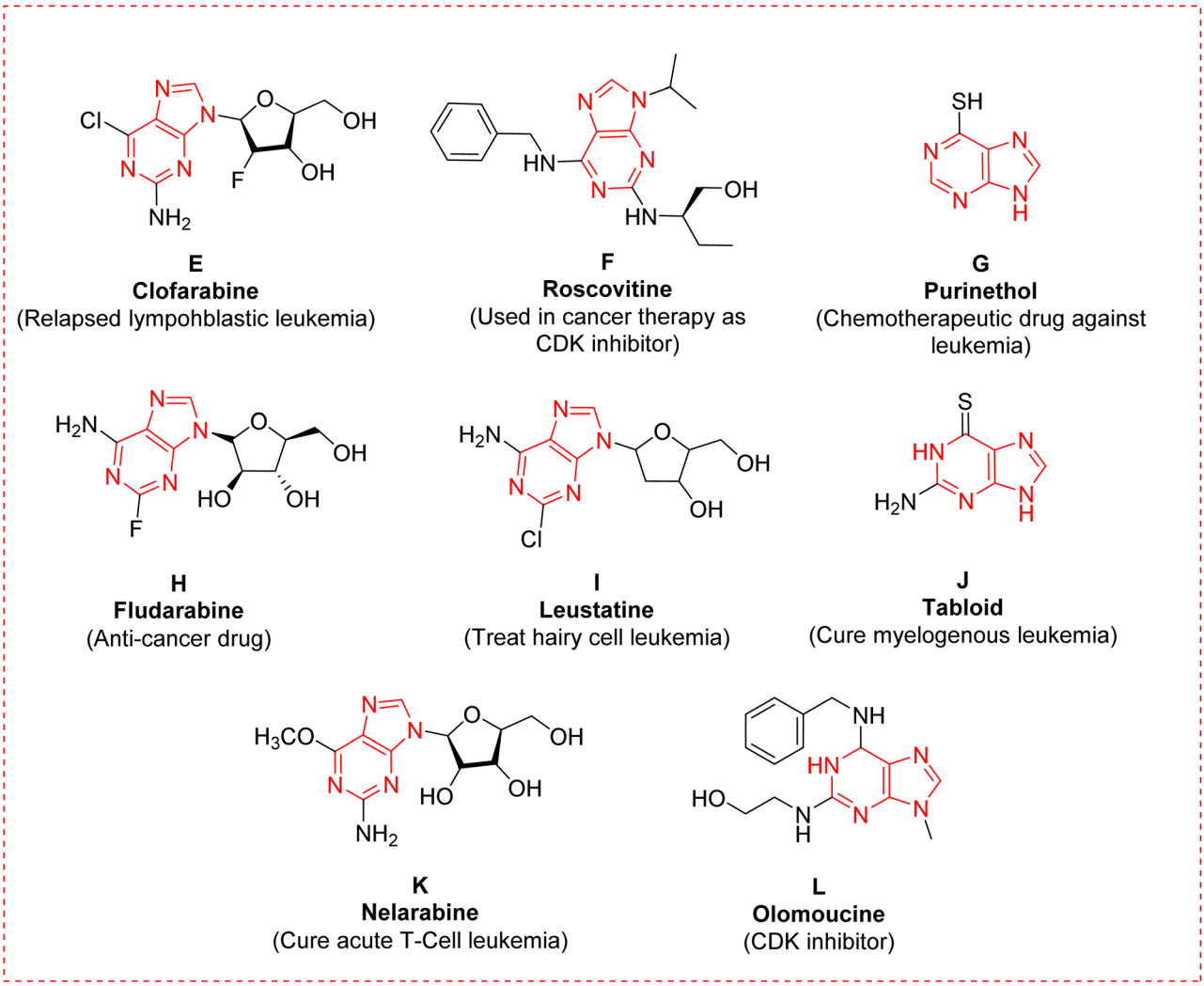
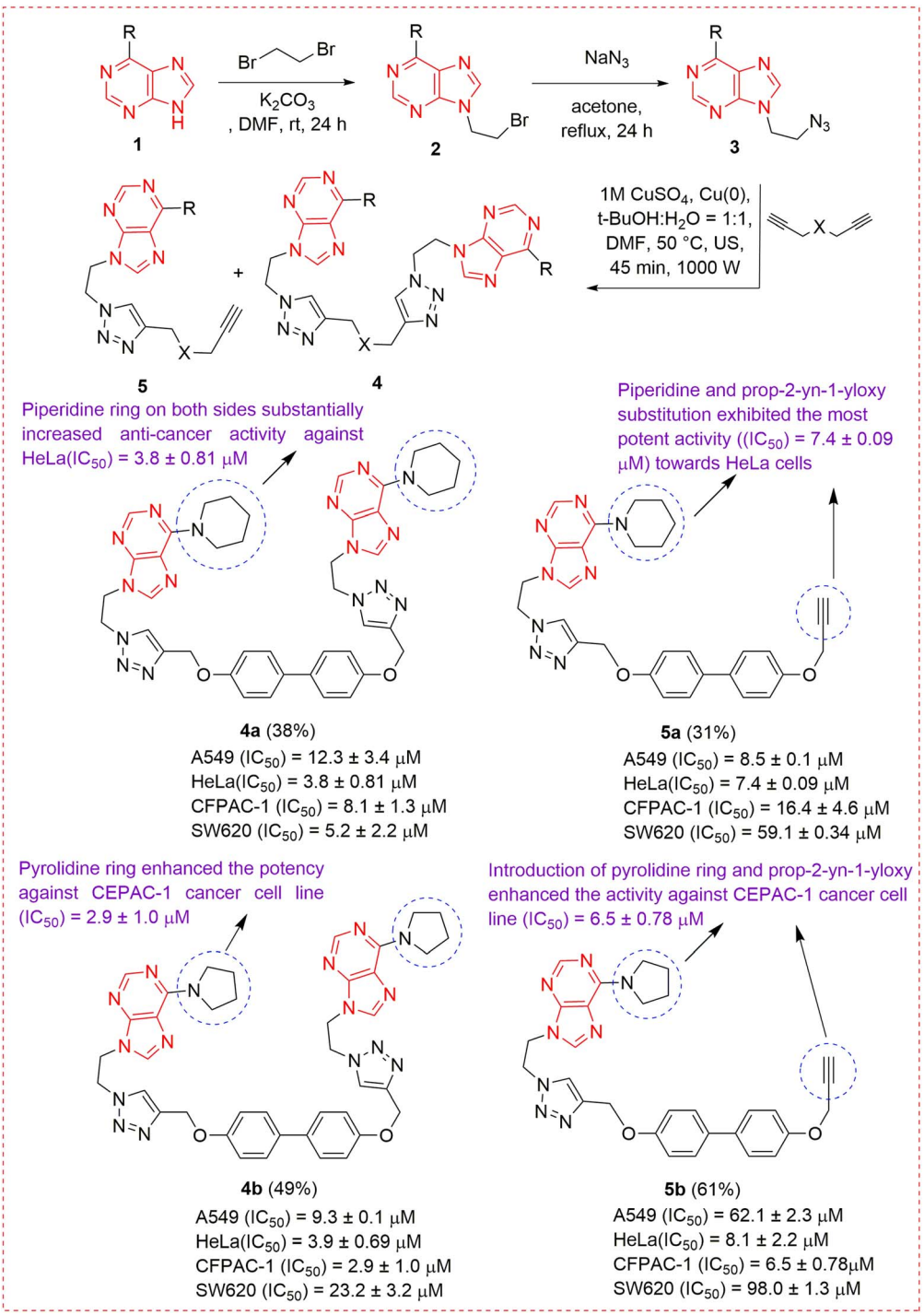


Fig. 3 FDA-approved purine-based anti-cancer drugs.[23–31]

ultrasound radiations to obtain target molecules (**4**) and (**5**). The anti-cancer properties of all the synthesized scaffolds were evaluated against cells for metastatic colorectal adenocarcinoma (SW620), ductal pancreatic adenocarcinoma (CFPAC-1), cervical carcinoma (HeLa), and lung adenocarcinoma (A549) (Scheme 1).[33] Recent studies confirmed that triazoles, purine and heterocyclic fused rings had played an important role in enhancing the anti-proliferative activity. According to SAR studies, 6-piperidinyl **4a** and **4b** and 6-pyrrolidinylpurines (**5a** and **5b**) containing 4,4-bis(oxymethylene)biphenyl demonstrated potent (although largely non-specific) inhibitory actions in the series of bis- and mono-purines. The most active bis-purines on the HeLa cell line were **4b** and **5b** (**4b**: IC_{50} = 3.8 μM; **5b**: IC_{50} = 7.4 μM). Compounds possessing a 1,4-bis(oxymethylene)phenyl linker showed reduced anti-cancer activity. Compounds with aliphatic linkers showed moderate activity.

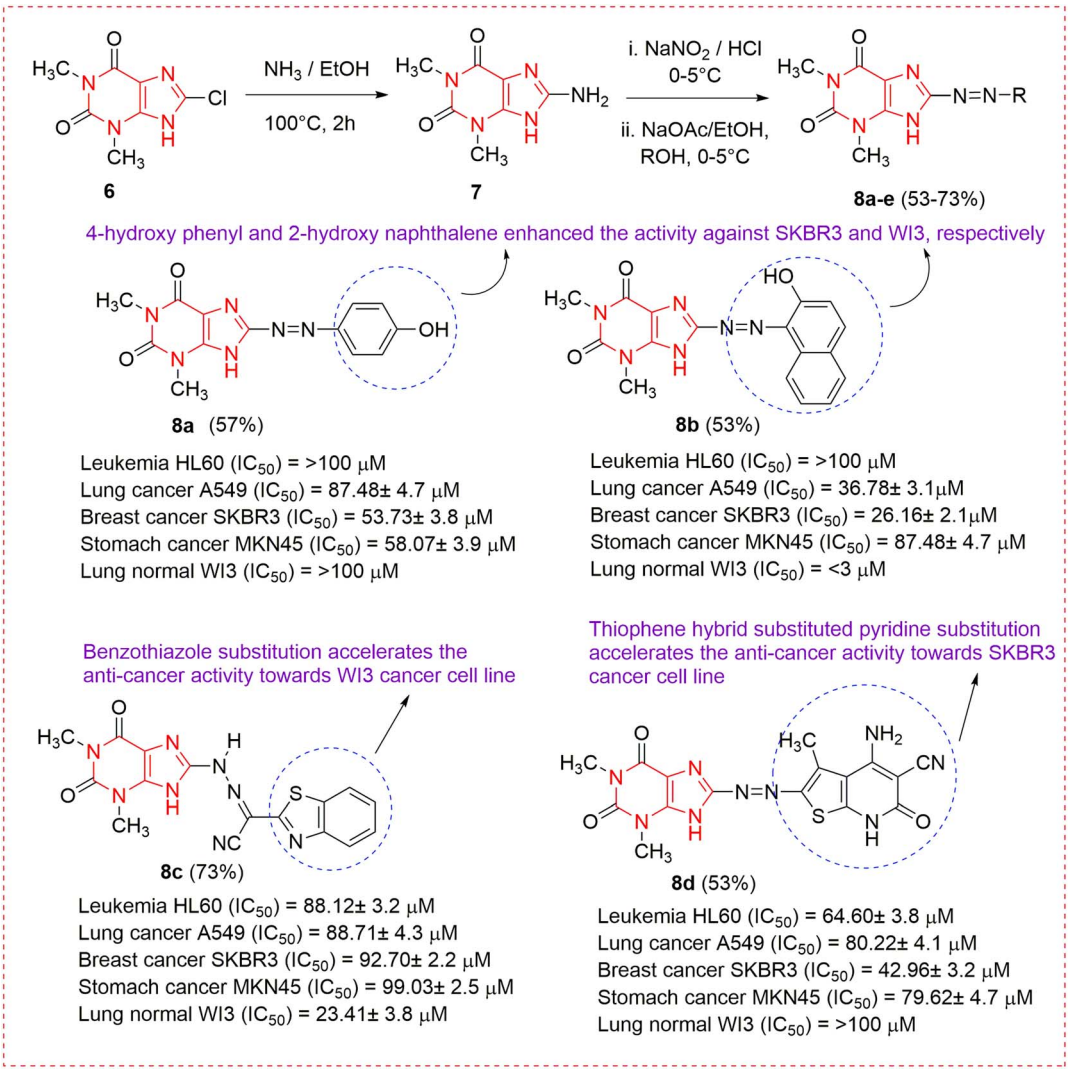


Scheme 1 Synthesis and anti-cancer evaluation for novel bis purine derivatives against A549, HeLa, CFPAC-1 and SW620 cancer cell lines.[33]

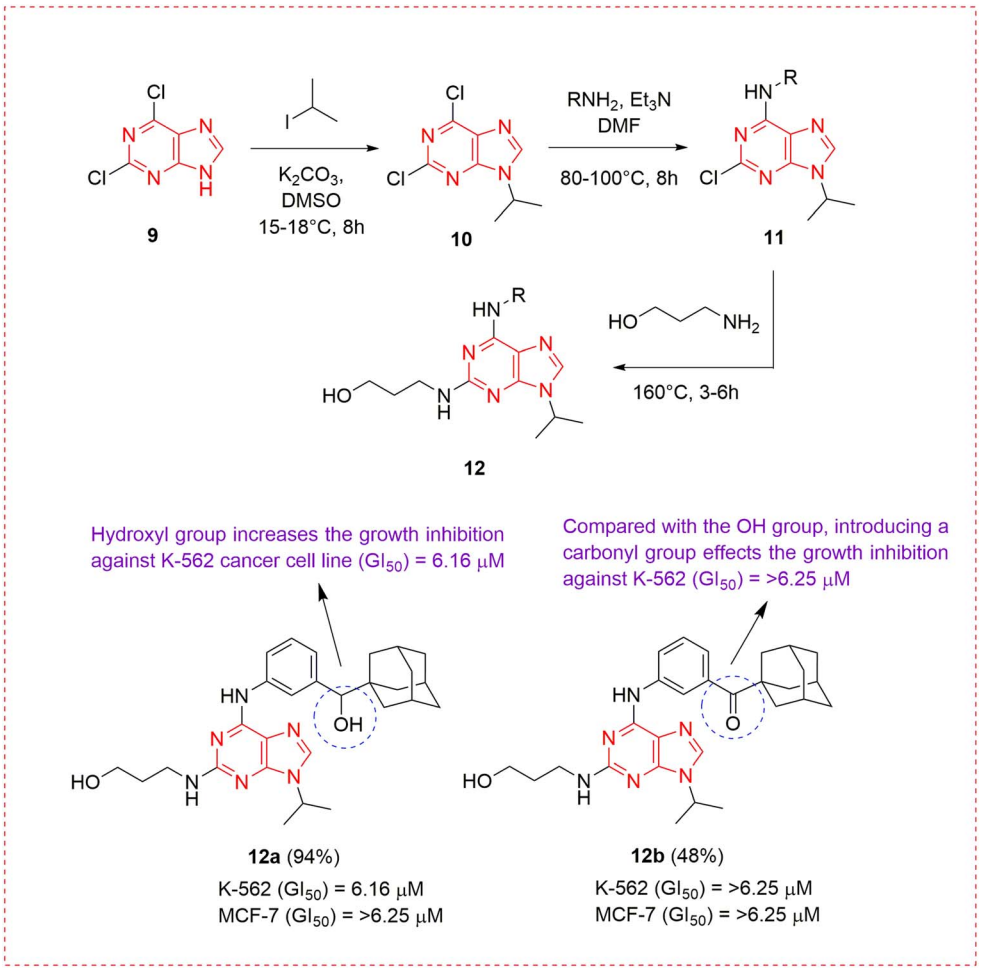
Introducing different R groups like piperidine and pyrrolidine increased its anti-cancer activity.

Mohamed E. Khalifa reported the synthetic routes to synthesize some purine derivatives and elucidated anti-cancer cell line activity.[34] The strong anti-cancer properties of each product were assessed *in vitro* against four distinct human cancer types: breast cancer (SKBR3), stomach cancer (MKN45), leukemia (HL60) and lung cancer (A549). 8-Amino-substituted purines (7) were synthesized using 8-chloro-1,3-dimethyl-3,9-dihydro-1*H*-purine-2,6-dione (**6**) in the presence of ethanolic ammonia at 100 °C for 2 h. Then, it was used to synthesize (**8**) by the addition of $NaNO_2$ in the presence of HCl. This was the basic precursor synthesized. A series of compounds were synthesized using different reagents and conditions (Scheme 2). Compounds **8a–8d** were the most active against breast cancer cells (SKBR3), having IC_{50} values of 53.73 ± 3.8, 26.16 ± 2.1, 25.11 ± 1.9 and 42.96 ± 3.2 μM, respectively. Compound **8c** proved to be the most effective against lung cancer cells (WI3), having an IC_{50} value of 23.41 ± 3.8 μM. According to molecular docking studies, these selected synthons bind with aurora kinase (a cancer-causing enzyme) to eradicate cancer cell lines. Superior tumor inhibition was demonstrated by inserting the hydroxyphenyl group at lower doses, particularly for breast cancer cell lines (Scheme 2).[34] Analysis of the structure–activity relationship proved that the benzothiazole moiety containing nitrogen possessed excellent anti-cancer activity.

M. Rouchal *et al.* demonstrated the design to synthesize adamantane-substituted purines that were considered the most potent anti-cancer drugs.[35] The anti-cancer activity of purine inhibitors may enhance by substitution of the adamantane moiety. The synthesis was initiated with alkylation of commercially available 2,6-dichloropurine (**9**) in the presence of K_2CO_3 base and DMSO solvent afforded 60% yield. In the next step, admentylated aromatic amines were introduced at the 6th position in the presence of Et_3N and DMF between 80 °C to 100 °C for 8 h to afford **11**. In the last step, C2 substitution using 3-aminopropanol afforded target molecule (**12**) (Scheme 3).[35] All the synthesized analogs were estimated for anti-cancer activity



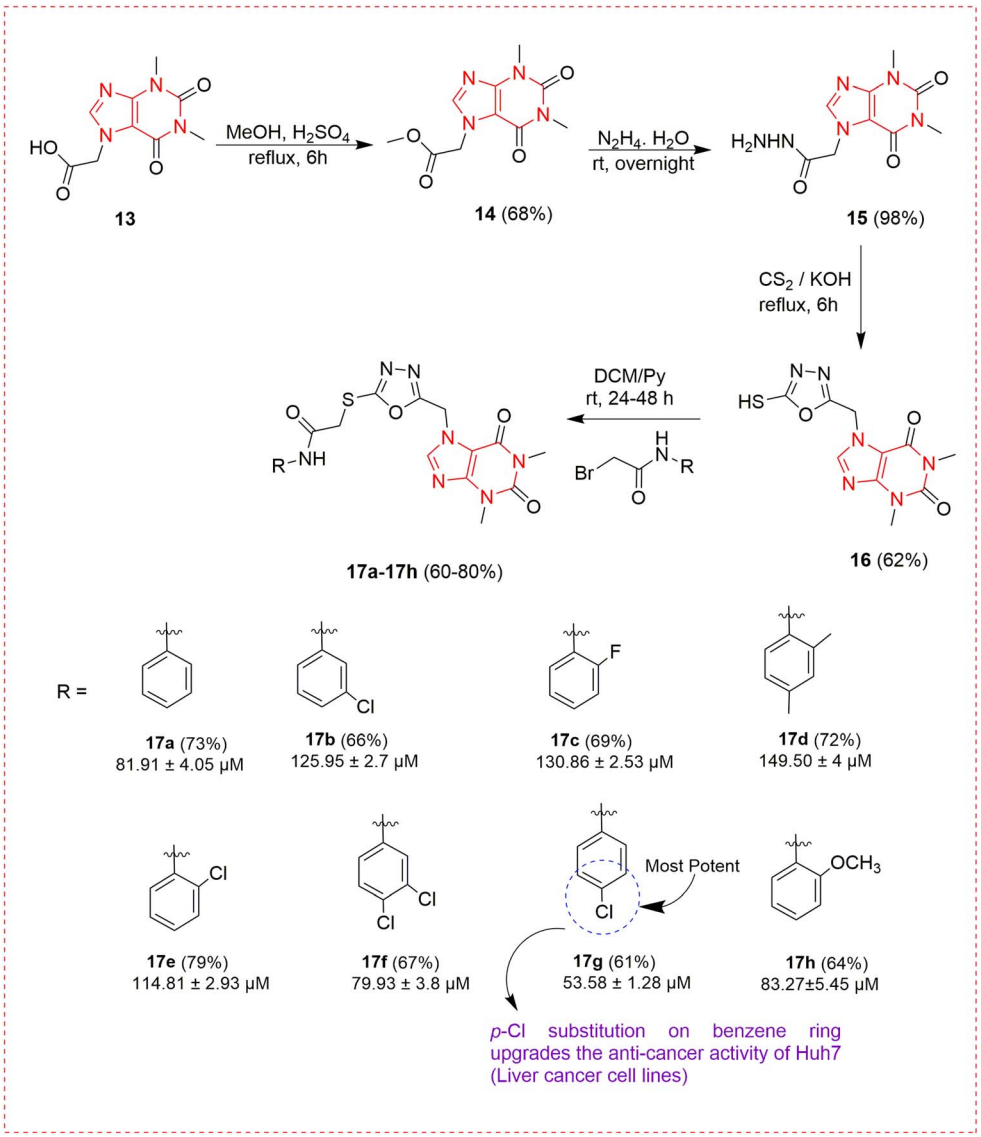
Scheme 2 Synthesis of diazenyl-based purine scaffolds against HL60, A549, SKBR3, MKN45 and WI3 cancer cell lines.[34]



Scheme 3 Synthesis of adamantane based purine scaffolds as strong anti-cancer agents.[35]

against 562 cells (chronic myelogenous leukemia) and MCF-7 cells (breast adenocarcinoma). The strongest activity was observed for purines **12a** (IC_{50} = 0.21 μM) and **12b** (IC_{50} = 0.58 μM). Bohemine and roscovitine were taken as the control group and used as a standard to compare all these synthesized drugs against cancer cell lines. According to SAR studies, the presence of oxo and hydroxyl groups at the 6th position and introduction of an adamantyl moiety enhanced the anti-cancer activity. A bulky adamantyl group with longer spaces formed tight complexes with active sites that reduced the risk of cancer.

