ChemInform Abstract: Synthesis of Indazole Motifs and Their Medicinal Importance: An Overview

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Mini-review

Synthesis of indazole motifs and their medicinal importance: An overview

Digambar D. Gaikwad [a, *], Archana D. Chapolikar [a], Chandrashekhar G. Devkate [a], Khandu D. Warad [a], Amit P. Tayade [a], Rajendra P. Pawar [b], Abraham J. Domb [c]

[a] Dept. of Chemistry, Govt. College of Arts & Science, Aurangabad 431001, India
[b] Dept. of Chemistry, Deogiri College, Aurangabad 431001, India
[c] School of Pharmacy, Department of Medicine, The Hebrew University of Jerusalem, Jerusalem 91120, Israel

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ABSTRACT

Indazoles is an important class of heterocyclic compounds having a wide range of biological and pharmaceutical applications. There is enormous potential in the synthesis of novel heterocyclic systems to be used as building blocks for the next generation of pharmaceuticals as anti-bacterial, anti-depressant and anti-inflammatory. Fused aromatic *1H* and *2H*-indazoles are well recognized for anti-hypertensive and anti-cancer properties. The present review focuses on novel routes of their synthesis and various biological activities.

1. Introduction

Indazole was first defined by scientist Emil Fisher as a “pyrazole ring fused with the benzene ring”. It has been extensively studied due to its interesting chemical and biological properties. Indazole belongs to the azoles family containing carbon, hydrogen and nitrogen atoms. Indazoles are also called as benzpyrazole or isoindazolone heterocyclic organic compounds, possessing two nitrogen atoms. Indazole having ten π-electron aromatic heterocyclic systems as like that of pyrazole molecule and indazoles resembles with pyridine and pyrrole. The structure of indazole in cylindrical bonds is as follows (Fig. 1).

Indazole derivatives are pharmacologically important as they form the basic structure of several drug molecules, such as Granisetron, $5HT_3$ receptor antagonist used as an anti-emetic in cancer chemotherapy and Benzydamine an anti-inflammatory agent. The indazole ring has two nitrogen atoms and can be functionalized with high selectivity at different positions. Planarity of the indazole ring, side chain length and fictionalizations at different positions can afford an enormous number of indazole derivatives, providing new molecules with biological and therapeutic properties.

World's largest selling drugs are nitrogen containing heterocycles [1]. It is because of their ubiquitous nature which is key scaffolds of many biological molecules and pharmaceutical products. Thus many chemists from all over the world were motivated and started developing different methods for the synthesis of these heterocycles. One of these which have biological, agricultural and an industrial application is Indazole [2]. Indazole and its derivatives possess several activities such as anti-inflammatory, anti-tumor, anti-HIV, anti-platelet and serotonin $5\text{-}HT_3$ receptor antagonist activities [3,4]. Indazole has potent affinity for $5\text{-}HT_{1A}$ receptor β and high affinity for I_2 receptor. Thus looking towards its important activities the methods for its synthesis should be developed [5]. This would help to explore the chemistry of *1H & 2H*-Indazole. Ortho-hydrazine benzoic acid (**1**) on heating results in the formation of (**2**) which was later named as indazolone, as reported by Emil Fisher in 1800 (Fig. 2).

Indazolone also called as the anhydride of (**1**), Emil Fisher and Kuzel attempted to apply the same strategy to obtain the anhydride of ortho-hydrazino cinnamic acid (**3**). Among the other products, they isolated a molecule that did not contain any oxygen. According

* Corresponding author.
E-mail address: gaikwad_dd@yahoo.com (D.D. Gaikwad).

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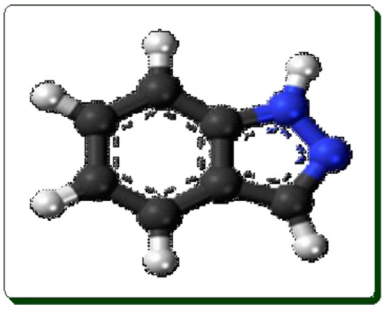
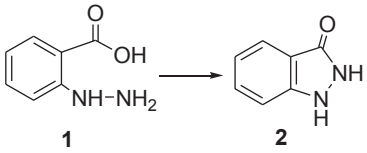


Fig. 1. Naturally accruing indazole nucleus.



First reported synthesis of indazolone

Fig. 2. Naturally accruing indazole nucleus.

to Fisher and Kuzel (1883), this was remarkable in the highest degree and they named it as indazole by analogy with the name of indole (Fig. 3).

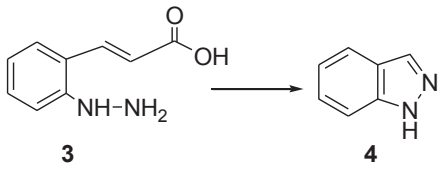
Most of the studies on indazole have been carried out by Karl Von Auwers during 1920s. His work and recent studies on indazole nucleus are reviewed in the following sections.

2. Tautomerism of indazoles

To understand the chemical reactivity of indazoles, it is important to know its tautomerism and aromaticity. Indazole may exist in two forms which result from the displacement of proton between two nitrogen atoms, a process described as proto-tropic annular tautomerism. Non substituted indazole exist predominantly as the *1H*-tautomer (**4**) based on the results from molecular refractivity studies. This was supported by the finding that, the UV and Raman spectra of non substituted indazole were similar to the spectra obtained for the 1H-substituted indazoles and different than the spectra of 2H-substituted indazole. Comparison between hydrogen and nitrogen NMR spectra of indazole with 1-methyl and 2-methylindazole and comprehensive study of ^{13}C and ^{1}H NMR studies provide the evidence for *1H*-tautomer [6].

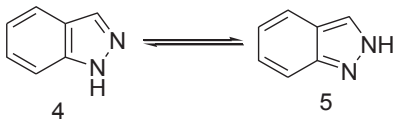
The indazole ring has two nitrogen atoms and annular tautomerism with regards to the position of the NH hydrogen atom. Due to the difference in energy between tautomers the benzenoid form (**4**) predominates in the gas phase solution. Solid state derivatives are usually found thermodynamically more stable than the corresponding *2H* forms, annular tautomerism of indazole benzenoid 1H-indazole tautomer (**4**) and quinonoid *2H*-indazole tautomers (**5**) [7] (Fig. 4).

Initially, the tricyclic structure (**6**) was suggested due to evidence for the presence of benzene ring based on the reactivity of *2H*-substituted indazoles in electrophilic aromatic substitution reactions and molecular refractivity measurements. However, a tricyclic formula creates a stereogenic center at C-3 and efforts to resolve the putative indazole-3-carboxylic acid (**7**) were



First reported synthesis of indazole

Fig. 3. Naturally accruing indazole nucleus.



Annular prototropic tautomerism of indazole

Fig. 4. Naturally accruing indazole nucleus.

unsuccessful. Eventually, Von Auwers proposed the quinonoid structure (**8**) for indazole (Fig. 5).

Another important observation reported by Von Auwers is related to the structure of 3-phenylindazole. 3-Phenylindazole is having a melting point 107–108 °C. On heating slightly above the melting point and allowed to resolidify, form crystals with a melting point of 115–116 °C. Acetylation of both compounds results in the formation of the same product which is converted to the low melting 3-phenylindazole on hydrolysis.

3. Indazoles as natural products

Indazoles are naturally occurring alkaloids *Nigellicine*, *Nigeglanine* and *Nigellidine*. *Nigellicine* was isolated from widely distributed plant *Nigella sativa*. *Nigeglanine* was isolated from extracts of *Nigella glandulifera*. Only few of the alkaloids studied upon isolation show the presence of indazole ring system. The first member of this alkaloid family *Nigellicine* (**9**) [8] was isolated in 1985 from the plant *N. sativa* an annual flowering plant, native to Southwest Asia. The seeds of this plant have been used for thousands of years as a spice and for the treatment of various diseases [9–11]. The structure of *nigellicine* has an intramolecular hydrogen bond between the carboxylate oxygen atom and the hydroxyl group. The structure of *nigellicine* is a pseudo-cross-conjugated heterocyclic mesomeric betaine, which means that it can be presented by dipolar canonical formula where both the positive and negative charge is delocalized in the structure [12] (Fig. 6).

Similarly other two alkaloids containing the same ring system, *Nigeglanine* (**10**) and *Nigellidine* (**11**) have been isolated from extracts of *N. glandulifera* and *N. sativa*. These two compounds can also be presented by their zwitterions formulae [13].

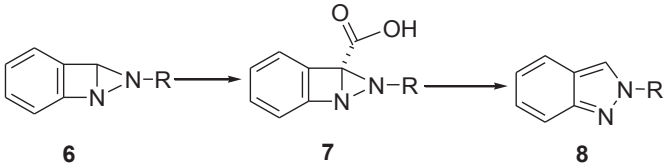


Fig. 5. Naturally accruing indazole nucleus.

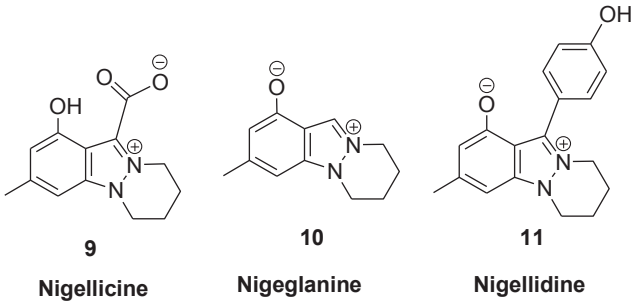
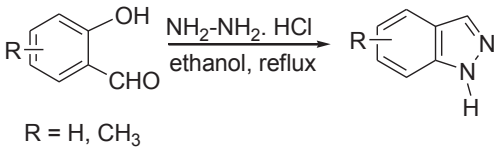
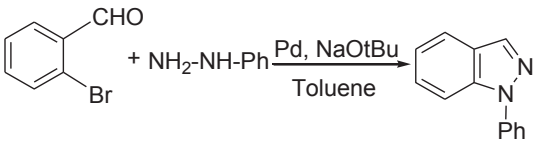


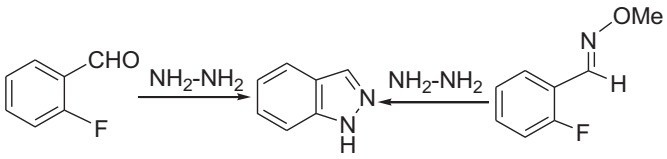
Fig. 6. Naturally accruing indazole nucleus.



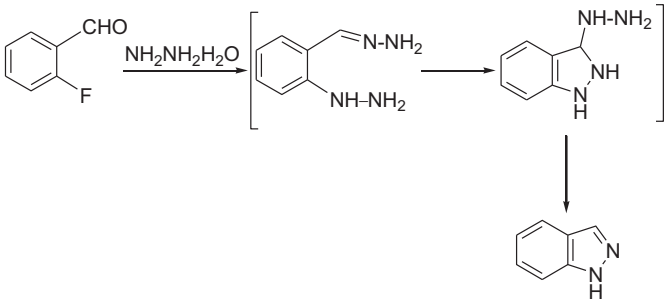
Scheme 1. Synthesis of indazole derivatives in different methods.



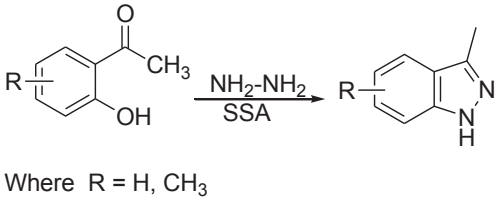
Scheme 2. Synthesis of indazole derivatives in different methods.



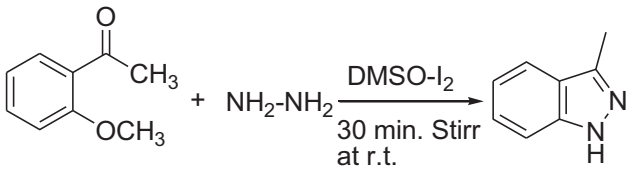
Scheme 3. Synthesis of indazole derivatives in different methods.



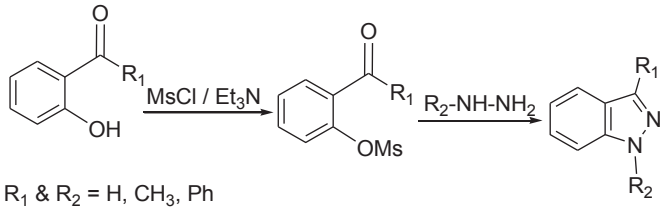
Scheme 4. Synthesis of indazole derivatives in different methods.



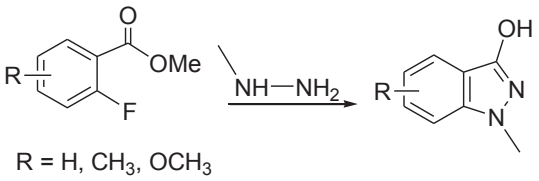
Scheme 5. Synthesis of indazole derivatives in different methods.



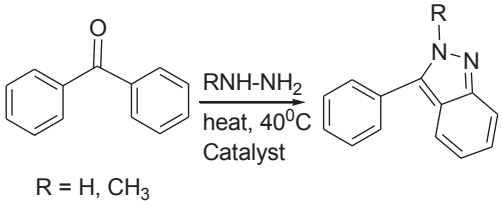
Scheme 6. Synthesis of indazole derivatives in different methods.



