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Review Article

Synthesis of Pharmacologically Active Indazoles and Its Analogues: A Review

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Abstract

Studies on heterocyclic compounds are an evergreen branch of organic chemistry and attract the attention of chemists working not only in the field of natural products but also in synthetic chemistry. Indazole and its derivatives are one of the most vital heterocycles in drug molecules. Diversely substituted indazole derivatives have gained considerable attention in the field of medicinal chemistry due to their versatile biological activities. This mini review aims to abridge the recent (2011-2021 till date) advances in various methods for the synthesis of indazole derivatives. Moreover, the current developments in the biological activities of indazole-based compounds are also presented.

Keywords: Indazole; Synthesis; Biological activities**.**

Introduction

Heterocycles are found in many natural products and biologically active compounds. Seven out of the top ten selling pharmaceutical drugs are Nitrogen heterocycles. Nitrogen-containing heterocycles are having a lot of importance due to their broad spectrum of pharmacological and biological activity. Structure and reactivity of small molecules, macromolecules knowledge is required in drug discovery and the ways in which molecules interact by means of both covalent and non-covalent recognition during signal transfer.

Indazoles are heterocyclic molecules, structurally pyrazole attached to benzene ring. Structurally Indazole has 10 π electrons, two nitrogen atoms presented in five-membered rings. Due to π electrons delocalization, it exhibits 3 tautomeric forms, i.e., 1*H*-Indazole, 2*H*-Indazoles, 3*H*-Indaoles as presented in **Fig. 1.** It acts as pyridine as well as pyrrole dual behavior. Indazole is generally considered as 1H-Indazole, the other two are potential tautomers.

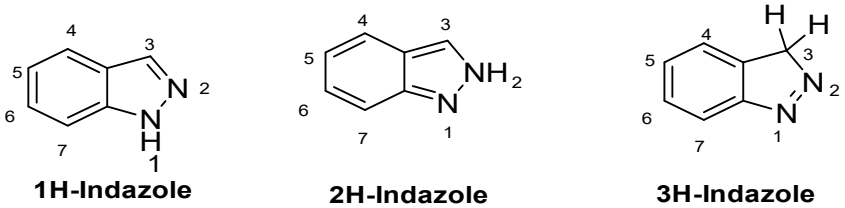


Fig. 1: Tautomeric forms of Indazole

The tautomeric form equilibrium between 1*H*-Indazole, 2H-Indazole in ground state as well as the excited state. Because of the difference in energy gap between the tautomers (**Fig. 1**), the 1*H*-tautomer (the benzenoid form **1a**) predominates in the gas-phase, solution and solid state is usually more stable 2.3 Kcal mol^{-1} than the corresponding 2*H*-forms (the quinonoid form **1b**). Both tautomeric forms can be identified by using solid state NMR-NQR spectroscopy. Indazole is a weaker base is having p*Ka*=1.31 but stronger acid is having p*Ka*=13.86. The dipole moment of the 2H-Indazole is more than the 1*H*-Indazole (**Table 1**).

Table 1: Basicity and dipole moment comparison of indazole tautomers.

Physical technique	1-methyl-1*H*-indazole	2-methyl-2*H*-indazole
Basicity (pK_b)	0.42	2.02
Dipole moment (D)	1.50	3.4

Unsubstituted indazole and its derivatives exist as a dimeric form, trimeric form due to the intramolecular hydrogen bonding between N-H…N (**Fig. 2**).

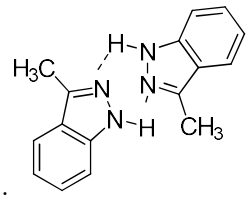
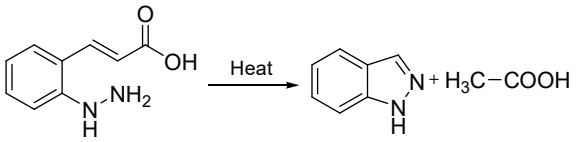


Fig. 2: Dimeric crystal structure of 3-methyl-1*H*-indazole

Indazoles were first synthesized by Nobel laureate Emil Fisher in the early 1880's from o-hydrazino cinnamic acid (**Scheme 1**).[1] The proceeds via the thermal cyclization of *o*-hydrazinocinnamic acid to yield 1*H*-Indazole. He made the initial attempts for the preparation of anhydride of o-hydrazinocinnamic acid, unexpectedly he got many products, out of these products he found one of the products is having without oxygen, later confirmed as Indazole.



Scheme 1: First report of synthesis of Indazole.

Pharmacological activity of indazoles

Indazole compounds are having a lot of importance due to their broad range spectrum of pharmacological and biological activity. Many researchers and academicians in the chemistry field, often "chemistry" is often used in a much narrower way and is synonymous with synthetic chemistry as a tool for the discovery of drugs. Drug discovery requires knowledge of the structure and reactivity of small molecules and macromolecules and the ways in which molecules interact by means of both covalent and non-covalent recognition during signal transfer.[2]

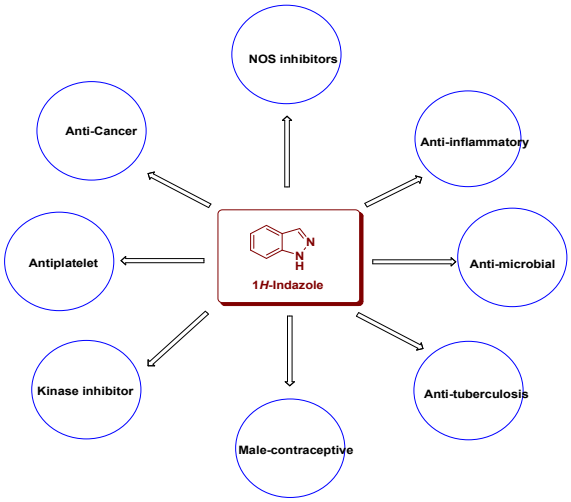


Fig. 3: Graphical presentation of pharmacological activities of indazoles.

Numerous publications, reviews, more than 400 patents or patent applications are reported due to their indazole core mediated privileged biological activity3-5. These compounds exhibit different biological activities such as nitric oxide synthase (NOS) selective inhibitors, effective agents to anti-inflammatory, anti-cancer, anti-microbial, kinase inhibitors, male-contraceptive (**Fig. 3**).

The Indazole motif is clearly identified as a highly valuable heterocyclic scaffold for the drug development of new biologically active compounds.

These are promising agents for nitric oxide synthase (NOS) selective inhibitors, especially selective NOS-II inhibition. NOS enzymes are divided into three classes, which are neuronal NOS (nNOS, type-I), inducible NOS (iNOS, Type-II), endothelial NOS (eNOS, Type-III) are responsible for the generation of nitric oxide from L-arginine[6]. The Indazole motif inhibits the biological effects of Nitric oxide, its role on the central nervous system, and influences processes connected with pain perception, convulsive behavior, and memory. Moreover, indazole derivatives can be used as estrogen receptor agonists, selective Farnesold-X-receptor agonists, and as anti-neoplastic agents (**Fig. 4**).[4-5]

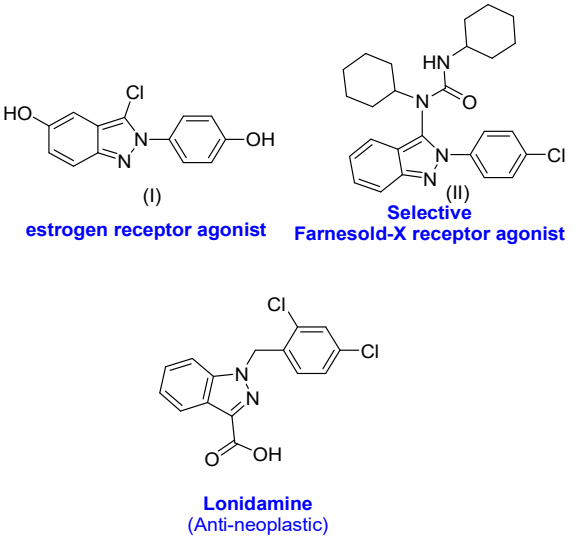


Fig. 4. Bioactive indazole derivatives.