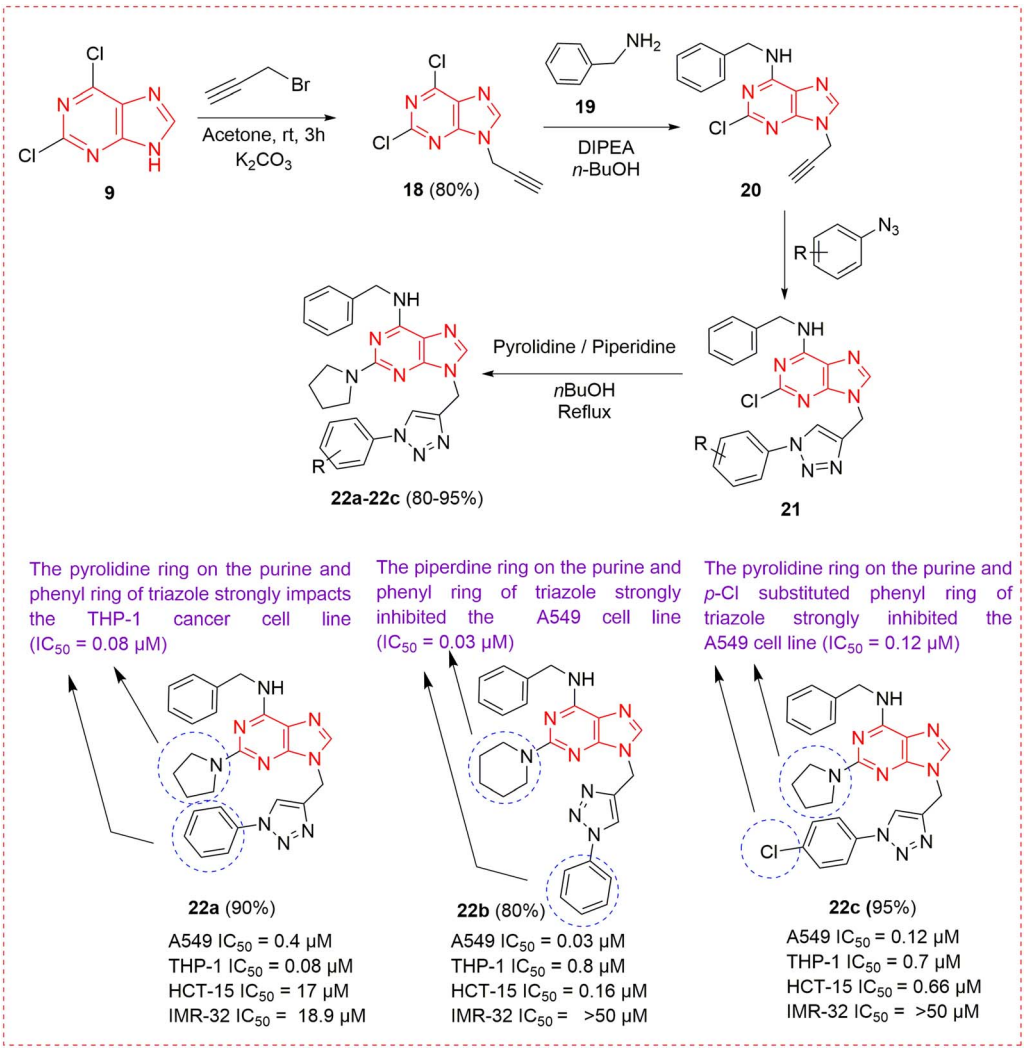
2.1.2 Five-membered heterocyclic hybrids. Acefylline derivatives were used to synthesize the oxadiazole purine derivative. Acefylline derivatives are considered to be excellent anti-cancer agents.[36] Xanthene theophylline derivatives based on purines exhibit a range of pharmacological and biological properties. In addition to serving as an anticancer, antibacterial, anti-inflammatory, and vascular relaxing agent, 7,8-alkyl substituted theophylline derivatives also improve their action at adenosine receptors. In the cardiovascular system, 7,8-disubstituted theophylline analogues act as hypotensive drugs.[37–39] Irum Shahzadi *et al.* reported the synthetic routes to synthesize 1,3,4-oxadiazole purine derivative and the anticancer activity against Huh7 (liver) cancer cell lines.[40] Acefylline derivative (2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7*H*-purin-7-yl)acetic acid) (**13**) was used, proceeded by a Fischer esterification reaction and refluxed for 6 h in the presence of methanol as a solvent and conc. H_2SO_4 catalyst to afford the product with a yield of 68% (**14**). Compound (**14**) was treated with hydrazine hydrate to synthesize theophylline-7-acetohydrazide (**15**) in 98% yield. Compound **15** was refluxed for 6 h in the presence of carbon disulfide and KOH base to afford substrate (**16**) in 62% yield. Substituted 2-bromo-*N*-phenyl acetamide reacted with compound **17** in the presence of base, *i.e.*, Py and DCM as the solvent to afford target molecules (**17a–17h**) in 60% to 80% yield (Scheme 4). Compound **17g** was the most effective against human liver cancer cell lines, with a cell viability IC_{50} value of 53.58 ± 1.28 μM. Among all the synthetic compounds, the most potent anti-cancer chemical had decreased cell viability whenever the chloro-substituent was present at *para* locations of the phenyl group. Structural activity relationship studies revealed that the most potent compound possessed the chloro substitution at the *para* position of the phenyl ring. Cell viabilities are determined by the MTT assay (Scheme 4).[40]



Scheme 4 Synthesis of 1,3,4-oxadiazole purine derivatives (**17a–17h**) showing cell viability against Huh7 (liver) cancer cells.[40]

Jabeena Khizer *et al.* proposed the synthetic routes of *N*-9 substituted 1,2,3-triazole analogs and demonstrated cytotoxic activity against THP-1 (leukemia), HCT-1 (colon), IMR-32 (neuroblastoma), and A-549 (lung) cells *in vitro*.[41] For anti-cancer activity, 5-fluorouracil is taken as a standard drug (5-FU). General preparation for the target molecule was initiated with 2,6-dichloropurines (**9**). Using propargyl bromide as the alkylating agent, potassium carbonate as the base, and acetone as the solvent, 2,6-dichloropurine was alkylated at room temperature to synthesize a mixture of alkylated purine regioisomers (**18**) at position *N*-9. A small yield of *N*-7-alkylated regioisomers was produced. In the next step, an S_NAr reaction was carried out using benzylamine (**19**) as the nucleophile in the presence of butanol and isopropylethylamine to synthesize substrate (**20**). Compound **21** was then formed by a [3 + 2] cycloaddition reaction in between different substituted aromatic azides and (**20**). Finally, intermediate **21** was treated with cyclic secondary amine bases such as piperidine and pyrrolidine and refluxed for 12 h to synthesize target molecules (**22a–22c**). Most triazole derivatives have the greatest activity against all the mentioned cancer cells with the IC_{50} value less than 10 μM. According to the SAR (structural activity relationship), piperidine and pyrrolidine substitution leads to the most promising anticancer potential. Chloro substitution at the *para* position (**22c**) also gives the most promising results (Scheme 5).[41]

K. Kapadiya *et al.* reported the design and synthetic routes for triazolo[3,4-e]purine derivatives against NCI-60 cell lines.[42] 2,6-dichloropurine (**9**) and 40% hydrazine hydrate were combined to create nitrogen-rich purine hydrazide (**23**). Purine hydrazide intermediate (**23**) synthesized the cyclized product (**24**) at the C-2 position with a good yield when it was treated with substituted phenylaldehyde in the presence of a small quantity of hydrochloric acid (Scheme 6). Nine distinct panels,

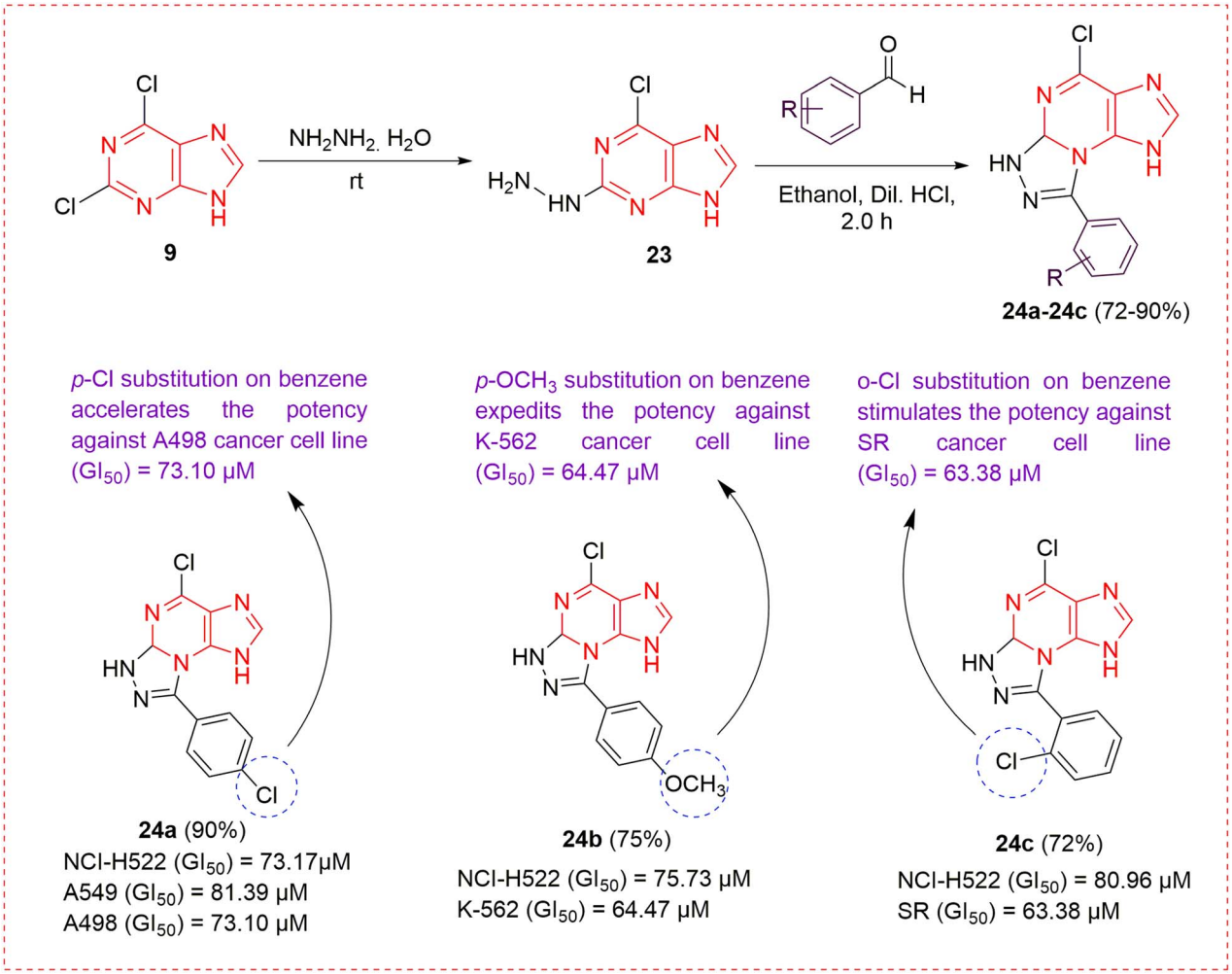


Scheme 5 Synthesis of trisubstituted triazole analogs and IC_{50} values against A549, IMR-32, HCT-15 and THP-1 cancer cell lines.[41]

including the leukemia cell line, *i.e.*, NSCLC, A549, A498, NCI–H522 and K562 were used to select and assess the *in vitro* anticancer activity of three compounds (**24a–24c**). There are more than three sub-panels in each cell line. Comparatively speaking, compound **18c** exhibited less activity than compounds **24a** and **24b**. It was determined that **24b** (mean GI_{50}: 99.09 μM; K-562: 64.47 μM and SR: 63.38 μM) was more effective than **24a** and **24c** (Scheme 6).[42] According to the structure–activity relationship, substituting the electron-withdrawing group (EWG) in **24a** and the electron-donating groups on the *para* position enhanced the anti-cancer activity.

E. R. Sucharita *et al.* reported the synthesis of innovative fused triazolo-pyrrolo purines as active anti-tumor agents.[43] A series of purine scaffolds were synthesized and checked for anti-cancer activity. The synthesis began with the reaction between 8-bromo-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (**25**) and propargyl bromide in the presence of K_2CO_3 and DMF at 60 °C for 6 h, resulting in the synthesis of molecule (**26**). In the last step, 1,3-cycloaddition reaction took place between the terminal alkyne and different aryl azides using an approximate amount of catalytic CuI in DMF for 35 to 45 minutes to synthesize target molecule (**27**) (Scheme 7).[43] All the synthesized derivatives were evaluated for their anticancer activity; compounds **27a** and **27b** had the highest anti-cancer activity. According to the structure–activity relationship studies, an electron withdrawing group on the phenyl group (Cl, Br, NO_2) possessed greater anti-cancer activity. Compound **27a** has two electron withdrawing groups on the phenyl ring, so it shows excellent anti-cancer activity, with an IC_{50} of 11.5 ± 0.64 μM for MCF-7, IC_{50} of 14.9 ± 0.64 μM for A-549 and moderate activity against HeLa (IC_{50}: 22.5 ± 1.14 μM). Similarly, substrate **27b** possessing a 4-NO_2Ph group on the triazole ring has probable anti-cancer activity against MCF-7 and A-549, and moderate activity against HeLa cancer cell lines.

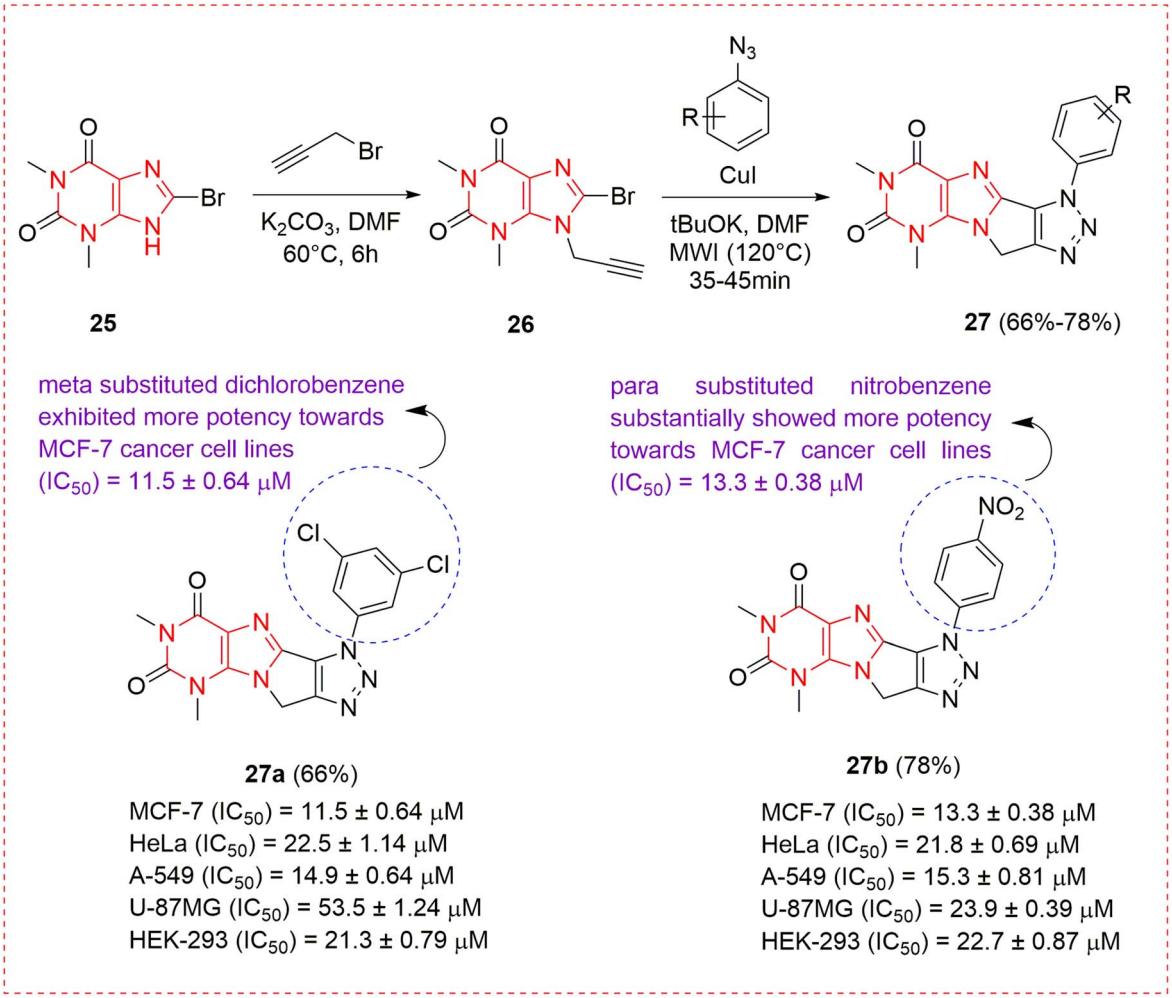
Afifi *et al.* synthesized innovative purine-pyrazole hybrids comprising thiazoles, thiazolidinones and rhodanines, and evaluated the anti-cancer activity against the malignant tumor.[44] Compound **28** was treated with different reagents in three steps to afford intermediate (**29**). This intermediate was



Scheme 6 Synthesis of the most active anti-cancer 1,2,4-triazole-containing purine scaffolds against lung (NCI–H522) and leukemia (K-562) cancer cell lines.[42]

coupled with 2-bromo-1-(4-bromophenyl) ethan-1-one and ethyl 2-bromoacetate to synthesize compounds **30** and **31**, respectively (Scheme 8).[44] These synthesized derivatives were effective against the 15-LOX enzyme. This enzyme is responsible for the development of cancer in the breast and prostate gland. 15-LOX overexpression is associated with increased angiogenesis, tumor size, and tumor formation frequency. The synthesized compounds were tested against five cancer cell lines *in vitro*: HepG-2 (liver), MCF-7 (breast), PC3 (prostate), Caco-2 (colon), and A549 (lung). 5-FU was taken as a reference drug to compare the IC_{50} values of the synthesized compound. Compound **31a** showed the strongest efficacy against the A549 cell line. Its potency was higher than that of standard medication using 5-FU alone (IC_{50} values of 18.85 and 83.03 μM, respectively). Furthermore, compound **31a** demonstrated strong anticancer activity against the MCF-7 (breast cancer) cell line. Compounds **30a** and **31a** showed strong activity against the HepG-2 cell line. The IC_{50} values of compound **31a** ranged from 36.51 to 95.39 μM, indicating its probable and broad-spectrum anticancer activity. Additionally, compound **31a** demonstrated broad-spectrum anticancer activity against all examined cell lines, with IC_{50} values ranging from 18.50–23.43 μM.

