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Applications of palladium-catalyzed C–N cross-coupling reactions in pharmaceutical compounds

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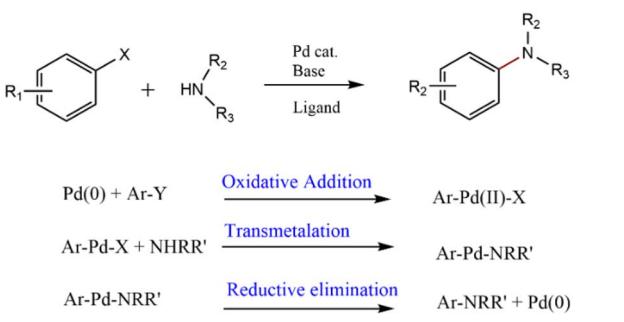
C–N cross-coupling bond formation reactions have become valuable approaches to synthesizing anilines and their derivatives, known as important chemical compounds. Recent developments in this field have focused on versatile catalysts, simple operation methods, and green reaction conditions. This review article presents an overview of C–N cross-coupling reactions in pharmaceutical compound synthesis reports. Selected examples of *N*-arylation reactions of various nitrogen-based compounds and aryl halides are defined for preparing pharmaceutical molecules.

1. Introduction

Pharmaceutical industries have undergone a wide variety of developments regarding new forms of active ingredients and their advances in formulation and preparation technology.[1,2] The development of tiny molecular drugs is a crucial driver of sales growth for large pharmacies and defines new research and development patterns for pharmaceutical firms.[3–11] Pharmaceutical industries strive to produce safe and inexpensive drugs while keeping pace with the pharmaceutical market. In this regard, investigating new synthetic approaches like "transition metal catalyzed reactions" for rapid access to massive hybrid libraries with facile and cost-effective operating methods is valuable.[12] During this time, cross-coupling reactions as significant synthetic transformations have revealed an abundance of uses in the generation of several biologically active compounds and natural compounds;[13,14] for instance, extensive studies have been reported on the application of Pd-based catalysts in the synthesis of critical medicinal compounds.[15–19] These encompass two different starting materials with active groups which reacted to each other in the presence of metal species catalysts.[20]

Amine is one of the most important functional groups in natural materials and pharmaceuticals; therefore, C–N bond formation reactions have attracted much attention. Ullmann and Goldberg introduced the C–N bond formation through the S_NAr reaction in the presence of copper salts suffering from serious disadvantages, such as poor substrate scope restricting its effectiveness in producing complex pharmaceuticals. These reactions need an activated functional group in the reactant, polar aprotic solvents, and a long reaction time. After that, Buchwald and Hartwig developed a C–N cross-coupling reaction using Pd-catalysts,[21–24] more improvements converted this reaction into a decent strategy in synthetic chemistry through the amination reaction of aryl, vinyl, and heteroaryl halides.[25–35] The constant development of substrate scope, ligands, and catalytic systems led to the generality of the *N*-arylation reaction. Now, many scientific reports on its utility and application are available.[36–39] The general mechanism of Pd-catalyzed C–N cross-coupling reaction, as described in Scheme 1, includes oxidative addition, insertion, transmetalation, and reductive elimination.[40–42]

C–N bond formation through Pd-catalyzed cross-coupling reactions has attracted much attention in scientific efforts and industry.[43–45] Numerous approved drugs and applicable



Scheme 1 General reaction scheme of Buchwald–Hartwig amination reaction.

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organic compounds have arylated amine functional groups. These cause significant development in employed catalytic systems comprising metal sources, ligands, and reaction performance techniques.[46–49] Different applications of this transformation in diverse scientific fields have inspired scientists to design new efficient ligands and study optimization reaction conditions to reach more efficient catalytic systems. Therefore, Pd-catalyzed coupling of amine with aryl halides was introduced as a pioneer of C–N bond formation reactions and promising alternating method to other traditional procedures, including nucleophilic aromatic substitution (S_NAr) and Cu-catalyzed Ullmann and Goldberg couplings.[50,51]

Numerous novel catalytic systems with excellent efficiency on hindered amines and low-activity compounds were achieved by developing structurally diverse ligands. For instance, phosphine ligands with distinct structural properties like large, bulky, and the sterically hindered group can perform the coupling of massive kinds of amines such as heterocyclic, primary, secondary, and electron-deficient with aryl halides or heteroaryl halides.[52,53] However, the investigation of the effects of the type of ligands and the detail of reaction conditions are not included in this review article to avoid the excessive length of the text.

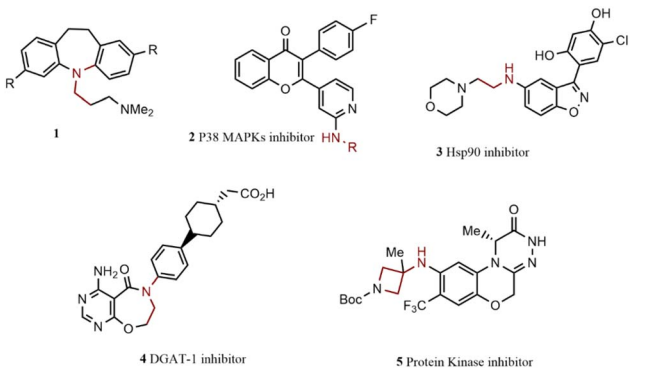
In recent years, these transformations have attracted much attention, especially in drug design approaches, considering the point that lipophilicity of the molecules can be modulated by the inclusion of nitrogen atoms in the molecular structure, which improves their pharmacokinetic profile such as solubility, permeability, and brain penetration.[54,55] These facts converted metal-catalyzed C–N formation reactions to general approaches and reliable procedures, especially in a systematic structure–activity relationship (SAR) exploration and medicinal chemistry efforts. Several review articles have been published about several cross-coupling reactions' usage in medicinal chemistry, emphasizing reaction conditions of multistep synthesis processes that have made the texts tedious and too long. Herein, this article provides a comprehensive report on applications of *N*-arylation reactions for the preparation of potential pharmaceutical compounds by depicting just their chemical structure and bolding newly formed bonds which made the text brief and useful.

Almost all available industrial synthesis methodologies contain C–N cross-coupling reactions employing Pd-based catalysts, and phosphine ligands are considered a limitation for them because of bearing ppm level threshold of Pd residual tolerance in active pharmaceutical ingredients and using expensive, unstable, and poisonous phosphine ligands.[56] Therefore, researchers have turned their attention toward employing less expensive, less toxic, and more effective metals as an alternative to Pd. Recently, numerous approaches have been reported for the C–N cross-coupling reaction in the presence of more sustainable and greener metal, base, solvent, and milder reaction conditions, which are valuable from the green chemistry point of view.[57–63]

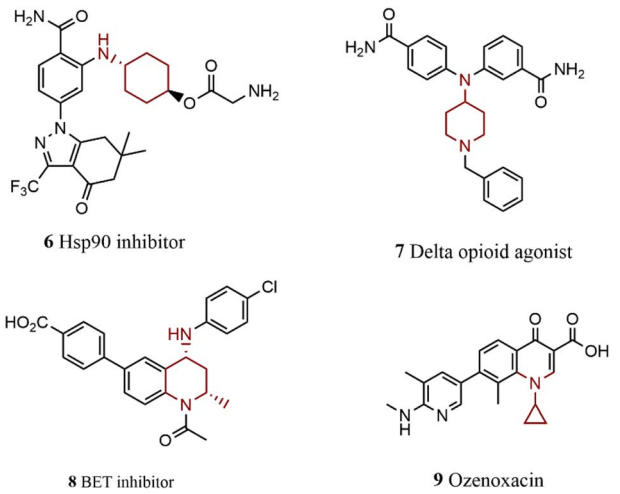
2. C–N cross-coupling reactions in pharmaceutical compounds

2.1. Primary alkylamine arylation

Primary alkylamine arylation is established as one of the most widely technologically advanced *N*-arylation reactions. Overcoming some drawbacks has converted this reaction into an efficient synthesis method for generating numerous pharmaceutical products.[64–69] The chemical structure of some drugs synthesized by harnessing primary alkylamines arylation reaction has been illustrated in Scheme 2. For instance, several 3,7-disubstituted tricyclic imipramine **1**, as an antidepressant agent, were synthesized by Jensen and co-workers through a one-pot procedure from bis-aryl bromides, microwave irradiation improved the reaction yields and reduced the production of an undesired product of monoamination.[70] Microwave heating was also used by Grøtli and co-workers to generate some chromone derivatives **2**, by the C–N cross-coupling reaction, products showed potential anti-cancer activity.[71] Hsp90 inhibitors are known as potential anti-tumor agents; Gopalsamy and colleagues synthesized compound **3** *via* C–N coupling of linear alkyl primary amines and aryl iodide as a new Hsp90 inhibitor.[72] DGAT-1 inhibitor **4** was prepared by Dow's team for obesity or type II diabetes treatment.[73] In another research work, aryl bromide was coupled with aminoazetidine to reach compound **5** as a protein kinase C_θ inhibitor, and its activity as an autoimmune disease drug was also investigated.[74] In continuation of the arylation reactions of primary alkylamines, a group of indazol-4-one-derived **6** was prepared through *N*-arylation of cyclohexyl amine by Huang and co-workers. Their anti-cancer activities were also confirmed as potential Hsp90 protein inhibitors.[75] δ-Opioid agonist **7** was synthesized through two sequential C–N bond-formation reactions.[76] In another scientific report, compound **8** was prepared through *N*-arylation of chiral amino-piperidine. More investigations exhibited that this compound acts as an anti-inflammatory agent.[77] Ozenoxacin is an approved antibiotic for treating contagious skin infections, it is also effective against various kinds of bacteria.[78] A successful synthetic procedure was described for



Scheme 2 Bioactive compounds synthesizing from primary alkylamine arylation.