Indazole moiety can be considered as a surrogate of the adenine of ATP, competitive kinase inhibitors be used for the identification of new ATP2. Indazole motifs are interesting targets to be used as protein kinase inhibitors belonging to the transferase group and allow the phosphorylation of the serine, tyrosine, and threonine residues of protein substrates. In addition, the indazole motifs were used as potential drug molecules. Some of the potent drugs having an indazole skeleton were presented below.

Anti-inflammatory activity

The indazole-based nonsteroidal anti-inflammatory drug benzadac (**Fig. 5**)[6], one of the widely used NSAIDs for muscular and joint pains.

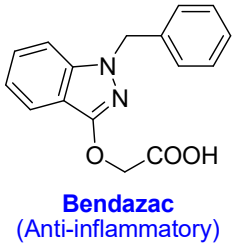


Fig. 5: Structure of anti-inflammatory drug benzadac.

Antiemetic activity

The serotonin 5-HT_3 receptor antagonist granisetron (**Fig. 6**) is used as an antiemetic. It mainly acts to decrease the activity of vagus nerve, that activates the vomiting center of the medulla oblongata.[7]

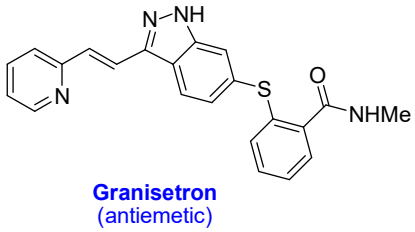


Fig. 6: Indazole containing antiemetic agent.

Anti-cancer activity

Axitinib is used in the treatment of renal cell carcinoma (RCC), Pazopanib is also classified as a Tyrosine kinase inhibitor also used in the treatment of RCC and advanced soft tissue carcinoma under the trade name of Votrient.[8-9] Chemistry has several different roles in the discovery and development of most new anti-cancer drugs. Improved understanding of the cellular, molecular and genetic bases of cancer have increased the number of drug targets available. During the first half of the twentieth century, compounds isolated from the mustard family were used for cancer chemotherapy. The first indazole family of such kind is Niraparib, Pazopanib, and Axitinib (**Fig. 7**).[10-12]

Moreover, many of the indazole-based heterocycles with a sundry mechanism of action have been patented by many pharmaceutical companies. For example, Samumed LLC, patented the compound (**I**) (**Fig. 5**), for the inhibition of the Wnt- signaling pathway. These motifs were developed for application in disorders due to dysregulation of the Wnt pathway like cancer, inflammatory and

neurological diseases.[13] Indazole analogs that also target the Wnt pathway were also explored by the research team of the University of Utah Research Foundation. The investigation of this team reveal that compound (**II**) (**Fig. 8**) was more potent than known inhibitors of the β-catenin/Wnt pathway[14] by Cell proliferation inhibition assay studies on colon cancer cell line.

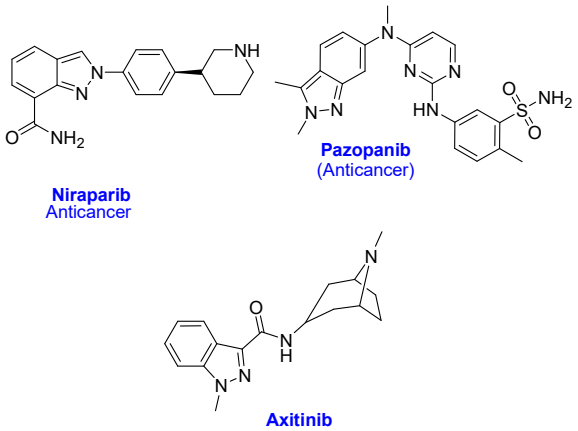


Fig. 7: Indazole containing anti-cancer drugs

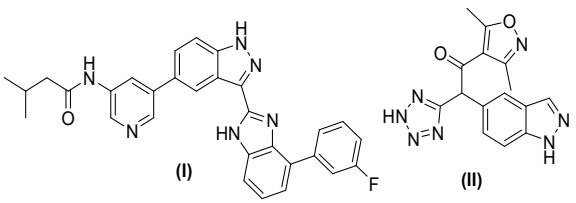


Fig. 8: Wnt signalling pathway modulated Indazole motifs patented by Samumed LLC

Antibacterial activity

A series of 1*H*-indazole and 1*H*-indole equivalents were invented by Actelion Pharmaceuticals as anti-bacterial agents. All these compounds comparatively exhibited more potency compared to ciprofloxacin across all assays.[15] Among these (R)-4-(4-fluoro-5-(((1S,2S)-2 (hydroxymethyl) cyclopropyl)buta1,3-diyn-1-yl)-1H-indazol-1-yl)-N-hydroxy-2-methyl-2- (methylsulfonyl) (Figure 9) was found to be the most active with excellent MIC values against diverse bacterial strains.

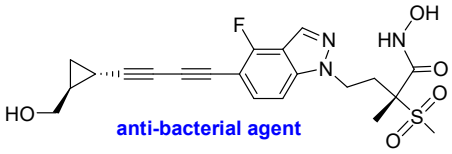


Fig. 9: Indazole scaffold patented by Actelion as anti-bacterial agent.

These broad range of biological applications of indazole and its derivatives attracted the attention of synthetic organic chemists around the world and encouraged them towards the development of efficient and novel protocols towards the construction of pharmacologically significant indazole scaffolds. Indazoles motifs are rarely available in nature; only three products have been isolated from a natural source such as Nigellicine,[16a,b] Nigeglanine,[16c] and Nigellidine[16d] **(Fig. 10).** Thus the synthesis of indazole motifs has engrossed substantial interest because these three naturally occurring compounds can be used in the treatment of various diseases.

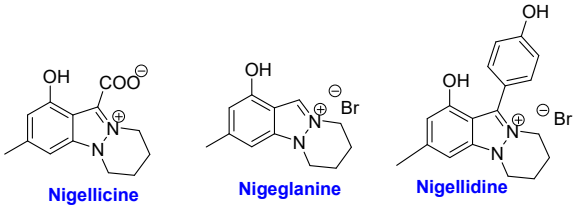
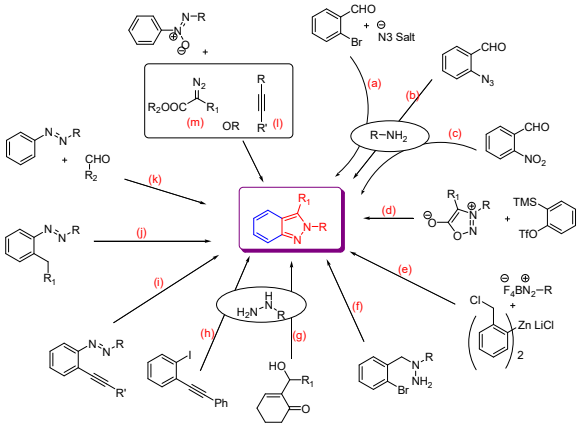


Fig. 10: Selected naturally occurring indazoles.