Hsp90 is an ATP-dependent molecular chaperone that plays a critical role in maintaining protein maintenance by controlling the proper portable, intracellular distribution, and activity of many powerful proteins. Oncoproteins are essential for the development of tumors and malignant transformation and make up a large portion of Hsp90 client proteins. These include receptor tyrosine kinases, Her2 receptor and EGFR. One promising cancer treatment strategy is inhibiting Hsp90. A powerful Hsp90 inhibitor with exceptional anticancer properties is BIIB021. To synthesize this inhibitor, S. C. Shin *et al.* investigated the design and synthetic routes of new purine-based derivatives which may act as Hsp90 inhibitors.[45] The general synthesis of target purine scaffolds was initiated with the reaction between 6-chloropurin-2-amine (**32**) and propargyl bromide in the environment of K_2CO_3 and DMF at room temperature. In the next step, compound **33** was treated with appropriate oxime in the presence of triethylamine and tetrahydrofuran to afford target molecule **34**. On the other hand, there was a side reaction with 4-methylbenzylchloride in the

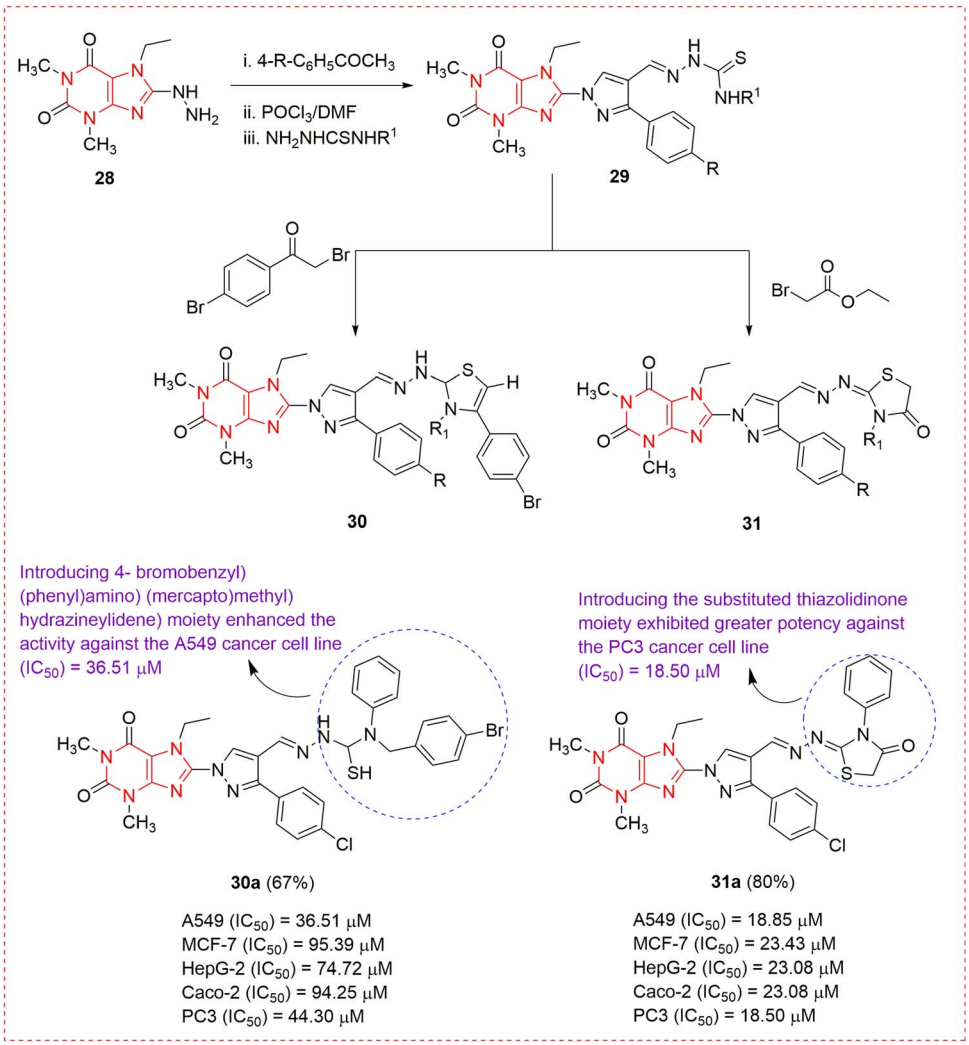


Scheme 7 Synthesis of the most promising anti-cancer triazole-pyrrole hybrid purine scaffolds.[43]

presence of K_2CO_3 and DMF that afforded another target molecule (**35**) (Scheme 9).[45] Using BIIB021 and 17-AAG as references, the *in vitro* anticancer activity of all the synthesized scaffolds was assessed against a panel of three human cancer cell lines that expressed high levels of Hsp90-related client proteins: EGFR-reliant colon (HCT116) cancer, (ER+) MCF-7, and Her-2 dependent SK-BR-3 breast cancer. Compound **35a** is the most hydrophobic isoxazole and it contains a *tert*-butyl moiety with good activity against SK-BR-3 breast cancer (GI = 45.76%) compared with 3-substituted isoxazole **34a** and **34b**. In contrast, **34b** is the most active member in the Hsp90α assay, producing moderate anticancer activity (SK-BR-3; GI = 33.17%, MCF-7; GI = 11.92%). The *p*-tolyl derivative (**35**) shows equipotent activity against breast cancer cells MCF-7 and SK-BR-3, with GI_{50} values of 16.22 ± 0.71 μM and 15.24 ± 2.08 μM, respectively.

Excess production of EGFR protien causes abnormal development of cancer cell in ovary and breast. Ovarian and breast cancer was considered as a prominent problem of time. The United States Food and Drug Administration (US FDA) authorized two first-generation EGFR tyrosine kinase inhibitors (EGFR-TKI) to treat non-small cell lung cancer: gefitinib and erlotinib. To eradicate these problems, Mashooq *et al.* reported the synthesis of purine-sulfonamide hybrids. These hybrids have shown great advancements in the pharmaceutical chemistry.[46] The synthesis of purine-sulfonamide hybrids gave scientists a new idea for innovative novel compounds. The synthesis involved a single-step reaction initiated by the treatment of commercially available 6-chloro purine (**36**) with a sulfonamide containing moiety (**37**) in the presence of ethanol for 4 h. This reaction afforded the target purine-sulfonamide hybrid molecule (**38**). The target molecule was the most potent anti-cancer agent. According to SAR studies, introduction of the *N*-(4,5-dimethyloxazol-2-yl)benzene sulfonamide moiety with a purine core nucleus enhances the anti-cancer activity of compounds (Scheme 10).[46]

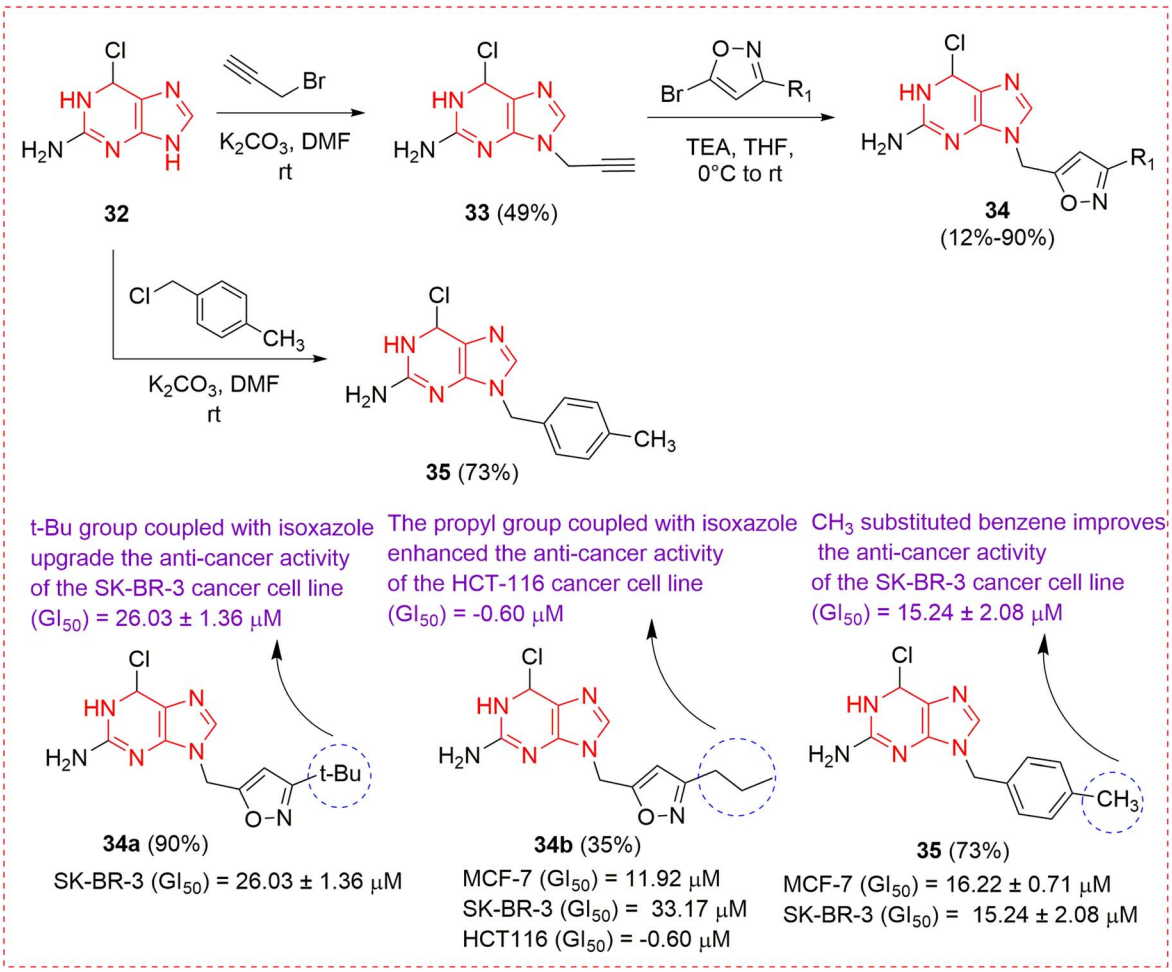
2.1.3 Six-membered heterocyclic hybrids. K. M. Kapadiya *et al.* reported the synthesis of purine hybridized quinoline



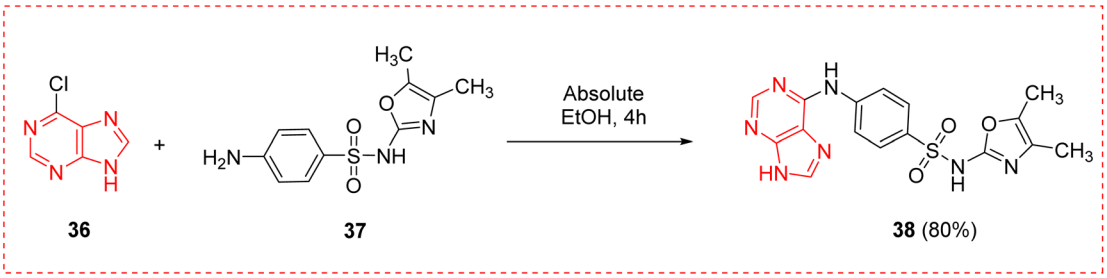
Scheme 8 Synthesis of most potent thiazoles and thiazolidinone containing purine hybrid and their IC_{50} values.[44]

scaffolds that were effective against lung cancer cells in 2019.[47] A convenient two-step approach was used for the synthesis of aryl amino-quinoline-purine nucleosides. First, 2,6-dichloropurine (**9**) and 3-aminoquinoline (**39**) undergo a highly intense reaction in the presence of isopropyl alcohol and concentrated hydrochloric acid (conc. HCl) when refluxed for 12 h at 80 °C to afford the chloroamine coupled intermediate (**40**). This was further treated with substituted aryl amines and refluxed for 24 h in *n*-butanol and HCl to synthesize **41** (Scheme 11). Among these, compound **41a** holds potential for growth inhibition. It has comparable GI_{50} values of 7.57 μM against the HOP-92 cell line (non-small cell lung cancer panel). SAR studies show that chloro *meta*-substitution on phenylamine attached to C-6 enhances the anti-cancer activity among all the synthesized derivatives. Electron-withdrawing groups show more effective anti-cancer evaluation than electron-donating groups (Scheme 11).[47]

J. Bertrand *et al.* reported the routes to synthesize novel 2,6,9-trisubstituted purine analogues that are the most potent against leukemia.[48] Leukemia is a blood disorder (cancer) that can cause the death of thousands of people every year. The synthesis of 2,6,9-trisubstituted purine analogues began through the alkylation of 2,6-dichloropurine (**9**) with bromomethylcyclopropane (**42**) in the presence of K_2CO_3 and DMF as the solvent at room temperature for 12 h to afford **43**. In the next step, regioselective aromatic substitution with anilines occurs by refluxing for 12 h in the presence of *n*-butanol as a solvent and *N, N*-DIPEA as a base to afford **44**. Finally, C–N coupling was done using a Buchwald-Hartwig cross coupling reaction with 4-(4-methylpiperazin-1-yl) aniline (**45**) catalyzed by microwave-assisted palladium(II) catalysis to afford purine derivative (**46**) in low to moderate yield (Scheme 12).[48] These synthesized derivatives were evaluated against three tyrosine kinases. These enzymes play an important role in activating cancer in the blood. Compounds **46a**, **46b**, and **46c** are considered the most

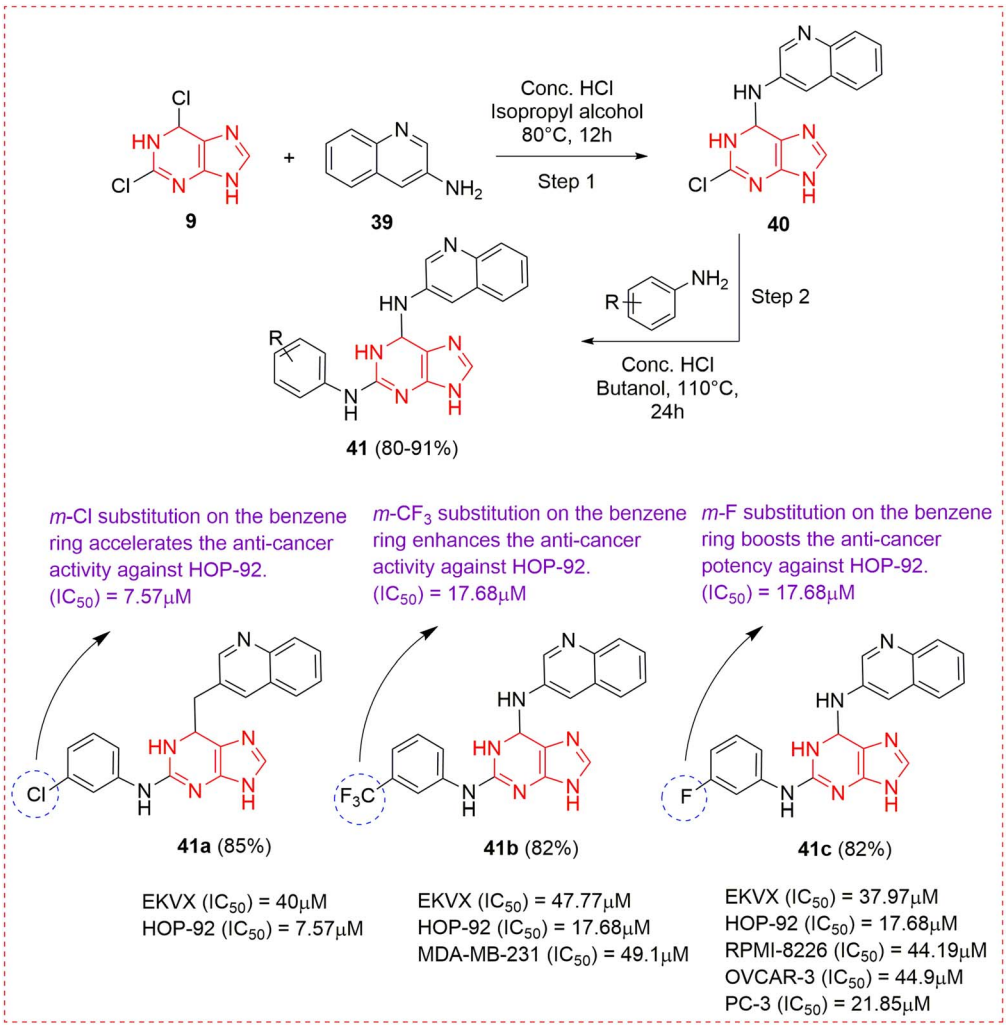


Scheme 9 Synthesis of isoxazole-based purine derivatives active against SK-BR-3 and MCF7 cancer cell lines.[45]



Scheme 10 Synthesis of sulfonamide-oxazole hybrid purine substrate as an anti-cancer agent.[46]

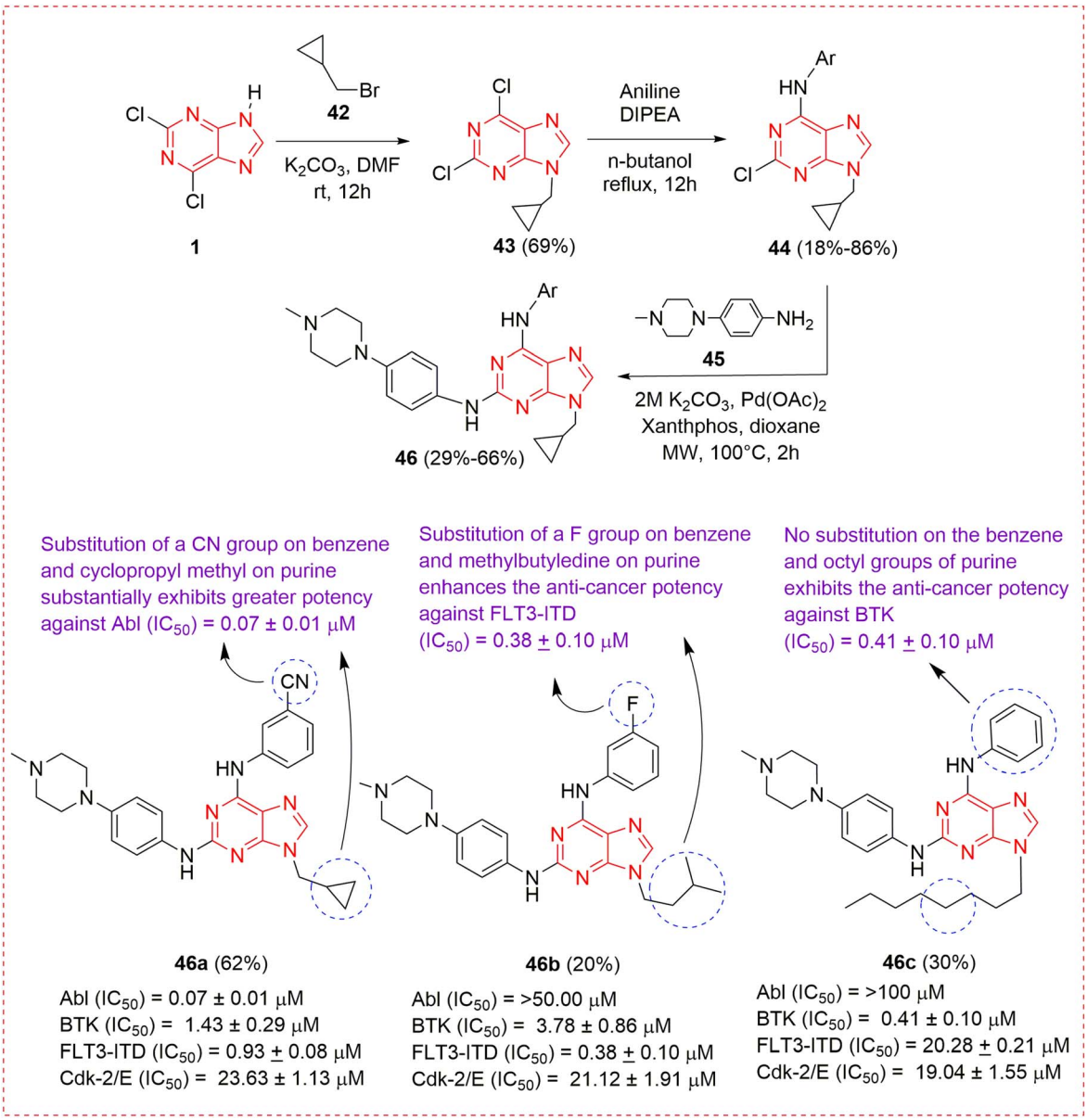
potent tyrosine kinases inhibitors. Tyrosine kinases may include BTK (Bruton's tyrosine kinase), Bcr-Abl (break-point cluster region-Abelson), and FLT3-ITD (FLT3-internal tandem duplication). The following IC_{50} values were determined for the most potent kinase inhibitors: **46a** (IC_{50} = 70 μM for Bcr-Abl), **46b** (IC_{50} = 0.41 μM for BTK) and **46c** (IC_{50} = 0.38 μM for FLT3-ITD). According to SAR studies, the most potent derivative for Abl has a small-sized substitution on the *meta* position. A bulky group on the *meta* position diminishes the potency. This study was similar to that of the two others tyrosine kinases. A *para* substitution enhances the anti-cancer activity compared with the *meta*-substitution. Also, the length and volume of alkyl chain affects the anti-cancer activity. For Abl, an alkyl chain longer than five carbons reduces its inhibitory effect against cancer. For BTK, a longer chain enhances its activity. Moreover,



Scheme 11 Synthesis of the most potent anti-cancer quinoline-based purine scaffolds.[47]