Scheme 7. Synthesis of indazole derivatives in different methods.



Scheme 8. Synthesis of indazole derivatives in different methods.

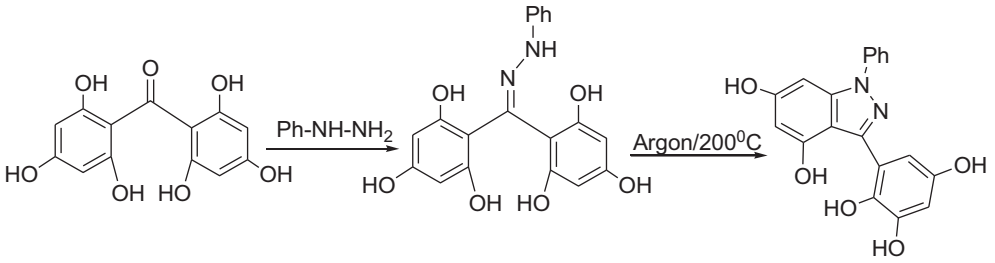


Scheme 9. Synthesis of indazole derivatives in different methods.

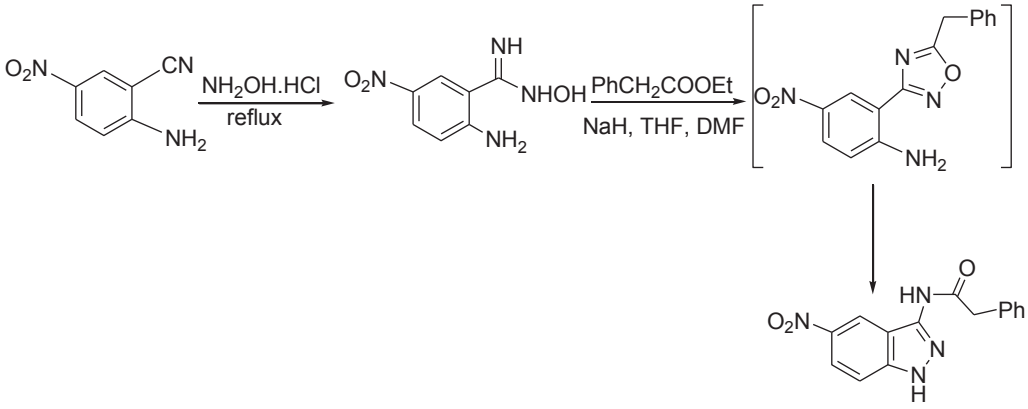
4. General importance of indazoles

Indazole nucleus is present in naturally occurring alkaloids and biologically active molecules. *Nigellidine* is a natural product containing an indazole nucleus, isolated from plant *N. sativa* and used in the treatment of various diseases. Commonly have carminative, stimulatory and diaphoretic properties. Indazole based heterocycles like indazolo pyrimidines and their derivatives are found to have a wide range of activities. Earlier findings on indazole derivatives are specifically known to be active as protein kinase inhibitors, cancer cell proliferative disorders, Alzheimer's disease, viral infections, auto immune and neuro degenerative disorders. In recent years, some of the indazole ring systems are being evaluated as potential drugs for variety of physiological activities with at least few compounds approved for clinical use. Further, pyrimidines ring in an organic molecule also shows prominent activity against several diseases.

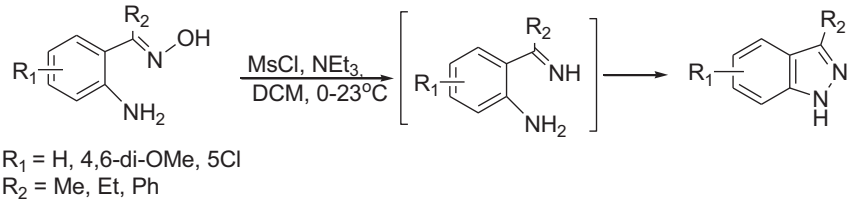
In addition, fluorine or trifluoro-methyl group at an appropriate position of molecule promotes lipophilicity to the molecule and results in increased solubility and transport of the drug in lipid system. Therefore indazole based compounds with fluorine or trifluoromethyl group at a specified position have gained significance as potent organic molecules, which ultimately serve like drugs.



Scheme 10. Synthesis of indazole derivatives in different methods.

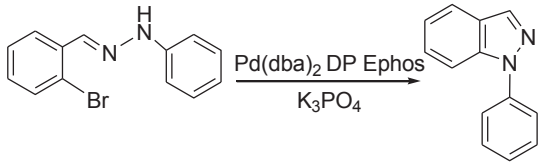


Scheme 11. Synthesis of indazole derivatives in different methods.

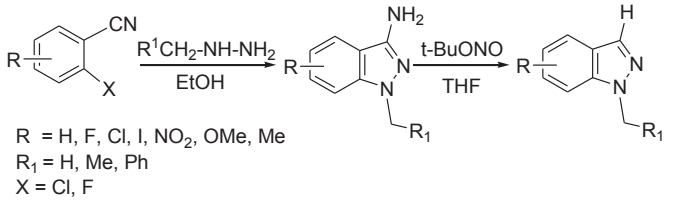


Scheme 12. Synthesis of indazole derivatives in different methods.

Some of the drug molecules containing indazole moieties are used as pharmaceutical agents.



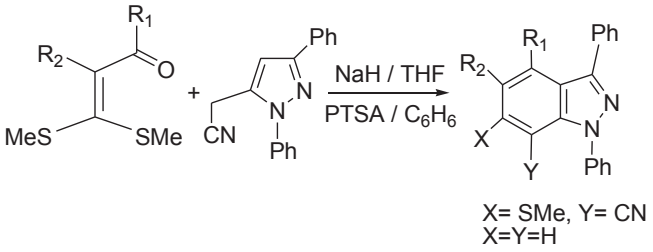
Scheme 13. Synthesis of indazole derivatives in different methods.



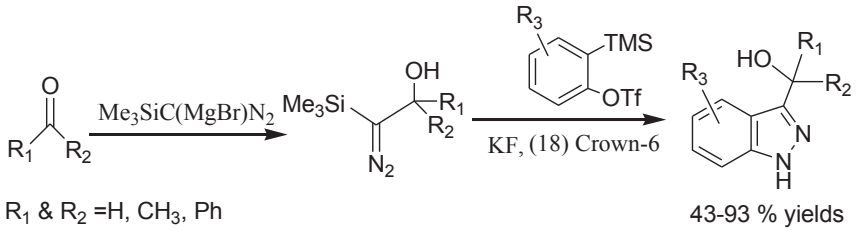
Scheme 14. Synthesis of indazole derivatives in different methods.

The importance of indazole nucleus has been given in biological and pharmacological properties. Our main aim is to exploit the medicinal properties using different synthetic approach. Accordingly the following outline has been proposed.

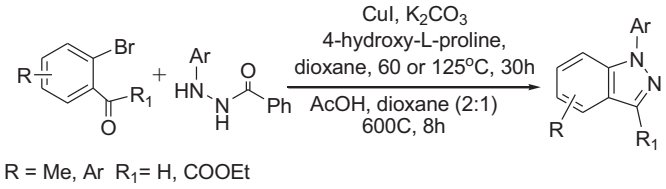
i. Synthesis of *1H*-indazoles
ii. Synthesis of *2H*-indazoles
iii. Indazole derivatives
iv. Medicinal importance
v. Drug design
vi. Miscellaneous



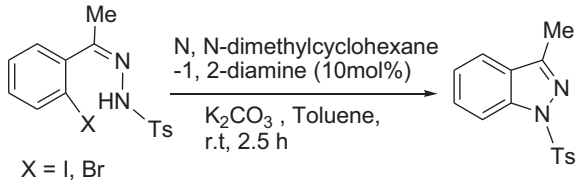
Scheme 15. Synthesis of indazole derivatives in different methods.



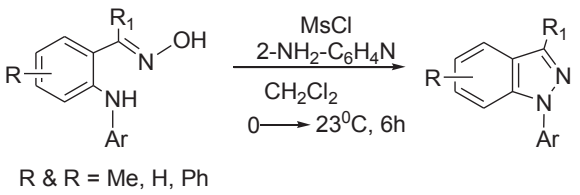
Scheme 16. Synthesis of indazole derivatives in different methods.



Scheme 17. Synthesis of indazole derivatives in different methods.



Scheme 20. Synthesis of indazole derivatives in different methods.



Scheme 18. Synthesis of indazole derivatives in different methods.

4.1. Synthesis of 1H-indazole

The *1H*-Indazoles represent an important class of heterocyclic compounds that exhibit a wide range of biological and pharmaceutical activities.

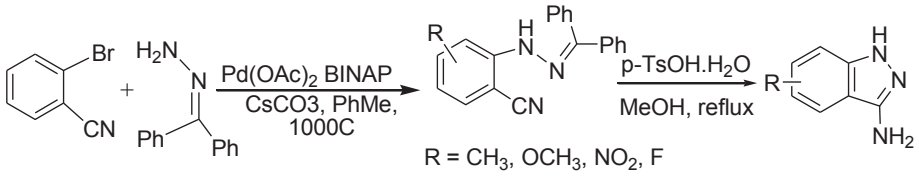
1H-indazoles were obtained by various synthetic methods such as substituted salicyladehydes react with hydrazine hydrochloride under reflux conditions. However, under the same reaction conditions benzaldehyde react with hydrazine hydrate to form hydrazones (Scheme 1) [14]. Ortho-bromo benzaldehyde react with arylhydrazines in toluene at 100 °C in the presence of catalytic amount of a palladium and phosphorus chelating ligands 1, 1-bis (diphenylphosphino) ferrocene and 1, 3-bis (diphenylphosphino)-propane along with NaO^tBu affords 1-aryl-1H-indazoles was reported (Scheme 2) [15]. The reaction of ortho-fluoro benzaldehydes and their ortho-fluro methyloximes with hydrazine has been reported for the synthesis of indazoles (Scheme 4) [16]. Similarly same product was obtained from ortho-fluoro benzaldehyde with hydrazine hydrate (Scheme 4) [17] (Scheme 3).

The synthesis of *1H*-indazoles have also been reported from reaction of ortho hydroxyl acetophenone on reaction with hydrazine hydrate in presence of silica sulfuric acid (SSA) acting as a catalyst which gives very good yields (Scheme 5) [18,19]. The synthesis of indazoles from ortho alkoxy acetophenone, hydrazine hydrates using DMSO and molecular iodine has been reported (Scheme 6) [20]. The reaction of aryl mesylate with hydrazine indicates the formation of arylhydrazone as an intermediate which further convert to indazoles. The presence of para-methoxy group in phenylhydrazine increases the yields of indazoles. Cyclized indazole was synthesized from phenylhydrazone in presence of acetic acid is reported (Scheme 7) [21]. However methyl ortho-benzoate react with methyl hydrazine to form 3-amino and 3-hydroxy indazole are reported (Scheme 8) [22]. Regioselective synthesis of 2,3-disubstituted tetrahydro-1H-indazoles has been reported by using catalyst zirconium sulfophenyl phosphonate methanephosphonate (Scheme 9) [23]. It was also observed that ortho hydrazophenone cyclized to indazoles using Argon at 200 °C reflux (Scheme 10) [24].

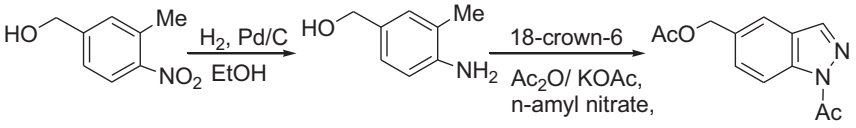
Lee et al. [25] prepared the key intermediate *1H*-indazole from 2-amino-5-nitro-benzonitrile. This reaction gives the transformation of benzonitrile into N-hydroxylamidine. The substituted *1H*-indazole obtained from 1, 2, 4-oxadiazole intermediate (Scheme 11).

The synthesis of *1H*-indazoles from ortho-amino benzoximes with creation of the N–N bond has been reported by Canceller et al. [26]. This reaction indicate the selective activation of the oxime group by reaction with a slight excess of methane sulfonyl chloride followed by cyclization to the *1H*-indazoles by exposure to triethylamine (Scheme 12).

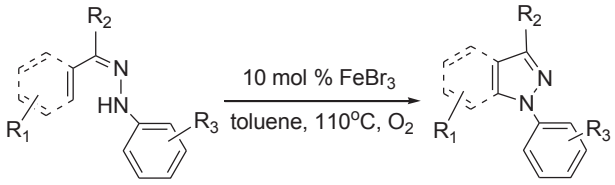
Cyclization of aryl hydrazones with ortho-bromo aldehydes and acetophenones using Palladium-catalyst gives 1-aryl-*1H*-indazoles. The cyclization of arylhydrazone of 2-bromobenzaldehydes performed by using $Pd(dba)_2$ and chelating phosphines DP Ephos in the presence of CS_2CO_3 or K_3PO_4 (Scheme 13) [27].



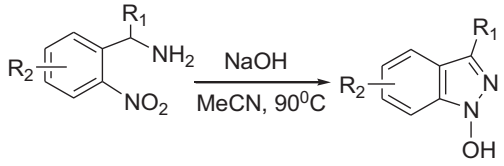
Scheme 19. Synthesis of indazole derivatives in different methods.



Scheme 21. Synthesis of indazole derivatives in different methods.