General synthetic methods of Indazole

Many synthetic routes are available for the synthesis of 2*H*-indazoles (**Scheme 2**).[17-24]



Scheme 2: Literature available methods for the synthesis of 2H-Indazoles.[17-24]

In route (a) one-pot three-component condensation reaction of 2-bromo-benzaldehyde, primary amine, and salt of azide to provide Indazoles. In this approach, copper-catalyzed C-N bond formation between the aryl bromide and the azide and N-N bond formation between the imine and the azide.[17] In route (b), condensation reaction between 2-azidobenzaldehyde and primary amine via *in situ* imine formation to afford indazoles.[18] In route (c) intramolecular reductive amination between 2-nitro benzaldehyde with a primary amine *to form N*-(2-nitrobenzylidene) anilines followed by *N*-hetero-cyclization to form indazoles.[19-20]

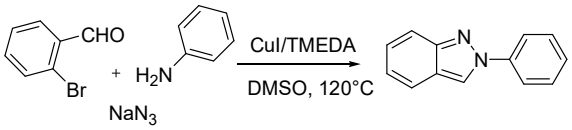
In other method route (d) [3+2] dipolar cycloaddition reaction between arynes and sydnones in the presence of TBAF to afford Indazoles.[21] Route (e) involves the reaction between aryldiazonium salt and bis(2-chloromethylaryl) zinc reagents to get Indazoles.[22] Route (f) reported Song *et al* intramolecular amination reaction of *N*-aryl-*N*-(*o*-bromobenzyl)-hydrazines in the presence of $Pd(OAc)_2$/dppf and NaO^{t}Bu as a base to yield Indazoles.[23] Route (g) reported by Kim research group cross-coupling reaction of aryl hydrazine with the Baylis-Hillman adduct to provide 2*H*-indazole.[24]

Another method (route h) reaction between 2-halophenyl acetylenes and aryl hydrazine to produce Indazoles. Route (i) Indazoles synthesized through palladium-catalyzed intramolecular C-N bond formation of *o*-alkyne azoarene. Route (j) denotes iodine mediated intramolecular oxidative annulation *o*-alkylazoarenes to yield Indazoles. Route (k) Rh (III)-catalyzed reaction between azobenzene and aldehyde with subsequent cyclization and aromatization. Route (l & m) tandem C−H alkylation and intramolecular decarboxylative cyclization of azoxy compounds with diazo esters in the presence of Rh(III)-catalyst. Some selected reactions for the synthesis of 2*H*-indazoles are described here.

Transition Metal Catalyzed synthesis of Indazoles

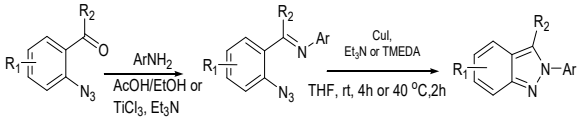
Cu catalyzed synthesis

Kumar *et. al.* has reported the synthesis of 2-aryl-2*H*-Indazoles through one-pot, three-component condensation reactions of 2-bromobenzaldehydes, primary amines, and sodium azide by using CuI (10 mol%)/TMEDA (10 mol%) as a homogeneous catalyst system in DMSO at 120°C for 12h resulted in good yields (**Scheme 3**)[25]. The protocol proceeds through condensation and Cu-catalyzed sequential C-N and N-N bond formation In contrast to existing methods, this method has several advantages like i) no need of special preparation of starting materials, as all the starting materials 2-bromobenzaldehydes, primary amines, and NaN_3 are readily available; ii) Easy separation of the final products, 2H-indazoles, by column chromatography due to large difference between the R_f values of the starting materials products and products; iii) broad substrate scope with a high functional group tolerance.



Scheme 3: Synthesis of 2-aryl-2*H*-Indazoles.

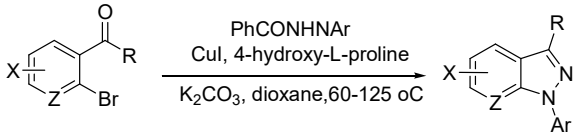
Rao group reported an efficient protocol to access of a wide variety of multi-substituted 2-aryl-2H-indazole through the formation of the N(1)–N(2) bond by Cu mediated intramolecular amination reaction of N-aryl-imines with azide activation by copper. Initially, the N-aryl-imines were obtained by the reaction of 2-azidobenzaldehyde with anilines (**Scheme 4**).[26] This method has been found to be generally useful for the preparation of a broad variety of 2*H*-indazole motifs some of which are difficult to make *via* conventional approaches. By employing a combination of CuI and tertiary amines, the Rao group developed a highly efficient catalyst system for this intramolecular *N–N* bond formation reaction.



Scheme 4: Syntheis of 2-aryl-2H-indazole

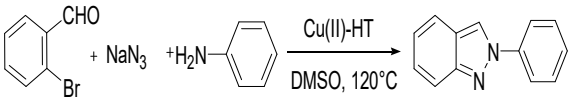
Ma and group described an effective protocol towards the synthesis of 1-aryl-1*H*-indazoles by the coupling reaction between *N*-Acyl-*N*′-substituted hydrazines and 2-bromoarylcarbonylic compounds using CuI/4-hydroxy-l-proline as catalyst at 60–125 °C (**Scheme 5).**[27]Conventional methods for preparing *N,N*-diarylhydrazines involve oxidation of diaryl amines and subsequent reduction of the resulting aryl diazoniums. This approach

normally suffers from multistep synthesis, harsh reaction conditions, and less yields. To overcome this drawback Ma and group described that *N*-acyl-*N*'-substituted hydrazines were excellent coupling partners, which could regioselectively react with aryl iodides and 2-bromoarylcarbonylic compounds under mild conditions for synthesizing 1-aryl-1*H*-indazoles.



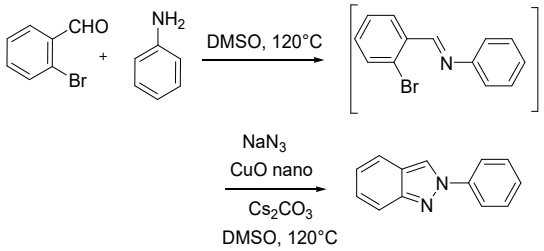
Scheme 5: Synthesis of 1-aryl-1*H*-indazoles

Reddy *et. al* described that a synthesis of 2*H*-indazoles was achieved from 2-bromobenzaldehydes, primary amines, and sodium azide through consecutive condensation, C–N and N–N bond formations copper catalyst (**Scheme 6**).[28] A number of 2*H*-indazoles derivatives were prepared by using Cu(II)–HT catalyst. Most of the previous methods exhibit several drawbacks, such as the formation of regioisomers, requirement of additives (expensive phosphine ligands, *etc.*), and low functional group tolerance, and also these methods require several steps to synthesize the starting materials. Furthermore, most of these methods are homogeneous in nature. Unlike the previous methods, this method proceeds *via* novel heterogeneous Cu–Al hydrotalcites (Cu^{II}–HTs) offer numerous advantages, such as being inexpensive and recoverable, and having a simple workup procedure by using readily available starting materials or precursors.



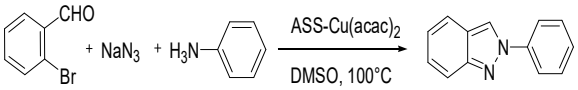
Scheme 6: Cu promoted synthesis of 2*H*-indazoles.

Khatun *et.al* have described a nano catalyzed CuO (2.5 mol%) of one-pot synthesis of 2-bromobenzaldehydes, primary amines, and sodium azide with Cs_2CO_3 as a base in DMSO at 120 °C to yield 2*H*-indazoles (**Scheme 7**).[29] The drawbacks in the previously reported methods such as the generation of a regio-isomeric mixture, requirement of pre-synthesised starting materials, use of ligands, high catalyst loading and longer reaction times, failure in large scale syntheses were addressed by this protocol. This method has certain advantages such as low catalyst loading, high yields, shorter reaction time and broad substrate scope tolerating a wide variety of functional groups, etc., and can be applicable to large scale synthesis also.



Scheme 7: Nano catalyzed CuO promoted synthesis of 2*H*-indazoles**.**

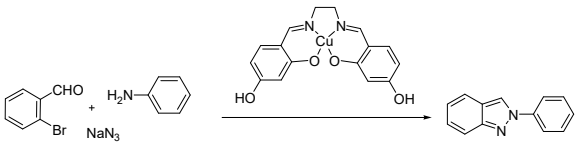
Sodhi and co-workers reported one-pot multicomponent synthesis of 2*H*-indazole from 2-bromobenzaldehyde, primary amines, and sodium azide through consecutive *C-N* and *N-N* bond forming reaction in the presence of silica/starch-M(acac)n (**Scheme 8**).[30] Among various catalysts, covalently anchored $Cu(acac)_2$ onto amine functionalized silica/starch composite [ASS-$Cu(acac)_2$] was found to be the most active and recyclable catalyst for the one-pot three component synthesis of 2*H*-indazoles via consecutive *C–N* and *N–N* bond formations. This protocol has certain advantages like is free from foul-odourous thiols and easy workup, eco-compatible and practical. The catalyst was found to be highly active and could be recycled for four consecutive runs without significant loss of activity.