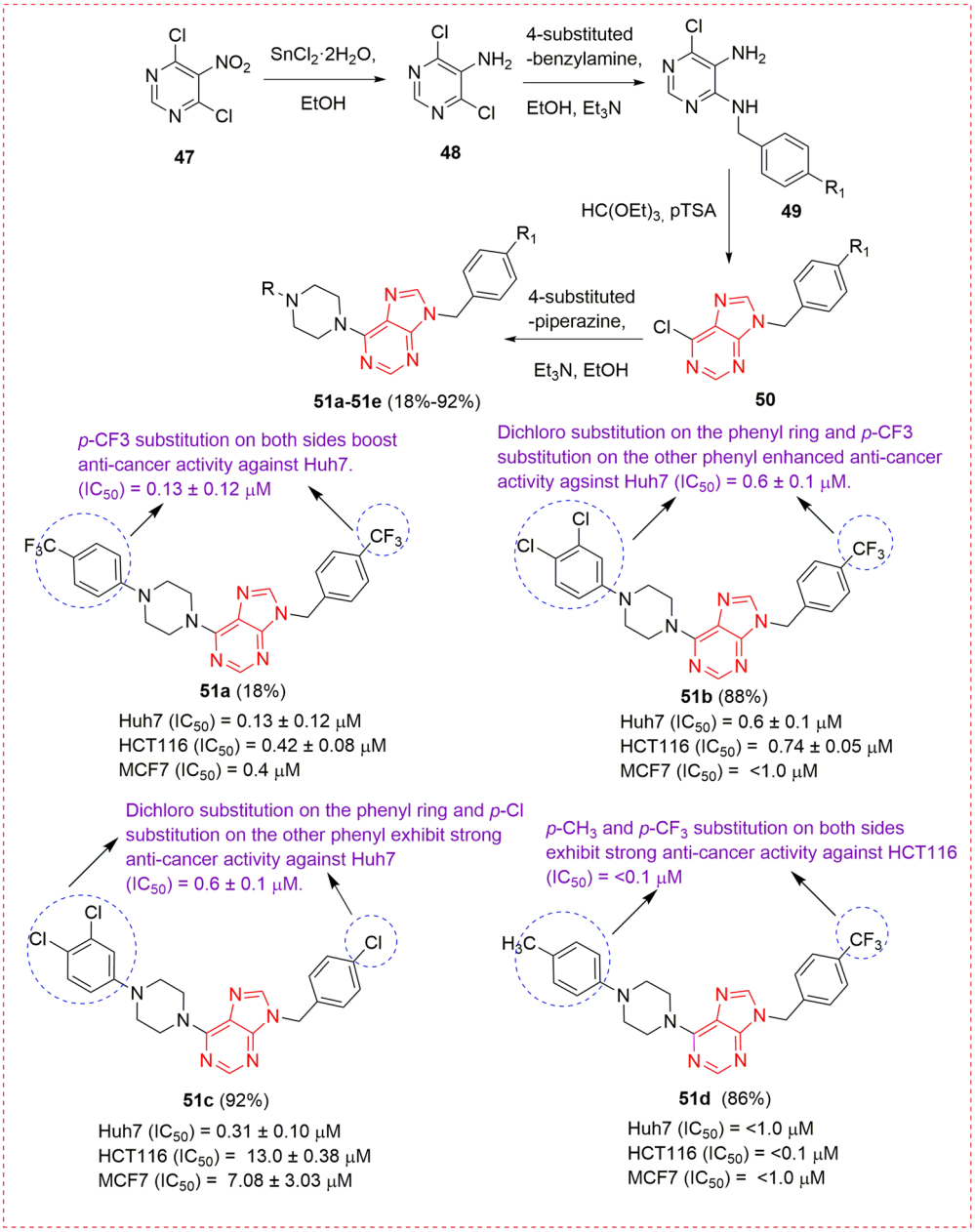
an iso-octyl chain shows promising anti-cancer effects for FLT3-IDK tyrosine kinase.

A. Kucukdumlu *et al.* stated the design, synthetic route, and cytotoxicity against cancer-causing cells of 6,9-disubstituted purine analogues.[49] Four steps were involved in the design and synthesis of a new family of 6,9-disubstituted purine analogues, featuring 4-substituted piperazine at C-6 and 4-substituted benzyl at *N*-9. First, the anticancer activity of all the synthesized compounds were assessed using the Huh7 liver, HCT116 colon, and MCF7 breast carcinoma cell lines. The cytotoxicity of all the compounds was evaluated and compared with commercially available 5-FU, cladribine, and fludarabine. The four-step synthesis of purine analogues (**51a–51e**) began with the commercially accessible 4,6-dichloro-5-nitropyrimidine (**47**). Dichloronitropyrimidine was converted into the equivalent dichloroaminopyrimidine (**48**) using ethanol and stannous chloride. In the next step, 5-amino-4,6-dichloropyrimidine (**48**) was aminated with 4-substituted benzylamine in the presence of ethanol and triethyl amine to synthesize 4-(4-substituted benzyl)pyrimidines (**49**). Substrate **49** was condensed with *p*-toluenesulfonic acid and triethyl-orthoformate to synthesize intermediate **50**. In the last step, 4-substituted piperazine was substituted at C-6 to afford target molecule scaffolds (**51a–e**) (Scheme 13).[49] The three 6-(trifluoromethylphenyl) piperazine purines (compounds **51a** and **51b**) show good cytotoxic effects on Huh7 cells compared with CPT, which are better than that of cladribine, fludarabine, and 5-FU. Furthermore, compounds **51b** and **51c** with a 3,4-dichlorophenyl group on piperazine have a greater cytotoxic effect on Huh7 cells than the established nucleoside medications (fludarabine, cladribine, and 5-FU), with IC_{50} values of 0.6 ± 0.1 and 0.31 ± 0.10 μM, respectively. Compounds **51d** and **51c** exhibit the highest level of cytotoxic activity among the purine analogues tested on HCT116 cells. The synthesized derivatives possess electron-withdrawing groups (EWG) on the phenyl ring. EWG enhances the anti-cancer activity but its activity changes by modifying the different substitutions on the phenyl ring.



Scheme 12 Synthetic routes for the preparation of the most potent piperazinyl purine and IC_{50} values against Abl, BTK, FLT3-ITD and Cdk-2/E cancer cell lines.[48]

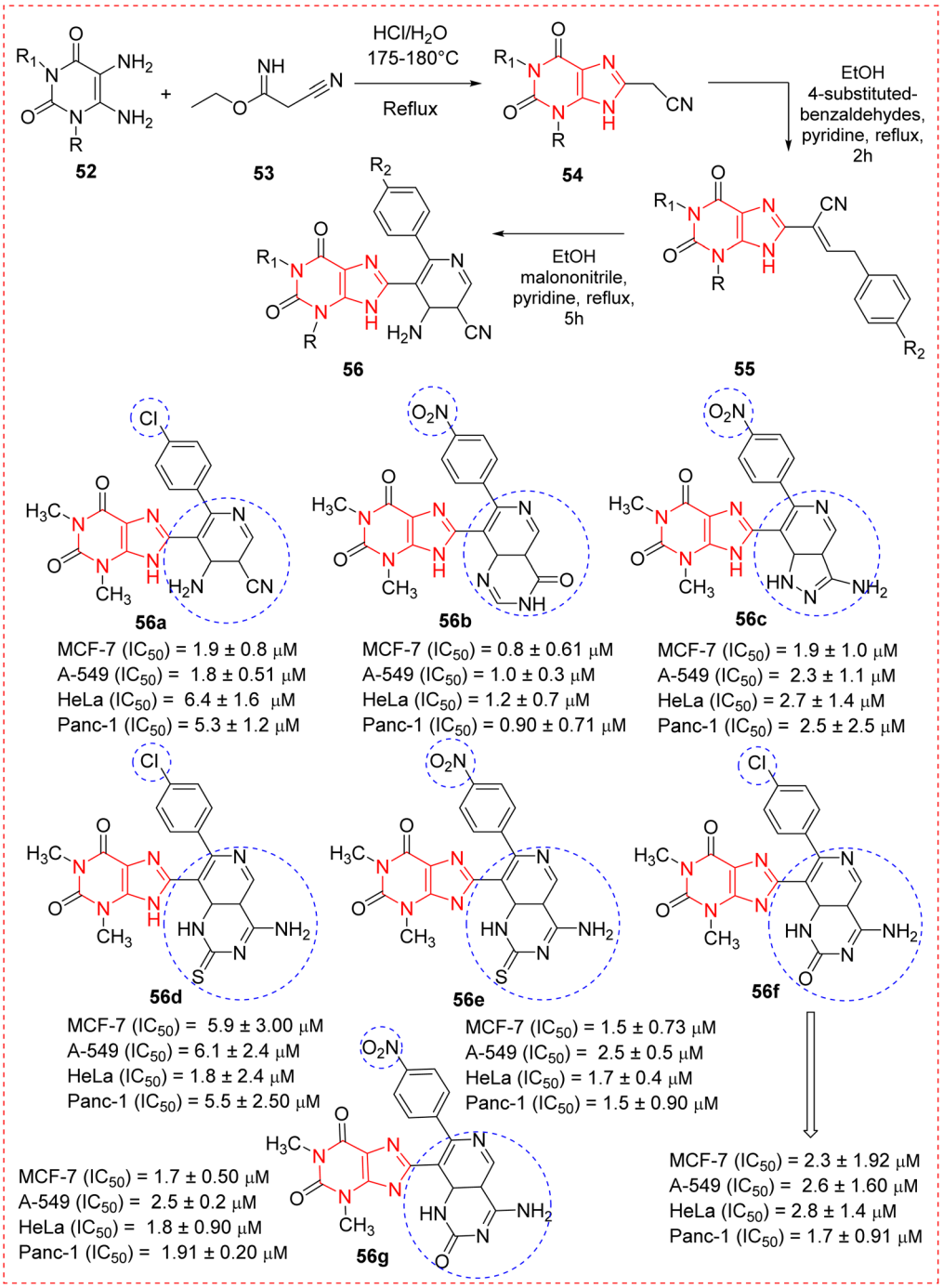
V. A. Verma *et al.* described the synthesis and anti-cancer assessment of purine derivatives.[50] Anti-cancer activity of these derivatives was evaluated against Panc-1 (pancreas), MCF-7 (breast), HeLa (cervical), and A-549 (Lungs) cancer cell lines. The synthesis of compound **56** was initiated with the pyrimidine containing moiety (**52**). Compound **52** was refluxed with 2-cyanoacetamidate (**53**) in the presence of aqueous acid at 175 °C–180 °C to synthesize substrate **54.** The next step included Claisen–Schmidt condensation. Molecule **54** was refluxed with 4-substituted benzaldehyde in the presence of a few drops of pyridine for 2 hours to afford **55.** Compound **55** was refluxed with malononitrile in the presence of EtOH as the solvent and a few drops of pyridine for approximately 5 hours to afford **56** (Scheme 14).[50] Derivatives of compound **55** were evaluated for their anti-cancer cytotoxic activity. All these derivatives were evaluated against doxorubicin as a standard drug. Substrate **55b** is the most potent against cancer cell lines MCF-7 (IC_{50}, 0.8 ± 0.61 μM), A-549 (IC_{50}, 1.0 ± 0.3 μM), and HeLa (IC_{50}, 1.2 ± 0.7 μM), whereas comparable effectiveness is observed against Panc-1 cancer cells with that of the standard anticancer agent doxorubicin. According to the structure activity relationship, substitution of a strong electron withdrawing group impacts cytotoxicity. In the below mentioned derivatives, compounds with NO_2 group and chloro



Scheme 13 Synthetic route to prepare the most potent anti-cancer piperazine-containing purine derivatives with their IC_{50} values against Huh7, HCT116 and MCF7 cancer cell lines.[49]

substitutions were more potent due to the presence of strong electron withdrawing groups.

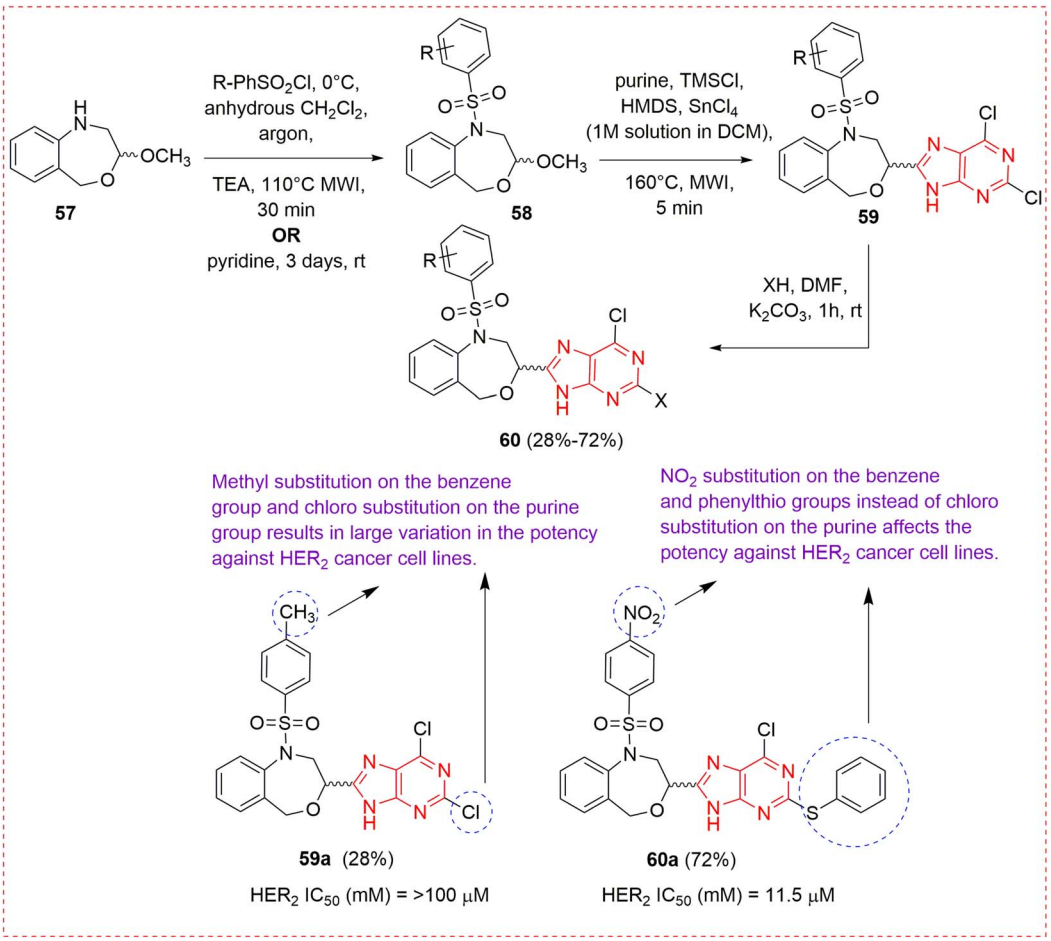
O. C Lupez *et al.* reported that the substitution of a nitro group or methyl group on the benzosulfonyl group and purine instead of benzotriazole enhanced the anti-cancer activity against various cancer cell lines.[51] This novel work started with the reaction between *N*-unsubstituted acetal (**57**) and substituted benzo sulfonyl chloride using anhydrous CH_2Cl_2 in an inert argon environment at 0 °C. Two methods were applied. The microwave irradiation[52] method was fast but afforded **58** in low yield. Compound **59** was prepared using a one-pot synthesis reaction with commercially available 2,6-dichloropurine (**9**) and (**58**) in the presence of DCM with $SnCl_4$, MWI and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) at 160 °C for 5 min. In the last step, nucleophilic substitution reaction at the 6th position was carried out using different nucleophiles in the presence of K_2CO_3 and DMF for 1 h at room temperature to afford **60** (Scheme 15).[51] All the obtained scaffolds were assessed for their anti-cancer activity as a HER2 inhibitor against MCF-7, SKBR3, HCT-116 and A-375 cancer cell lines. HER2 (human epidermal growth factor receptors) were approximately 20% overexpressed in breast cancer. Compounds **59a** and **60a** were the most potent



Scheme 14 Synthesis and cytotoxic evaluation (IC_{50}) of some novel pyridopyrimidine, pyrazolopyridine, and pyranonapthyridine ring containing purine derivatives.[50]

against the growth of cancer cell lines. Compound **59a** was more effective for all cancer cell lines with IC_{50} values ranging from 0.42–0.86 μM. Compound **60a** was effective against HER2 enzyme inhibition. According to SAR studies, the substitution of a phenylthio group (bulky group) on the 6th position enhanced the inhibitory effect of the HER2 receptor. Halogen-substituted purine derivative (**59a**) enhanced the anti-proliferative activity against all cancer cell lines. Also, the nitro and methyl substitution on the phenyl ring induced anti-cancer activity.

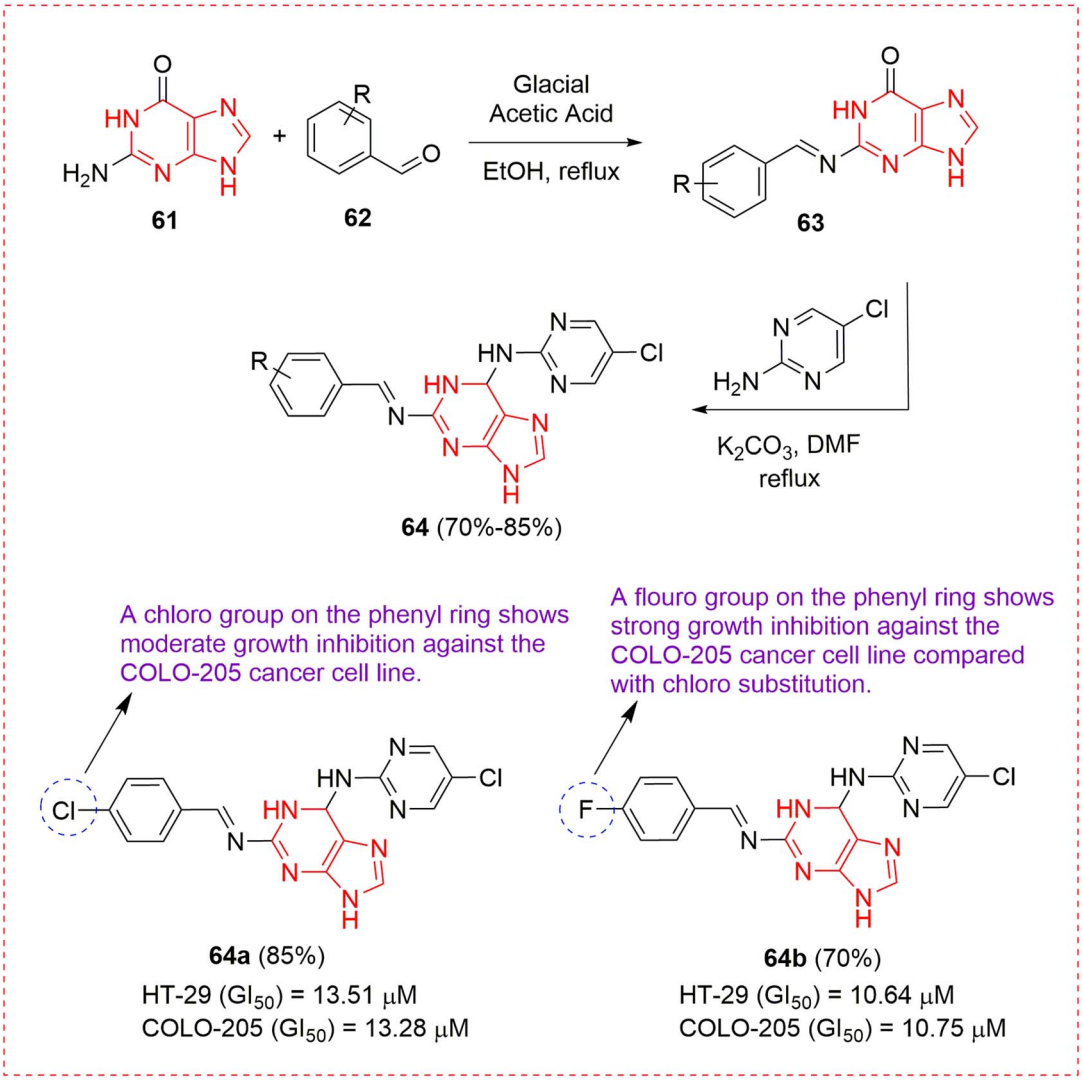
S. More *et al.* demonstrated the synthetic route to develop pyrimidine-hybrid purine derivatives that act as angiogenesis inhibitors.[53] Angiogenesis is a process of formation of new vessels in the body that may spread the cancer throughout the



Scheme 15 Synthesis of benzo-oxazepine based purine derivatives s anti-cancer agents.[51]

body, causing metastasis. These designed derivatives were subjected to examine their angiogenesis inhibition. The Raf-1/MAPK/ERK signaling pathway was activated by VEGFR-2 phosphorylation, leading to angiogenesis, improved vascular permeability, and tumor migration. Consequently, blockage of the VEGFR-2 signaling pathway was taken into consideration when developing the most crucial pathway for tumor treatment. The synthesis began with the reaction between guanine (**61**) and substituted aldehyde (**62**) in the environment of ethanol and glacial acetic acid as a catalyst to synthesize intermediate **63**. In the next step, **63** was reacted with 2-amino-5-chloropyrimidine refluxed in the presence of DMF and K_2CO_3 to afford target molecule (**64**) (Scheme 16).[53] Compounds **64a** and **64b** are considered the most potent against angiogenesis with GI_{50} values of 13.28 μM and 13.51 μM against HT-29 and COLO-205, respectively, for **64a**, while **64b** had GI_{50} values of 10.64 μM and 10.75 μM against HT-29 and COLO-205, respectively. The structure–activity relationship revealed that halogen groups substituted with a phenyl ring showed active participation in the inhibition of angiogenesis (metastasis). The synthesized derivatives inhibit the VEGFR-2 receptor that may enhance angiogenesis.