Scheme 22. Synthesis of indazole derivatives in different methods.



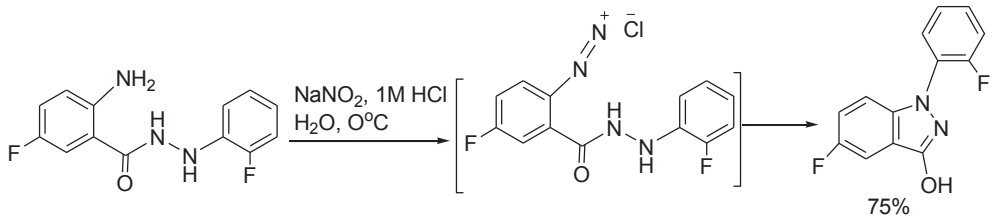
Scheme 23. Synthesis of indazole derivatives in different methods.

The regioselective synthesis of substituted *1H*-indazoles, from ortho-halobenzonitriles and alkyl hydrazine was described. The two-step reaction pathway proceeds through the intermediacy of 1-alkyl-3-amino-*1H*-indazoles (Scheme 14) [28].

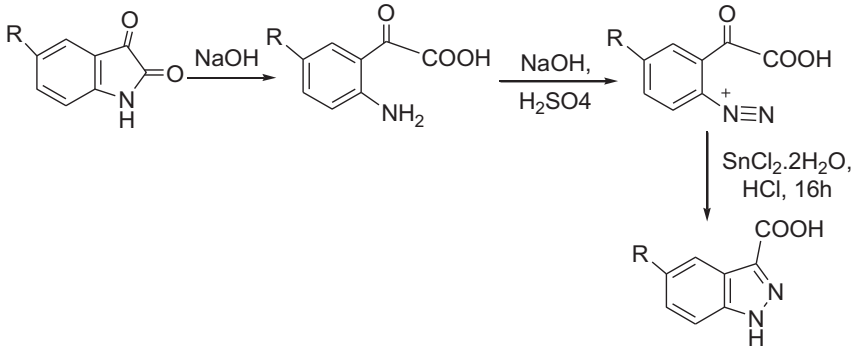
An efficient synthesis of highly substituted and annulated indazoles involving base induced addition elimination of 1,3-diphenyl-5-cyanomethylpyrazole to a variety of acyclic and cyclic α-oxoketene, followed by acid assisted cycloaromatization of the resulting conjugate adducts has been reported (Scheme 15) [29].

In this method different aldehydes and ketones are reacted with Diazo (trimethyl silyl) methyl magnesium bromide to give 2-diazo-(2-trismethylsilyl) ethanol. These were efficiently converted to indazoles gives hydroxymethyl units at 3-position by intermolecular [3 + 2] cycloaddition with benzynes (Scheme 16) [30].

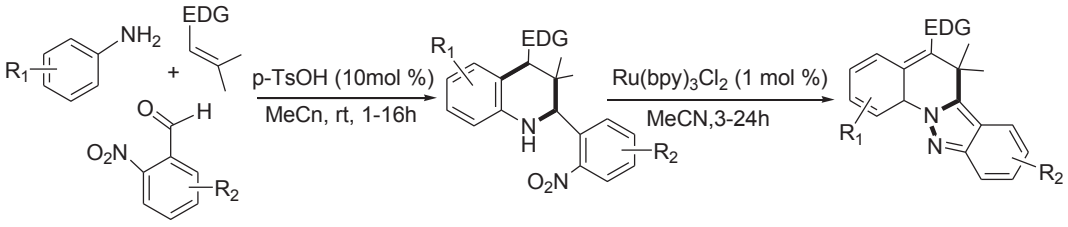
The substituted hydrazine with aryl iodides catalyzed by CuI gives disubstituted hydrazines regioselectively. The substituted hydrazine can also react with 2-bromo arylcarbonylic compounds



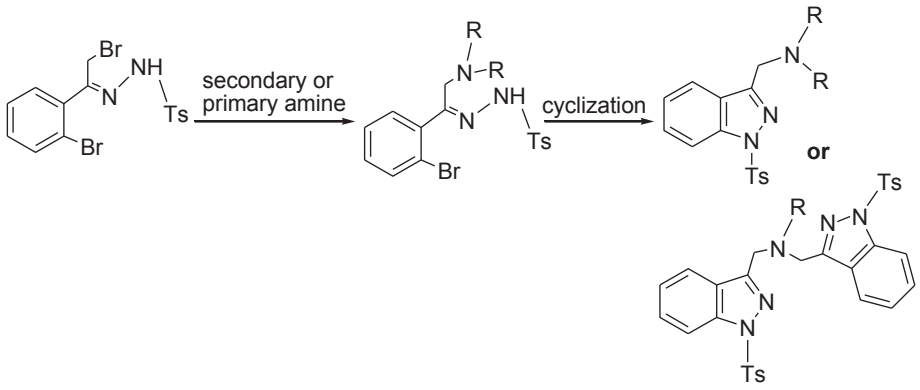
Scheme 24. Synthesis of indazole derivatives in different methods.



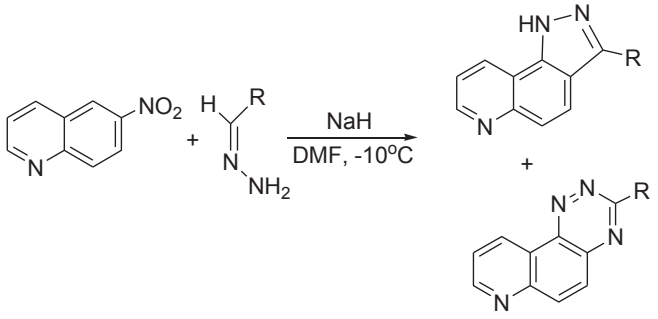
Scheme 25. Synthesis of indazole derivatives in different methods.



Scheme 26. Synthesis of indazole derivatives in different methods.

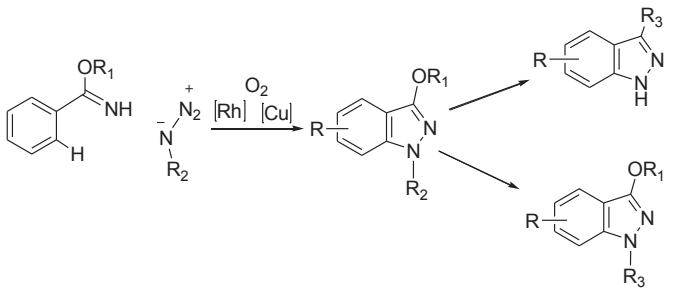


Scheme 27. Synthesis of indazole derivatives in different methods.



Scheme 28. Synthesis of indazole derivatives in different methods.

with acetic anhydride, followed by nitrosation with n-amyl nitrate



Scheme 30. Synthesis of indazole derivatives in different methods.

in the presence of 4-hydroxy-L-proline as ligand to provide 1-aryl-*1H*-indazoles (Scheme 17) [31].

The reaction of N-aryl-*1H*-indazoles and benzimidazoles synthesized from common arylamino oximes gives excellent yield. Triethylamine promoted the formation of benzimidazoles, where as 2-aminopyridine promoted the formation of N-arylindazoles (Scheme 18) [32].

The two-step synthesis of 3-aminoindazoles from 2-bromobenzonitriles involves a palladium-catalyzed arylation of benzophenone hydrazones followed by an acidic deprotection/cyclization sequence. This procedure offers efficient alternative to the typical SNAr reaction of hydrazine with *o*-fluorobenzonitriles (Scheme 19) [33].

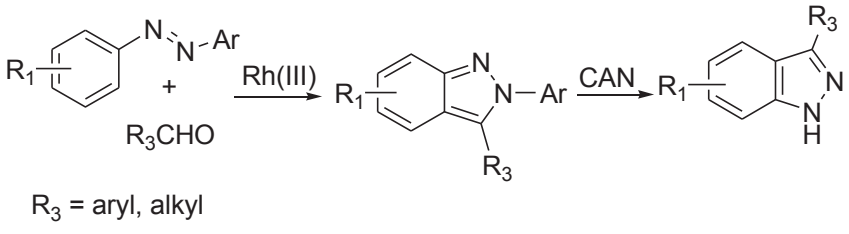
The transition-metal free method is reported for the synthesis of indazoles which involves an inexpensive catalytic system composed of a diamine and K_2CO_3. In this method isomerization with UV light has been done when *E*/*Z* isomeric mixtures of the starting material were used (Scheme 20) [34].

The reduction of the nitro group using hydrogen and 10% palladium on carbon provided the aniline. Performing the diacetate in the presence of catalytic amounts of 18-crown-6, gave the desired indazole (Scheme 21) [35].

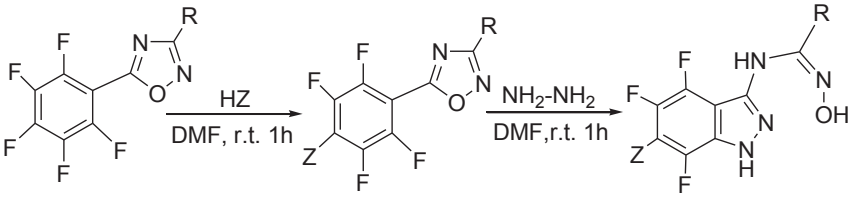
The synthesis of substituted *1H*-indazoles and *1H*-pyrazoles from arylhydrazones via $FeBr_3/O_2$ mediated C–H activation/C–N bond formation reactions was reported. The corresponding 1, 3-diaryl-substituted indazoles and trisubstituted pyrazoles were obtained in moderate to excellent yields (Scheme 22) [2].

A new and versatile cyclization reaction affording rare 1N-hydroxyindazoles is presented. Treatment of 2-nitrobenzylamines with methanolic sodium hydroxide furnishes 1N-hydroxy indazoles regioselectively and in high yield. The reaction tolerates a range of functional groups and electronic effects (Scheme 23) [36].

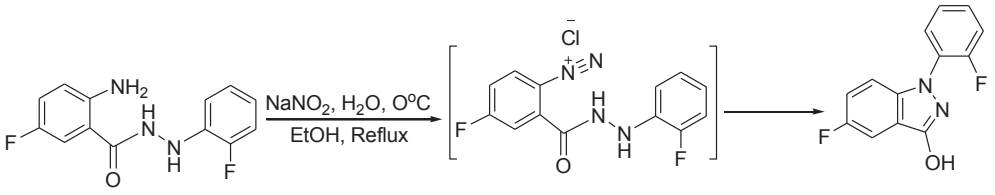
A different protocol preceding the intermediacy of a diazonium ion has also been reported. Thus, in the course of the preparation of *1H*-indazolone derivatives showed neoepiephedrine/serotonin reuptake inhibitory activity and it is used for the treatment of fibromyalgia. The construction of the *1H*-indazolone core structure of precursor has been accomplished via the decomposition of a



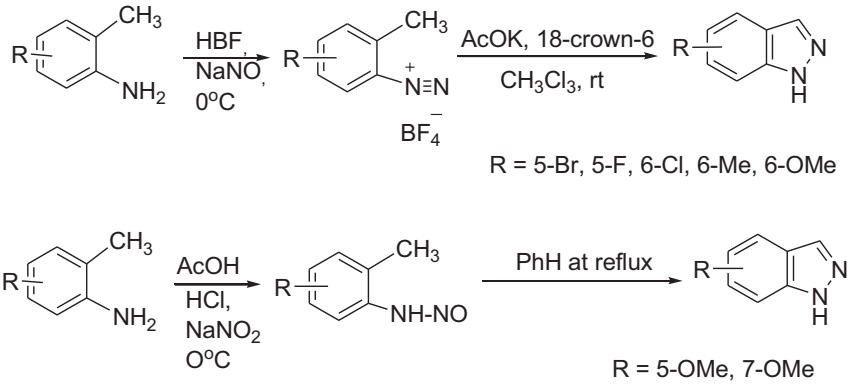
Scheme 29. Synthesis of indazole derivatives in different methods.



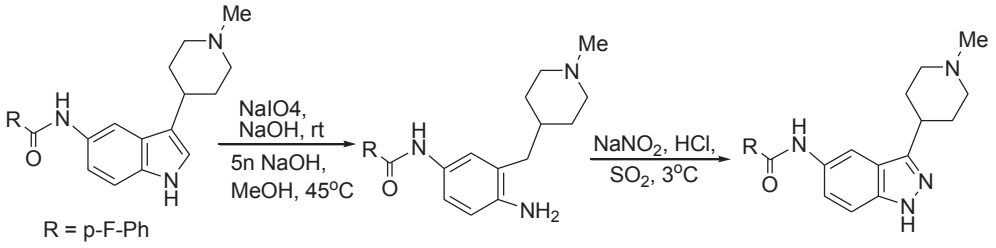
Scheme 31. Synthesis of indazole derivatives in different methods.



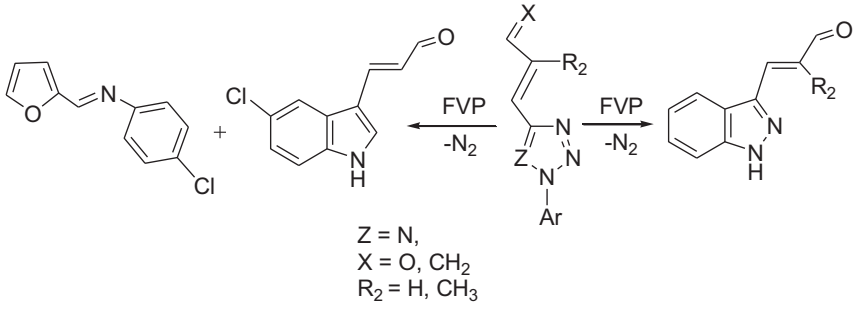
Scheme 32. Synthesis of indazole derivatives in different methods.