Scheme 8: Silica/starch-M(acac)n catalyzed of 2*H*-indazoles**.**

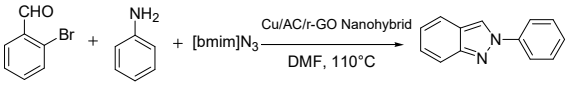
Sharghi *et. al.* reported the air stable, one-pot multi-component condensation of 2-bromobenzaldehyde, primary amine with sodium azide by using a highly reusable support-free Cu(II)–salen complex at 120°C to yield 2*H*-indazole (**Scheme 9**).[31] We report our attempts to develop *C—N* bond forming reactions using a mononuclear Cu(II)–salen complex as an inexpensive, efficient and versatile catalyst. This method is a highly active, air-stable, and versatile procedure for *C—N* bond

forming reactions for the synthesis of N-aryl compounds under nearly solvent-free conditions. This system shows several advantages including commercially available starting materials, easy purifications, and nearly solvent-free and mild conditions.



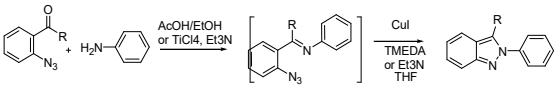
Scheme 9: Cu(II)–Salen complex catalyzed synthesis of 2*H*-indazole.

Behrouz group described multicomponent condensation of 2-bromobenzaldehyde, amines, [Bmim]N_3in the presence of Cu/amino clay/reduced graphene oxide nanohybrid (Cu/AC/r-GO nanohybrid) as a heterogeneous catalyst at 110°C in DMF to afford 2*H*-indazoles with good yields (**Scheme 10**).[32] This is a straightforward and highly efficient synthesis of 2H-indazoles *via* one-pot three component reaction of readily available 2-bromobenzaldehydes, structurally diverse amines, and [bmim]N_3 as the green source of azide in the presence of Cu/aminoclay/reduced graphene oxide nanohybrid (Cu/AC/r-GO nanohybrid).The protocol proceeds through a consecutive condensation, *C–N* and *N–N* bond formations using Cu/AC/r-GO nanohybrid. Cu/AC/r-GO nanohybrid proved to be a thermal and chemical stable nano catalyst with the ease of handling, recovery and excellent reusability properties. The mild reaction conditions, low catalyst loading, short reaction time, using available precursors, ease of operation, minimization of by-products and chemical wastes, and reusability of the catalyst make this method attractive and suitable for synthesis of different 2H-indzaole derivatives.



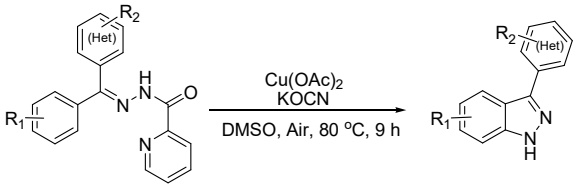
Scheme 10: (Cu/AC/r-GO nanohybrid) catalyzed synthesis of 2*H*-indazoles.

Hu *et. al.* have reported an intramolecular amination reaction of 2-azidobenzaldehyde with a primary amine in the presence of CuI–TMEDA/TEA to yield a wide range of Indazoles (**Scheme 11**).[33]



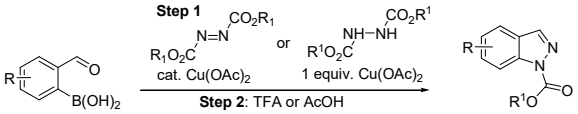
Scheme 11: CuI–TMEDA/TEA mediated synthesis of indazoles.

Ding and group[34] described a traceless directing group assisted Cu-mediated oxidative intramolecular *C-H* amination of hydrazones towards the construction of 1H-indazoles (**Scheme 12**). Various 1*H*-indazoles were obtained *via* traceless directing group assisted Cu promoted oxidative intramolecular *C-H* amination of hydrazones. Using picolinamide as a traceless directing group and the inexpensive Cu salts as the oxidant, it has been proved to be an efficient method for the direct construction of N-heterocycles.



Scheme 12: Cu promoted synthesis of 1H-indazoles.

Very recently, Jirgensons and coworkers reported[35] an effective $Cu(OAc)_2$ catalyzed one pot two step protocol for the synthesis of 1*N*-alkoxycarbonyl indazoles by the reaction of 2-formylboronic acids with diazadicaboxylates followed by acid or base induced ring closure *via* the *C–N* bond formation step (**Scheme 13**). The protocol required a stoichiometric amount of copper(II) acetate for the *C–N* bond formation step. The method is based on readily available building blocks and can be performed at relatively mild reaction conditions.

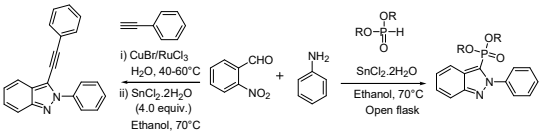


Scheme 13: $Cu(OAc)_2$ catalyzed synthesis of 1*N*-alkoxycarbonyl indazoles

Sn catalyzed synthesis

Sudhapriya *et. al.*[36] reported the cyclization of $SnCl_2.2H_2O$ mediated-coupling followed by reductive cyclization of 2-nitrobenzaldehyde, primary amine, and phenylacetylene or dialkyl phosphonates to afford 3-Alkynyl-2-Aryl-2*H*-Indazole or 2-aryl-2*H*-indazole-3-phosphonates (**Scheme 14**).[36] The

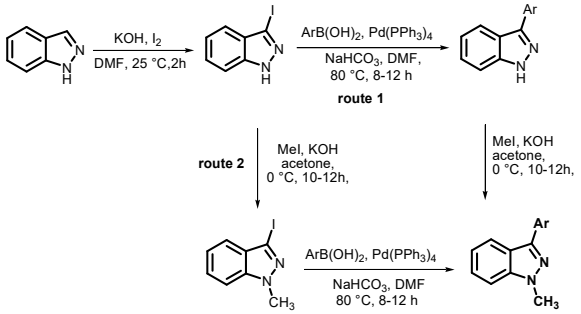
same group reported the synthesis of 2H-indazole derivatives through *N-N* bond formation using $SnCl_2.2H_2O$ as eco-friendly catalyst. The proceeds under, mild reaction conditions, one-pot operation, open flask condition, transition metal free reaction, and have wide substrate scope with good yields, thus proceeds with high atom economy *via* the formation of α-aminophosphonates followed by the generation of indazole ring through *N-N* bond formation eliminating water as a by-product.



Scheme 14: Synthesis of3-Alkynyl-2-Aryl-2*H*-indazole or 2-aryl-2*H*-indazole-3-phosphonates

Pd catalyzed synthesis

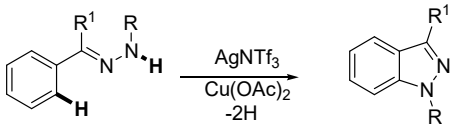
Recently our group has reported an efficient Pd catalyzed synthesis of *N*-methyl-3-aryl indazoles by two dissimilar approaches starting from 1*H*-indazole *via* iodination, Suzuki-Miyauracoupling and methylation reactions (**Scheme 15**).[37] The prepared indazole derivatives exhibited moderate anticancer activity.



Scheme 15: Pd catalyzed synthesis of *N*-methyl-3-aryl indazoles

Ag catalyzed synthesis

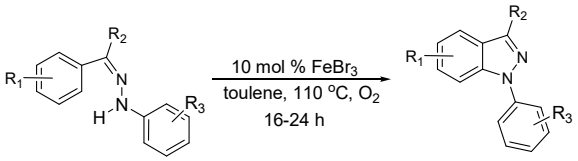
Lee and co-authors reported the construction of 1*H*-indazole by a Ag(I)-promoted intermolecular oxidative *C–H* amination. The method involves the effective amination for the construction of a variety of 3-substituted indazoles that are otherwise difficult to be prepared by other means of *C–H* aminations (**Scheme 16**).[38] The beginning mechanistic investigation suggest that it proceeds through an outer-sphere electron transfer mediated by the employed Ag(I) oxidation . This protocol was found to be predominantly proficient for the synthesis of various medicinally relevant 1*H*-indazoles having amide ester, olefin, ketone, -CF_3, and aryl groups at 3-position.