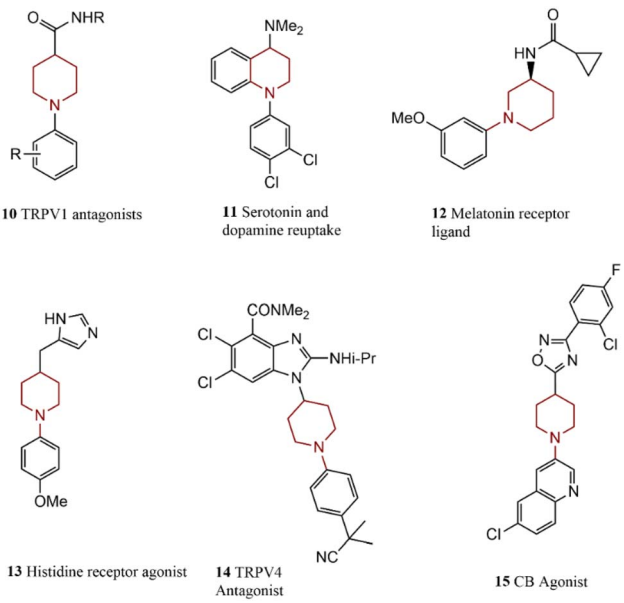


Scheme 3 More bioactive compounds synthesizing from primary alkylamines arylation.

generating ozenoxacin **9** through a C–N bond formation reaction catalyzed by Pd. Cyclopropanamine coupled to aryl bromide in the first step, followed by a Stille coupling reaction to reach the final product.[79] The chemical structure of these compounds is illustrated in Scheme 3.

2.2. Bioactive compounds containing piperidine

Piperidine is one of the most regular nitrogen heterocycles in pharmaceutical compounds.[80] The chemical structure of some medicinal compounds synthesized using piperidine is depicted in Scheme 4. Player and co-workers prepared a series of carboxamide piperidines **10** by using a weak base that avoids side product creation. The activity of these compounds in pain management has been approved.[81]



Scheme 4 Bioactive compounds containing piperidine.

Tetrahydroquinoline **11** is a potential anti-depressant medicine prepared by coupling aryl iodide with protected piperidine.[82] Melatonin receptor ligand **12**, as an agent for treating sleep disorders, was also synthesized *via* coupling of amide-substituted piperidine.[83]

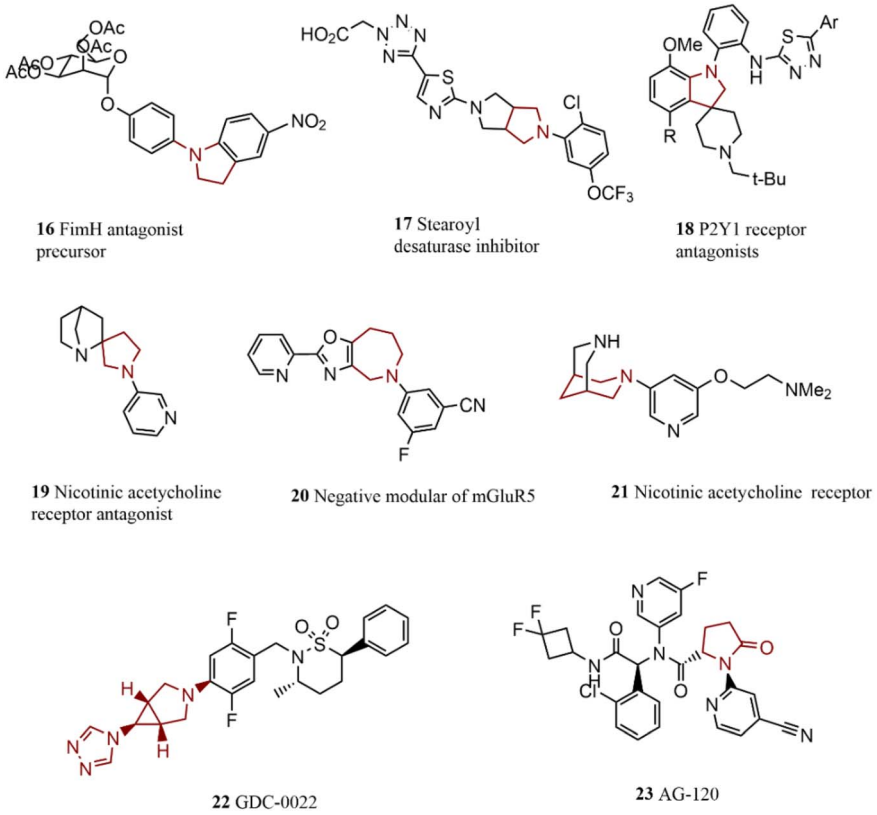
The Pd-catalyzed coupling of piperidine and 4-bromoanisole for preparing **13** acting as an H3 receptor agonist and potential agent against anxiety disorders and inflammation was presented.[23] The reaction of benzimidazole-based piperidine gave a TRPV4 antagonist **14**; its efficiency against lung injuries has been studied. Another research work; synthesized a CB2 agonist **15** as a pain management agent *via* a selective *N*-arylation reaction.[84]

2.3. Pharmaceuticals compounds containing pyrrolidine, pyrrolidine-2-one, azepine, and piperidine

The most abundant nitrogen-containing heterocycles in pharmaceuticals include pyrrolidine, pyrrolidine-2-one, azepine, and piperidine. The chemical structure of some synthesized compounds comprises them are illustrated in Scheme 5. Ernst *et al.* discovered an indoline-based heterocyclic compound **16** acting as an anti-urinary infection.[85] Lachance and co-workers synthesized an agent **17** for treating diabetes through bis-pyrrolidine coupling reaction by taking advantage of the protection process to achieve selectivity in C–N bond formation transformation.[86]

A P2Y1 receptor agonist **18** used for the treatment of thrombosis was prepared by employing spiro-indoline in the presence of a special catalytic system.[87] Moreover, a nicotinic acetylcholine receptor agonist **19** was also prepared by employing spiro-pyrrolidines. The therapeutic effect of this compound was studied in neurodegenerative and schizophrenia diseases.[88] Compound **20** was produced through the coupling of azepine, its activity in the treatment of peripheral was also explored.[89] Tomassoli and co-workers coupled a di-aza-bi-cyclic compound with 3-bromopyridine under microwave irradiation **21**, in which one nitrogen protection caused to mono-arylation reaction.[90] Compound GDC-0022 **22** is a potential inhibitor of orphan receptor γ (RORγ) containing two chiral centers; therefore, its production route needs to be mild.

Previously reported procedures, including *N*-arylation reactions catalyzed by Pd, suffered from problems, such as low yield, formation of undesired side products, and a very challenging purification process. Sirois and co-workers improved available Pd-catalyzed *N*-arylation methods by optimizing various reaction conditions, such as the kind of solvent and base that successed in overcoming drawbacks and achieve excellent conversion yields.[91] Popovici-Muller and co-workers discovered compound AG-120 **23** named ivosidenib,[92] as a specific IDH1 (the isocitrate dehydrogenase-1) inhibitor, a mutation that overexpresses in numerous kinds of cancers. The presented multistep synthetic process includes an *N*-arylation reaction in the last step. An enantiomerically pure product was achieved easily by crystallization. Due to the success of large-scale synthesis, further clinical investigations are in progress.



Scheme 5 Bioactive compounds containing pyrrolidine, azepine, piperidine, and pyrrolidin-2-one.