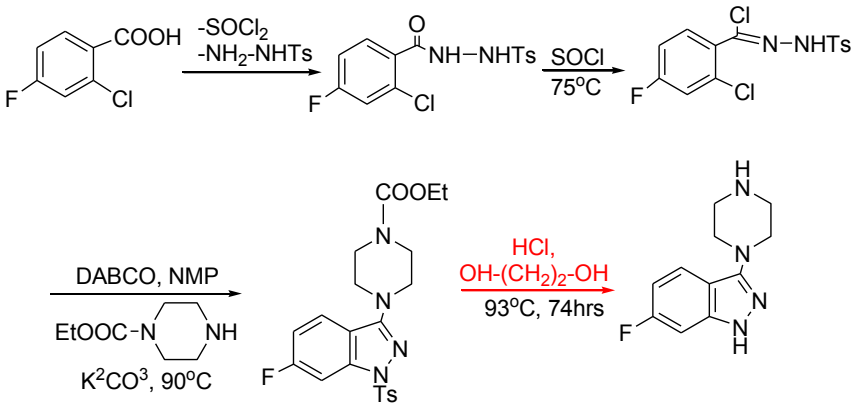
Scheme 33. Synthesis of indazole derivatives in different methods.



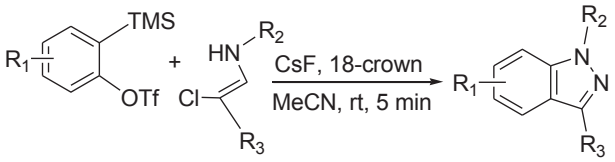
Scheme 34. Synthesis of indazole derivatives in different methods.



Scheme 35. Synthesis of indazole derivatives in different methods.



Scheme 36. Synthesis of indazole derivatives in different methods.



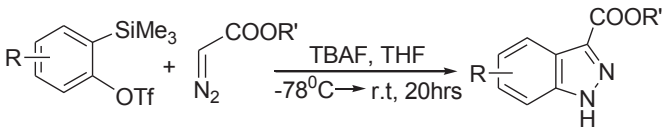
Scheme 37. Synthesis of indazole derivatives in different methods.

diazonium salt and capture of the resulting aryl cation by an ortho-disposed hydrazide (Scheme 24) [37].

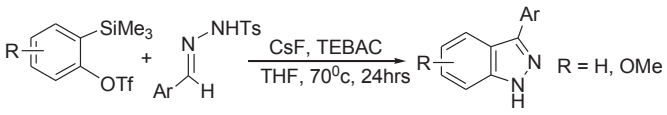
Reduction of a diazonium ion, or N-nitroso species, to the corresponding hydrazine and intramolecular reaction of the latter with ortho-disposed carbonyl functionality is another way to reach 3-substituted-*1H*-indazoles. Following this protocol, 5-bromo and 5-methoxy-3-carboxy-*1H*-indazoles have been prepared from properly substituted isatins (Scheme 25) [38].

An emerging technology using flow chemistry is used by pharmaceutical industry for development of novel drugs using indazole derivatives (Scheme 26) [22].

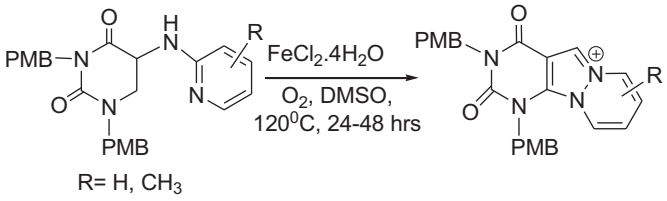
The 3-aminomethyl-*N*-tosyl-indazoles is synthesized by reacting amines with vinyl azines (Scheme 27) [39]. Thus, by the reaction of 1, 3-dinitrobenzene with 4-nitrobenzaldehyde hydrazone the cyclocondensation occurred by replacement of one of the nitro



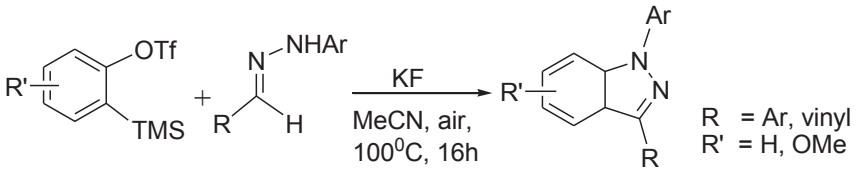
Scheme 40. Synthesis of indazole derivatives in different methods.



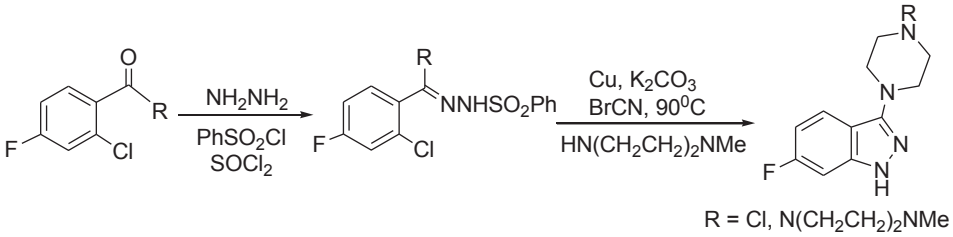
Scheme 41. Synthesis of indazole derivatives in different methods.



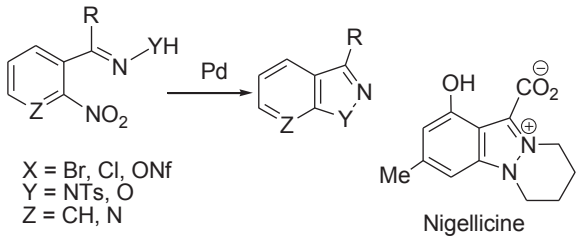
Scheme 42. Synthesis of indazole derivatives in different methods.



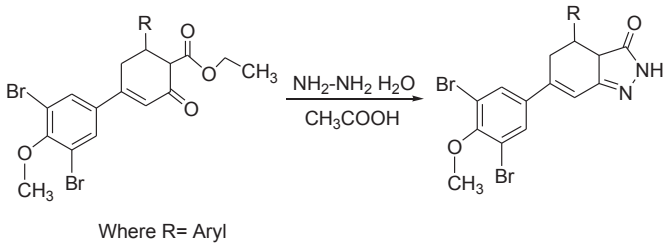
Scheme 38. Synthesis of indazole derivatives in different methods.



Scheme 39. Synthesis of indazole derivatives in different methods.



Scheme 43. Synthesis of indazole derivatives in different methods.



Scheme 47. Synthesis of indazole derivatives in different methods.

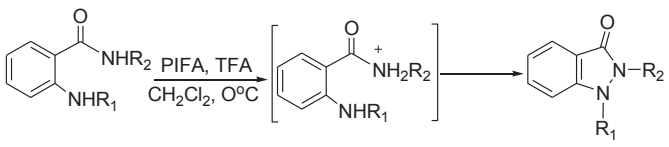
group, giving 5-nitro-3-(4-nitrophenyl) benzopyrazole as the main product (Scheme 28) [40].

An efficient synthesis of highly functional group-compatible synthesis of substituted *N*-aryl-*2H*-indazoles is reported via the rhodium (III)-catalyzed C–H bond addition of azobenzenes to aldehydes currently reported (Scheme 29) [41].

An efficient, facile and general synthesis of *1H*-indazoles by 1,3-dipolar cycloaddition of arynes with diazomethane derivatives were obtained by using Rh^{III}/Cu^{II} Cocatalyzed (Scheme 30) [42].

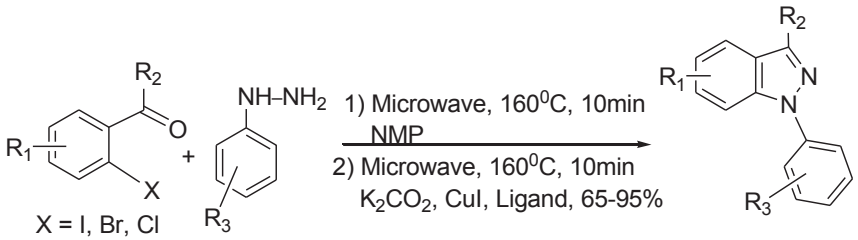
For the synthesis of fluorinated indazoles the bi-dentate nucleophile was added to the electrophilic 1, 2, 4-oxadiazole ring. Functionalization of the indazole was achieved through a nucleophilic aromatic substitution on the starting 5-pentafluorophenyl-1, 2, 4-oxadiazole (Scheme 31) [43].

The different protocol proceeding using the diazonium salt has also been reported. Thus, in the course of the preparation of *1H*-indazolone compound acting as the construction of the *1H*-indazolone core structure of precursor has been accomplished via the

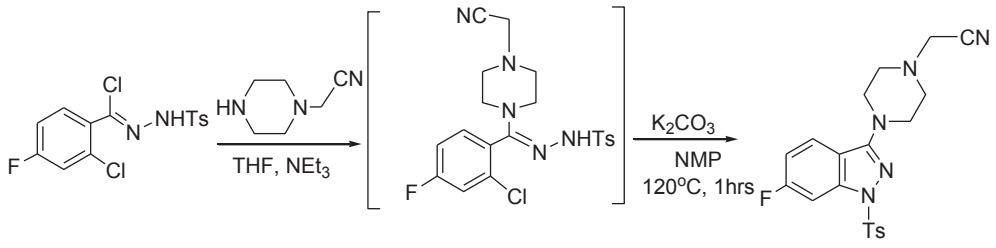


Scheme 48. Synthesis of indazole derivatives in different methods.

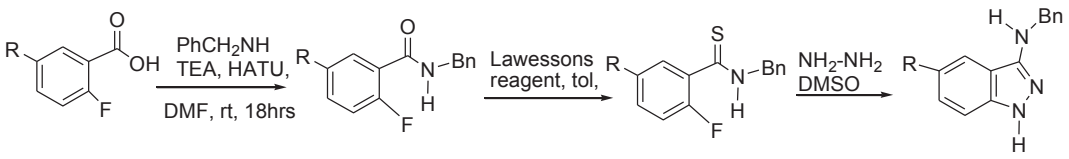
Scheme 49. Synthesis of indazole derivatives in different methods.



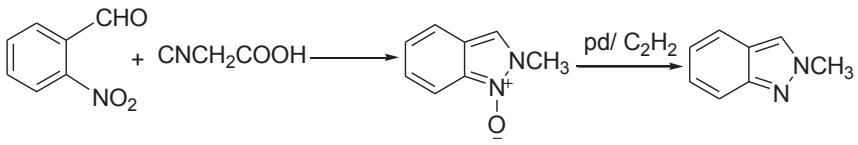
Scheme 44. Synthesis of indazole derivatives in different methods.



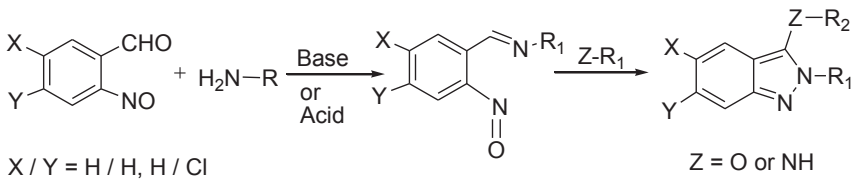
Scheme 45. Synthesis of indazole derivatives in different methods.



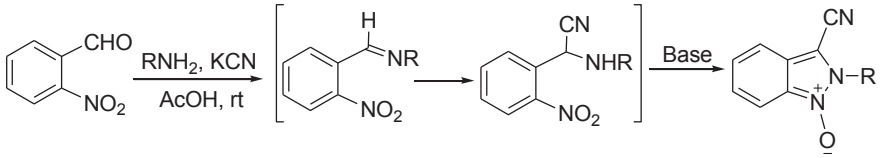
Scheme 46. Synthesis of indazole derivatives in different methods.



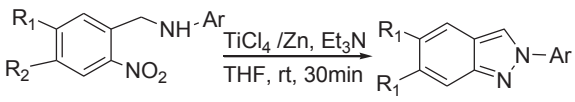
Scheme 50. Synthesis of indazole derivatives in different methods.



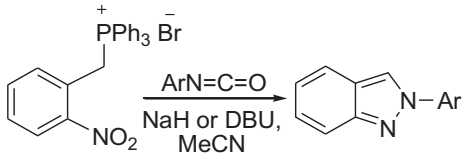
Scheme 51. Synthesis of indazole derivatives in different methods.



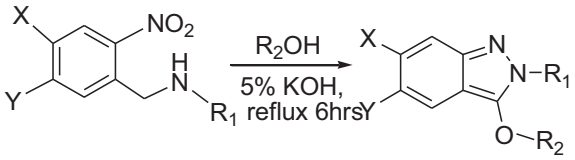
Scheme 52. Synthesis of indazole derivatives in different methods.



Scheme 53. Synthesis of indazole derivatives in different methods.