Scheme 16: Ag(I)-catalyzed synthesis of 3-substituted indazoles

Fe catalyzed Synthesis

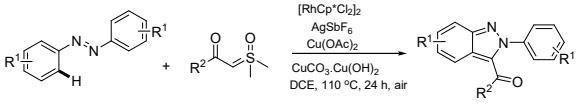
Bao group described[39] a simple and effective $FeBr_3/O_2$ promoted C–H activation/C–N bond formation reactions to access numerous 1,3-diaryl-substituted indazoles from aryl hydrazones under mild conditions (**Scheme 17**). In this method an inexpensive, abundant, and less toxic iron is used in place of precious metals, especially for practical large scale preparation. The molecular oxygen was used as an eco-friendly oxidant and the inexpensive and nontoxic iron(III) as the catalyst, this protocol is effective for direct construction of *N*-heterocycles and also can be used for industrial applications.



Scheme 17: Fe promoted synthesis of1,3-diaryl-substituted indazoles

Rh cayalyzed synthesis

Kim *et al* reported[40] a high level chemo selective synthesis of 3-acyl (2H)-indazoles from azobenzenes and sulfoxonium ylides *via* the Rh(III)-catalyzed C–H functionalization and intramolecular annulation reactions **(Scheme 18).** This protocol allows the generation of an array of C3-acylated (2H)-indazoles with high level of chemoselectivity and functional group tolerance.

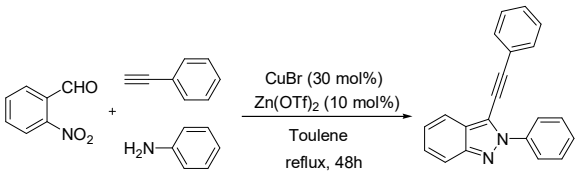


Scheme 18: Rh(III)-catalyzed synthesis of 3-acyl (2*H*)-indazoles.

Bimetallic-catalyzed synthetic methodologies

Cu/Zn cayalyzed synthesis

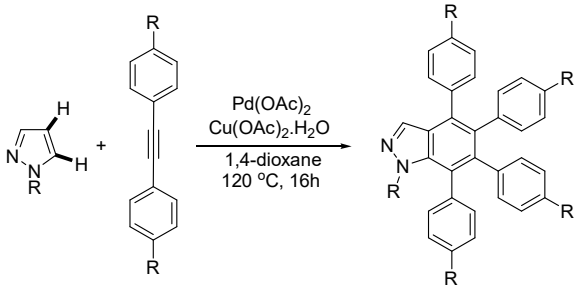
Saikia *et. al.* reported the synthesis of 3-(Arylethynyl)-2*H*-indazoles from one-pot three-component condensation reaction between 2-nitroarylaldehydes, primary mines and alkynes in the presence of zinc(II) triflate and copper(I) bromide (**Scheme 19**).[41]



Scheme 19: Synthesis of 3-(Arylethynyl)-2*H*-indazoles.

Pd/Cu cayalyzed synthesis

Joo and group[42] described an efficient synthesis of fluorescent indazoles *via* Pd-promoted benzannulation of Pyrazoles with internal alkynes. In this approach indazoles were obtained from readily available pyrazoles *via* the reaction of the C−H bonds of the heterocyclic ring. This convergent strategy leads to the development of tetra aryl indazoles as new fluorophores (**Scheme 20**).

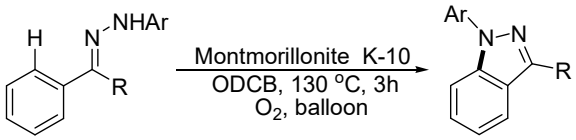


Scheme 20: Pd catalyzed synthesis of indazole.

A catalytic amount of $Pd(OAc)_2$ along with a stoichiometric oxidant, $Cu(OAc)_2 \cdot H_2O$, enabled the construction of indazoles possessing different substituents on the benzene ring. Complementary to many cyclization methods that form heterocyclic rings from functionalized arenes, this new strategy based on the direct conversion of simple diazoles is useful for providing benzo-fused heteroarenes having multiple substituents on the benzene ring.

Transition Metal Free synthesis

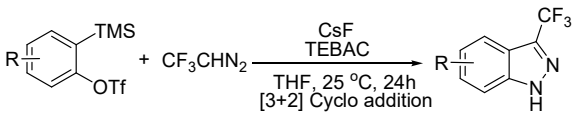
Kim *et al* described[43] an effective transition-metal-free protocol towards the construction of 1*H*-indazoles from aryl hydrazones at 130 °C througha chronological intramolecular nucleophilic cyclization and an aerobic oxidation path in the presence of montmorillonite K-10 in 1,2-dichlorobenzene (**Scheme 21).** This is an efficient method for the synthesis of 1H-indazoles from aryl hydrazones in the presence of montmorillonite K-10 in ODCB at 130 °C in a short time.



Scheme 21: Synthesis of1*H*-indazoles from arylhydrazones.

By Cyclo addition reaction

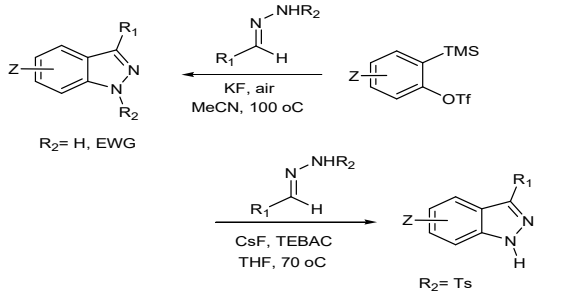
Ma and group reported[44] the simple method towards the synthesis of potential biologically active 3-trifluoromethyl-indazoles by an efficient [3 + 2] cycloaddition of *in situ* generated arynes and CF_3CHN_2 in the presence of fluoride in conjunction with TEBAC. The arynes were *in situ* generated from *O*-(trimethylsilyl)aryl triflates and CF_3CHN_2 acts as a 1,3-dipole in the cycloaddition with alkynes **(Scheme 22).** This reaction provided a general and practical protocol for the synthesis of 3-trifluoromethyl-indazoles under mild reaction conditions.



Scheme 22: Synthesis of 3-trifluoromethyl-indazoles.

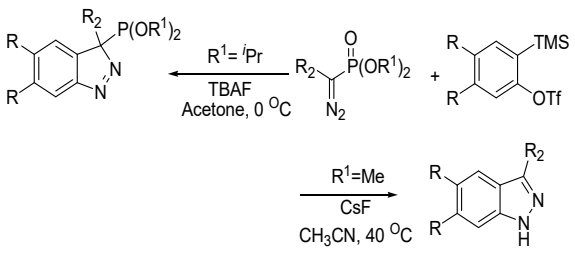
Shi *et al*[45] described an efficient a [3 + 2] annulation approach from arynes and hydrazones to access 1*H*-indazoles. Under suitable reaction conditions, N-tosylhydrazones afford 3-substituted

indazoles either *via in situ* generated diazo compounds or through an annulation/elimination process where as the N-aryl/alkylhydrazones leads to 1,3-disubstituted indazoles by an annulation/oxidation process (**Scheme 23**). These methods allow for indazoles bearing a more diverse combination of substitutions at the 1- and 3-positions compared with the previous discoveries in aryne reactions to indazoles. The introduction of aryl and vinyl groups have been successful, and the introduction of alkyl groups has been partially resolved.



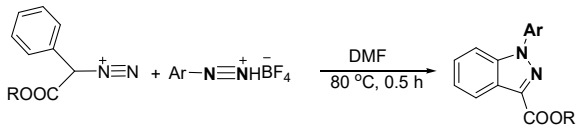
Scheme 23: Synthesis of1,3-disubstituted indazoles.