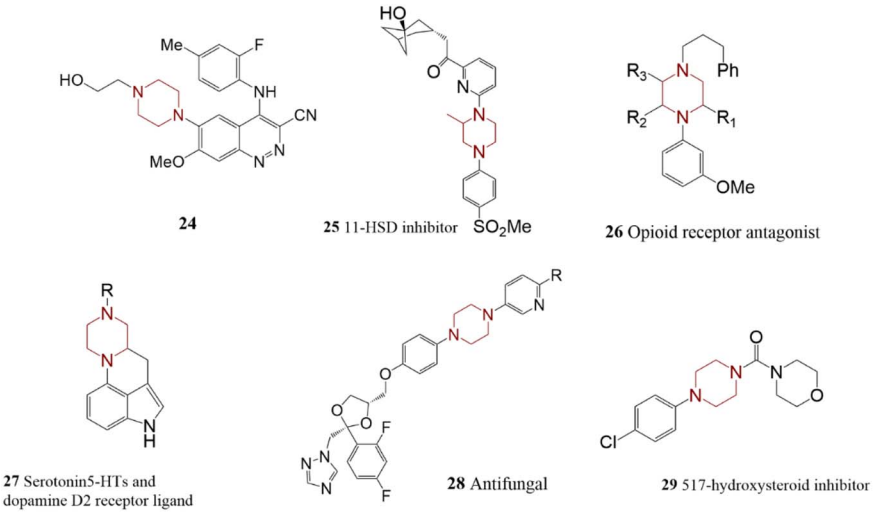
2.4. Bioactive compounds containing piperazine or morpholine

Another abundant nitrogen-contained heterocycle compound is piperazine which is found as a part of numerous biologically active materials. Piperazine rings often are functionalized in the N1- and N4-positions using protected or functionalized versions. Compound **24** (Scheme 6) was synthesized through the reaction of aryl bromide and piperazine in polar media and harsh reaction conditions as an intermediate in preparing anticancer treatment agents.[93] Park *et al.* reported functionalization of unprotected piperazine in less crowded nitrogen. Two C–N bond formation reactions were performed in the overall synthesis process. They also investigated the efficiency of product **25** in the treatment of type II diabetes.[94]

To couple piperazine in more crowded nitrogen, Carroll and co-workers had to protect it; in continuous, protecting agent was removed, and an opioid receptor antagonist **26** was achieved.[95] Compound **27** containing piperazine has exhibited acceptable activity against schizophrenia and Parkinson's disease. Kehler and co-workers succeeded in its synthesis through a cross-coupling reaction of 4-bromoindole and *N*-carbamate piperazine.[96]

In another research effort, the reaction of aryl bromide with a piperazine-based heterocyclic compound led to an antifungal agent **28** with excellent solubility properties.[97] An approved antileukemia agent **29** was prepared by harnessing urea-containing piperazine's C–N bond formation reaction in one step of its synthesis process.[98] Tang and co-workers synthesized some derivatives of piperazines such as compound **30** through the coupling of 4-bromobenzamide with functionalized piperazine by using a Pd catalyst. The product is a candidate for the treatment of type II diabetes by acting as MCD (malonyl-CoA decarboxylase) inhibitor.[99] Batey *et al.* prepared a fluoroquinolone as an antibacterial agent, by applying cyclopropane ring-fused piperazine.[100] These modifications improve the piperazine core's chemical and biological properties. In the same way, a potential B-Raf kinase inhibitor **31**, as an antitumor treatment candidate, was generated by Wang and co-workers *via* an *N*-arylation reaction.[101] The coupling of indoles with piperazinone led to the preparation of compound **32**, a potential triple reuptake inhibitor and anti-depression agent.[102] In another research effort, the reaction of 1,4-dibenzodiazepine and 4-iodobenzotrifluoride was employed for the synthesis of **33** by Tafesse and co-workers, and the effectiveness of the product as a painkiller was investigated.[103] In studies for discovering orally bioavailable treatment agents, Ku *et al.* succussed in the synthesis of venetoclax 5 **34**. The reported procedure comprising Pd-catalyzed Buchwald–Hartwig coupling reaction between aryl bromide derivatives and piperazine derivatives led to large-scale and high-yield products. Venetoclax was introduced as suitable medicine for the treatment of chronic lymphocytic leukemia.[104–106]

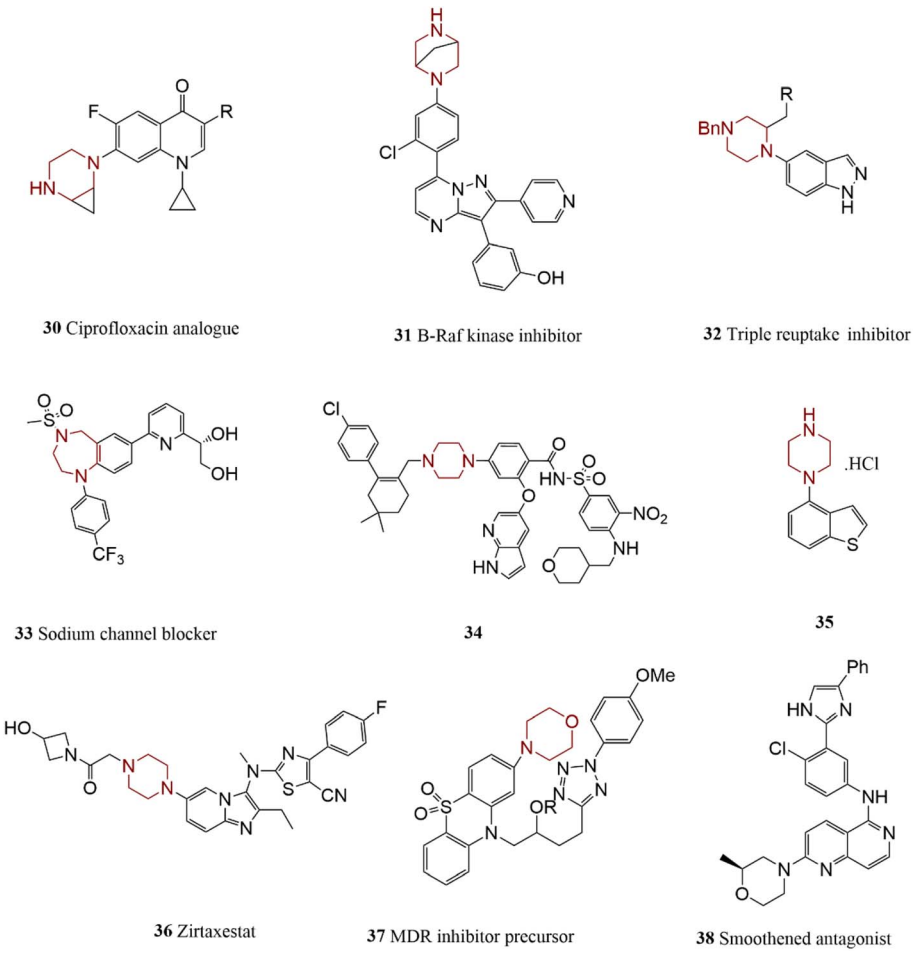
Brexpiprazole **35** is an approved drug for the treatment of schizophrenia.[107] Brexpiprazole was generated through an *N*-arylation reaction between 4-bromobenzo-[*b*]-thiophene and



Scheme 6 The chemical structure of some biologically active compounds synthesized *via* the coupling of piperazine.

piperazine employing Pd catalyst. This reaction was performed at a large scale with excellent yields of product.[108]

Lei and co-workers discovered a new process for the synthesis of autotoxin inhibitor ziritaxestat **36**, a potential drug for the treatment of chronic obstructive pulmonary. In this technique, through widespread screening, a piperazine-free base was used instead of *N*-Boc piperazine, omitting the re-protective step and improving the overall reaction efficiency



Scheme 7 Bioactive compounds containing piperazine or morpholine.

are considered the strengths of the presented method.[109] Morpholine is one of the other common heterocyclic moieties in commercially available drugs. The chemical structure of some biologically active compounds containing piperazine and morpholine has depicted in Scheme 7. A thiazine and morpholine-based N-heterocycle compound **37** was synthesized through C–N coupling reactions by harnessing a Pd-based catalyst. This new compound and its congeners were introduced as efficient potential anticancer agents.[110] In the exploration of medulloblastoma therapy, C–N cross-coupling of morpholine was applied to provide some antagonists molecules such as compound **38**.[111]

2.5. Bioactive compounds containing piperazinen and aniline

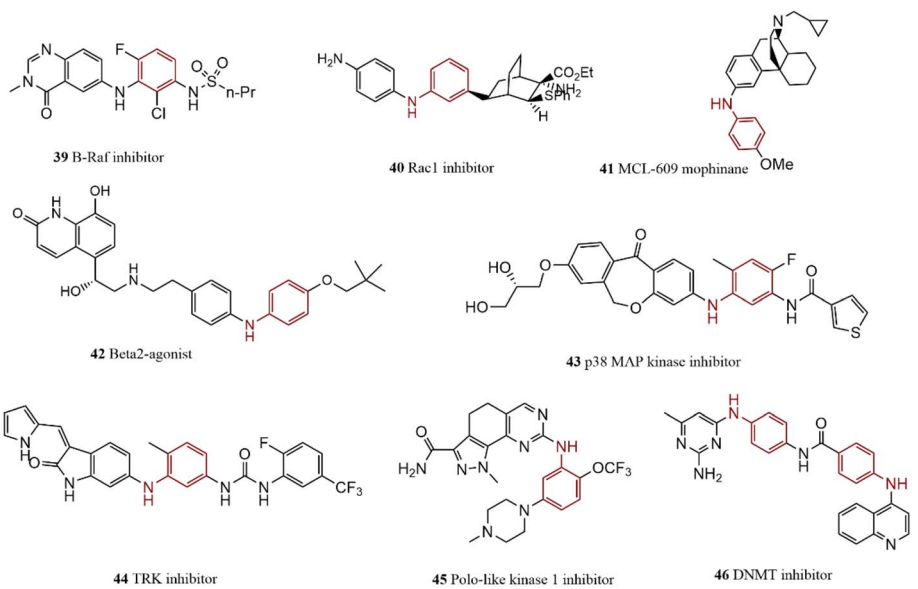
Several B-RafV600E inhibitors with excellent selective anticancer activity have been synthesized.[112] One of the most promising candidates **39** was generated *via* the reaction of functionalized anilines and quinazolinone by using Pd-catalyst. In another research report, cycloaddition and C–N coupling reactions were employed to synthesize potent Rac1 inhibitors, including norbornene unit **40**.[113] In this work, various stereoisomers of aniline were reacted with aryl iodide, and compound **41** was recognized as the most biologically active case. The relationship between chemical structure and biological activities was evaluated, and *p*-anisidine was coupled with different enantiomers of aryl triflate. The anticancer properties of these synthesized compounds were studied and compared. The chemical structure of more promising compounds, comprising functionalized anilines, has been depicted in Scheme 8, **42**.[114,115] This coupling reaction was harnessed to synthesize a series of potentially β2-agonists agents **43**, acting against respiratory disorders.[116] A candidate for inflammatory diseases treatment **44** was synthesized *via* coupling of a tricyclic core with diverse anilines, the product including a biologically stable dibenzoxepinones unit.[117] A serious TRK inhibitor was prepared, acting as a tumor growth inhibition factor **45**. Pd catalytic system was employed for the performance of aniline coupling.[118]