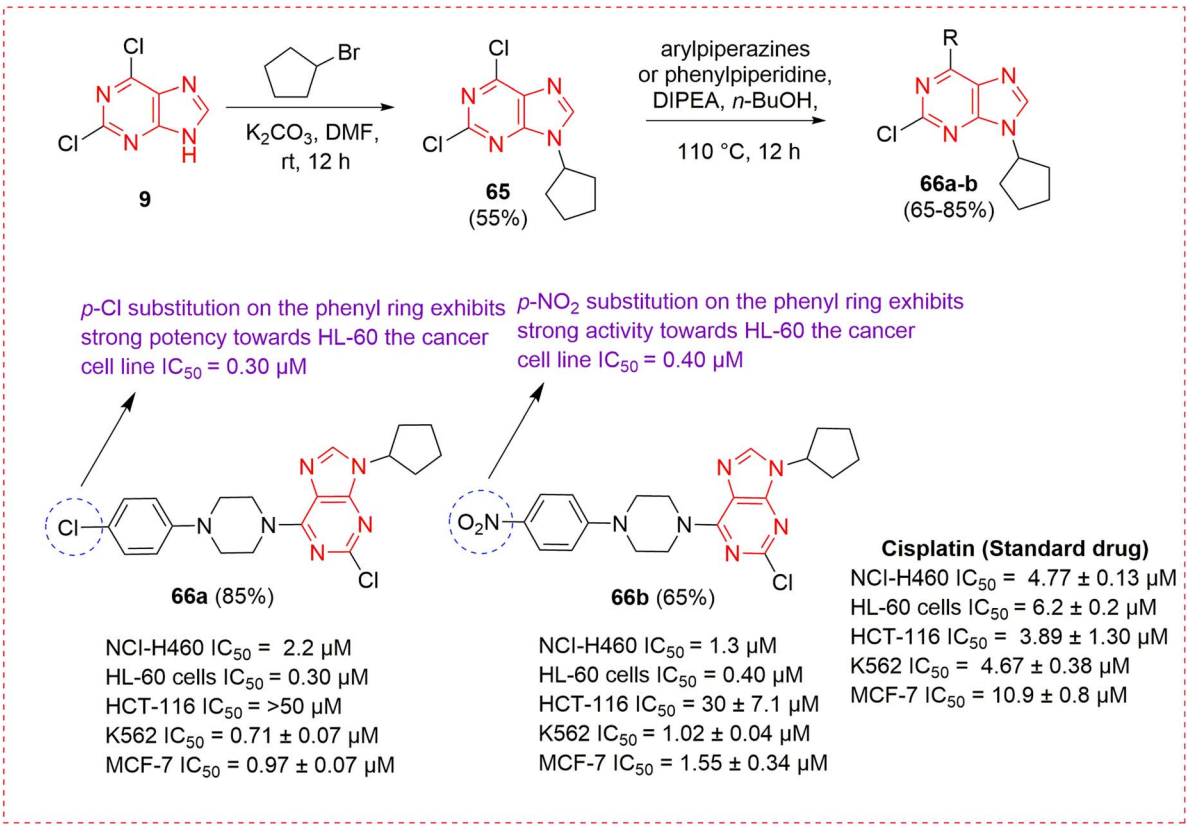
2.1.4 Non-heterocyclic and chalcone type hybrids. Cristian O. Salas *et al.* designed the routes to synthesize the most promising 2,6,9- trisubstituted purine derivatives and examined their anti-cancer activity against cisplatin (standard drug).[54] 2,6,9-trisubstituted purines are nitrogen-containing and have strong anti-cancer activities against different cancer cell lines.[55] The synthesis began with commercially available 2,6-dichloro purine (**9**) that was coupled with cyclopentyl bromide in an environment consisting of K_2CO_3 and DMF at room temperature for 12 h to afford 2,6-dichloro-9-cyclopentyl-9*H*-purine (**65**). This intermediate was treated with substituted arylpiperazine in the presence of *n*-BuOH and DIPEA at 110 °C for 12 h, yielding the most promising molecules (**66a–66b**) (Scheme 17). However, compound **66b** has 70 times greater selectivity against NCI-460 cancer cells, and has the maximum potency and selectivity to kill K562 and MCF-7 cancer cells with $IC_{50} = 1.4$ μM. According to the structure–activity relationship (SAR) and cytotoxicity reports, substitution of aryl piperazine at the *meta* or *para* position with an electron-withdrawing moiety may enhance its anti-cancer activity (Scheme 17).[54]



Scheme 16 Synthesis and IC_{50} values of most active pyrimidine hybrid purine derivatives against HT-29 and COLO-205 cancer cell lines.[53]

El-Kalyoubi and F. Agili reported the synthesis of target molecules (**69**) as anti-cancer agents against the mammalian lung cancer cell line (A-549).[56] The synthesis was initiated with the formation of diazonium salt followed by the reduction of compound **67** to afford a 5,6-diaminouracil compound (**68**). In the last step, compound **68** was reacted with different aromatic aldehydes and refluxed for 7–8 h in the presence of triethyl orthoformate to obtain target molecule **69** (Scheme 18).[56] All the synthesized substrates were evaluated as anti-cancer agents. Compounds **69a**, **69b** and **69c** were the most potent anti-cancer drugs. All these synthesized derivatives were compared with commercially available Methotrexate. Compounds **69a**, **69b** and **69c** possessed IC_{50} values of 27.0 ± 1.1, 23.1 ± 0.6 and 26.3 ± 1.3 μM, respectively. According to SAR studies, a donating group on benzene enhances the anti-cancer activity more significantly than substitution with an electron withdrawing.

Polat *et al.* demonstrated the synthetic routes and anti-cancer assessment of novel 6,8,9-trisubstituted purine analogues.[57] 4,6-dichloro nitro pyrimidine (**70**) was used as the starting material. In the first step, the nitro group was reduced to amine (NH_2) using $SnCl_2$ in the presence of ethanol. In the next step, compound **72** was obtained by heating **71** with cyclopentylamine in the presence of ethanol in a sealed tube at 125 °C. Compound **73** was afforded through the cyclization reaction when treated with 4-substituted benzaldehyde containing *p*-TSA catalyst and DMF as the solvent. In the final step, compound **74** was obtained in good yield (91–95%) through the nucleophilic aromatic substitution reaction using substituted piperazines. A series of different compounds was obtained. The biological activities of all these derivatives were compared with 5-flourouracil. Compounds **74a**, **74b** and **74c** are considered the most potent compounds against liver, breast, and colon cancer

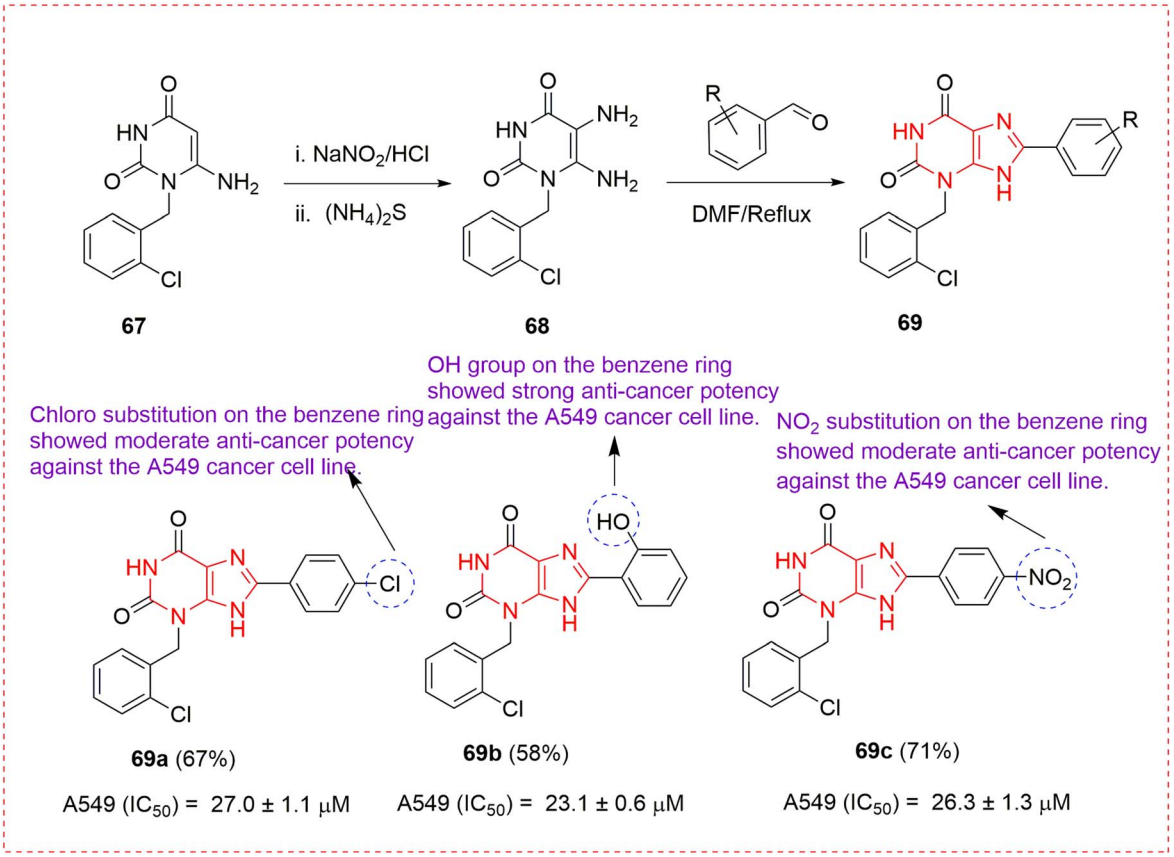


Scheme 17 Synthesis of the most promising arylpiperazine purine derivatives (**66a–66b**) resulting in *in vitro* cytotoxicity of cancer cell lines NCI–H460, HL-60, HCT-116, K562, and MCF-7.[54]

cell lines. Compound **74b** demonstrates superior cytotoxic effects against Huh7 cells (14.2 μM) compared with 5-FU (30.6 μM) and fludarabine (28.4 μM). Furthermore, the cytotoxic effects of non-substituted and methoxyphenyl analogues **74a** (17.9 μM) and **74c** (23.6 μM) on Huh7 cells are greater than those of 5-FU (30.6 μM) and the therapeutically utilized nucleoside medication fludarabine (28.4 μM). The presence of electron-donating groups on benzene improve the anti-cancer activity (Scheme 19).[57]

T. Q.-Zhao *et al.* demonstrated the synthesis and anti-cancer evaluation of novel chalcone hybrid purine derivatives.[58] Chalcones are natural compounds extracted from some natural sources and are also prepared in the laboratory. Analysis of the structure–activity relationship (SAR) proved that chalcones possess high anti-cancer activity. The reaction between 4,6-dichloro-2-(propylthio)pyrimidin-5-amine (**75**) and primary amine affords the chalcone-based purine derivative compound (**76**). Compound **76** was countered with an aldehyde under different conditions to synthesize intermediate compound (**77**). In the next step, intermediate **78** was synthesized by treating **77** with primary amine in the presence of K_2CO_3 and ethanol at 80 °C. Compound **78** was reacted with selenium oxide in the presence of DMSO to afford (**79**). The last step involved the synthesis of target molecule (**80**) by treating **79** with 1-(4-methylphenyl)ethenone (Scheme 20). These derivatives (**80a**) and (**80b**) were compared with 5-fluorouracil (5-FU). The synthesized molecule (**80b**) containing a phenylpropyl group at the purine *N*-9 position and a 4-methylphenyl group of the chalcone region demonstrates the greatest activity against the MGC803 cell line, according to the structure–activity relationship studies. The toxicity of compounds **80a** and **80b** was examined against the GES-1 cell line. Substrate **80b** exhibits significant cytotoxicity against GES-1, with IC_{50} values of 35.58 μM and 23.35 μM, respectively (Scheme 20).[58]

Abou-Zied *et al.* reported that chalcones and xanthine hybrid structures improved the anti-cancer activity of compounds.[59] This was considered a very helpful method. The synthesis began with a Claisen–Schmidt rearrangement reaction of 4-aminoacetophenone (**81**) with substituted benzaldehyde derivatives (**82**). The intermediate chalcone (**83**) was stirred with bromoacetyl bromide in the presence of DCM to afford acylated chalcones (**84**). In the last step, xanthine (purine derivative) was alkylated with acylated chalcone to afford chalcone–xanthine hybrid molecule (**85**). Twenty innovative hybrid scaffolds were created and evaluated for their anti-cancer activity using four different cancer cell lines: the epithelial cancer cell line (A-549), the breast cancer cell line (MCF-7), the colon cancer cell line (HT-29), and the human pancreatic cancer cell line (Panc-1). All these derivatives were compared with commercially available doxorubicin medicine. Among all the synthesized derivatives, seven of them showed the most potent anti-cancer activity (Scheme 21).[59] Compounds **85a**, **85b**, **85c**, **85d**, **85e** and **85f** were

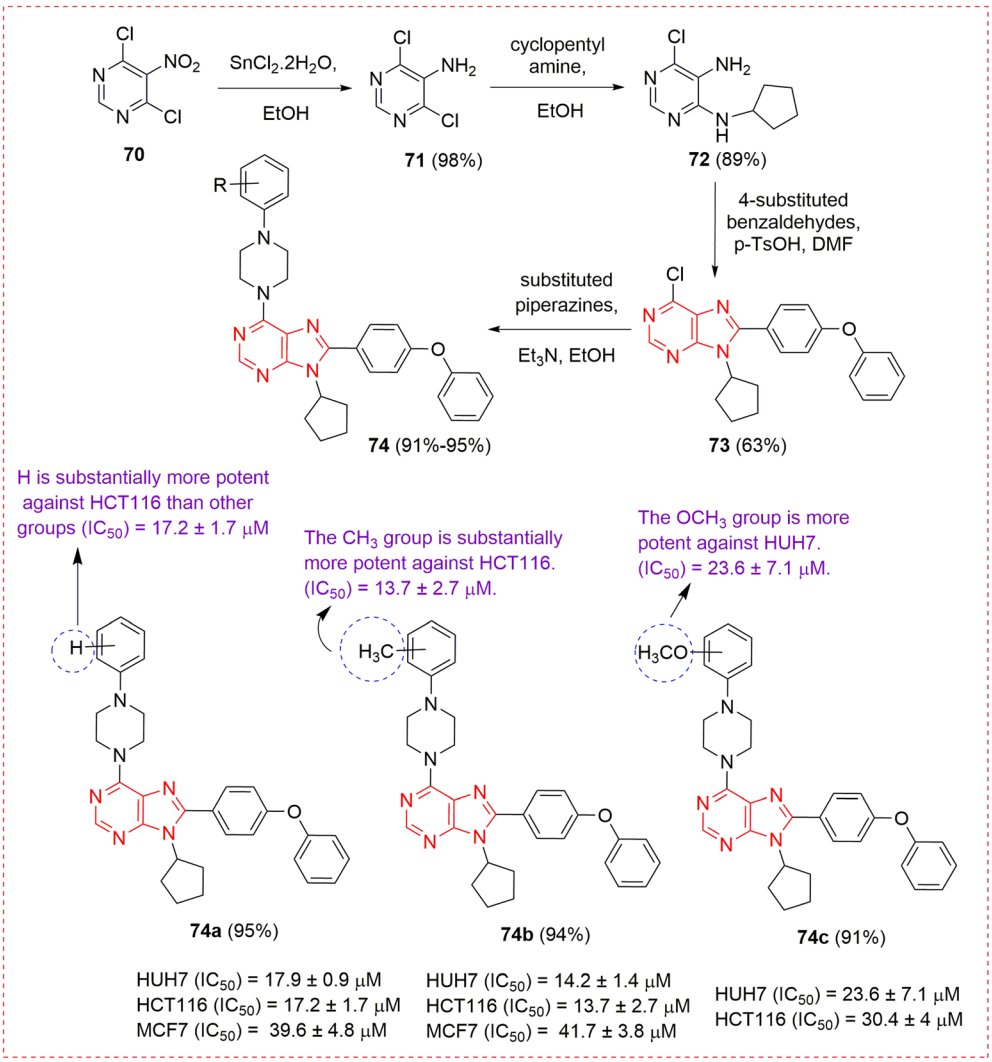


Scheme 18 Synthesis of novel 3,8-disubstituted purine derivatives and cytotoxic evaluation against the A549 cancer cell line.[56]

the most potent anti-cancer agents. According to SAR studies, 1,3-dimethylxanthine analogs were considered 7-fold more active than 1-methylxanthine. Also, substitution of the R_3 group with an electron withdrawing group shows better anticancer activity but electron donating groups OMe and Cl have the best anti-cancer activity.

2.1.5 Miscellaneous and natural product-based hybrids. El. Kalyoubi *et al.* reported the synthetic routes for purine/pteridine based analogues which are dual EGFR/$BRAF^{V600E}$ inhibitors.[60] These two enzymes bind with the active sites of cancer cells and activate cancer. These inhibitors are utilized for cancer treatment. The synthesis began with nitrosation of 6-amino-1-alkyluracils (**86**) in the presence of HNO_2 to afford compound **87**. This intermediate was reduced with ammonium sulfide to synthesize 5,6-diaminouracil (**88**). In the next step, compound **88** acted as a nucleophile and its amine group attacked the carbonyl group of 2,7-dibromo-9*H*-fluoren-9-one (**89**) and underwent aza-Michael addition to afford target molecule **90** (Scheme 22).[60] Compounds **90a** and **90b** were considered the most effective and potent anti-cancer agents. The synthesized derivatives were evaluated for cytotoxicity of HT-29 (colon cancer cell line), A-549 (lung cancer cell line), Panc-1 (pancreatic cancer cell line) and MCF-7 (breast cancer cell line). Analysis of the structure activity relationship revealed that the substitution of sulfur with oxygen at position 2 and methyl with ethyl at position 3 in compound **90a** results in a 2.3-fold less effective anti-cancer agent. Compound **90b** has 2-chlorobenzyl in place of methyl. This substitution has 1.2-fold lower anti-cancer activity than **90a**, but there is improved activity if 2-chlorobenzyl is substituted with an ethyl group. Therefore, the decreasing order of substitution for anticancer activity is methyl >2-chlorobenzyl.