Peng and coauthors[46] reported the primary results on the efficient synthesis of 3-Alkyl/aryl-1*H*-indazoles and 3-alkyl/aryl-3*H*-indazole-3-phosphonates *via* a 1,3-dipolar cycloaddition reaction between α-substituted α-diazo methyl phosphonates and arynes under mild reaction conditions. This protocol involve introduction of both aryl and alkyl group at C3 position of the indazoles. The phosphoryl group controlled the selectivity for the synthesis of 1H- and 3H-indazoles (**Scheme 24**).



Scheme 24: Synthesis of 3-Alkyl/aryl-1*H*-indazoles and 3-alkyl/aryl-3*H*-indazole-3-phosphonates

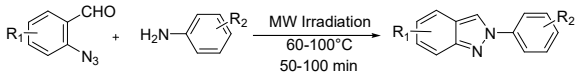
Shi *et. al.* reported a reagent and catalyst free donor/acceptor diazo activation strategy that proceeds *via* condensation with diazonium salts. The key intermediate diazenium intermediate was formed by diazo activation by diazonium salt. This diazenium intermediate was found to undergo cyclization to give indazoles in excellent yields (**Scheme 25**).[47] This protocol is the first example of donor/ acceptor diazo activation by diazonium salts under metal-free conditions.



Scheme 25: Synthesis of indazoles by diazo activation strategy.

Microwave-assisted Synthesis

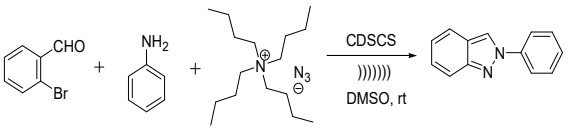
Sharada *et. al.* reported[48] a microwave-assisted, catalyst free consecutive C=N and N=N bond formation from 2-azidobenzaldehyde with various primary amines at 110 °C to provide 2*H*-indazoles in excellent yields (**Scheme 26).** This method features for its high yields, mild conditions, and operational simplicity.



Scheme 26: Microwave-assisted synthesis of 2*H*-indazoles.

Ultrasonic promoted synthesis

Soltani Rad *et. al* reported[49] the synthesis of indazoles from an ultrasonic promoted one-pot three-component reaction of 2-bromobenzaldehyde, primary amine, and tetra-butyl ammonium azide (TBAA) in presence of copper-doped silica cuprous sulphate (CDSCS) at room temperature with good yields (**Scheme 27**).The method is an ultrasound promoted one pot, three component synthesis of 2*H*-indazoles through consecutive condensation, *C-N* and *N-N* bond formations under ultrasonic irradiation using tetrabutylammonium azide (TBAA) as an azide source and CDSCS as a heterogeneous nano-catalyst.The advantages of this approach involve the high yields of products, low catalyst loading, mild reaction conditions, short reaction times, readily available precursors, operation and separation simplicity, no use of supplementary ligand, minimization of by-products and chemical wastes, reusable catalyst, etc.

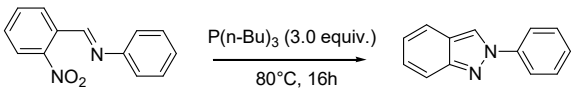


Scheme 27: Ultrasonic promoted synthesis of2-aryl indazoles.

By Cadogan reductive cyclization/ Phospha-catalyzed synthesis

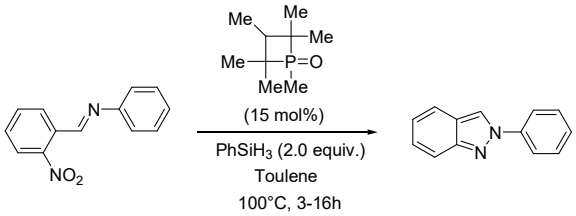
Reductive cyclization method of nitro groups was established by Cadogan group. Especially, the synthesis was functional to get five-membered rings with nitrogen such as carbazole derivatives, as shown in schemes 28 and 29. This ring closure protocol has an advantage in that it is not affected by the electronic state of the substrate and thereby it can possibly occur in both electron-poor and electron-rich systems.

Genung *et. al.* reported[50] the condensation of aryl aldehyde and aniline at elevated temperature, it was envisioned that simply adding tri-n-butyl phosphine after the condensation was completed, followed by heating, would afford the Cadogan reductive cyclization product indazoles. Fortunately, this method proved effective as the one-pot process for the synthesis of indazole (**Scheme 28**). The use of tri-n-butylphosphine and protic solvent afforded mild conditions for the reductive cyclization in a media compatible with imine formation. This method enhanced the synthetic practicality of the transformation and improved the safety of the process by decreasing the temperature profile and restraining the quantity of reducing reagent contrast to preceding reports.



Scheme 28: Cadogan indazole synthesis *via N-N* bond formation

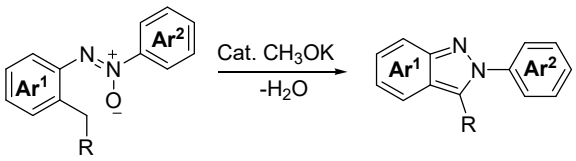
Nykaza *et. al.* described[51] the Cadogan synthesis of Indazoles from *o*-nitrobenzaldimines/*o*-nitroazobenzenes with small-ring phosphacycle, 1,2,2,3,4,4-hexamethyl-phosphetane, through *N-N* bond-formation. The method provides a simple phospha-catalytic approach to a valuable *N–N* bond-forming mode (**Scheme 29**). Unlike the previous methods involving stoichiometric reagent chemistry, transition-metal catalysis, or alternative high energy azide substrates this process provides a simple phospha catalytic approach to an important *N–N* bond-formation. Earlier studies involving $P^{III}/P^{V}=O$ redox cycling have predominantly focused on ring strain arguments underpinning catalytic turnover of phosphine oxides by silane reductants. But this method proceeds *via* a dominant electronic component to the overall biphilic function of the phosphetane catalyst.



Scheme 29: Cadogan synthesis of 2-aryl Indazoles.

Base (CH_3OK) catalyzed synthesis

Zhou and coworkers described[52] a simple and effective base-catalyzed benzyl *C–H* deprotonation and cyclization method to afford for the synthesis of 2-aryl-2*H*-indazoles from *ortho*-alkyl substituted azoxy benzenes (**Scheme 30**).[50] This is an efficient green protocol for the synthesis of 2-aryl-2*H*-indazoles *via* a base-catalyzed benzyl C-H deprotonation and cyclization of ortho-alkyl substituted azoxy benzenes. Unlike, to the previously reported transition-metal-catalyzed strategies, this approach used an inexpensive CH_3OK as the base, that eradicates the requirement of oxidants and transition-metal catalysts. This protocol envisages the presence of a strong base would trigger the nucleophilic cyclization of ortho-alkyl substituted azoxybenzenes, leading to a wide range of 2-aryl-2H-indazoles along with the release of H_2O.



Scheme 30: CH_3OK catalyzed synthesis of 2-aryl-2*H*-indazoles.

The authors also reviewed[53-55] various other biologically important heterocyclic compounds so as to provide new scopes for developing different

structure dependent active moieties for interesting authors.

Conclusion

Indazole and its derivatives have a pivotal role in medicinal chemistry due to its wide spectrum of pharmacological activities. This motif is a highly useful synthon for the synthesis of many bridgehead heterocycles having significance in the pharmaceutical industry. Thus there has been an emergent interest in the development of indazole motifs against various types of diseases. A wide range of bioactive moieties can easily be integrated into indazole derivatives and gigantic efforts have been devoted to the investigation of their synthesis and evaluation of their medicinal properties. This mini review covers updates in the synthesis of indazole compounds from 2011-2021. The present review portrayed the recent synthetic strategies and the progress of new concepts along with conventional methods to prepare various indazole derivatives. Thus we believe that this review will encourages the researchers and medicinal chemists to develop novel protocols for the synthesis of diversely substituted indazoles having medicinal significance.