One alternative process of coupling heteroaryl amines with aryl halides is the reaction between hetero-aryl halides and anilines which is valuable when low conversion is achieved, or precursors are not available. A series of antitumor compounds were synthesized by Beria and co-workers by using the coupling of anilines with a hetero-aryl halide consuming a catalytic system including Pd species and specific ligands.[119]

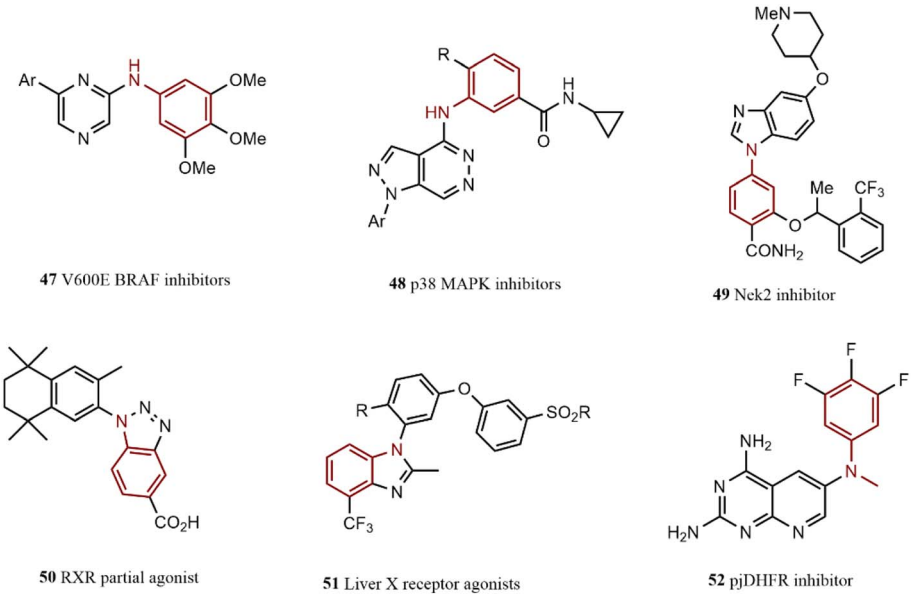
In searching for new antileukemia, DNMT inhibitor agents, compound **46** was discovered and synthesized through a multistep synthesis route including S_NAr reactions, low conversion, and harsh reaction conditions motivated researchers to employ a more efficient strategy. Therefore, Pd-catalyzed C–N cross-coupling reactions of 4-chloroquinoline and ethyl 4-aminobenzoate were carried out, and excellent yield of the desired product without any side reactions was achieved besides other benefits of this new synthesis technique.[120]

Pd-catalyzed arylation of 1,2-dichloropyrazine led to the generation of compound **47**, identified as a BRAF inhibitor agent.[121] Wurz and co-workers explored the reaction of pyridazine and substituted aniline; they introduced compound **48** as an anti-inflammatory agent.[122] This strategy can use to generate a large number of similar compounds. This route was applied to synthesize compound **49** *via* an *N*-arylation reaction; this compound acts as a Nek2 inhibitor.[123]

The reaction of *o*-nitroaryl iodide with substituted aniline to reach RXR partial agonist **50**, as an example of a new group of anti-diabetes drugs, was represented by Kakuta and co-workers.[124] Similarly, a liver X receptor agonist **51** was prepared by Bernotas and co-workers through an *N*-arylation reaction.[125] A series of pjDHFR inhibitors, potential anti-infection drugs, were synthesized by Gangjee and colleagues by employing a wide range of substituted *N*-methyl anilines coupling with aryl



Scheme 8 Bioactive compounds containing aniline.



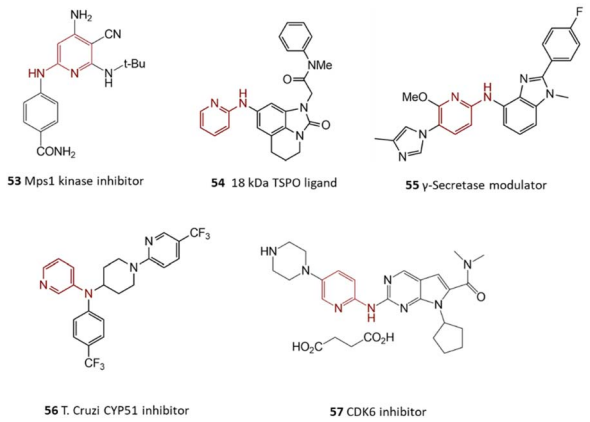
Scheme 9 Bioactive compounds containing *N*-arylation products.

bromide. Compound **52** was identified as the most potent analog in this series.[126] The chemical structure of some *N*-arylation products is depicted in Scheme 9.

2.6. Biologically active compounds containing 2-aminopyridine

Several biologically active compounds containing 2-aminopyridines generated by the harnessing of C–N cross-coupling reaction have been illustrated in Scheme 10. In studies about anti-cancer promising drugs, medicinal chemists have reached a group of selective Mps1 inhibitors produced by the selective reaction of substituted 2,4-diaminopyridine and methyl 4-iodobenzoate in which compound **53** was identified as the most effective analog.[127]

In another research effort, the reaction of 2-aminopyridine with polycyclic aryl bromide was investigated by Fukaya and coworkers. Product **54** was found as a promising agent for the treatment of psychiatric disorders.[128] Moreover, the final product of a coupling of pyridine and substituted-aryl bromide led to the formation of γ-secretase modulator **55** acting as an anti-Alzheimer drug.[129] Compound **56** was distinguished as one of the promising agents for the treatment of Chagas disease. Trisubstituted amine was synthesized by using commercially accessible precursors *via* a C–N cross-coupling reaction of secondary 3-aminopyridine and substituted aryl bromide catalyzed by Pd-based homogenous species. It was found that the order of steps and protecting processes in total synthesis are critical factors to achieving success in this synthesis strategy.[130] Ribociclib **57** was recognized as a CDK6 inhibitor agent and is used for the treatment of breast cancer in combination with aromatase inhibitors like letrozole. Various preparation techniques for its preparation are available; however, a significant development was archived *via* microwave-assisted C–N bond formation reaction between substituted piperazine and substituted 2-chloro-pyrimidine employing a Pd catalyst.[131] Abemaciclib **58** is an approved cyclin-dependent kinase (CDK) inhibitor that could be used against breast cancer cells. The industrial synthesis approach of abemaciclib contains a Pd-catalyzed Suzuki and a C–N bond cross-coupling reaction.

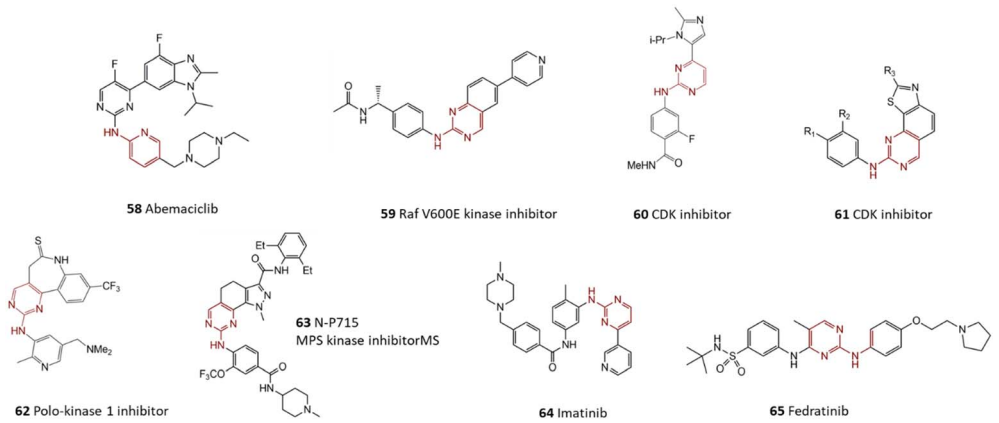


Scheme 10 Bioactive compounds containing 2-aminopyridine.