M. N. S. Rad *et al.* reported the synthetic routes and characterization of novel caffeine-triazolyl methoxy scaffolds (purine derivative) as a strong anti-cancer agent.[61] Caffeine (**91**) was brominated to raise the positive charge density on C(8) for the ensuing SNAr-type reaction, which initiated this synthesis. NBS (*N*-bromosuccinamide) prepared in a solution of DCM and room temperature water allowed for the bromination of caffeine to afford compound **92**. In a different procedure, the necessary alkyl azides (**94**) were easily produced by combining excess sodium azide with alkyl halides (**93**) in an acetone–water combination and refluxed to produce the appropriate alkyl azides nearly quantitatively. The 'Click' Huisgen alkyl-azide cycloaddition reaction was carried out using propargyl alcohol in the synthesis of **95**. To obtain the target products (**96**) in good yields, **95** was finally combined with 8-bromo caffeine (**92**) using a SNAr-type reaction employing KOH in DMSO at 100 °C

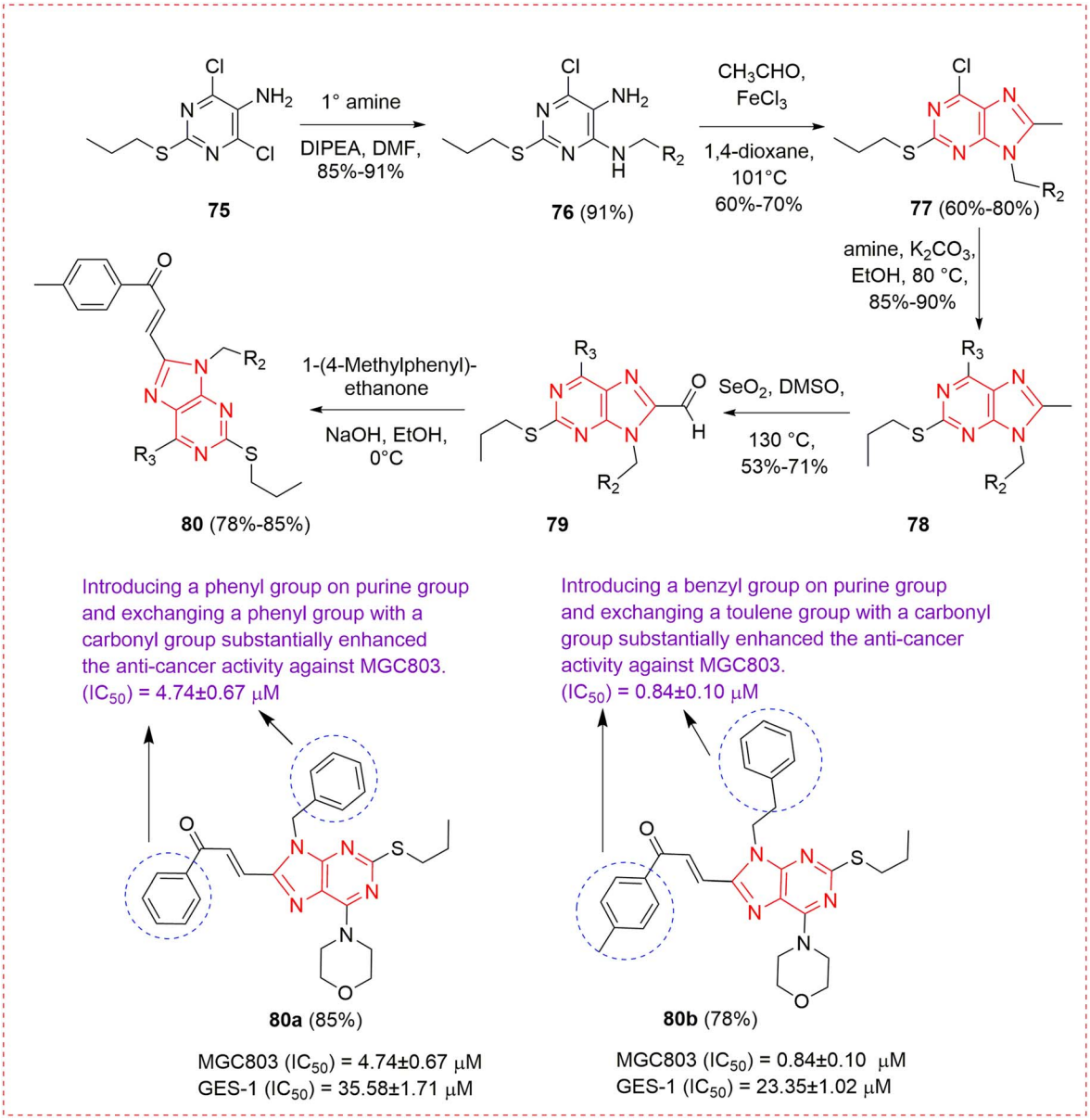


Scheme 19 Synthesis of novel trisubstituted purine analogues and evaluation of anti-cancer activity (IC_{50} values) against HUH7, MCT116 and MCF7 cancer cell lines.[57]

(Scheme 23).[61] The synthesized derivatives were assessed for their anti-cancer activity against A357 (melanoma cells), MCF-7, MDA-MB-468, and HEK-293 (kidney cancer cell line). Compounds **96a**, **96b**, and **96c** were the most active anti-cancer agents. Compound **96a** displayed the maximum and lowest anti-cancer activity against A375 and HEK-293 compared with methotrexate (MTX) as a reference medication. Although compounds **96b** and **96c** showed the strongest effects against MCF-7 and MDA-MB-468, MTX outperformed them in activity. SAR studies revealed that triazole substitution by phenyl and straight chain alkyl group improves the anti-cancer activity.

M. N. S. Rad *et al.* described the design, synthetic routes and antiproliferative activity of the chalcone-caffeine hybrid.[62] It was proved that substituted chalcones enhanced the anti-cancer activity. Caffeine (**91**) was brominated to raise the positive charge density on C(8) for the ensuing SNAr-type reaction, which initiated this synthesis. NBS in a solution of DCM and water afforded the bromination of caffeine. Compound (**97**) was substituted with different chalcones (**98**) in the environment of K_2CO_3 and DMF at 60 °C for 12–18 h to synthesize target molecules (**99**) (Scheme 24).[62] Among all the synthesized derivatives, compound **99a** was the most active against cancer cells A357 and MCF-7. Structure–activity relationship studies reveal that the most effective molecule (**99a**) replicating the glutamate residue in folic acid and its antimetabolic derivatives have a hydrolyzable ester moiety in the *para* position that enhances the compound's activity (**99a**). Compound **99a** possesses IC_{50} values of 92 ± 3.2 μM (A357) and 34 ± 3.5 μM (MCF-7), which are 10 times more effective than the standard commercially available MTX drug.

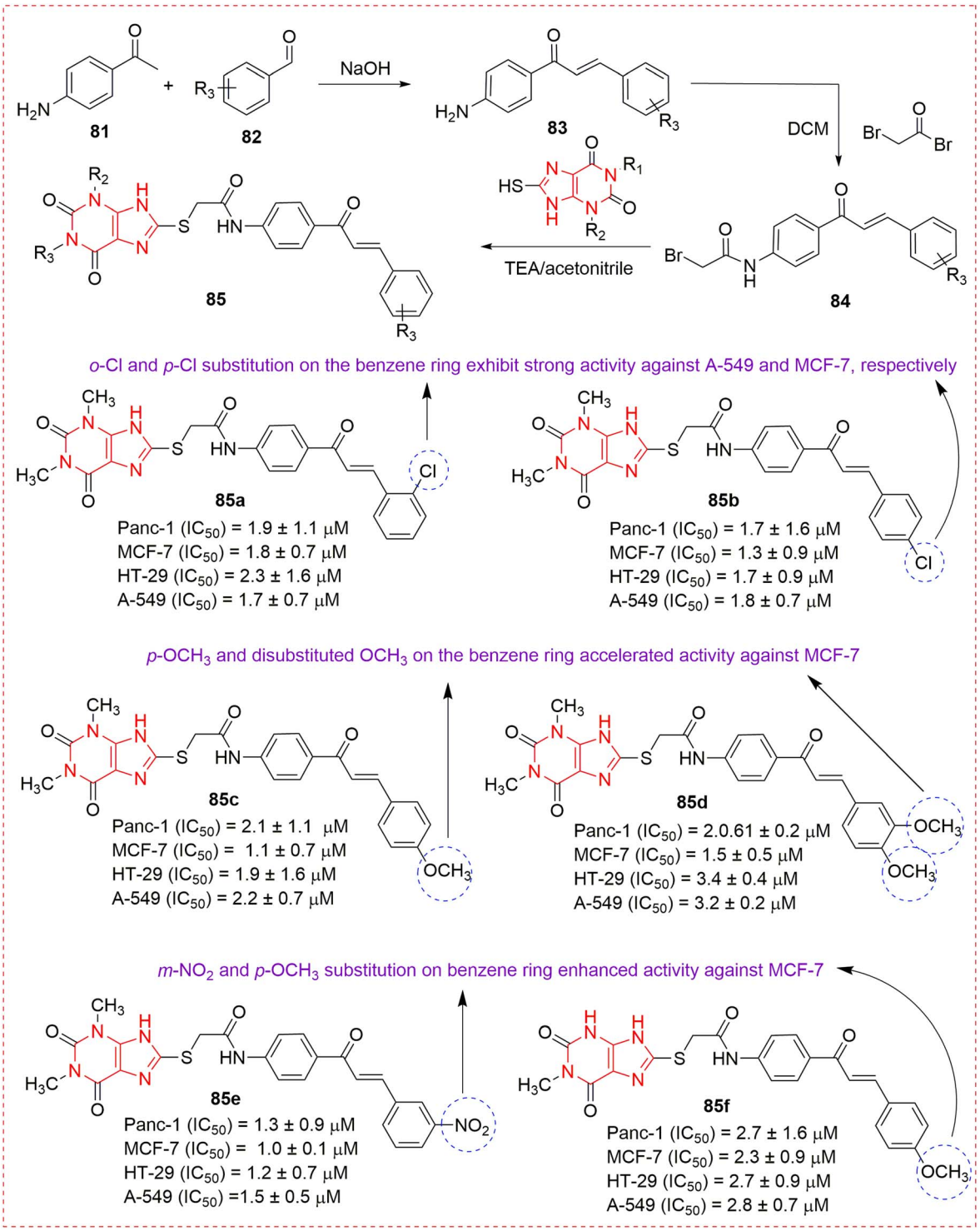
Z. Xu *et al.* reported the C–H enaminylation of purine derivatives with ketenimines with the help of eco-friendly



Scheme 20 Synthesis and IC_{50} values of novel chalcone hybrid purine scaffolds[58]

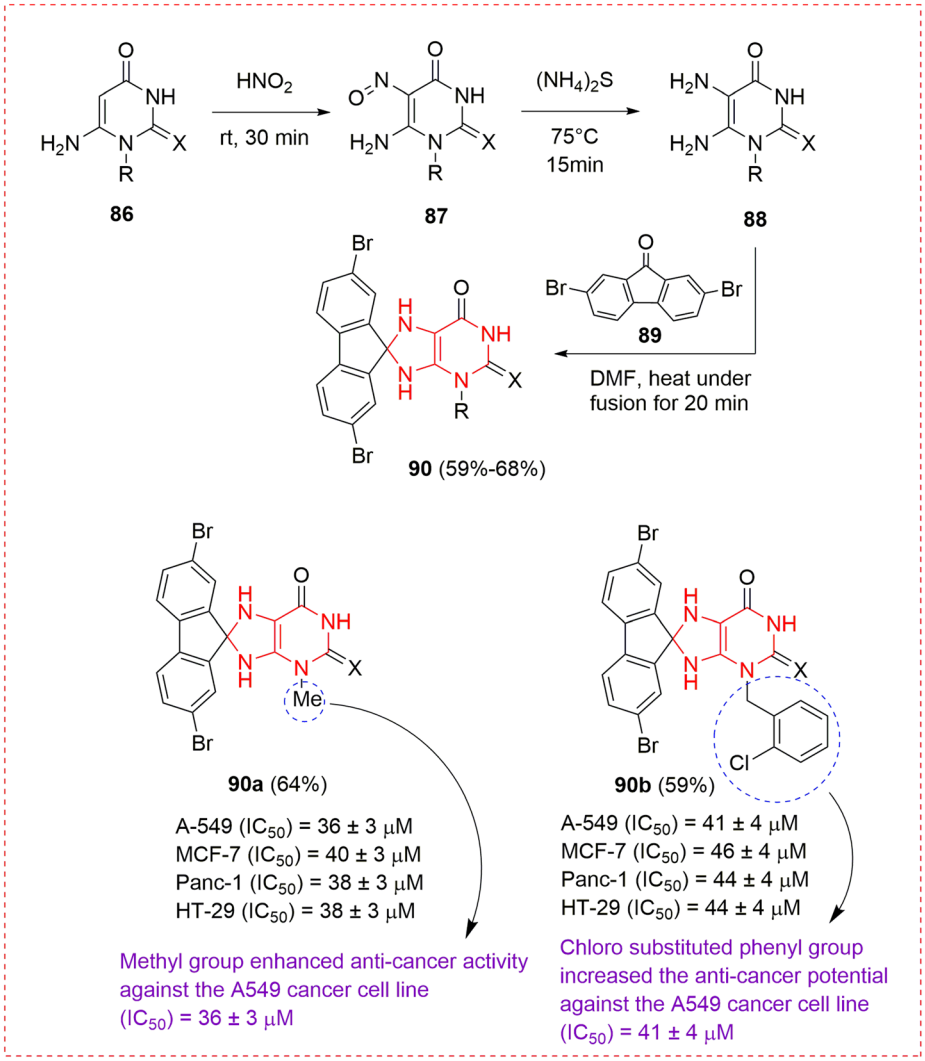
rhenium and manganese catalysts.[63] The synthesis was initiated with the reaction between indole-based purine (**100**) and substituted ketenimines (**101**) in the presence of NaOAc for 16 h by loading a small amount of manganese or rhenium catalyst to afford enaminylated product **102.** To explore the further diversification of compound **102**, a series of compounds (**103**) were prepared using mild Lewis base in dichloromethane as solvent at 40 °C for 2 h (Scheme 25).[63] Compounds **102a**, **102b** and **103a** were considered the most potent against A548 and MCF7 cell lines with the IC_{50} values shown in Scheme 25. According to the structure–activity relationship, introducing a small-sized electron donating group on a phenyl ring increases the anti-cancer activity of the compound. The reported compounds have small-sized electron-donating groups that enhance its activity: fluorine acts as an electron donating group due to its conjugation with the phenyl ring.

E. B. Elkaeed *et al.* demonstrated the synthetic routes to synthesize theobromine derivatives as strong anti-cancer agents.[64] In the previous literature, theobromine derivatives were considered active agents that bind with the cancer-causing enzyme to diminish its activity. The synthesis was initiated with the potassium salt formation on imidic nitrogen (**105**) using KOH and absolute ethanol for 15 min. In the next step, *N*-benzyl-2-chloroacetamide (**107**) reacted with theobromine potassium salt (**105**) which was produced by the reaction of benzylamine (**106**) with 2-chloro acetyl chloride in the presence of DMF and $NaHCO_3$ to produce the corresponding target molecule **108** (Scheme 26).[64] The obtained substrates were



Scheme 21 Synthesis and IC_{50} values for chalcone–xanthine-based purine derivatives.[59]

thought to be the most effective anti-cancer agents against the HCT-116 and A549 cancer cell lines. In an *in vitro* cytotoxicity test, EGFR inhibition against cancer was evaluated using compound **91** with erlotinib as the reference. Compound **108** showed IC_{50} values of 21.99 and 22.02 μM against A549 and HCT-116, respectively, and its anticancer potentials were very similar to those of erlotinib (6.73 and 16.35 μM, respectively). The cytotoxic potential of compound **108** against the W138 normal human cell line was assessed to validate it's *in silico* safety results and selectivity against cancer cell lines. Substrate

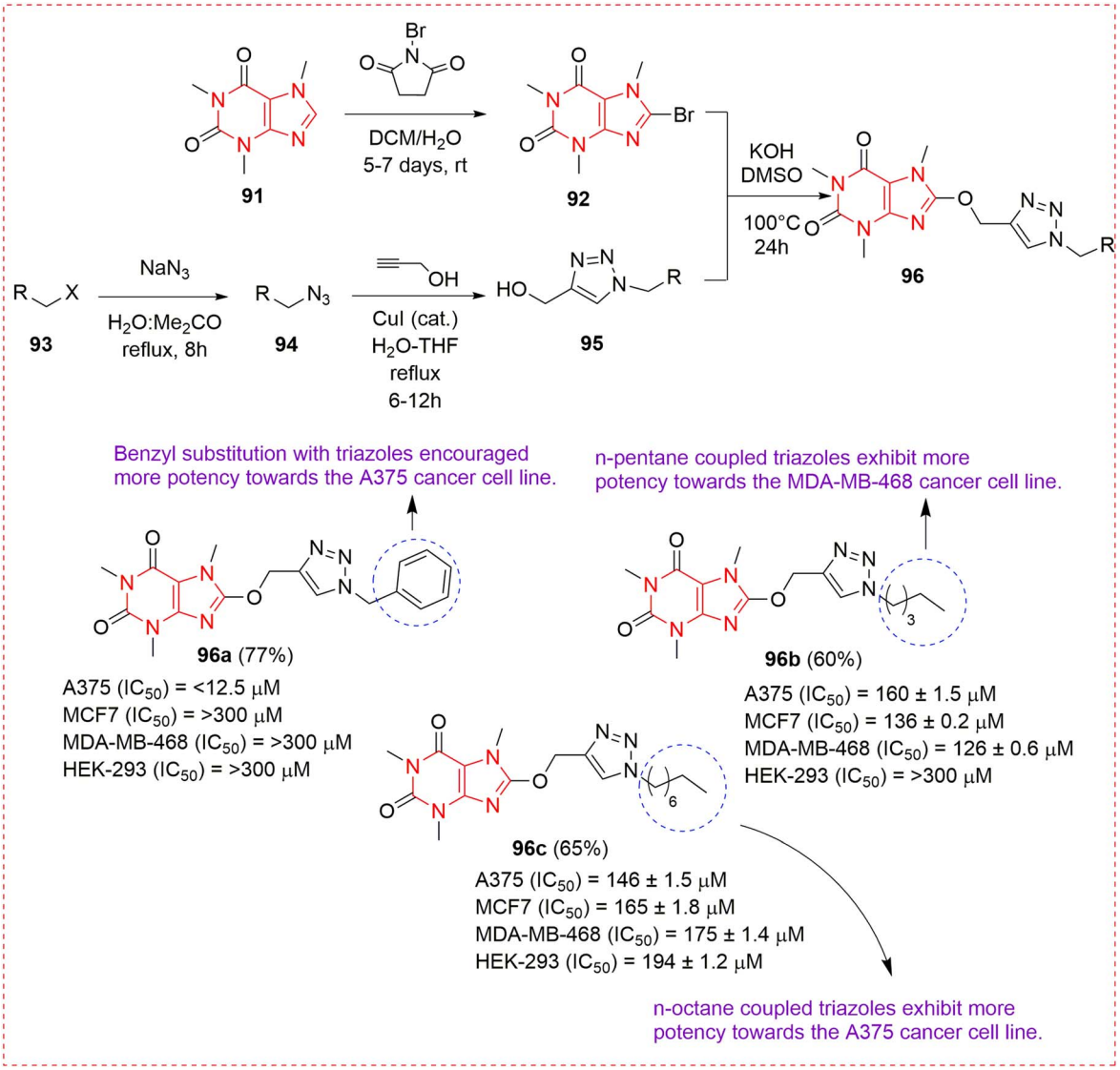


Scheme 22 Synthesis of the most active pteridine based purine analogues as anti-cancer agents.[60]

108 demonstrated the highest cytotoxicity, with a high IC_{50} value of 49.44 μM (safer than erlotinib). Concerning SAR studies, theobromine derivatives were considered more potent against intestinal cancer but the introduction of a benzylacetamide moiety enhanced the anti-cancer activity.

M. A. Dahab *et al.* outlined the semi-synthesis of theobromine-based analogues that may act as VEGFR-2 receptor inhibitors. This receptor enhances metastasis (spreading of cancer).[65] The target theobromine derivatives were synthesized in various steps. In the first step, 4-aminobenzoic acid (**109**) reacted with chloroacetyl chloride to afford chloroacetamide intermediate which was further reacted with thionyl chloride ($SOCl_2$) to produce 4–(2-chloroacetamido) benzoyl chloride (**110**). Compound **110** was treated with substituted anilines in the presence of acetonitrile, DMF, and triethyl amine to produce compound **111**. In the last step, the target molecule (**112**) was synthesized followed by the reaction of the potassium salt of theobromine (**105**) and compound **111** (Scheme 27).[65] All the synthesized scaffolds were assessed against MCF-7 and HepG2. Compounds **112a** and **112b** were the most potent, with IC_{50} values of 4.32 ± 0.2 and 5.84 ± 0.3 μM, respectively. Compound **112a** was the most powerful, with more potent cytotoxic activity against MCF-7 and HepG2 than that of sorafenib (IC_{50} = 7.26 ± 0.3 and 9.18 ± 0.6 μM). Additionally, compound **112b** demonstrated encouraging antiproliferative activity against MCF-7 and HepG2, with IC_{50} values of 19.35 ± 1.3 and 27.89 ± 2.0 μM, respectively. SAR studies revealed that methyl substitution (electron donating group) enhanced the anti-cancer activity more than fluorine substitution (electron-withdrawing group). Furthermore, it was preferable to substitute electron-donating groups rather than electron-withdrawing groups at position 2 to enhance anti-cancer activity.