Acknowledgements

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Conflict of interest

No conflicts to declare.

References

1. Fischer, E.; Tafel, J. **I.** Ueber die Hydrazine der Zimmtsäure. *Justus LiebigsAnnalen der chemie,* **1885**, *227*, 303-340.
2. Wiley, R. H. Pyrazoles and reduced and condensed pyrazoles, vol. *22*. The chemistry of heterocyclic compounds, John wiley& sons: Newyork, NY, **2009**.
3. Cankarova, N.; Halavac, J.; Krchnak, V. Recent Synthetic Approaches to 1H- and 2H-Indazoles. A Review.*Org. Prep. Proced. Int.,* **2010**, *42*, 433-465.
4. Schmidt, A. Heterocyclic mesomeric betaines and analogs in natural product chemistry. betainic alkaloids and nucleobases.*Adv. Heterocyclic. Chem.,* **2003**, 85, 67.
5. Schmidt, A.; Beutler, A.; Snoydoych, B. Recent Advances in the Chemistry of Indazoles.*Eur. J. Org. Chem.,* **2008,** 2008, 4073-4075.
6. Balfour, J.A.; Clissold, S.P. Bendazac lysine. (1990). A review of its pharmacological properties and therapeutic potential in the management of cataracts. *Drugs*, **1990**, *39 (4)*, 575–596.
7. Fischer J.; Ganellin C. R. Analogue-based Drug Discovery, *John Wiley & Sons*. **2006**, p. 448.
8. Denya, I.; Malan, S.F.; Joubert, J. Indazole derivatives and their therapeutic applications: a patent review (2013-2017). *Expert Opin. Ther. Pat.,* **2018**, *28*, 441-453.
9. Takeuchi, A.; Hori, M.; Sato, S.; Ban, H. S.; Kuchimaru, T.; Kizaka-Kondoh, S.; Yamori, T.; Nakamura, H. Synthesis and biological activity of furanylindazoles as inhibitors of hypoxia inducible factor (HIF)-1 transcriptional activity.*Med. Chem. Comm.,* **2012**, *3*, 1455-1461.
10. Scott, L.J.Niraparib: First global approval. *Drugs*, **2017**, *77*, 1029–1034.
11. Zivi, A.; Cerbone, L.; Recine, F.; Sternberg, C.N. Safety and tolerability of pazopanib in the treatment of renal cell carcinoma. *Expert Opin. Drug Saf.*, **2012**, 11, 851–859.
12. Escudier, B.; Gore, M. Axitinib for the Management of Metastatic Renal Cell Carcinoma. *Drugs R D*, **2011**, 11, 113–126.
13. Samumed, Llc. Indazole inhibitors of the Wnt signal pathway and therapeutic uses thereof. AU2016203274B2. **2016**.
14. University of Utah Research Foundation. Substituted 1H-indazol-1-OL analogs as inhibitors of beta catenin/Tcf protein-protein interactions, US 9,738,628. 201.
15. Actelion Pharmaceuticals Ltd. Antibacterial 1H-indazole and 1H-indole derivatives, US 9, 624, 206. **2017**.
16. (a) Atta-ur Rahman, S.; Malik, H.; Cun-heng H.; Clardy, J. Isolation and structure determination of nigellicine, a novel alkaloid from the seeds of nigella sativa. *Tetrahedron Lett.,* **1985**, *26*, 2759-2762; (b) Schmidt, A. Biologically Active

Mesomeric Betaines and Alkaloids, Derived from 3- Hydroxypyridine, Pyridin-N-oxide, Nicotinic Acid and Picolinic Acid: Three Types of Conjugation and Their Consequences. *Curr. Org. Chem.,* **2004,** *8*, 653-670; (c) Liu, Y.M.; Yang, J.S.;. Liu. Q.H. A New Alkaloid and Its Artificial Derivative with an Indazole Ring from Nigella glandulifera. *Chem. Pharm. Bull.,* **2004**, *52*, 454-455; (d) Attaur-Rahman, S.; Malik, S. S.; Hasan, M. I.; Choudhary, C. Z. Ni and J. Clardy. Nigellidine-A new indazole alkaloid from the seeds of Nigella sativa. *Tetrahedron Lett.,* **1995**, *36*, 1993-1996.

17. Ruiz-Castillo, P.; Buchwald, S L. Applications of Palladium-Catalyzed *C–N* Cross Coupling Reactions. *Chem. Rev.,* **2016**, *116*, 12564–12649.
18. Vidyacharan, S.;.Murugan, A.; Sharada, D. S. C(sp2)–H Functionalization of 2H-Indazoles at C3-Position *via* Palladium(II)-Catalyzed Isocyanide Insertion Strategy Leading to Diverse Heterocycles. *J. Org. Chem.,* **2016**, 81, 2837-2848.
19. Akazome, M.; Kondo, T.; Watanabe, Y. Palladium Complex-Catalyzed Reductive N-Heterocyclization of Nitroarenes: Novel Synthesis of Indole and 2H-Indazole Derivatives. *J. Org. Chem.,* **1994,** 59, 3375-3380.
20. Abed, H. B.; Schoene, J.; Christmann, M.; Nazare, M. Contemporary Organic Synthesis.*Org. Biomol. Chem.,* **2016**, *14*, 8520.
21. Wu, C.; Fang, Y.; Larock, R. C.; Shi, F.; Facile, A. (2010). One-Pot Synthesis of β-Substituted (Z)-Acrylonitriles Utilizing an α-Diaminoboryl Carbanion. *Org. Lett.,* **2010**, 12, 2171-2173.
22. Haag, B.; Peng, Z.; Knochel, P. Preparation of Polyfunctional Indazoles and Heteroarylazo Compounds Using Highly Functionalized Zinc Reagents.*Org. Lett.,* **2009**, *11*, 4270-4273.
23. Song, J. J.;.Yee, N. K. A Novel Synthesis of 2-Aryl-2H-indazoles *via* a Palladium-Catalyzed Intramolecular Amination Reaction. *Org. Lett.,* **2000**, *2*, 519-521.
24. Lee, K. Y.; Gowrisankar, S.;Kim, J. N. Facile synthesis of 2H-indazole derivatives starting from the Baylis–Hillman adducts of 2-cyclohexen-1-one. *Tetrahedron Lett.,* **2005**, *46*, 5387-5391.
25. Kumar, M. R.; Park, A.; Park, N.; Lee, S. Consecutive Condensation, C–N and N–N Bond Formations: A Copper-Catalyzed One-Pot Three-Component Synthesis of 2H-Indazole. *Org. Lett.,* **2011**, *13*, 3542-3545.
26. Hu, J.; Cheng, Y.; Yang, Y.; Rao, Y. (2011). A general and efficient approach to 2H-indazoles and 1H-pyrazoles through copper-catalyzed intramolecular N–N bond formation under mild conditions.*Chem. Commun.,* **2011**, *47*, 10133-10135.
27. Xiong, X.; Jiang, Y.; Ma, D. Assembly of N,N-Disubstituted Hydrazines and 1-Aryl-1H-indazoles via Copper-Catalyzed Coupling Reactions. *Org. Lett.,* **2012**, *14*, 2552–2555.
28. Prasad, A. N.; Srinivas, R.; Reddy, B. M. Cu^{II}–hydrotalcite catalyzed one-pot three component synthesis of 2H-indazoles by consecutive condensation, C–N and N–N bond formations. Catal. Sci. Technol., **2013***, 3*, 654-658.
29. Khatun, N.; Gogoi, A.; Basu, P.; Das, P.; Patel, B. K. CuO nanoparticle catalysed synthesis of 2H-indazoles under ligand free conditions. *RSC Adv.,* **2014**, *4*, 4080-4084.
30. Sodhi, R. K.; Changotra, A. Metal Acetylacetonates Covalently Anchored onto Amine Functionalized Silica/Starch Composite for the One-Pot Thioetherification and Synthesis of 2H-Indazoles. *Catal. Lett.,* **2014**, *144*, 1819-1831.
31. Sharghi, H.; Aberi, M.; Shiri, P. Highly reusable support-free copper(II) complex of para-hydroxy-substituted salen: Novel, efficient and versatile catalyst for C─N bond forming reactions. *Appl. Organometal. Chem.,* **2017**, *31*, e3761.
32. Behrouz, S. (2016). Highly Efficient One-Pot Three Component Synthesis of 2H-Indazoles by Consecutive Condensation, C–N and N–N Bond Formations Using Cu/Aminoclay/Reduced Graphene Oxide Nanohybrid. *J. Heterocyclic Chem.,* **2016,** *54,* 1863-1871.
33. Hu, J.; Cheng, Y.; Yang, Y.; Rao, Y. A general and efficient approach to 2H-indazoles and 1H-pyrazoles through copper-catalyzed intramolecular N–N bond formation under mild conditions. *Chem. Commun.,* **2011**, *47*, 10133-10135.
34. Zhang, G.; Fan, Q.; Zhao, Y.; Ding. C. Traceless Directing Group Assisted Copper-Promoted Oxidative intramolecular C-H Amination of