Screening various reaction conditions achieved excellent optimization that led good conversion yield of the final product.[132–134] In continuation, paying attention to the goals of green chemistry encouraged researchers to investigate abemaciclib synthesis by Pd-free catalytic systems and in more sustainable reaction conditions. Successful outcomes of magnetic cobalt-catalyzed C–N coupling in the abemaciclib preparation process have opened new horizons in the development of green chemistry in medicinal chemistry.[135,136]

2.7. Bio-compounds containing 2-aminopyrimidines

2-Aminopyrimidines coupled with aryl bromides have constructed some medicinal compounds. A series of B-Raf inhibitor



Scheme 11 Bioactive compounds containing 2-aminopyrimidines.

agents Vasbinder and co-workers were synthesized through the microwave-assistance coupling of 2-aminopyrimidine with enantiomerically pure aryl bromide, a more promising analog marked as **59**.[137]

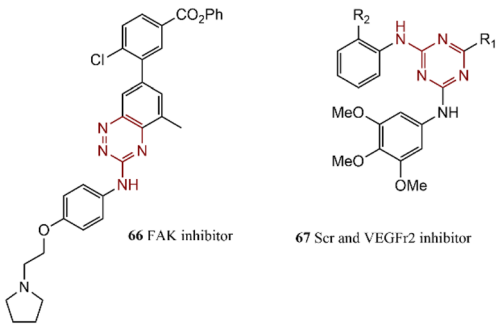
Jones and co-workers coupled some imidazole to pyrimidine, the products introduced as potential anticancer drugs, the structure of more efficient compounds are given in Scheme 11, **60**, **61**.[138,139] More examples of 2-aminopyrimidine containing heterocyclic compounds are represented. Duffey and co-workers generated some compounds with the tricyclic core as antitumor polo-like kinase inhibitors **62**.[140] Investigations have specified that coupling of aminopyrimidine with aryl bromide takes more advantages compared to other approaches such as condensing enamines and aryl guanidines. A Pd-catalyzed C–N bond formation reaction using Pd and supported ligands was used for the preparation of some tumor growth inhibitors such as **63**.[141]

In the same way, imatinib **64** was synthesized through a coupling reaction of aryl bromide and 2-aminopyrimidine in typical reaction conditions including the Pd complex, a solvent that can solve the reagents with excellent high reaction temperatures tolerate. Afterward, this synthesis route was improved as a two-step synthesis process using a lower Pd amount.[142] Fedratinib **65** was known as a Janus kinase 2 (JAK2) inhibitor, and its efficiency in the treatment of myelofibrosis has been approved.[143]

The chemical structure of fedratinib has depicted in Scheme 11. The synthesis procedure contains a Pd-catalyzed Buchwald–Hartwig amination reaction.[144] Further, the fedratinib synthesis in Pd-free conditions was investigated. Moreover, *in silico* evaluations exhibited the potential antitumor activities of some derivatives.[135]

2.8. Bioactive compounds containing 1,2,4-triazin-3-amine and 1,3,5-triazine-2,4-diamine

Nucleophilic substitution reaction is a traditional way to functionalize 1,3,5-triazine. Afterward, a more advanced technique including a C–N bond formation reaction was used to obtain some complex substituted 1,3,5-triazine. Microwave-assistance *N*-arylation of 1-bromo-2-nitrobenzene was carried out by Chen and co-workers for the generation of a group of FAK



Scheme 12 Bioactive compounds containing 1,2,4-triazin-3-amine and 1,3,5-triazine-2,4-diamine.

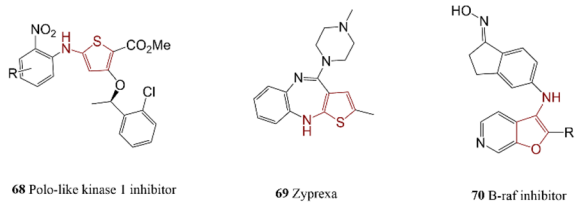
inhibitor candidates with angiogenic effect compounds **66** and **67** (Scheme 12).[145] Compound **67** was recognized as a potential VEGFR, Src kinase inhibitor, and anti-macular degeneration agent. It was prepared by cross-coupling 3-amino-1,2,4-triazine and aryl bromide.[146]

2.9. Bioactive compounds containing thiophene-2-amine and furan-2-amine

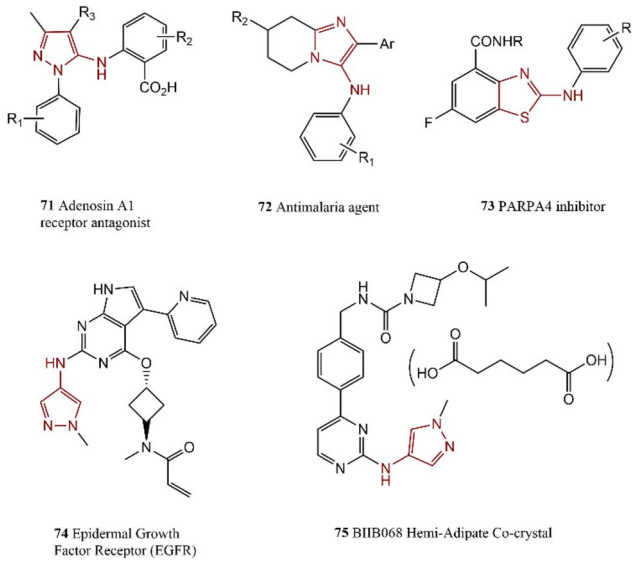
Sulfur-containing five-membered heterocycles amines are one of the more stable heterocyclics with low participation of nitrogen in resonance contribution, this makes them ideal for facile C–N cross-coupling reactions. Thiophene-based intermediates such as **68** were synthesized as PLK1 inhibitors under mild reaction conditions.[147] The employed procedure exhibited good selectivity and excellent overall efficiency; product **69** can be used potentially as anti-schizophrenia. Compound **70** was generated *via* the reaction of aminothiophene with 2-fluoronitrobenzene (Scheme 13).[148]

2.10. Bioactive compounds containing imidazole, pyrazole and thiazole

Benzimidazole, imidazole, and thiazole are five-membered rings with two heteroatoms that are found frequently in biologically active molecules. C–N cross-coupling reaction of 5-aminopyrazoles and aryl bromides in the presence of a weak



Scheme 13 Bioactive compounds containing thiophene-2-amine and furan-3-amine.



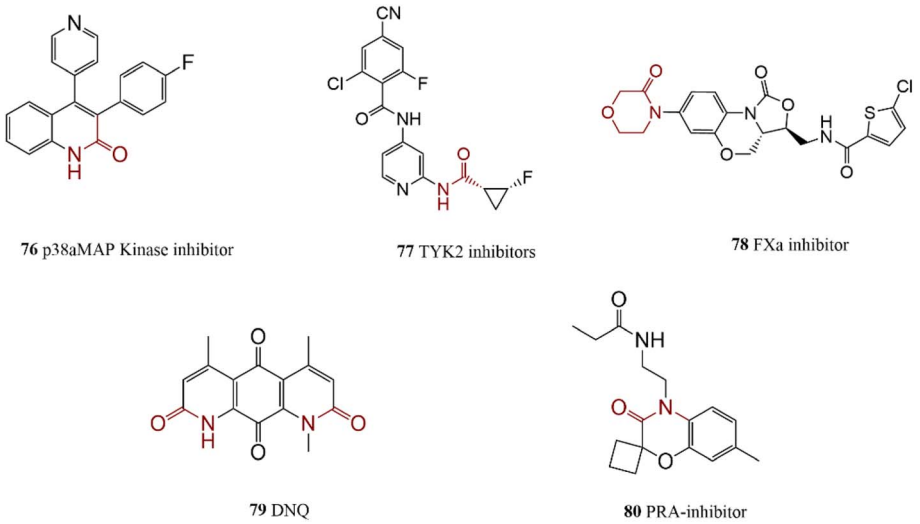
Scheme 14 Bioactive compounds containing imidazole, pyrazole, and thiazole.

base and supported ligand led to the preparation of some compounds such as **71** and **72** which potentially improved the renal function.[149]

2-(Arylamino)thiazoles and 2-aminothiazoles containing nitrogen and sulfur atoms are other abundant five-membered heterocyclic compounds in the field of medicinal chemistry. 2-Amino(benzo)thiazoles can directly couple to aryl halide by employing a suitable catalytic system.[150] In this regard, 2-arylaminobenzothiazoles **73** was synthesized as potent PARP14 inhibitors.[151] In another research report, an effective synthesis approach for the preparation of an inhibitor of Epidermal Growth Factor Receptor (EGFR) T790 M **74** was presented which can use as a potential treatment for lung cancer.[152] They employed palladacycle for the reaction of 1-methyl-1*H*-pyrazol-4-amine with a functionalized aryl halide. Li and co-workers synthesized BIIB068 **75**, a BTK (Bruton's Tyrosine Kinase) inhibitor that probably can act as a drug against autoimmune diseases.[153] The presented efficient method employed for coupling reaction of 1-methyl-1*H*-pyrazol-4-amine with substituted 2-chloropyrimidine (Scheme 14).

2.11. Bioactive compounds containing primary amide

A series of 3,4-diarylquinolinones was generated through primary amides coupling with aryl bromides and base-catalyzed aldol condensation.[154] Among synthesized compounds, **76** gave the most effectiveness in inflammation treatment. In a research project to find new TYK2 inhibitors as anti-inflammatory agents, medicinal chemists reached compound **77**.[155] In the final step of its multistep reaction syntheses process, primary amide was coupled to aryl bromide. In the presented procedure, the reaction was carried out under microwave heating by applying a Pd complex, supported ligand, and weak base. A series of potent anticoagulant drugs such as **78** was prepared,[156] similar to the previous report of cyclic amides and tricyclic oxazolidinone combination. The multistep synthesis contains Suzuki coupling, Miyaura borylation, and double ring closure including two intramolecular amidation reactions developed by Hergenrother and co-workers, and the synthesis of product **79** with potential anti-cancer activity was also reported.[157] Nonoyama and co-workers synthesized a new renin inhibitor candidate **80**.[158] Plasma renin activity (PRA) has a significant role in hypertension



Scheme 15 Bio-active compounds containing primary amide.

pathogenesis, and PRA-inhibitor decreases the danger of myocardial infarction (Scheme 15).