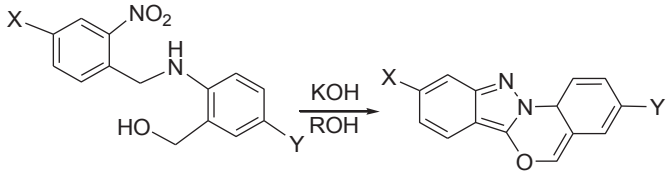


Scheme 54. Synthesis of indazole derivatives in different methods.



Scheme 55. Synthesis of indazole derivatives in different methods.

decomposition of a diazonium salt and capture of the resulting aryl cation by an ortho-disposed hydrazide (Scheme 32) [37].



Scheme 56. Synthesis of indazole derivatives in different methods.

Diazotation of an ortho-toluidine followed by capture of the generated diazonium salt is an old yet common way of synthesis of *1H*-indazoles. This can be realized by following two routes the first and most common proceeds by a phase transfer-catalyzed reaction from ortho-methyl-benzendiazonium tetrafluoroborates; the second takes place via N-nitroso derivatives (Scheme 33) [44].

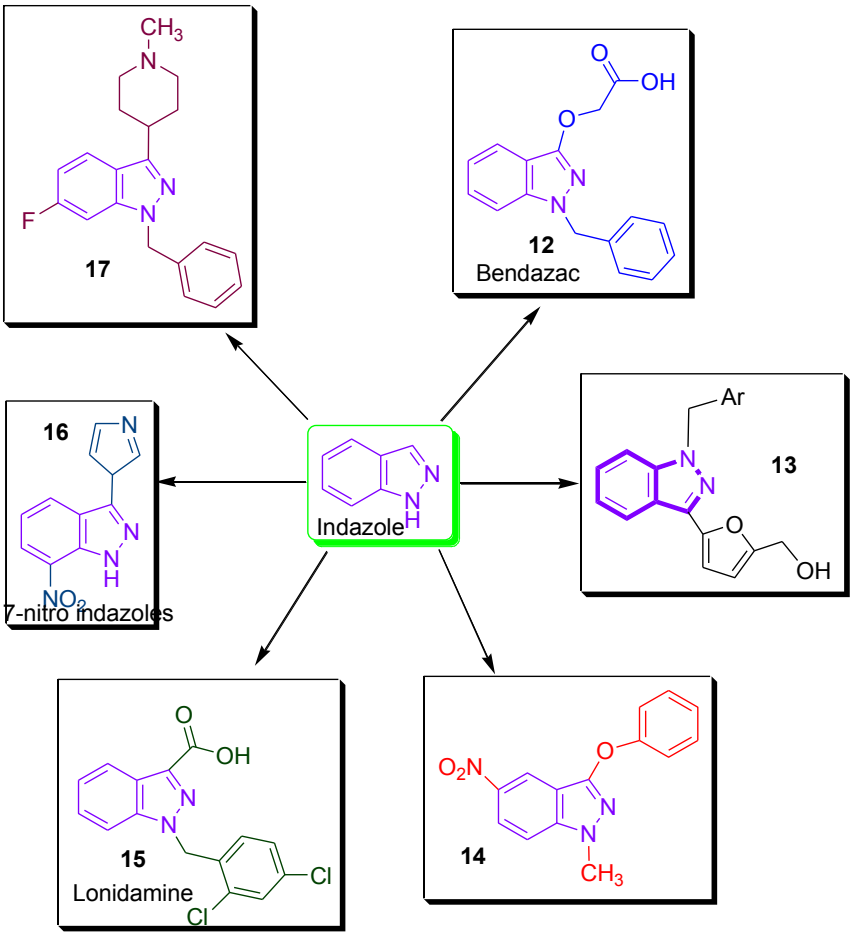
Zhang et al. [45] which, in the course of a study aimed at preparing bicyclic benzamides as novel 5-HT1F receptor agonists have reported the preparation of *1H*-indazole. It is worth noting that this example features an indole to indazole conversion and reduction of the diazo intermediate with SO_2 (Scheme 34).

The flash vacuum pyrolysis of azolylacroleins and azolylbutadienes from 2-Aryl-5-acroleinyl-1,2,3,4-tetrazoles and 2-aryl-5-butadienyl-1,2,3,4-tetrazoles resulted in nitrogen extrusion to give nitrile imines followed by ring closure to give the corresponding indazoles in good yields was reported (Scheme 35) [46].

One common synthetic route to *1H*-indazoles is the condensation of an aryl ketone, substituted in ortho by a leaving group (halogen, OMs), with hydrazine, followed by cyclization of the resulting hydrazones by simple heating or in the presence of a base. For example a short and convenient synthesis of the 3-(1-piperazinyl)-*1H*-indazole derivative has been successfully achieved. 3-(1-piperazinyl)-*1H*-indazole derivative was obtained in 67% overall yield without the need for chromatographic purification (Scheme 36) [47].

The synthesis of *1H*-indazoles via 1,3-dipolar cycloaddition of nitrile imines to benzyne is described (Scheme 37) [4]. [3 + 2] annulation approach from arynes and hydrazones constructs the skeleton of *1H*-indazole under different reaction conditions, N-tosylhydrazones and N-aryl/alkylhydrazones can be used to afford various indazoles (Scheme 38) [48].

Sulfonylation of phenylsulfonyl chloride in pyridine gave 90% yield of sulfonamide. Formation of the corresponding imidoyl chloride was achieved in 72% yield using thionyl chloride. Imidoyl chloride was treated with 2 equiv of 1-methylpiperazine to afford imidate in 73% yield. Cyclization with potassium carbonate in DMF using a copper catalyst gave indazole (Scheme 39) [49].



Drug molecules containing indazoles moiety

Fig. 7. Naturally accruing indazole nucleus.

The [3 + 2] cycloaddition of variety diazo compounds with ortho (trimethylsilyl) aryl triflates in the presence of CsF or TBAF at room temperature provides a direct, efficient synthesis for a wide range of biologically and pharmaceutically interesting substituted indazoles (Scheme 40) [50] (Table 1).

Readily available, stable, and inexpensive *N*-tosylhydrazones react with arynes under mild reaction conditions to afford 3-substituted indazoles in good yields. The reaction involves a 1,3-dipolar cycloaddition of in situ generated diazo compounds and arynes (Scheme 41) [51] (Table 2).

1,3-diaryl-substituted indazoles and trisubstituted pyrazoles were obtained in moderate to excellent yields under mild conditions (Scheme 42) [52]. By using Pd-catalyzed the synthesis of 3-substituted indazoles of benzoisoxazoles which is a Pd-catalyzed

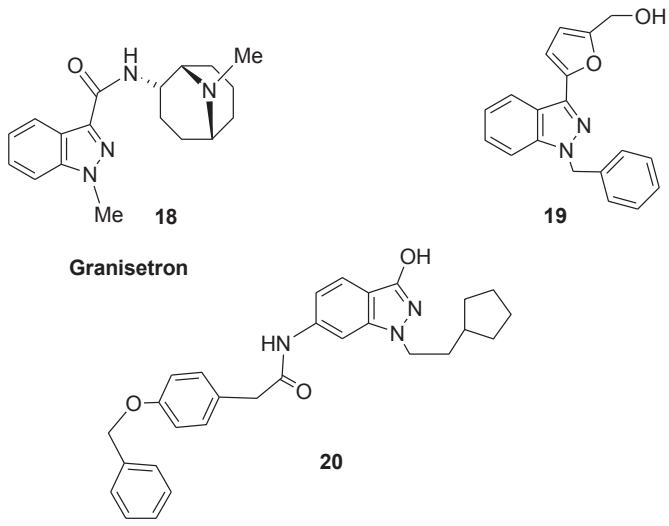
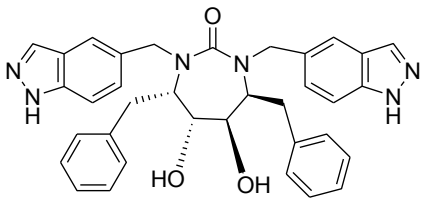


Fig. 8. Naturally accruing indazole nucleus.



Indazolyl substituted Urea (21)

Fig. 9. Naturally accruing indazole nucleus.

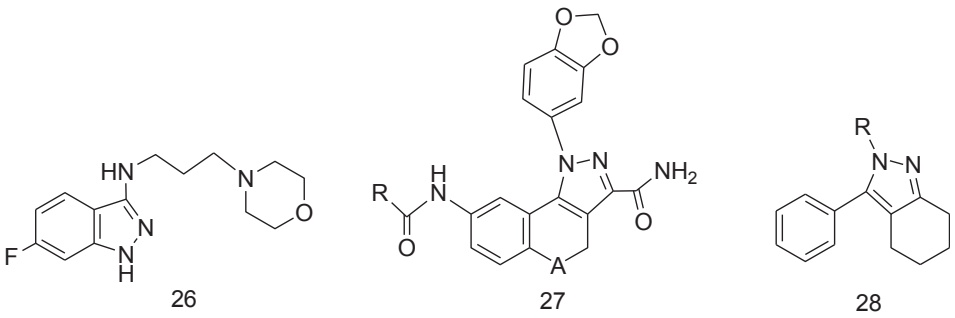


Fig. 10. Naturally accruing indazole nucleus.

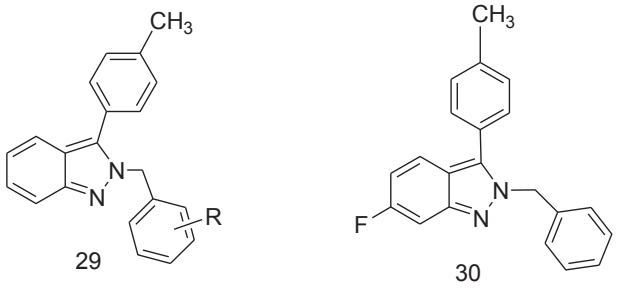


Fig. 11. Naturally accruing indazole nucleus.

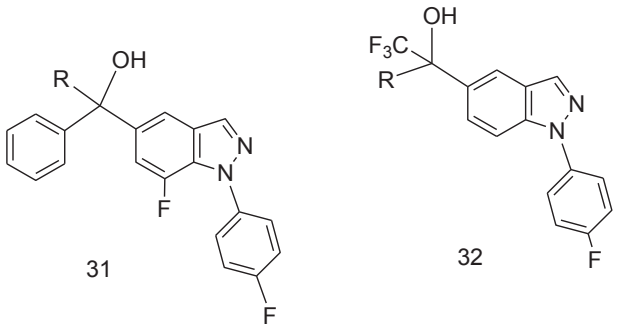


Fig. 12. Naturally accruing indazole nucleus.

intramolecular carbon–nitrogen and carbon–oxygen bond formations (Scheme 43) [53].

Microwave heating of ortho-halobenzaldehydes or ortho-haloacetophenones with phenylhydrazines are heated in microwave at 160 °C for 10 min and gives arylhydrazones, which on further cyclized to give 1-aryl-*1H*-indazoles using CuI/diamine-catalyzed (Scheme 44) [54].

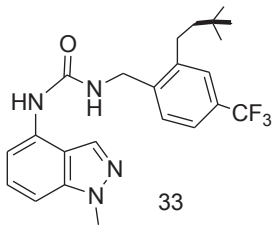


Fig. 13. Naturally accruing indazole nucleus.

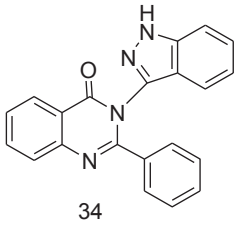


Fig. 14. Naturally accruing indazole nucleus.

The cyclization of tosylhydrazone gives the corresponding 3-(1-piperazinyl)-*1H*-indazole under the reaction condition NMP at 120 °C in the presence of K_2CO_3 was reported (Scheme 45) [55].

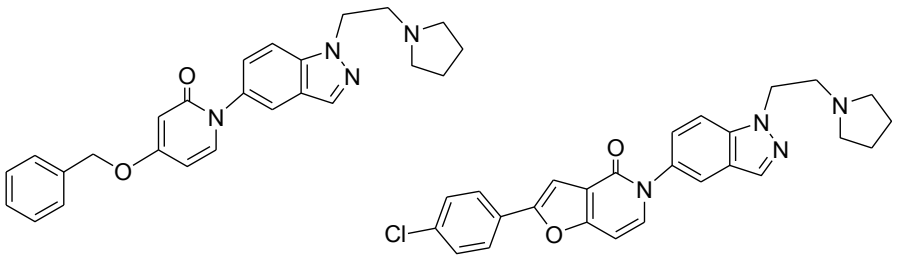
Based on the same strategy, the following example depicts a slightly different route for the synthesis of *1H*-indazoles. Three other examples of preparation of 3-amino-*1H*-indazoles can be found in references giving additional examples of preparation of various substituted *1H*-indazoles (Scheme 46) [56].

Joshi H. S. et al. the synthesis of 6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-2,3,4,5-tetrahydro-3H-indazole-3-one from (2E)-1-(3,5-dibromo-4-methoxyphenyl)-aryl-prop-2-en-1-one by using hydrazine hydrate in acidic condition (Scheme 47) [57]. The synthesis of a series of *1H*-indazol-3-ones with creation of the N–N bond has been achieved via the intra-molecular trapping of an N-acylnitronium intermediate by an ortho-disposed amino group. Starting from an o-aminobenzamide the N-acylnitronium cation was best generated by action of the hypervalent iodine reagent PIFA in DCM at 0 °C was reported (Scheme 48) [58].