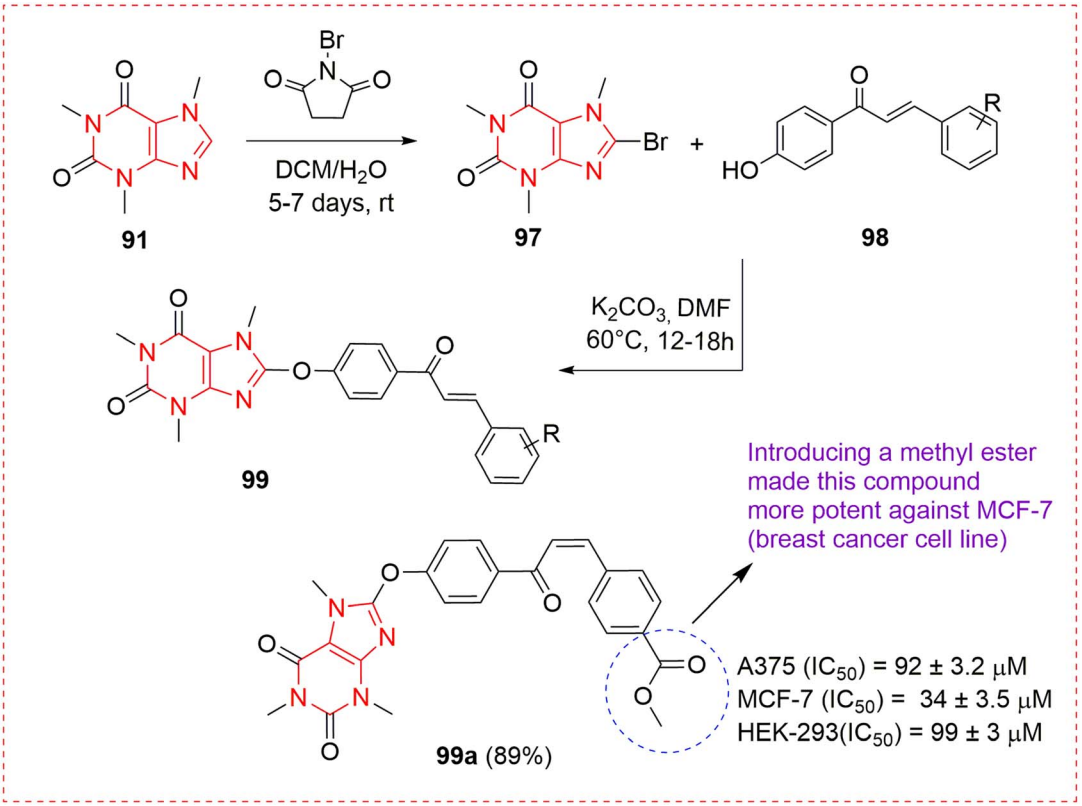
One of the most pertinent classes of chemotherapeutic medicines are mock nucleosides and nucleotides (often called



Scheme 23 Synthesis of caffeinyl-triazolyl methoxy hybrid derivatives as strong anti-cancer agents against A357, MCF7, MDA-MB-468 and HEK-293 cancer cell lines.[61]

scaffolds) to distinguish them from their physiological equivalents. These kinds of chemicals are mostly prodrugs that function as antimetabolites of nucleic acids in therapeutic settings. The use of nucleoside and nucleotide analogues has certain drawbacks despite their notable efficacy in clinical settings, including their limited oral bioavailability and the inherent and acquired confrontation of cancer cells. Considering the lack of nucleoside and nucleotide derivatives as anti-metabolites, N. M. Xavier *et al.* demonstrated the design to synthesize novel purine derivatives that contain a dodecyl azido and glucuronamide moiety.[66] Diacetone-D-glucose (**113**) was the starting point for the synthesis of target molecule nucleosides. In the presence of NaH, diacetone-D-glucose was nucleophilically displaced with dodecyl bromide to obtain the 3-*O*-dodecyl derivative. The 5,6-diol (**114**) was obtained by treating the primary acetonide with aqueous acetic acid (70%) and its selective hydrolysis. By creating a good leaving group, an azide moiety was added to diol (**114**) to afford **115**. The protected diol in **115** was deprotected using tri-fluoroacetic acid (TFA) and protected with acetyl using pyridine at room temperature for 1 h to afford (**116**). In the last step, pre-stimulated by silylation using BSA was followed by nucleosidation reactions involving 2-acetamido-6-chloropurine carried out at 65 °C under MWI in the presence of TMSOTf. Thus, 2-acetamido-6-chloropurine was *N*-glycosylated with **116** to obtain N_1-linked nucleoside (**117**) in 41% yield (Scheme 28).[66]

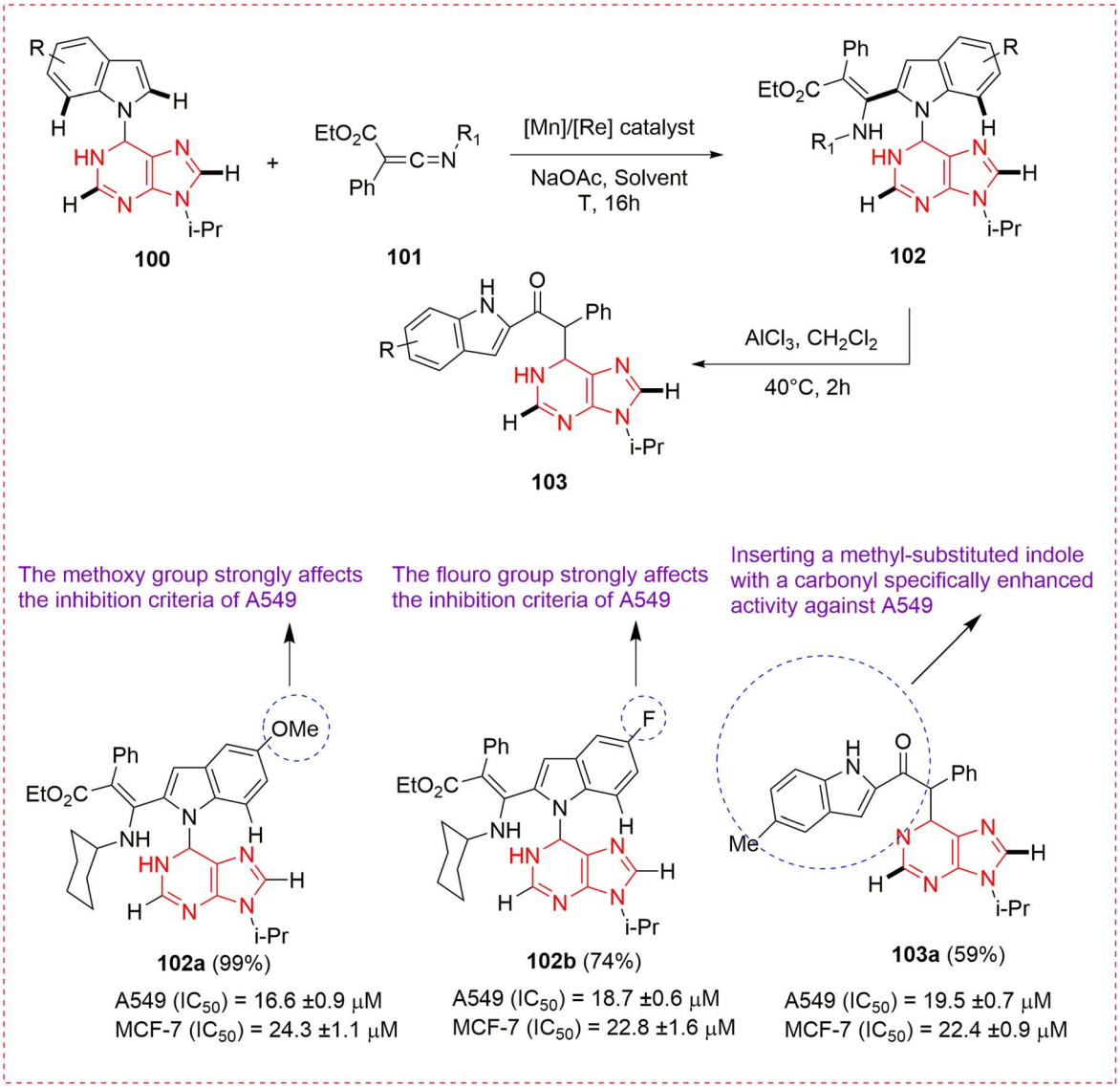
Substrate **119** was used as a glycosyl donor in the fusion of *N*-dodecyl glucuronamide-based nucleosides with *O*-benzylated furanose moieties. From the *N*-dodecyl furanuronamide



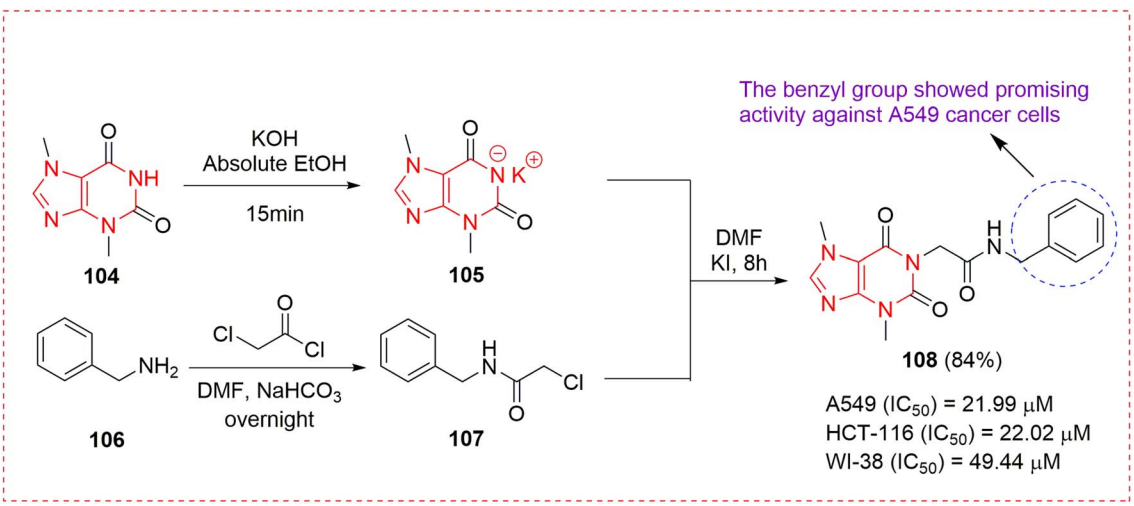
Scheme 24 Synthesis of the most potent chalcone-caffeine hybrid purine derivatives.[62]

derivative (**118**), this intermediate was obtained in three stages: acetylation, acetonide cleavage, and benzylation. However, both *N*-9 and *N*-7-linked purine nucleosides (**120**) and (**121**) were produced by nucleosidating **119** with 2-acetamide-6-chloropurine through the microwave irradiation method resulting in yields of 26% and 11%, respectively[52] (Scheme 29).[66] The azido and glucuronamide derivatives were evaluated for anti-cancer activity against chronic myeloid leukemia cell line K562, and breast adenocarcinoma cell line MCF-7. The most potent compound in this group was **117**, with GI_{50} values of 3.2 μM in both cell lines. This is roughly three times lower than that of the anticancer medication 5-fluorouracil in MCF-7 cells and seven times more than that of the antileukemic agent imatinib in K562 cells. The *N*-7-linked purine derivative (**121**) was the most potent molecule, having the same efficacy as compound **117** towards both lines of cancer cells ($GI_{50} = 3.3$ μM). Analysis of structure–activity relationships (SAR) reveal that purines containing a heterocyclic nitrogen are excellent biologically active compounds. Along with this, the addition of an azido and glucuronamide moiety enhances anti-cancer activity two to three-fold more than commercially available compounds.

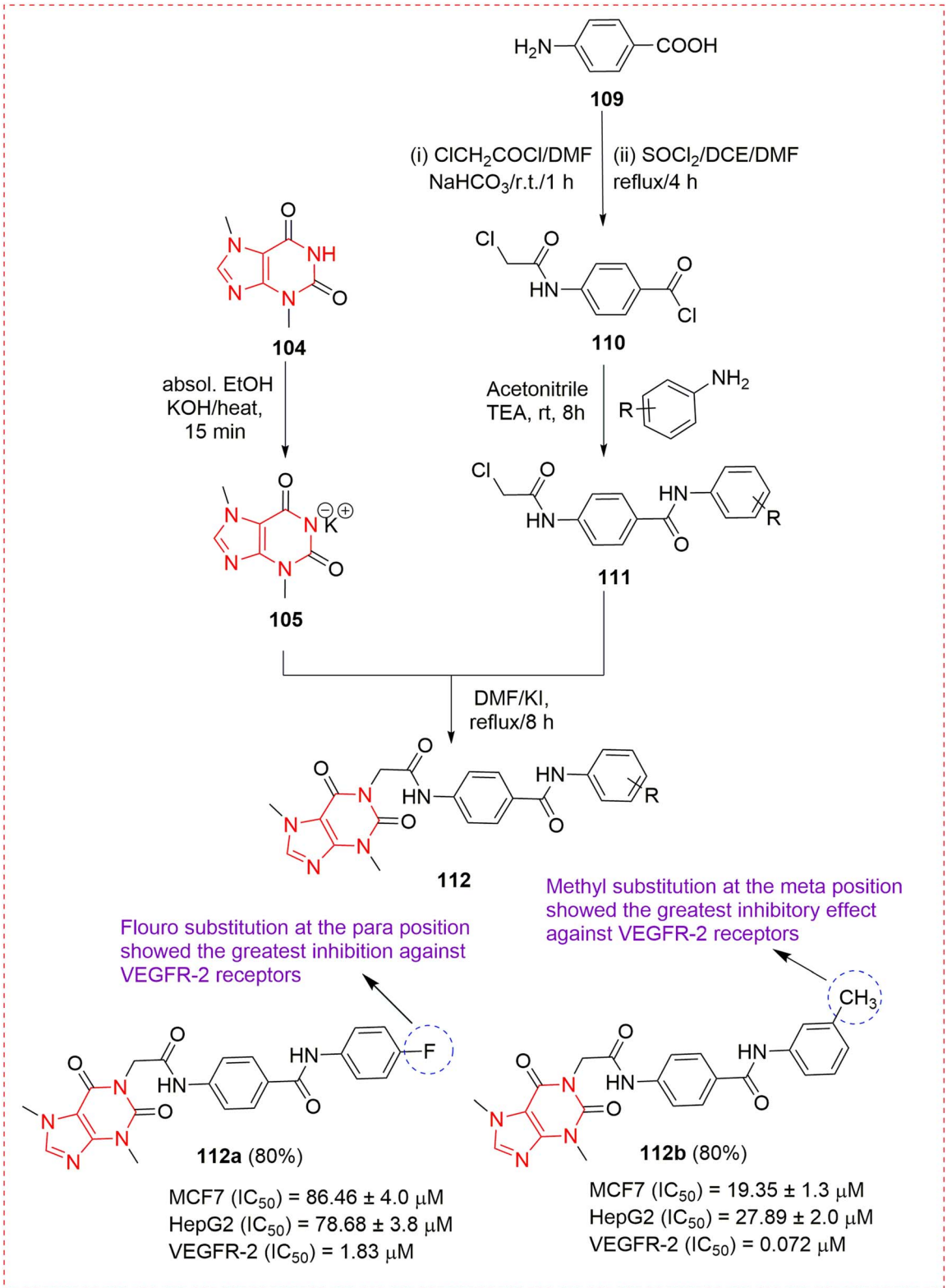
According to the survey, approximately 18 HDACs are identified in humans. HDAC enzyme mainly regulates histone acetylation, possibly leading to cancer. By altering the chromatin structure, histone acetylation plays a crucial part in the epigenetic control of gene expression. HDACs are closely linked to tumor growth, as evidenced by reports showing that their levels are overexpressed in cancer cells and vary depending on the kind of tumor. Tumor cell migration, death, cellular differentiation, and proliferation can all be inhibited by blocking HDACs. Prostate, esophageal, and other malignancies overexpress class I HDACs. To resolve this issue, P.T. Mao *et al.* synthesized and evaluated aminobenzamide purine scaffolds as HDAC inhibitors that may reduce the risk of cancer.[67] The synthesis began with the commercially available 2,6-dichloro purine (**9**) which was substituted by amine at C2. This compound (**122**) was subsequently reacted with 4-(bromomethyl)-benzoate to afford **123**, an ester. This intermediate ester was converted into carboxylic acid using an alkali base in ethanol. In the final approach, substituted phenylenediamine was treated with intermediate **124** to synthesize the required target molecule (**125**) (Scheme 30).[67] A series of derivatives with different substitutions were synthesized. According to the *in vitro* activities, compound **125a** had outstanding inhibitory effects on cancer cells, including HCT-116, MDAMB-231, and K562 cell lines, and was 12 times more potent than MS275 against the HDAC1 isoform. Compound **125a** had strong antiproliferative effects with IC_{50} values of 0.50, 0.38, and 0.12 μM for HCT116, MDA-MB-231, and K562 cell lines, respectively. The metabolic stability of compound **125a** was significantly



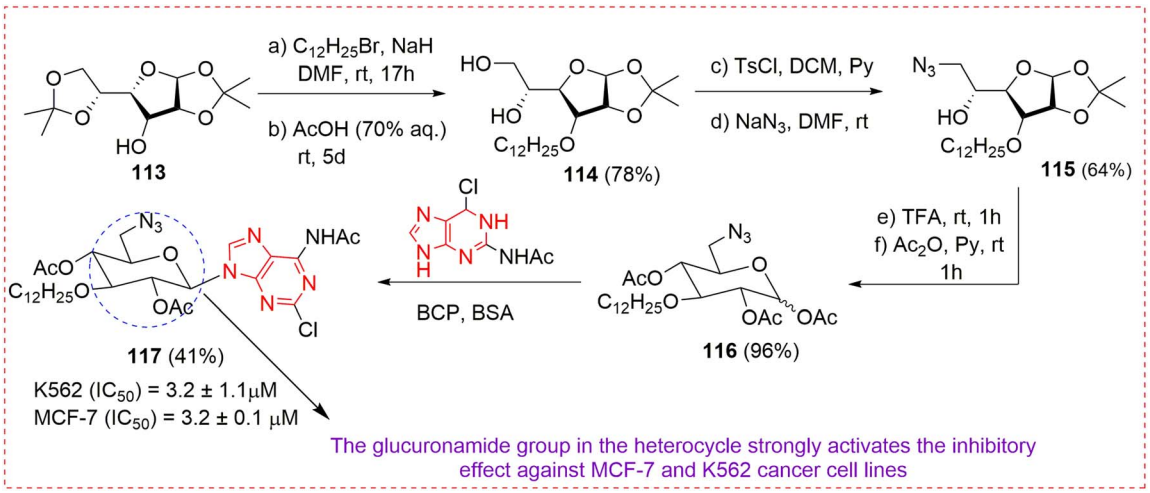
Scheme 25 Synthesis of the most potent indole-based purine derivatives and IC_{50} values of the synthesized scaffolds against A549 and MCF-7 cancer cell lines.[63]



Scheme 26 Synthesis of most promising anti-cancer theobromine scaffolds.[64]



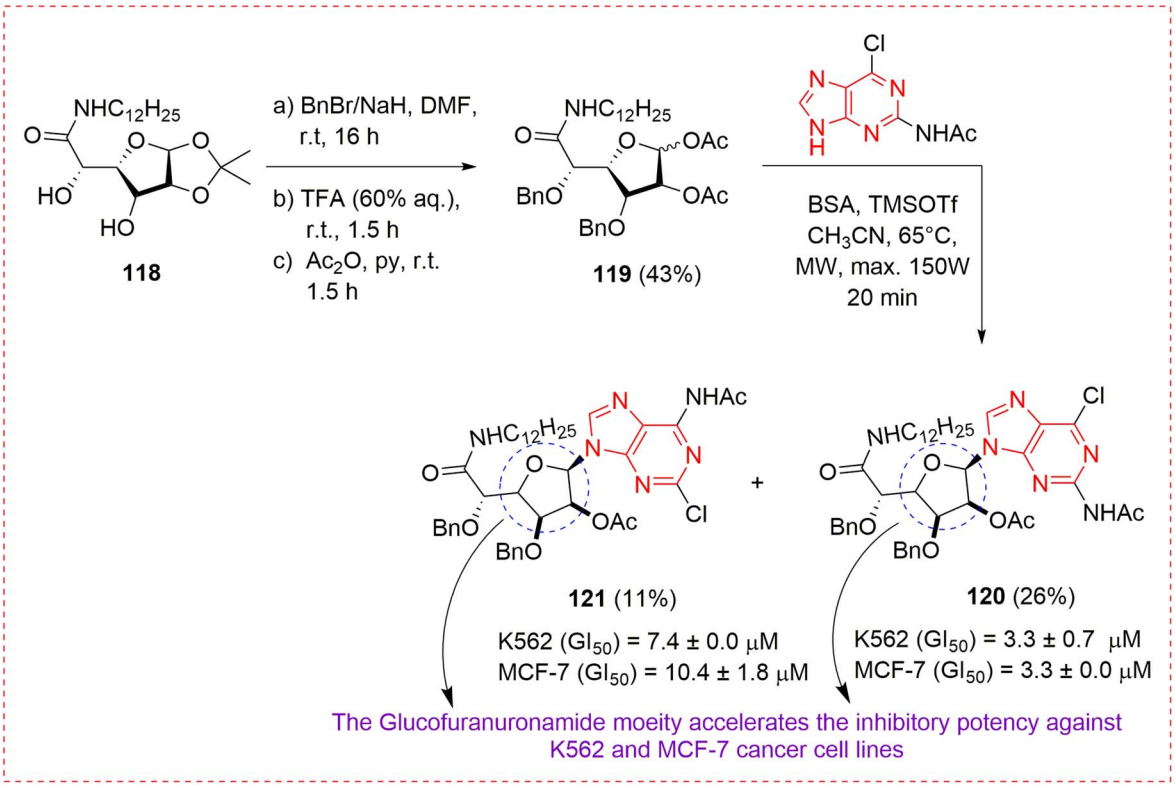
Scheme 27 Synthesis and IC_{50} values of theobromine-based scaffolds against MCF7, HepG2 and VEGFR-2 cancer cell lines.[65]