2.12. Bio-active compounds containing primary sulfamide

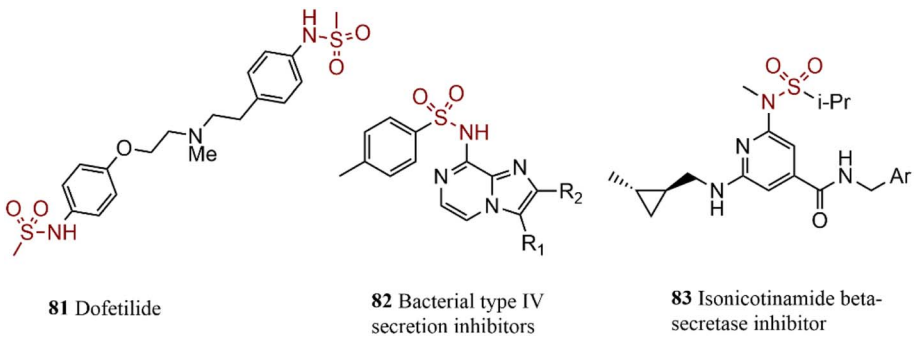
In the reported procedure, the benzoxazine core was generated through an intermolecular C–N cross-coupling reaction, after screening different reaction conditions, the reaction was performed in optimized conditions using Pd and Pt-based catalyst, xylene as a solvent, and K_2CO_3 as a base. The product dofetilide **81** is one of the FDA-approved antiarrhythmic medicine that was synthesized by Ruble *et al.* through a new procedure by employing Pd-catalyzed *N*-arylation reactions in two steps with an excellent yield of product at suitable industrial reaction conditions.[159] A group of 8-sulfamide imidazopyrazines was synthesized by coupling *p*-toluenesulfonamide with various heteroaryl chlorides in the presence of Pd salt and heterogeneous ligands. Product **82** was introduced as a potent antibacterial agent.[160] Secondary sulfonamides were coupled to dichloroisonicotinate in the initial steps of the total synthesis of nicotinamide **83**, a candidate for Alzheimer's treatment (Scheme 16).[161]

2.13. Bio-active compounds containing urea

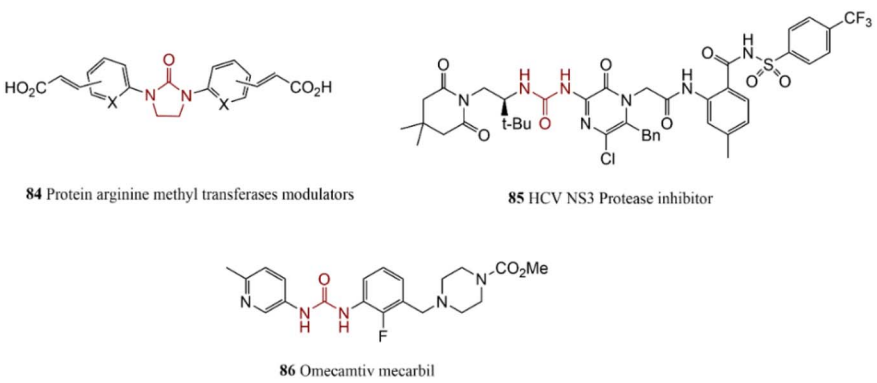
A group of modulators of PRMTs (protein arginine methyltransferases) was prepared by C–N cross-coupling of symmetrical ureas inhibitor **84**. This excellent process was used for the synthesis of a structural unit of complex protease inhibitors. This method contains the coupling of chloropyrazinone with monosubstituted ureas using a Pd catalyst and specific bidentate ligands.[162] Compound **85** was generated by applying this reaction to couple urea, as an inhibitor of hepatitis C virus (HCV) NS3 protease.[163] Omecamtiv mecarbil **86** is unsymmetrical diaryl urea that was generated by Buchwald and co-workers in a two-step selective C–N coupling reaction using Pd salt and dialkylbiaryl phosphine ligand as a catalyst (Scheme 17).[164]

2.14. Bioactive compounds synthesized *via* the coupling of protected amine

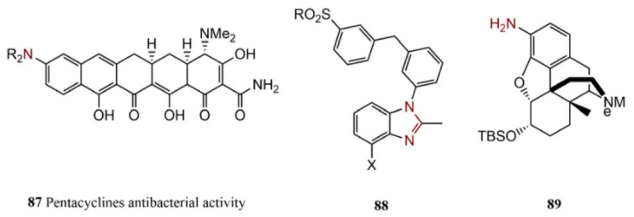
The protected aniline is used to prevent undesirable reactions during the synthesis process and can be removed in the final step. A group of 9-aminopentacyclines including **87** was prepared by Xiao and co-workers using Pd-catalyzed to connect polycycle amines where the protected group was removed in the last stage.[165] Pd-catalyzed C–N cross-coupling reaction between benzophenone imine and aryl triflates was introduced as a successful strategy to gain amine derivatives. Herein compound **88** is a precursor of the total synthesis of an antiheroin addiction.[166] Similarly, **89** was generated to reach an opioid receptor antagonist.[167] *N*-Arylation of LHMDS, lithium bis(trimethylsilyl)amide, applying a Pd-based catalyst, and dialkylbiarylphosphines ligand is known as one of the practical ways to synthesize primary anilines (Scheme 18).



Scheme 16 Bio-active compounds containing primary sulfamide.



Scheme 17 Bio-active compounds containing urea.



Scheme 18 Bioactive compounds synthesized *via* the coupling of protected amine.

2.15. Bioactive compounds synthesized *via* *N*-arylation of LHMDS

Heteroarylamine was provided by the reaction of 2-bromopyridine and LHMDS in the initial step of total synthesis of compound **90** which was recognized as a c-Met inhibitor with potential activity against cancer cells.[168] Heteroarylamines **91** and **92** were also generated by harnessing the reaction of 2-chloropyridines and LHMDS. Products are important precursors for the synthesis of valuable anticancer agents.[169,170] The prodrug of antitumor seco-CBI-indole **93**, containing a stable cyclic carbamate, was synthesized through primary aniline preparation by Pd-catalyzed reaction of Ph_3SiNH_2 and LHMDS.[171] Lasmiditan **94** is an approved anti-migraine drug synthesized employing benzophenone in a C–N cross-coupling reaction in the presence of a Pd-catalyst. The following hydrolysis attained primary aniline.[172] Technique solved the difficulties of primary aniline preparation besides the merits of mild reaction conditions.[173] Product **95** exhibited selective 5-HT1F agonist activity with minimum side effects (Scheme 19).

2.16. Bio-active compounds containing indazol, indole, and imidazole

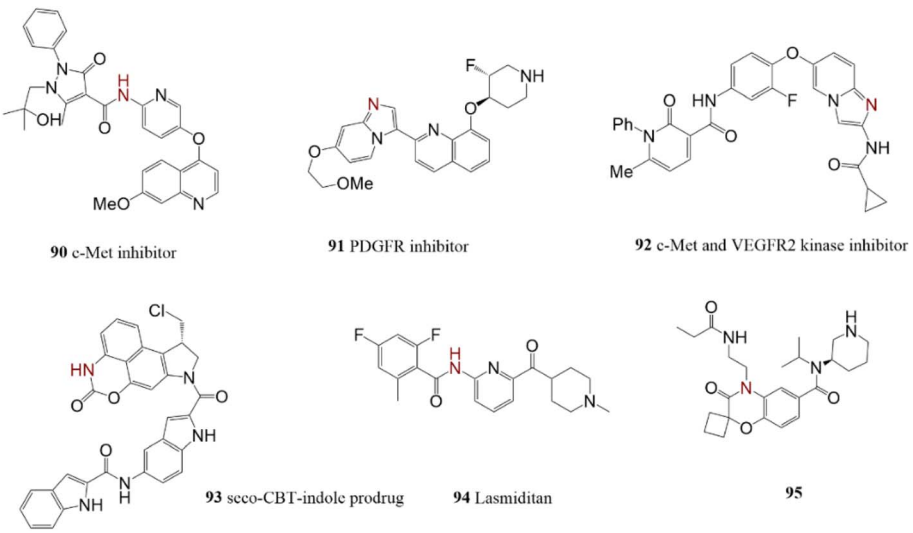
In this regard, protected (*s*)-pyrrolidine-2-carboxamide was coupled to bis-aryl chloride derivative applying Pd catalyst during the synthesis of pibrentasvir **96**. This compound was recognized as an effective anti-viral drug and employ in the treatment of hepatitis C patients.[174]

Pibrentasvir was commercialized in 2017 under the trade name of Mavyret. Qian and co-workers presented a method for the reaction of substituted aryl bromide with *N*,*N*-disubstituted hydrazines to produce 2-*N*-substituted imidazolines **97** as a candidate for the treatment of type II diabetes.[175] Tomoo and co-workers described the successful C–N coupling of indole and aryl bromides by Pd catalyst. The product belongs to cytosolic phospholipase A2α inhibitors acting as an anti-inflammatory agent.[176] Nilotinib **98**, an approved drug for chronic myelogenous leukemia, has been prepared by arylation of unsymmetrical imidazoles catalyzed by a Pd-based catalytic system.[177]