4.2. Synthesis of 2H-indazole compounds

The chemistry of *2H*-indazoles as well as *1H*-indazoles has not been explored. However, the discovery of N_2 substituted 2H-indazole compounds may exhibit biological activities has generated recent interest in their simple and efficient preparation.

The synthesis of *2H*-indazoles using copper catalyst by the reaction of 2-bromo benzaldehyde, primary amines and sodium azide three component reaction in which the catalyst plays the key role in the formation of C–N and N–N bonds. This gives a broad scope with a high tolerance for various functional groups (Scheme 49) [59]. The ortho nitro-benzaldehyde react with 2-cyno acetic acid give intermediate indazole-N-oxide then again treated with Pd/C_2H_2 to give *2H*-indazoles as products (Scheme 50) [60]. The Davis–Beirut reaction shows the synthesis of *2H*-indazoles from o-nitroso benzaldehyde and primary amines under both acid and base catalysis. This reaction synthesizes a number of novel 3-amino-*2H*-indazole derivatives (Scheme 51) [61]. Similarly 3-cyano-*2H*-indazole N-oxides has been synthesized it gives the trypanocidal and



5-(pyridinon-1-yl) indazoles (35) **5-(furopyridinon-5-yl) indazoles (36)**

Fig. 15. Naturally accruing indazole nucleus.

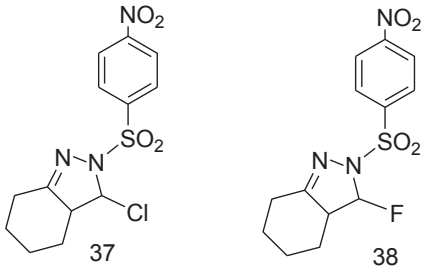


Fig. 16. Naturally accruing indazole nucleus.

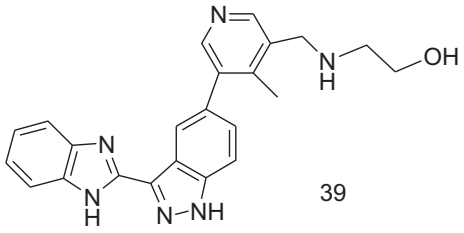
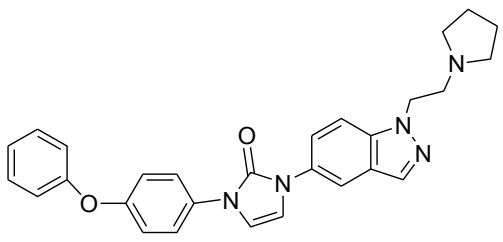


Fig. 17. Naturally accruing indazole nucleus.

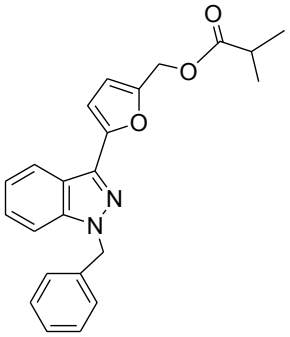
leishmanocidal activities of each derivative. Following the route shown in (Scheme 52), ortho-nitro benzaldehyde was first transformed via a Schiff base to a α-aminonitrile derivative which was next cyclized to a 3-cyano-*2H*-indazole N-oxide by treatment with a base (Et_3N or $NaHCO_3$) [62]. All ortho-substituted aldehyde react with different reagents to form *2H*-indazoles reports good yield.

The *2H*-indazoles are synthesized by the reductive cyclization of 2-nitrobenzylamines in presence of titanium reagent ($TiCl_4$/Zn) in triethylamine are reported (Scheme 53) [63]. The substituted indazoles are synthesized from 2-nitrobenzyl triphenyl



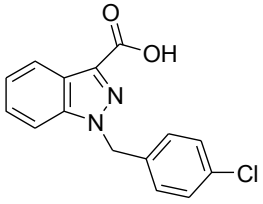
***N-1*-(2-aminoethyl)-indazoles (40)**

Fig. 18. Naturally accruing indazole nucleus.



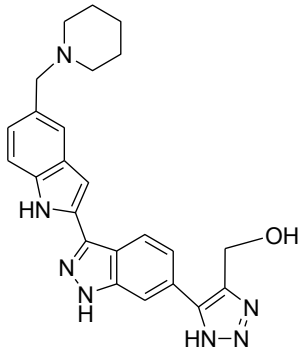
1, 3-disubstituted indazoles (41)

Fig. 19. Naturally accruing indazole nucleus.



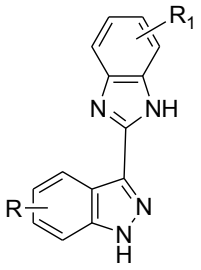
1-p-chlorobenzyl-*1H*-indazole-3-carboxylic acid (42)

Fig. 20. Naturally accruing indazole nucleus.



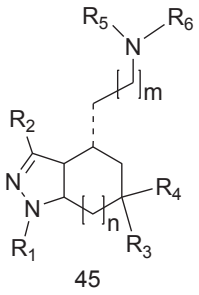
3-(indol-2-yl) indazole (43)

Fig. 21. Naturally accruing indazole nucleus.



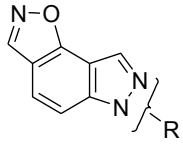
3-Benzimidazol-2-yl-1H-indazole (44)

Fig. 22. Naturally accruing indazole nucleus.



45

Fig. 23. Naturally accruing indazole nucleus.

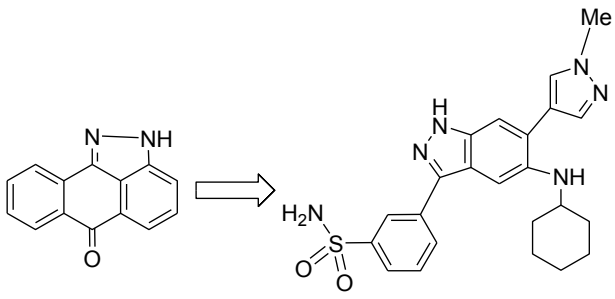


[1, 2] oxazolo[5,4-*e*] indazoles (46)

Fig. 24. Naturally accruing indazole nucleus.

phosphonium bromide and aryl isocyanates, catalyzed by sodium hydride or DBU (Scheme 54) [64]. The 3-alkoxy-2H-indazoles is prepared by the cyclization of nitro phenyl group using alcoholic solvent of 5% KOH (Scheme 55) [65]. All nitro substituted reactant gives very effective final yields are reported bellow.

The parent *2H*-indazolo[3,2-b] benzo[d]-1,3-oxazine heterocycles as well as a series of novel analogs have been synthesized utilizing two subsequent intramolecular hetero cyclizations in one pot. A variety of diversity groups were added to explore the scope of this reaction and to provide a number of new compounds for biological screening (Scheme 56) [66].



47 48

Fig. 25. Naturally accruing indazole nucleus.

The *N*-(2-nitrobenzylidene) anilines gives a mixture of 2,1-benzisoxazoles and 3-anilino-2-aryl-2*H*-indazoles in the presence of indium and iodine in MeOH, *N*-(2-nitrobenzylidene) anilines were transformed into 3-anilino-2-aryl-*2H*-indazoles as the predominant major product through the change of the solvent from protic MeOH to aprotic THF were reported (Scheme 57) [67]. A copper-catalyzed intramolecular amination reaction has been newly developed to synthesize a variety of multi-substituted *2H*-indazole and *1H*-pyrazole derivatives from easily accessible starting materials under mild conditions (Scheme 58) [68].

2H-indazoles is synthesized rapidly by [3 + 2] dipolar cycloaddition of arynes and sydnones, which proceeds under mild reaction condition and the product is reported. (Scheme 59) [69].

German scientists observed that several oxidation procedures, such as the Kornblum oxidation, applied to benzyl bromide instead of giving the expected aldehyde to from 2-phenyl-*2H*-indazole compound (Scheme 60) [70].

Starting from Baylis–Hillman adducts of cyclohexenone a two-step procedure for the formation of N-Ph-*2H*-indazoles featuring DDQ oxidation of pyrazoles intermediates has been reported (Scheme 61) [71].

Readily available 2-chloromethylaryl zinc reagents react with functionalized aryldiazonium tetrafluoroborates providing polyfunctional indazoles. Selective metalations of the 2-aryl-*2H*-indazoles afford new polycyclic aromatics. The performance of a chemoselective addition of diheteroarylzincs to aryldiazonium salts allows an efficient preparation of new heterocyclic azo compounds (Scheme 62) [72].

The synthesis of 2H-indazoles using palladium-mediated intramolecular amination reaction of N-aryl-N-(ortho-bromobenzyl)-hydrazines has been reported by Song and Yee. The conditions required for this transformation were heating in toluene at 90 °C for 15 h in the presence of $Pd(OAc)_2$, dppf and t-BuONa (Scheme 63) [73].

Using non-traditional methods Schiff bases are prepared from several amines and 2-nitrobenzaldehydes. Thus reacting nitro compounds with triethyl phosphite under microwave irradiation for the generation of nitrenes which gives insertion reactions to form indazoles (Scheme 64) [74].

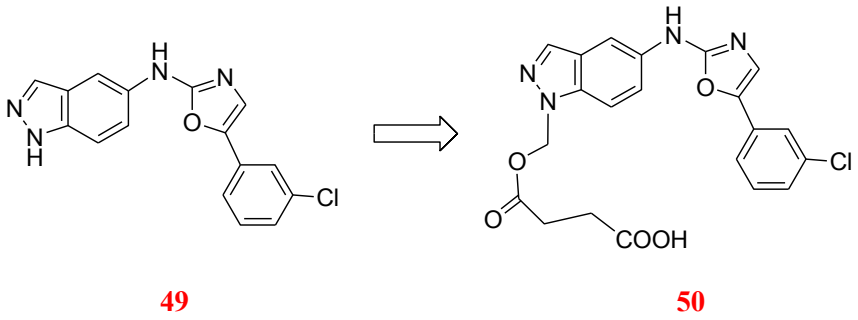
On the basis of experimental observations and deuterium labeling experiments, a mechanism involving the formation of a nitrene intermediate, strongly coordinated to the metal, was postulated (Scheme 65) [75].

Akazome et al. [76] reported the palladium-catalyzed intramolecular reductive N-heterocyclization of (2-nitro-benzylidene) amines to give the corresponding *2H*-indazole products in 48–75% isolated yields. Reactions were conducted in a stainless reactor at 100 °C for 16 h under 20 kg cm^{-2} of initial CO pressure and in the presence of a $PdCl_2(PPh_3)_2$ (5 mol%)-$SnCl_2$ (50 mol%) system. Few examples are shown in (Scheme 66).

4.3. Indazoles derivatives

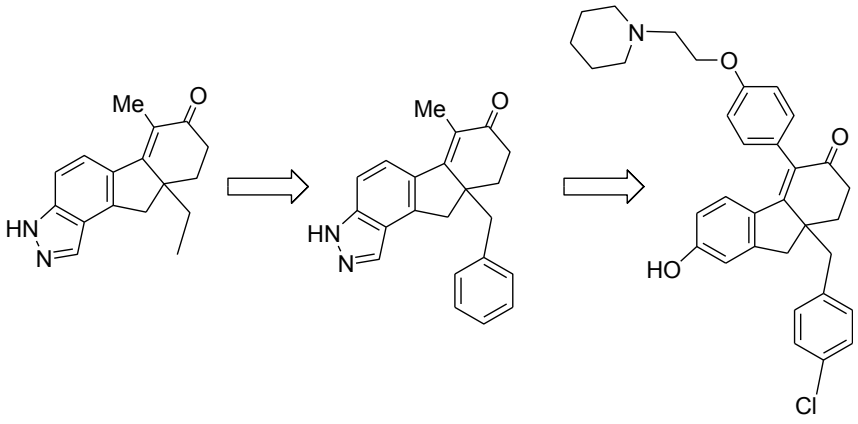
Indazole derivatives are important nitrogen containing bicyclic ring compounds having biological activity and agrochemical potential besides possessing important pharmacological activities. The indazole ring system is also present in many other compounds such as herbicides, dyes, sweeteners etc. There are many useful applications of indazole derivatives as follows:

Regioselective is very important part for the synthesis of different indazole derivatives. This selectivity is obtained using N-arylation and desilylation from 3-trimethyl silylindzoles (Scheme



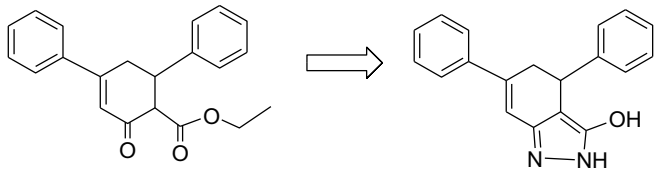
49 50

Fig. 26. Naturally accruing indazole nucleus.



51 52 53

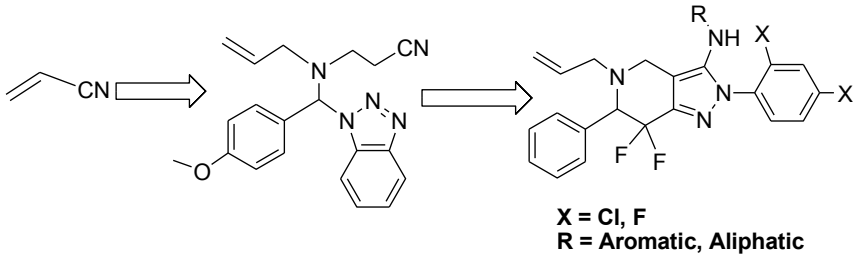
Fig. 27. Naturally accruing indazole nucleus.