Hydrazones to Synthesis of 1HIndazoles or 1H-Pyrazoles. *Eur. J. Org. Chem.*, **2019**, *2019*, 5801-5806.

35. Solomin, V V.; Seins, A .; Jirgensons, A. Synthesis of indazoles from 2-formylphenylboronic acids. *RSC Adv.,* **2021**, *11*, 22710-22714.
36. (a) Sudhapriya, N.; Nandakumar, A.; Perumal. P. T. Facile synthesis of 2-substituted quinolines and 3-alkynyl-2-aryl-2H-Indazole via $SnCl_2$-mediated reductive cyclization. *RSC Adv.,* **2014,** *4*, 58476-58480; (b) Sudhapriya, N.; Balachandran, C.; Awale, S. Perumal, P. T. Sn(II)-Mediated facile approach for the synthesis of 2-aryl-2H-indazole-3-phosphonates and their anticancer activities. *New J. Chem.,* **2017**, *41*, 5582-5594.
37. Saketi, J.M.R.; Boddapati, S.N.M.; M., R.; Adil, S.F.; Shaik, M.R.; Alduhaish, O.; Siddiqui, M.R.H.; Bollikolla, H.B. $Pd(PPh_3)_4$ Catalyzed Synthesis of Indazole Derivatives as Potent Anticancer Drug. *Appl. Sci.,* **2020**, *10*, 3792-3906.
38. Park, A.; Jeong, KS.; Lee, H.; Kim. H. Synthesis of 1H-Indazoles via Silver(I)-Mediated Intramolecular Oxidative C–H Bond. *ACS Omega*, **2021**, *6*, 6498–6508.
39. Zhang, T.; BaoW. Synthesis of 1*H*-Indazoles and 1*H*-Pyrazoles *via* $FeBr_3/O_2$ Mediated Intramolecular C–H Amination. *J. Org. Chem.,* **2013**, *78*, 1317–1322.
40. Oh, H.; Han, S.; Pandey, A.K.; Han, S.H.; Mishra, N.K.; Kim, S.; Chun, R.; Kim, H. S.; Park, J.; Kim, I.S. Synthesis of (2H)-Indazoles through Rh(III)-Catalyzed Annulation Reaction of Azobenzenes with Sulfoxonium Ylides. *J. Org. Chem.,* **2018**, *83*, 4070–4077.
41. Saikia, A. K.; Unnava, R.; Indukuri, K.; Sarkar. S. Regioselective one-pot, three-component synthesis of substituted 2H-indazoles from 2-nitroarylaldehyde, alkyne and amine catalyzed by the CuBr/$Zn(OTf)_2$ system. *RSC Adv.,* **2014**, *4*, 55296-55299.
42. Kim, O.S.; Jang, J. H.; Kim, H.Y.; Han, S.J.; Tsui, G.C.; Joo, J. M. Synthesis of Fluorescent Indazoles by Palladium-Catalyzed Benzannulation of Pyrazoles with Alkynes.*Org. Lett.,* **2017**, *19*, 1450–1453.
43. Yu, J.; Lim, J.W.; Kim, S.Y.; Kim, J.; Kim, J.N. An efficient transition-metal-free synthesis of 1H-indazoles from arylhydrazones with montmorillonite K-10 under O_2 atmosphere. *Tetrahedron Lett.,* **2015**, *56*, 1432-1436.
44. Sun, L.; Nie, J.; Zheng, Y.; An Ma. J. [3 + 2] Cycloaddition of arynes with CF_3CHN_2: Access to 3-trifluoromethyl-1H-indazoles.Journal of Fluorine Chemistry, **2015**, *174*, 88-94.
45. Li, P.; Wu, C.; Zhao, J.; Rogness, D.C.; Shi, F. Synthesis of Substituted 1H-Indazoles from Arynes and Hydrazones. *J. Org. Chem.,* **2012**, *77*, 3149–3158.
46. Chen, G.; Hu, M.; Peng, Y. Switchable Synthesis of 3-Substituted 1H-Indazoles and 3,3-Disubstituted 3H-Indazole-3-phosphonates Tuned by Phosphoryl Groups. *J. Org. Chem.,* **2018**, *83*, 1591–1597.
47. Li, X.; Ye, X.; Wei, C.; Shan, C.; Wojtas, L.; Wang, Q.; Shi, X. Diazo Activation with Diazonium Salts: Synthesis of Indazole and 1,2,4-Triazole.*Org. Lett.,* **2020**, *22*, 4151–4155.
48. Vidyacharan, S.; Sagar, A.; Chaitra, N. C.; Sharada, D. S. A facile synthesis of 2H-indazoles under neat conditions and further transformation into aza-γ-carboline alkaloid analogues in a tandem one-pot fashion. *RSC Adv.,* **2014**, *4*, 34232-34236.
49. Soltani Rad, M. N. Ultrasound promoted mild and facile one-pot, three component synthesis of 2H-indazoles by consecutive condensation, C-N and N-N bond formations catalysed by copper-doped silica cuprous sulphate (CDSCS) as an efficient heterogeneous nano-catalyst. *Ultrason. Sonochem.,* **2017**, *34*, 865-872.
50. Genung, N. E.; Wei, L.; Aspnes. G. E. Regioselective Synthesis of 2H-Indazoles Using a Mild, One-Pot Condensation–Cadogan Reductive Cyclization. *Org. Lett.,* **2014**, *16*, 3114-3117.
51. Nykaza, T. V.; Harrison, T. S.; Ghosh, A.; Putnik, R. A.; Radosevich, A. T. A BiphilicPhosphetane Catalyzes N–N Bond-Forming Cadogan Heterocyclization via P^{III}/P^{V}═O Redox Cycling. *J. Am. Chem. Soc.,* **2017,** *139*, 6839-6842.
52. Jin, G. Q.; Gao, W. X.; Zhou, Y. B.; Liu, M. C.; Wu, H. Y. Efficient synthesis of 2-aryl-2H-indazoles by base-catalyzed benzyl C–H

deprotonation and cyclization. *Chem. Commun.,* **2020**, *56*, 14617-14620.

53. John, V.; Raju, G. P.; Lakshmi, G.; Rani, B. L.; Bollikolla, H. B. Developments on 1,2,4-triazine scaffold substitutions for possible anticancer agents. *Carib. J. Sci. Tech. (CJST)*, **2020**, *8*(1), 060–081.
54. Reddy, M. S. N., Bollikolla, H. B. Synthesis and biological significance of 2H-chromene analogs: A Review. *Carib. J. Sci. Tech. (CJST)*, **2016**, *4*(1), 963–971.
55. Anandam, R., Khandapu, B. M. K.., Kasturi, J. K.., Thripuram, V. D., Ala, V. B., Mannam, K. M., Bollikolla, H. B. C-dimethylated Chalcones: Towards Possible Dual Acting Agents- Against Tuberculosis and cancer (A549) and an SAR study. *Carib. J. Sci. Tech. (CJST)*, **2020**, *8*(1), 053–059.