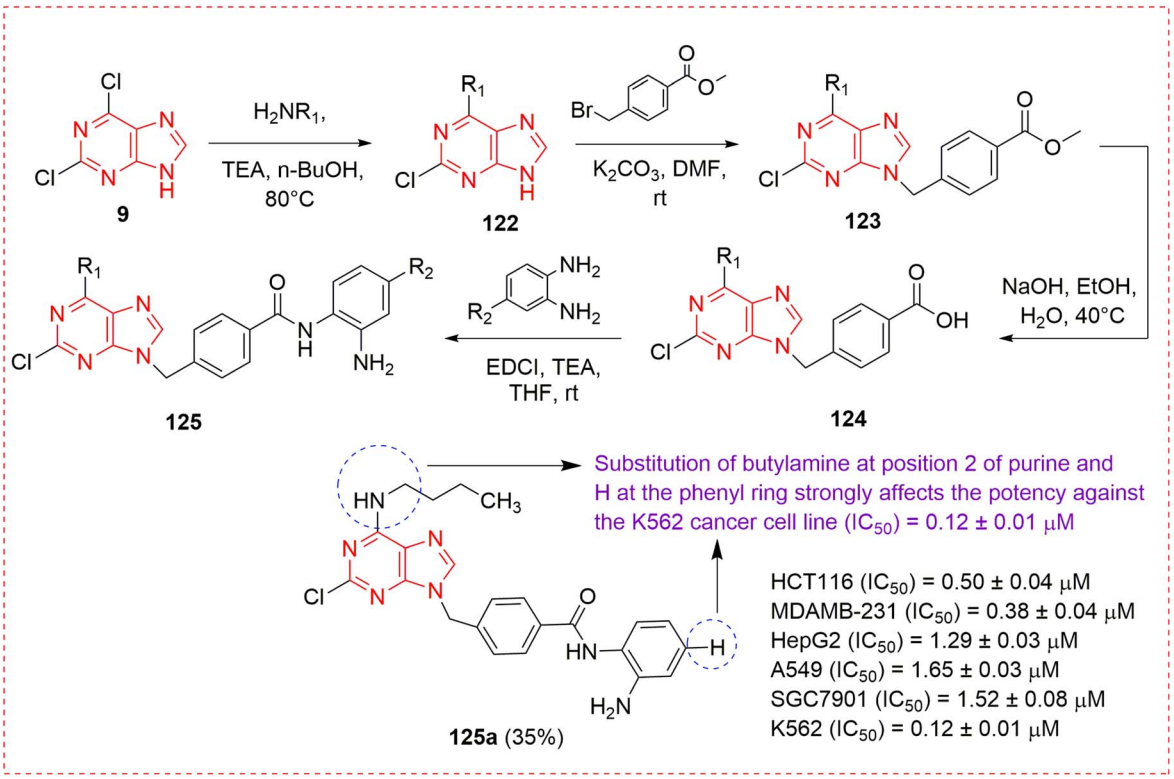
Scheme 28 Synthetic routes to glucuronamide based purine substrate as a potent anti-cancer agent against K562 and MCF-7 cancer cell lines.[66]

higher than the well-known HDAC inhibitor, SAHA. Analysis of the structure–activity relationship (SAR) among the series concluded that the compound that possessed *N*-butyl amine substituted on the C2 of purine enhanced the anti-cancer activity. Along with this, halo-substituted products showed diminish activity.

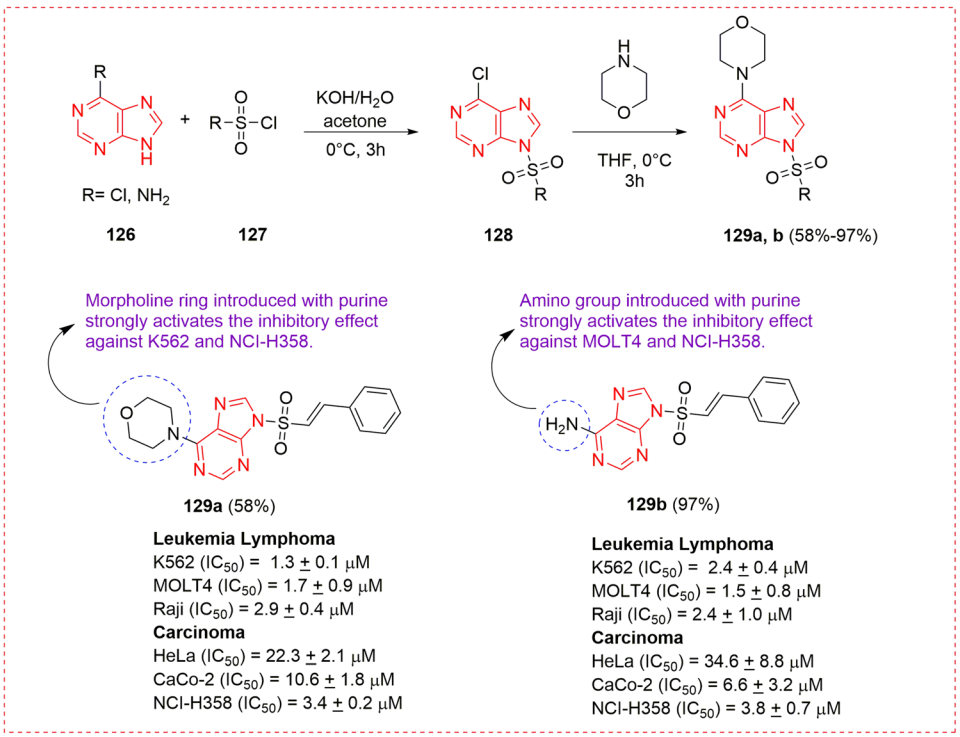
Matic *et al.* described the synthesis and anti-cancer elucidation of 6-amino and 6-morpholino-9-sulfonylpurines derivatives.[68] Sulfonyl purines contain the sulfonamide group which is an imperative class of biologically active compounds. These compounds may act as powerful anti-microbial, anti-thyroid, anti-tumor agents. 6-Substituted purine (**126**) was countered with aryl sulfonyl chloride (**127**) in the presence of aqueous potassium hydroxide and acetone at 0 °C for 3 h to afford 6-chloro-*N*-9-sulfonypurines (**128**). Compound **128** was modified with morpholine to afford 6-morpholino-*N*-9-



Scheme 29 Synthetic routes to glucofuranuronamide based purine substrate as potent anti-cancer agents against K562 and MCF-7.[66]



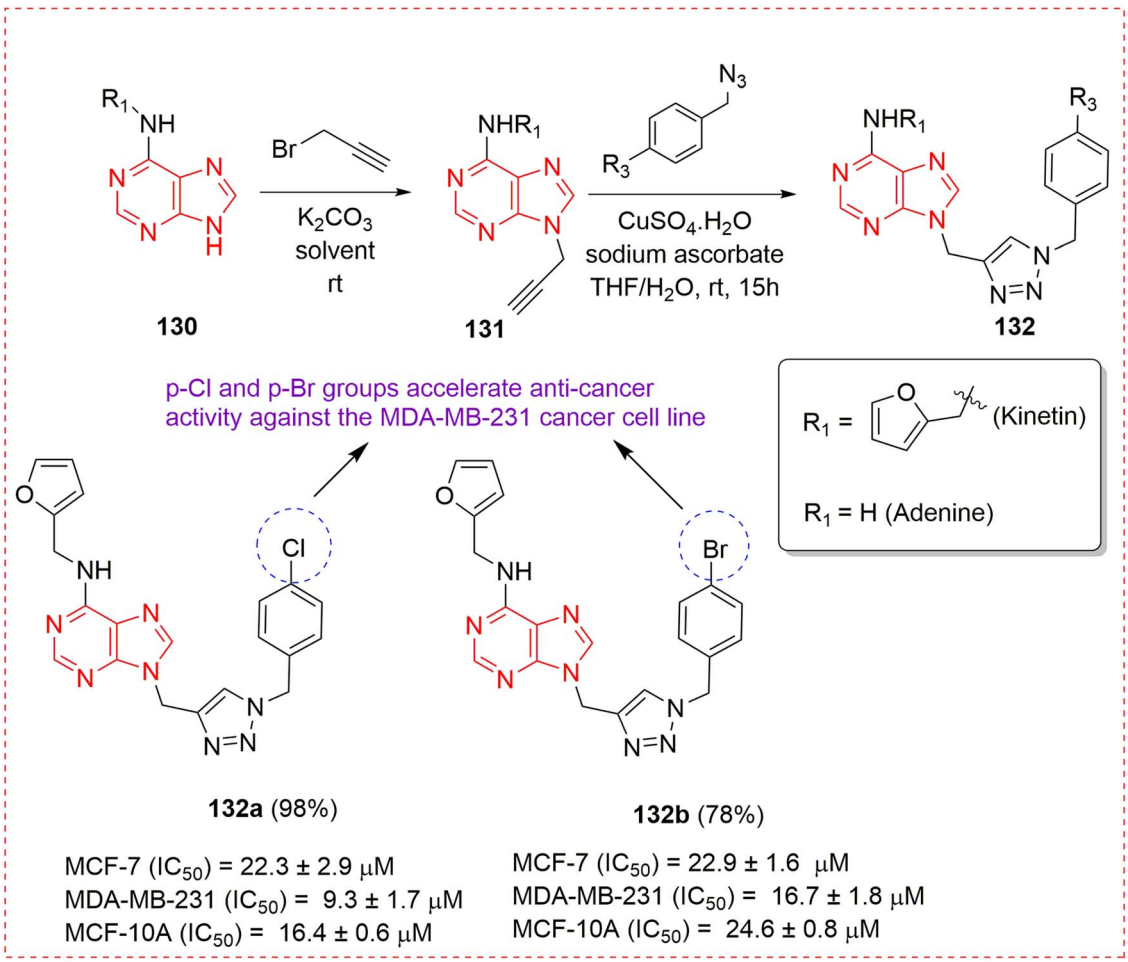
Scheme 30 Synthesis of the most active purine scaffolds containing an aminobenzamide moiety as the anti-cancer agent.[67]



Scheme 31 Synthesis of 6-amino and 6-morpholino sulfonyl hybrid purine derivatives as strong anti-cancer agents.[68]

sulfonylpurines (**129a** and **129b**). The anti-proliferative activity (anti-cancer) of derivatives of compounds **129a** and **129b** were tested against 5-FU (fluorouracil) as a standard drug (Scheme 31).[68] Compounds **129a** and **129b** were considered the most effective anti-cancer agents on the normal (BJ), leukemia lymphoma (K562, MOLT4, Raji) and carcinoma (HeLa, NCI–H358, CaCo-2) cell lines. Compound **129a** revealed an IC_{50} of 3.4 ± 0.2 μmol dm^{-3} on NCI–H358 cells and less than 24 μmol dm^{-3} on HeLa and CaCo-2 cells. Leukemia and lymphoma cell lines (K562, MOLT 4, and Raji) were used to achieve the optimum inhibitory concentration of substrate **129a** at applied concentrations ranging from 1.0 to 1.7 μmol dm^{-3}. Compound **129b** has a remarkable selectivity index of 10 on acute lymphoblastic leukemia (MOLT4) cells and an IC_{50} of less than 2.4 μmol dm^{-3} against leukemia and lymphoma cells. Analysis of the structure–activity relationship demonstrated that binding of a styryl group to purine scaffolds had significant anti-tumor potential and no disturbing effect on normal cells. The strong anti-cancer activity of synthesized derivatives was detected against carcinoma (CaCo-2 and NCI–H358) cells.

O. Torres *et al.* demonstrated the design to synthesize new kinetin-based purine scaffolds that were effective for breast cancer.[69] Among women, the leading cause of death is breast cancer. Synthesis of benzyl substituted-1,2,3-triazolo-purines scaffolds began with the reaction between *N*-substituted-9*H*-purin-6-amine (**130**) and 3-bromoprop-1-yne. An intermediate (**131**) was obtained which was further reacted with substituted phenyl azides in the presence of copper sulphate, sodium ascorbate, and THF at room temperature for 15 h to afford purine triazole-based scaffolds (**132**). These obtained derivatives were evaluated for their cytotoxic activity against different cancer cell lines, *i.e.*, MCF-7, MDA-MB-231 (breast cancer cell line), and MCF-10A (non-cancer cell line) (Scheme 32).[69] According to SAR studies, kinetin derivatives showed no activity against cancer cells. However, the derivative of the furan ring of kinetin showed observable anti-cancer activity. Also, anti-cancer activity was enhanced with addition of a halogen group. Compared with doxorubicin, compounds **132a** and **132b** showed a strong anti-cancer activity among all the synthesized derivatives. Compounds **132a** and **132b** have chloro and bromo substitutions at the *para* position, respectively. Furthermore, compound **132a** with a chlorine atom in the structure has IC_{50} values of 22.3 ± 2.9 μM (MCF-7) and 9.3 ± 1.7 μM (MDA-MB-231) [p-Cl] among the kinetin derivatives. The most active compound was **132b**, which contains a bromine atom [p-Br: IC_{50} = 22.9 ± 1.6 μM (MCF-7) and IC_{50} = 16.7 ± 1.8 μM (MDA-MB-



Scheme 32 Synthesis and anti-cancer evaluation (IC_{50} values) of the most primitive substituted triazole-based purine derivatives.[69]

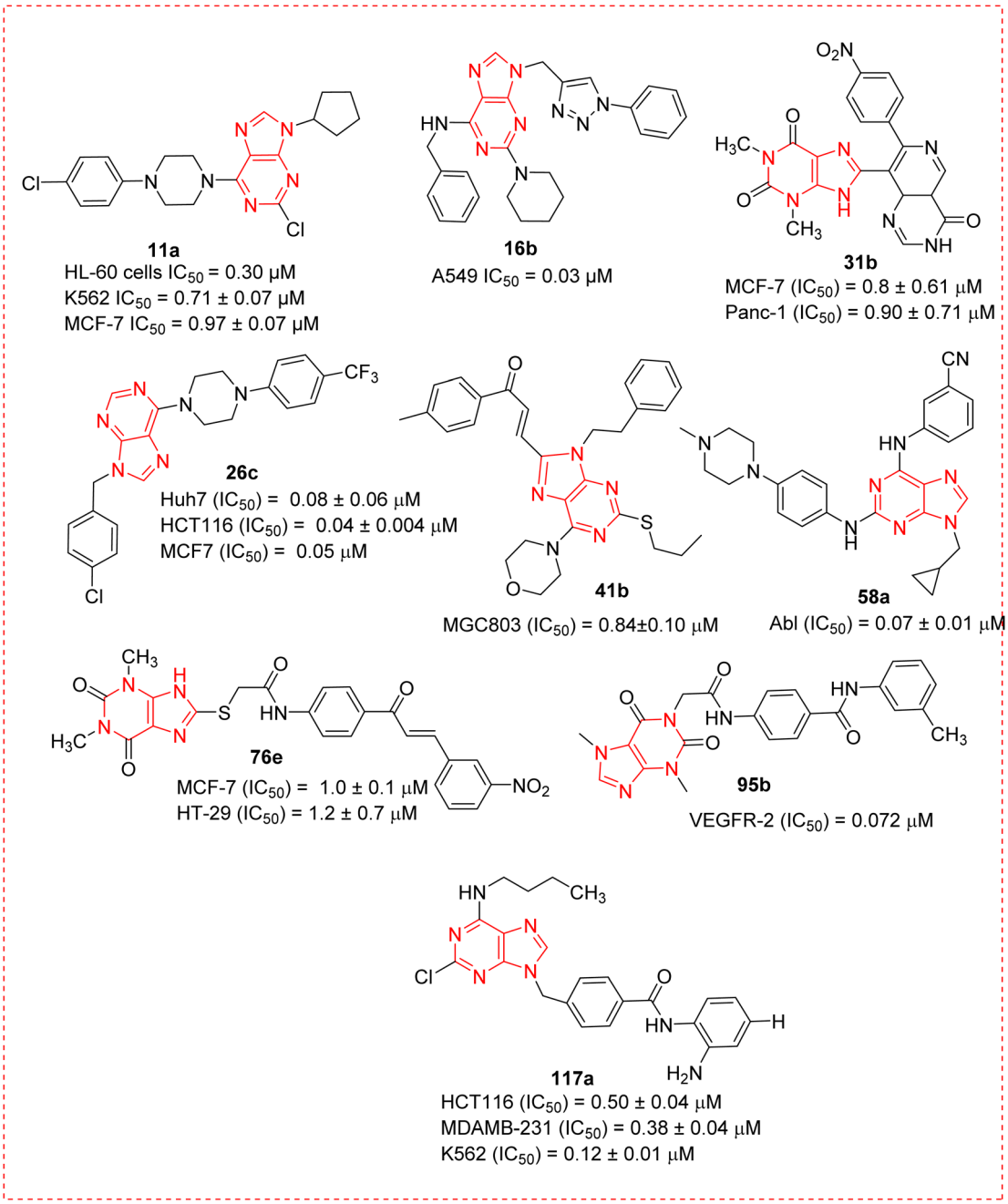


Fig. 4 Selected most potent anticancer molecules from the current review for future study.

231)], underscoring the significance of the halogens in enhancing the biological activity of kinetin derivatives.

Most potent molecules to study in the future (Fig. 4).

3 Conclusion

The ongoing study of purine-based hybrids has resulted in the development of highly potent and selective anticancer molecules that address significant problems such as drug resistance and toxicity. Over the last five years (2020–2024), significant progress has been made in the synthesis of structurally diverse purine derivatives such as aryl piperazine, triazole-hybrid piperidine/pyrrolidine, diazenyl, pyridopyrimidine, pyrazolopyridine, pyranonaphthyridine, and various linker-based bis-purine analogues. Comparative structure–activity relationship (SAR) studies have shown that tailored modifications such as piperazine, triazoles, thiazoles, and xanthine-chalcone hybrids increase cytotoxic efficacy against a wide range of cancer cell lines, including HCT-116, A549, MCF-7, and HeLa. Purine molecules based on theobromine and adamantane have also demonstrated exceptional therapeutic potential against HepG2 and VEGFR-2. These findings demonstrate the purine scaffolds' versatility in anticancer drug development, as well as the significance of rational hybrid design in improving

selectivity, effectiveness, and safety. Future research will focus on improving pharmacokinetics, combating drug resistance, and designing novel drug delivery systems to effectively bring these promising purine-based anticancer medicines into clinical applications.

4 Future perspectives

Cancer inhibition medication is a serious concern in the world. According to the world report given by WHO, there are 20 million new cancer cases and 9.7 million deaths between 2022 to 2025. To resolve this issue, a wide range of studies must be conducted to understand the therapeutic effects of the known scaffolds and determine the mode of action for various purine-based scaffolds that can be targeted during the synthesis of novel analogues. In this current review, more than 133 molecules were synthesized. All the scaffolds were important because of their diverse target interactions, structural diversity, and various mechanisms of action. These molecules will be essential for the future eradication of cancer. Also, the anti-cancer evaluation (IC_{50} values) and structural activity relationships (SAR) of these synthesized derivatives are described to show their effectiveness against different cancer cell lines. Both synthetic and medicinal chemists would benefit from this review since it would help them comprehend the new scaffolds and structural elements that might provide ideas for creating novel compounds that would combat drug resistance.

Abbreviations

CLL	Chronic lymphocytic leukemia
HIV	Human immunodeficiency virus
RTI	Reverse transcriptase inhibitor
DIPEA	Diisopropyl ethyl amine
CPT	Camptothecin
THF	Tetrahydrofuran
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
5-FU	5-Fluorouracil
P-TSA	*Para*-Toluenesulfonic acid
BTK	Bruton's tyrosine kinase
Bcr-Abl	Break-point cluster region-Abelson
ITD	Internal tandem duplication
EGFR	Epidermal growth factor receptor
US	Ultra sound irradiations
TEA	Triethylamine
DCM	Dichloromethane
MWI	Microwave irradiation
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
Her2	Human epidermal growth factor-2
HDAC	Histone deacetylases
VEGFR-2	Vascular endothelial growth factor receptor-2
Raf1	Rapidly accelerated fibrosarcoma-1
MAPK	Mitogen-active protein kinase
ERK	Extracellular signal-regulated kinase
MTX	Methotrexate
Hsp90	Heat shock protein 90
ER+	Estrogen receptor-positive
US FDA	The United States Food and Drug Administration
TMSOTf	Trimethylsilyl triflates
BSA	Bis(trimethylsilyl)acetamide
TFA	Trifluoroacetic acid
Py	Pyridine
NBS	*N*-Bromosuccinimide
ATP	Adenosine triphosphate
BCP	Bathocuproine
17-AAG	17-*N*-Allylamino-17-demethoxygeldanamycin
SAHA	Suberoylanilide hydroxamic acid
WHO	World Health Organization

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Author contributions

M.A. Hashmi: writing–review and editing. A. Malik: supervision, validation, and investigation. U. H. Siddiqua: validation and investigation. A. Kanwal: review and editing.

Conflicts of interest

"There are no conflicts to declare".

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