Antifungal and antibacterial agents **Antibacterial and antioxidant agents**

54 55

Fig. 28. Naturally accruing indazole nucleus.



56 57

Fig. 29. Naturally accruing indazole nucleus.

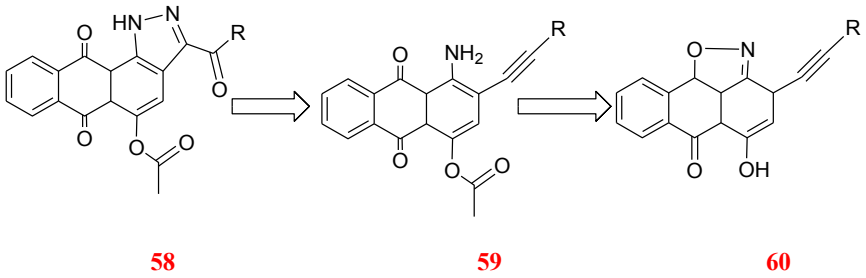


Fig. 30. Naturally accruing indazole nucleus.

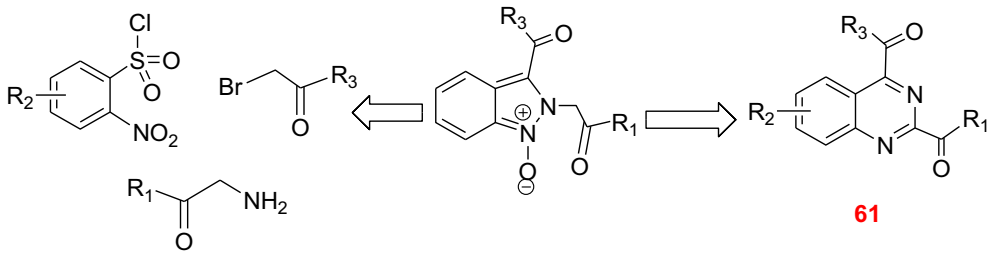


Fig. 31. Naturally accruing indazole nucleus.

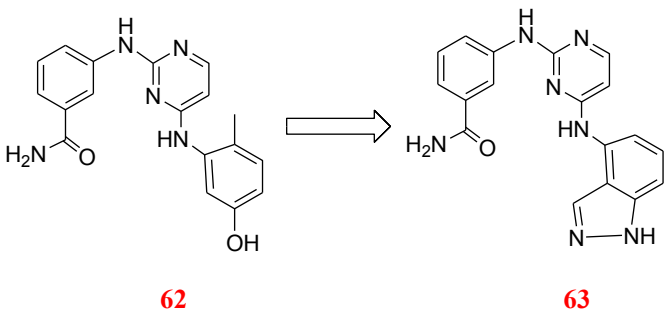


Fig. 32. Naturally accruing indazole nucleus.

67) [15]. 1-Arylindazoles obtained from 3-trimethylsilyl indazoles using 10% KOH in ethanol solution (Scheme 68) [16]. Similarly 2-methyl-2*H*-indazoles are reported using a methyl 2, 2, 2-trichloroacetimidate (Scheme 69) [77].

The synthesis of sulfonamide indazole derivatives using $SnCl_2$/$ArSO_2Cl$/Pyridine in ethanol is reported and it gives anti-proliferative activities (Scheme 70) [78]. In other example 1, 6-dihydro indazole derivatives synthesized via Larock indole annulations (Scheme 71) [79].

The derivatives of indazoles such as Nigellidine hydrobromide are synthesized using $Pb(OAc)_2/CS_2CO_3$ in toluene (Scheme 72) [80]. Similarly another reagent $Br-(CH_2)_4-Br$ in acetonitrile is reported in good yield (Scheme 73) [81].

Lewis acid promoted elimination of *p*-toluenesulfonic acid from sulfonyl indazoles and sulfonyl indoles generates the

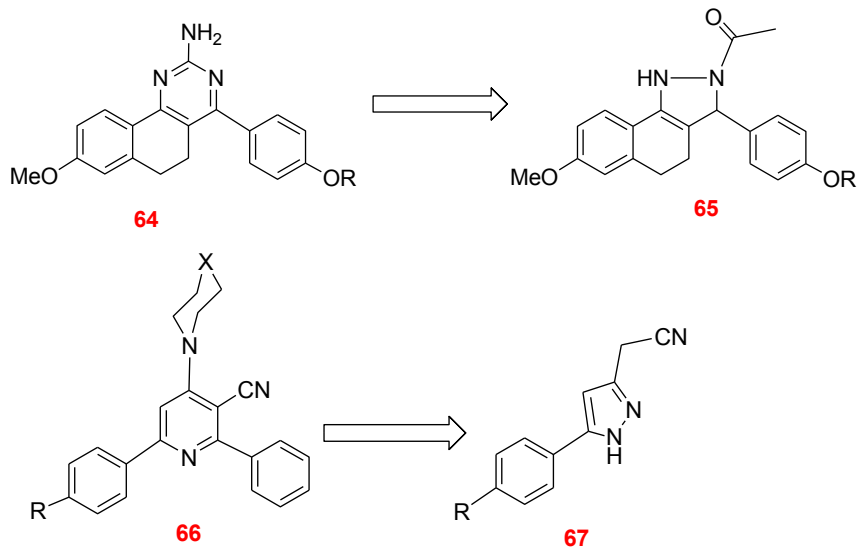


Fig. 33. Naturally accruing indazole nucleus.

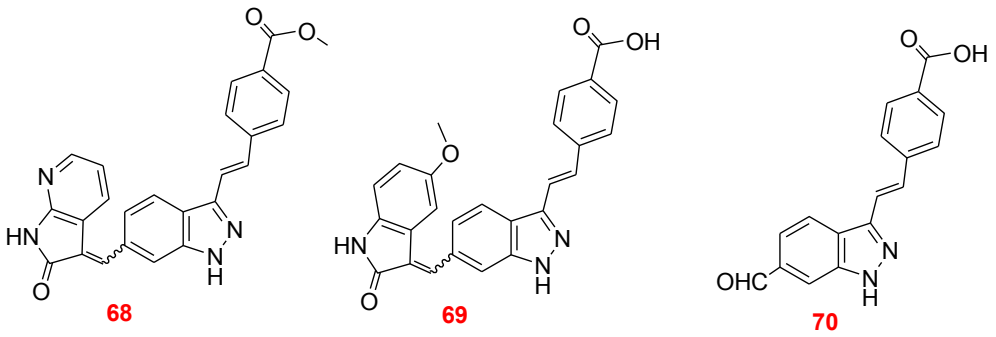


Fig. 34. Naturally accruing indazole nucleus.

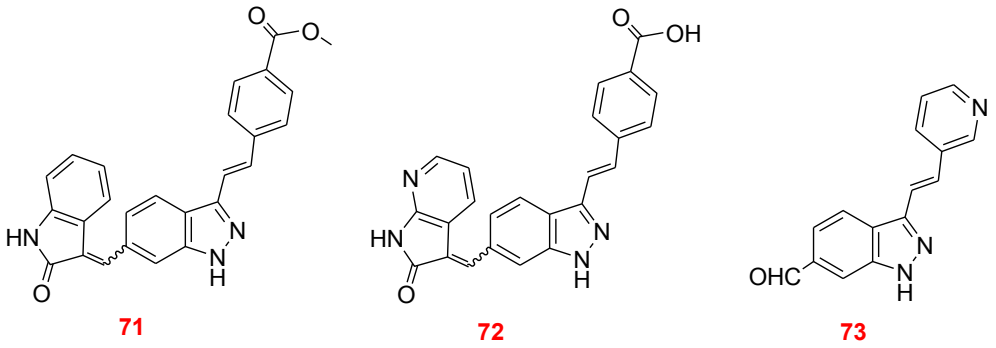


Fig. 35. Naturally accruing indazole nucleus.

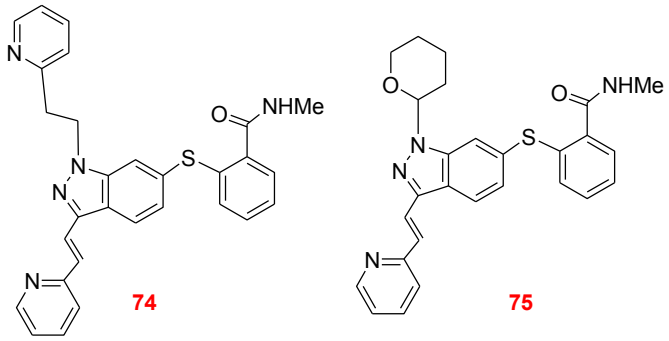
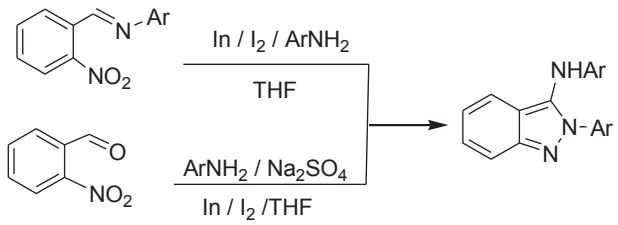


Fig. 36. Naturally accruing indazole nucleus.

corresponding iminium ion that reacts with allyltin reagent, silyl enol ethers, silyl ketene acetals and electron-rich aromatics leading to the synthesis of indazole derivatives (Scheme 74) [82].

Synthesis of 1, 3-diaryl substituted indazoles utilizing a Suzuki cross-coupling/deprotection/N-arylation processed has been studied (Scheme 75) [83].

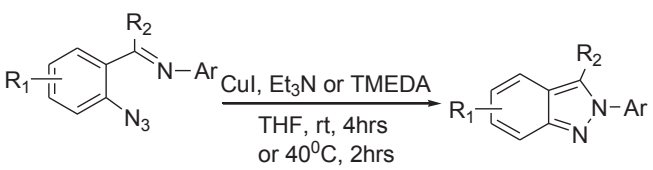


Scheme 57. Synthesis of indazole derivatives in different methods.

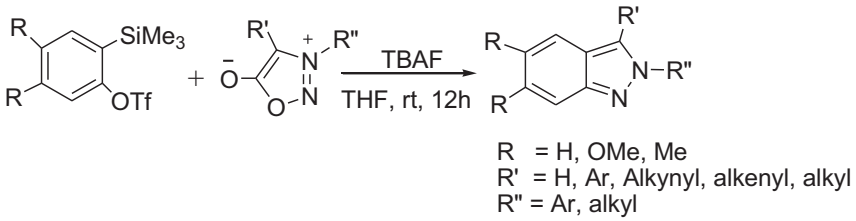
4.4. Medicinal importance of indazoles

Among the known heterocyclic compounds the indazole nucleus is potentially valuable as building-blocks in medicinal chemistry. Even so, a large number of synthetically prepared indazoles derivatives have displayed biological and pharmacological properties [84]. Such as Bendazac (**12**) is a non-steroidal anti-inflammatory agent, used as an anti-cataract drug [85]. New YC-1 indazole derivative (**13**) were synthesized and evaluated with HIF-1 transcriptional activity, in vivo [86]. Furthermore, for the mechanistic study of the YC-1 derivatives, shows the anti-proliferative activity against human cancer cells and 1, 3, 5-trisustituted indazole derivative (**14**) as an extremely potent anti-oxidant [87]. Recently it has been reported that a combination of lonidamine (**15**) was shown to have antitumor properties in phase-II and phase-III studies for the treatment of advanced breast, ovarian and lungs cancer are encouraging [88]. The 7-nitro indazoles derivative (**16**) was tested for the treatment of alcohol dependence, anti-mutagenesis and anti-oxidant properties [89]. Similarly piperidine derivative of indazole (**17**) has been patented as a non-narcotic, analgesic and antipsychotic drug [90] as shown below (Fig. 7).

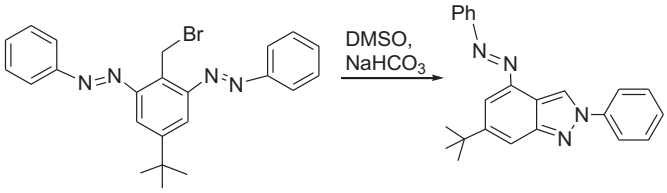
Apart from this indazoles constitute an important class of heterocycles that display interesting biological and pharmacological



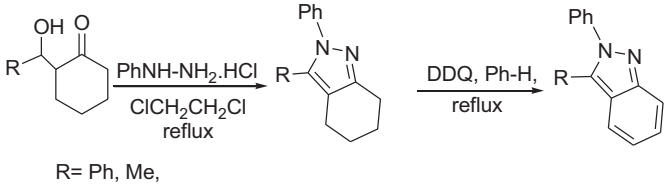
Scheme 58. Synthesis of indazole derivatives in different methods.



Scheme 59. Synthesis of indazole derivatives in different methods.