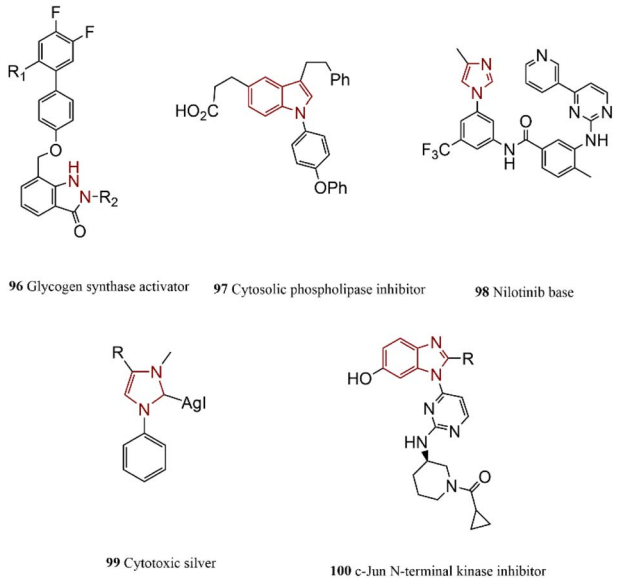
Traditional S_NAr reactions in the presence of Cu catalyst suffered from some disadvantages such as poor selectivity and low product yield that were resolved by this new strategy using imidazole in excess and aryl halide in low amounts. Regioselective C–N coupling of functionalized imidazole gave **99** in an excellent conversion method, an anti-leukemia drug.[178] In another report, a series of benzimidazole derivatives were formed by a selective *N*-arylation reaction between 4-chloropyrimidine and benzimidazole, the final product **100** is known as a candidate for the treatment of neurodegenerative diseases (Scheme 20).[179]

2.17. Bioactive compounds synthesized *via* *N*-arylation of sulfur-containing five-membered rings

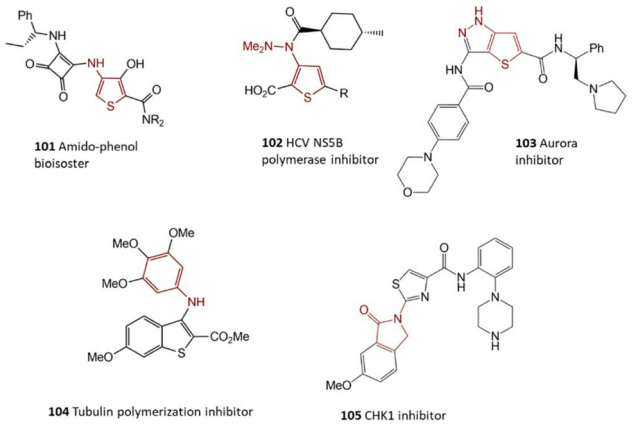
The five-membered rings containing sulfur and nitrogen are found in many heterocyclic drugs. These compounds are also synthesized *via* C–N coupling reactions. Potent anti-inflammatory agent **101** was synthesized using the coupling of aryl bromide and benzophenone imine.[180] In the same way, Canales and co-workers described the C–N coupling of benzophenone hydrazone alkyl hydrazines with halothiophenes.[181] According to these reactions, a potential HCV inhibitor 102 and



Scheme 19 Bioactive compounds synthesized *via* *N*-arylation of LHMDS.



Scheme 20 Bio-active compounds containing indazol, indole, and imidazole.

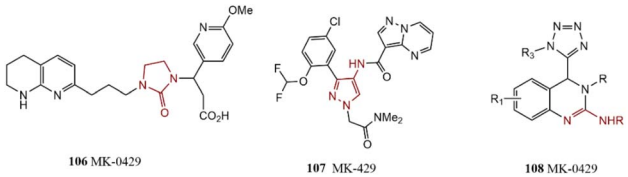


Scheme 21 Bioactive compounds synthesized *via* *N*-arylation of sulfur-containing five-membered rings.

anticancer drug 103 were produced.[182] C–N coupling of benzothiophene at the C3-position was also reported for the preparation of compound **104**.[183] Moreover, 2-bromothiazole was applied in a C–N coupling reaction where coupled with amides to generate a biologically active compound **105** (Scheme 21).

2.18. Bio-active compounds containing other N-heterocyclic

MK-0429 is a potent pan-integrin inhibitor that successfully passed human clinical trials and has been introduced as anti-prostate cancer and anti-osteoporosis agent. A short and efficient synthesis method comprising the carbon–nitrogen bond formation process has been reported to reach **106**.[184] GDC-4379 is a well-known JAK1 inhibitor for the therapy of asthma. To synthesize, Stumpf *et al.* discovered a new method comprising condensation, nitro reduction by $NaBH_4$ in the presence of copper, amidation, and C–N bond cross-coupling of pyrazole.



Scheme 22 Bio-active compounds containing N-heterocyclic.

Their reported method delivered GDC-4379 crystals **107** with a high yield of product and an easy purification process.[185] A series of 4-tetrazolyl-substituted 3,4-dihydroquinazoline derivatives were prepared through cascade cross-coupling of azide-isocyanide and cyclization reaction in the presence of a Pd catalyst. Compound **108** was recognized as an efficient anti-breast cancer cell agent *via* broad biological investigations (Scheme 22).[186]

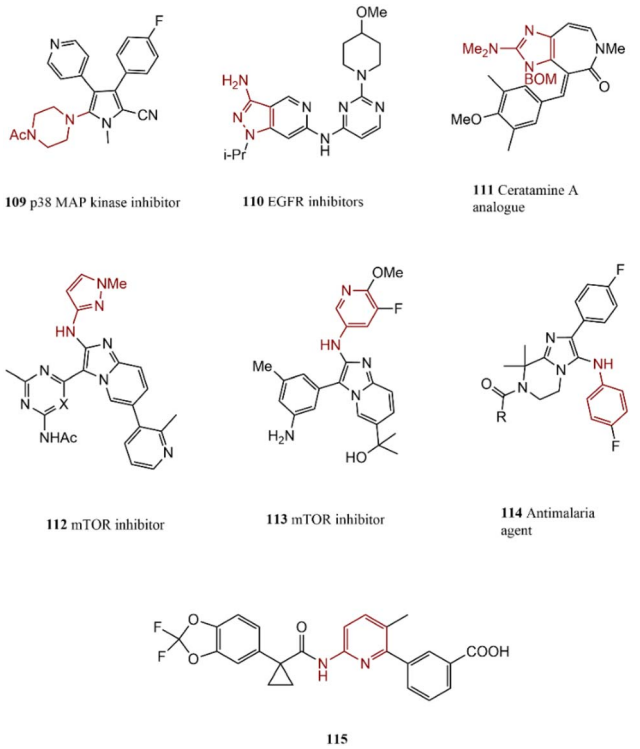
2.19. Biologically active compounds synthesized using LiHMDS

C–N coupling reactions of halo-imidazoles, -pyrazoles, -pyrroles, and their derivatives have attracted much attention due to the usefulness of the final products in medicinal chemistry; however, such these reactions suffer from some difficulties because of their free NH group. A p38 map kinase inhibitor **109** was synthesized by Bullington and co-workers as an anti-inflammatory agent. Pd catalysts promote the C–N coupling reaction of 2-bromopyrrole and acetylpiperazine in excellent yields.[187] In another research report, epidermal growth factor receptor (EGFR) inhibitors such as **110** were synthesized through two following C–N coupling steps.[188]

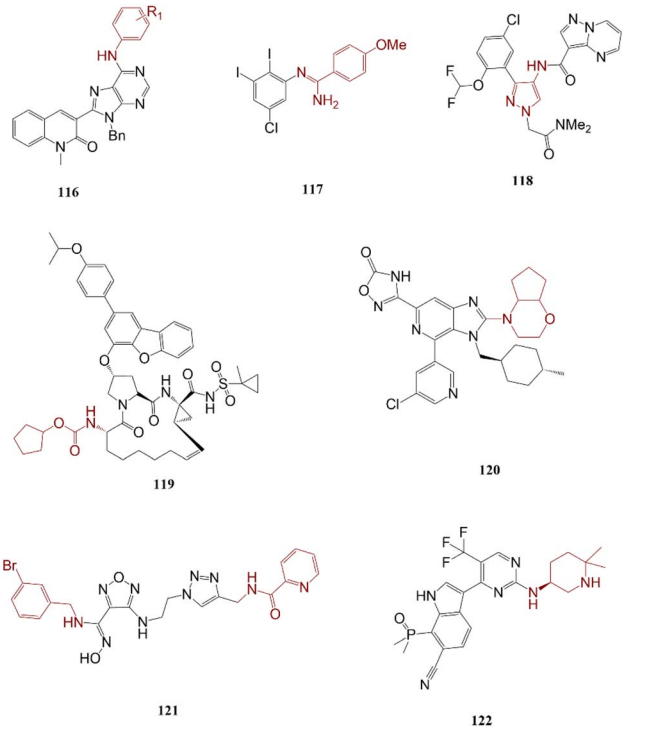
N-Arylation reactions can be performed in haloimidazole in every position;[189] for example, Roberge and co-workers presented a new procedure for the preparation of ceratamine A **111**, a potential oncology medicine, *via* *N*-arylation of fused imidazole in the presence of Pd catalytic system by using LiHMDS/Ph_3SiNH_2 as ammonia source for conversion of 2-chloroimidazole to its primary aniline.[190] Pd-catalyzed *N*-arylation of imidazopyridines led to the formation of tumor inhibitor drugs including **112** and **113**.[191] Moreover, a series of promising antimalarial agents **114** was synthesized *via* C–N cross-coupling reaction. Compound **115** is a small-molecule CDK4/6 inhibitor approved for the therapy of advanced-stage breast cancer. The Buchwald–Hartwig amination is an essential step in its synthesis process; LiHMDS was applied to the generation of protected amine without any impurities and by-products. Chloropicoline derivative formed a C–N bond *via* coupling with amide by employing a Pd catalyst and xantphos ligand (Scheme 23).[192]

2.20. More biologically active compounds constructed from amination reaction

Larghi and co-workers reported a development in Liebeskind–Srogl cross-coupling reaction in the presence of Pd catalysts as a facile process to access compounds containing purine. Compound **116** was identified as a biological active against PC-3



Scheme 23 Biologically active compounds synthesized using LiHMDS.



Scheme 24 The chemical structure of biologically active compounds is constructed from an amination reaction.

and MDA-MB231 cancer cell lines.[193] A series of 2,3-diiodinated *N*-arylbenzimidamide derivatives was synthesized through a highly regioselective Buchwald–Hartwig amination reaction. Compound **117** was introduced as the most effective derivative as a potential compound for MDM2 and MDM4 activity-related disease therapy.[194] Its large-scale synthesis comprises two main steps C–N bond formation and ring-closing metathesis reaction.

Furaprevir **118**, **119** was found as a safe and effective drug in clinical trials phases I and II.[195] Compound **120**, MK-4688, is an HDM2–p53 protein–protein interaction inhibitor whose generation procedure involves a metal-catalyzed C–N bond formation reaction.[196]

One of the well-known inflammatory autoimmunity treatment options is an immunomodulatory enzyme, indoleamine 2,3-dioxygenase 1 (IDO1). IDO2 is its other homolog with a lower expression. However, researchers have revealed that IDO1/IDO2 dual inhibitors have very good *in vitro* inhibitory activity (IC_{50} = 112 nM) and it was introduced as a potential drug for rheumatoid arthritis. **121** was prepared on a large scale through a double C–N bond formation reaction in high yields.[197]

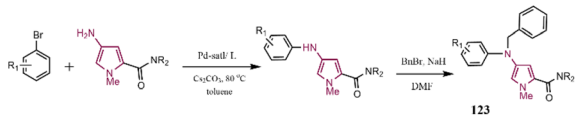
CDK7 has a role in transcription and the cell cycle of cancer cells; therefore, research on CDK7 inhibitors and their action mechanism has attracted much attention. A synthesis technique to gain SY-5609 **122** was described based on C–N bond formation reactions. SY-5609 is an FDA-approved CDK7 inhibitor agent with high selectivity and metabolic stability.[198]

Zang and co-workers discovered a macrocyclic ATP citrate lyase inhibitor, which is a metabolic enzyme acting in fatty acid and cholesterol synthesis. Therefore, ATP citrate lyase inhibitor agents were identified as a candidate for the treatment of several metabolic diseases and malignancies. The biological evaluation confirmed the excellent binding affinity of this compound, leading to good inhibitory activity. Its synthesis contains a ring-closing C–N bond formation reaction.[199]

Fibroblast growth factor receptors (FGFRs) have a bold pattern in numerous cancers. Currently, the effectiveness of selective FGFRs-inhibitors is being evaluated in clinical trials as potential ant-cancer agents. Compound **122** was generated easily through a C–N bond formation reaction as an effective anti-FGFR agent (Scheme 24).[200]

2.21. Examples of N-contain pharmaceutical drug molecules synthesis routes

Herein, the most important pragmatical compounds synthesized through C–N cross-coupling reaction have been presented; however, considering the importance of reaction sequence and conditions some examples of synthesizing various pharmaceutical drug molecules of N-contain heterocyclic compounds have been reviewed. Developing synthesized methods to get effective drug compounds have converted them into a hot topic and their importance has excited researchers to investigate C–N bond formation as one of the most employed reactions.[201–205] Tanatani and co-workers reported the arylation of N-protected 3-amino pyrroles to synthesize a five-membered heterocycle. The synthesized compound **123** was identified as an anti-tumor agent (Scheme 25). The employed catalytic system consists of Pd salt, a phosphorus ligand, and Cs_2CO_3 as

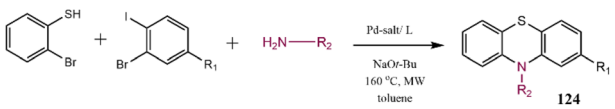


Scheme 25 Synthesis route for preparation of functionalized N-contain heterocyclic.

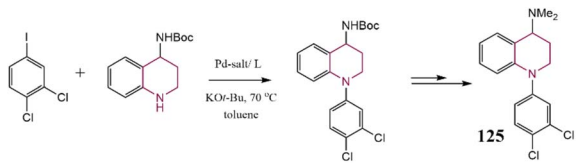
the base leading to a good yield of product.[206] In another research report, synthesis methods were described for the production of nitrogen-based heterocycles **124** *via* coupling primary alkylamines in the presence of a Pd-based catalyst. In the presented strategy, 2-bromothiophenol, a primary amine, and a functionalized 1-bromo-2-iodobenzene were coupled together by using a single catalyst (Scheme 26), further this procedure was applied to synthesize a series of disubstituted phenothiazines.[207]

Tetrahydroquinoline **125** was synthesized by employing *N*-Boc-protected piperidine, the synthesis route has been depicted in Scheme 27. This compound was recognized as an antidepressant agent.[208]

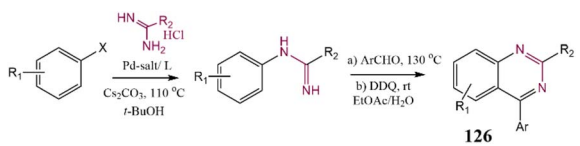
By using a catalytic system consisting of $Pd_2(dba)_3$, ligand, and base, a series of alkyl and aryl amidines were coupled with aryl chlorides, bromides, and triflates. Notably, monoarylated products were gained as the main product by applying *N*-unsubstituted amidines. After optimization examination, the free base conditions were found as the best conditions. This procedure was used for the one-pot synthesis of 4-arylquinazolines, this transformation has been illustrated in Scheme 28. In the second step, electrocyclization was performed by DDQ



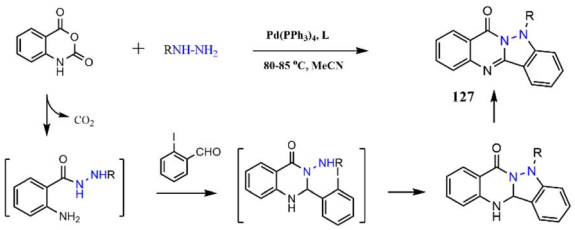
Scheme 26 Synthesis rout for preparation of a series of phenothiazines.



Scheme 27 Synthesis route for the preparation of a functionalized tetrahydroquinoline.



Scheme 28 Synthesis route for the preparation of a 4-arylquinazolines.



Scheme 29 Schematic of one-step protocol synthesis of indazolo quinazolinones derivatives.

oxidation, and 4-quinazolines **126** were generated in moderate yield. Several 4-arylquinazolines derivatives with diverse electronic natures were successfully prepared.[209]

In another research report, varied indazole quinazolinones were prepared through a one-step protocol. This process started with a reaction of the isatoic anhydride and hydrazine, generating an intermediate formed by trapping CO_2, and further cyclization with *o*-iodobenzaldehyde led to the creation of quinazolinone. In the next step, Pd-catalyzed intramolecular coupling occurred. The final fused heterocycle **127** was obtained by air-oxidation reaction (Scheme 29).[210]

3. Conclusions

Over the past few decades, compounds containing nitrogen have been in high demand, which has encouraged the progress of C–N bond formation reactions catalyzed by metals in line with the production reactions of amines. This review article focused on published works that have demonstrated the academic and industrial valuable use of C–N coupling reactions in aniline derivatives synthesis. Numerous research areas on this topic have been attractive; however, herein application of this transformation in medicinal chemistry has been highlighted. It is anticipated that this article will help medicinal chemists working on C–N coupling reactions synthesize more potent structures with higher yields and lower side effects in treating either simple or more complicated diseases. We hope this review will inspire chemists to improve *N*-arylation conditions of more challenging synthetic reactions to reach novel high-tech pharmaceutical products. This inspires researchers to investigate the possibility of performing the C–N cross-coupling reaction on a large scale. The new wave of reaction performance in mild reaction conditions using lower-cost materials will lead to more eco-friendly and economic advantages in industrial processes. Palladium and traditional phosphine ligands are poisonous and precious; therefore, Pd-precursors with optimized reaction conditions or palladium-free catalysts have been widely considered. Moreover, studying and investigating the chemical structures of compounds with desirable biological activity can support medicinal chemists in new drug design processes.

Conflicts of interest

There are no conflicts to declare.

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