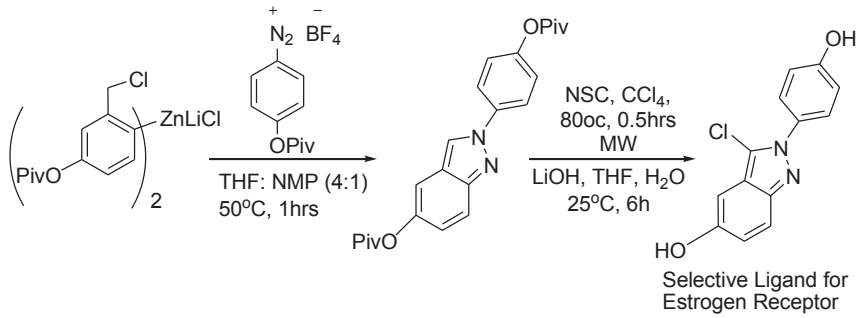
Scheme 60. Synthesis of indazole derivatives in different methods.



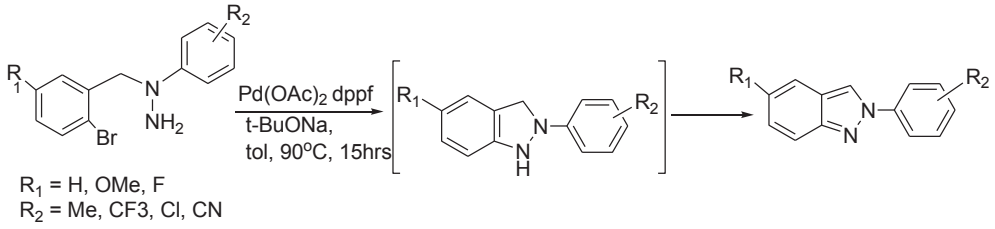
Scheme 61. Synthesis of indazole derivatives in different methods.

properties. Literature survey reveals that there are various molecules containing indazoles moiety gives an anti-depressant, anti-inflammatory, analgesic, anti-pyretic, dopamine antagonistic, anti-tumor, anti-emetic and anti-HIV activities. The indazole ring system is also present in many other compounds such as herbicides, dyes and sweeteners. Granisetron (**18**), serotonin 5-HT_3 receptor antagonist used to treat and prevent nausea and vomiting induced by cancer chemotherapy [91]. The other compounds of interest are YC-1(**19**) used [92] for the treatment of cardiovascular diseases or erectile dysfunction. Similarly the melamine concentrating hormone receptor antagonist (**20**) is believed to have a number of biological functions, including in the regulation of appetite [93] (Fig. 8).

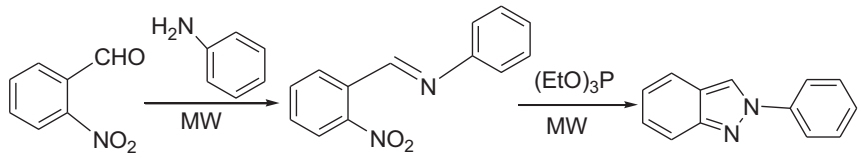
Compound (**21**) an indazolyl substituted urea derivatives is extremely potent HIV protease inhibitors. Molecular modeling studies underline the biological importance of the hydrogen bond donor properties of indazolyl nitrogen atoms [35,94,95] (Fig. 9, Table 3).



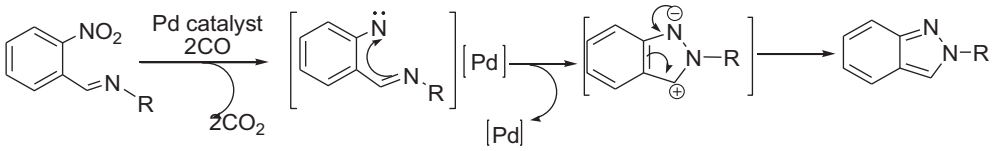
Scheme 62. Synthesis of indazole derivatives in different methods.



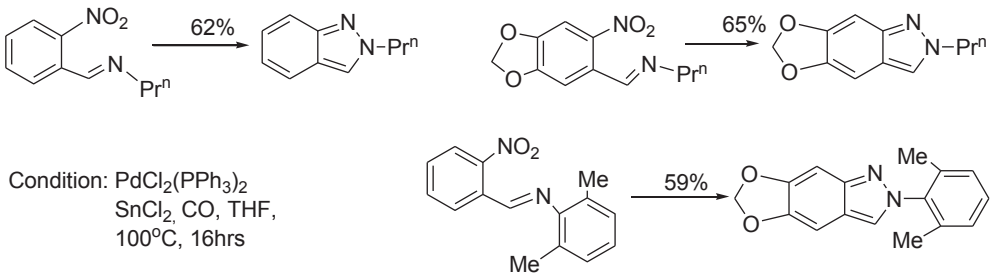
Scheme 63. Synthesis of indazole derivatives in different methods.



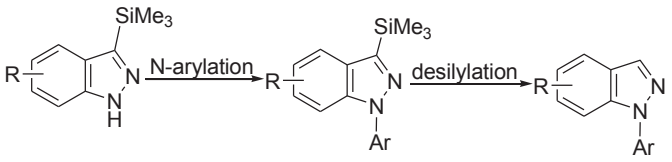
Scheme 64. Synthesis of indazole derivatives in different methods.



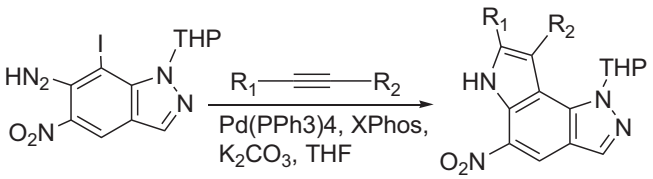
Scheme 65. Synthesis of indazole derivatives in different methods.



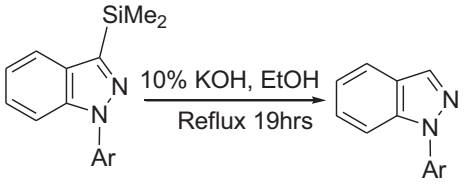
Scheme 66. Synthesis of indazole derivatives in different methods.



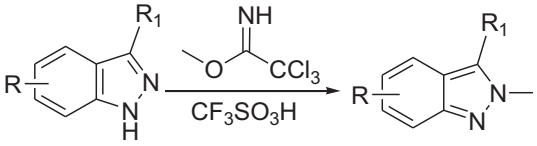
Scheme 67. Synthesis of indazole derivatives in different methods.



Scheme 71. Synthesis of indazole derivatives in different methods.

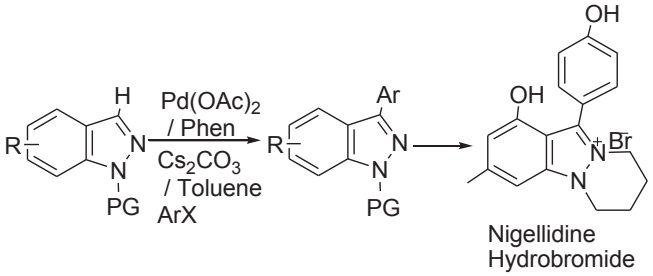


Scheme 68. Synthesis of indazole derivatives in different methods.

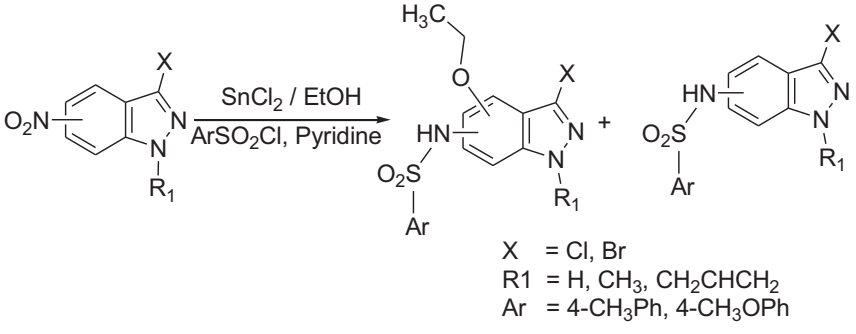


Scheme 69. Synthesis of indazole derivatives in different methods.

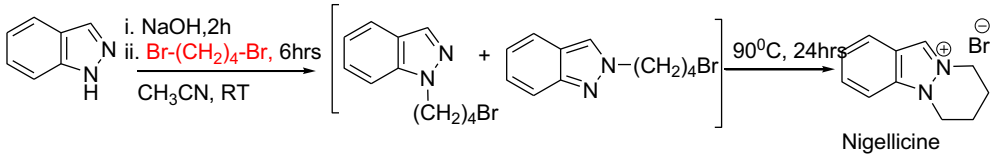
Indazole derivatives (**26**) have significant anti-inflammatory properties [100]. Metz, S. et al. [101] described fused pyrazole compounds (**27**) for the treatment of inflammation. Their physiologically acceptable salts also possess anti-inflammatory and



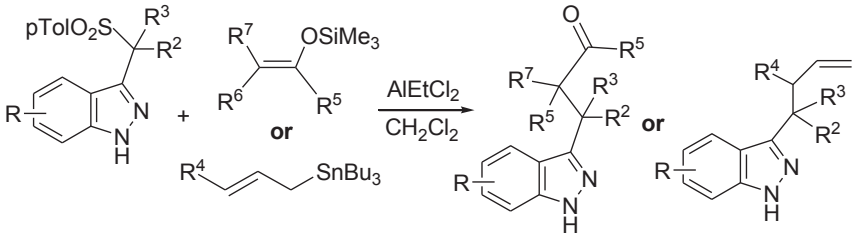
Scheme 72. Synthesis of indazole derivatives in different methods.



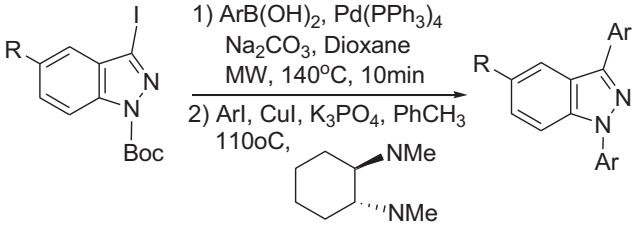
Scheme 70. Synthesis of indazole derivatives in different methods.



Scheme 73. Synthesis of indazole derivatives in different methods.



Scheme 74. Synthesis of indazole derivatives in different methods.



Scheme 75. Synthesis of indazole derivatives in different methods.

analgesic properties. A (**28**) number of in vivo biological assays were done to identify novel anti-inflammatory agents among the class of 2, 3-diaryl-4, 5, 6, 7-tetrahydro-*2H*-indazoles [60] (Fig. 10).

The 3-(4-Methylphenyl)-*1H*-indazole (**29**) of *N*-substituted derivatives are evaluated for anti-angiogenic activity.Synthesis of N-(substituted benzyl)-3-(4-methylphenyl) indazoles (**30**) has been reported as novel anti-angiogenic agents [102] (Fig. 11).

Indazole (**31**, **32**) based series of glucocorticoid receptor antagonist reported by M. Bai et al. [103]. Glucocorticoid the receptor antagonist. The SAR exploration of this scaffold yielded compounds with nanomolar affinity were reported for the glucocorticoid receptor with indications of selectivity for the preferred trans-repression mechanism (Fig. 12).

Brian S. Brown et al. [87] carried out the synthesis and SAR study of indazole (**33**) against TRPV1 antagonists leading to the discovery is described. Biological studies demonstrated potent in vitro and in vivo activity for suitable physicochemical and pharmacokinetic (Fig. 13).

Salvatore Plescia et al. [104] describes the new indazole derivatives (3-(1-ethyl-*1H*-indazol-3-yl)-2-phenylquinazolin-4(3H)-one) (**34**) and tested to evaluate antimicrobial, anti-proliferative activity. They were showed moderate anti-proliferative activity and some inhibitory activity against COX-1 and COX-2 (Fig. 14).

The synthesis and SAR study of 5-(pyridinon-1-yl) indazoles (**35**) and 5-(furopyridinon-5-yl) indazoles (**36**) as potent MCH-1 antagonists are described [105] (Fig. 15).

Maninder M. T. et al. [106] described the synthesis of new 2,3-disubstituted-3,3a,4,5,6,7-hexahydro-*2H*–indazole derivatives, and indicated that 3-(4-chlorophenyl)-2-(4-nitrophenylsulfonyl)-3,3a,4,5,6,7-hexa hydro *2H*-indazole (**37**) and 3-(4-fluorophenyl)-2-(4-nitrophenyl sulfonyl)-3,3a,4,5,6,7-hexahydro-*2H*–indazole (**38**) shows the prominent antimicrobial activity (Fig. 16).

Synthesis, modeling and structure–activity relationship of indazole as inhibitors of Tpl2 kinase are described. Through SAR modifications at the C3 and C5 positions of the indazole (**39**), we discovered compound with good potency in LANCE assay (0.047 μM) and cell-based *p*-Erk assay (0.079 μM) [107] (Fig. 17).

A series of urea-based *N-1*-(2-aminoethyl)-indazoles (**40**) were synthesized and evaluated for melanin-concentrating hormone

Table 1
Excellent yield were reported from the above Reaction Conditions.

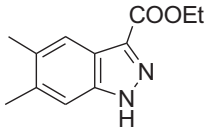
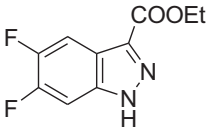
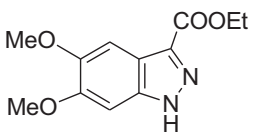
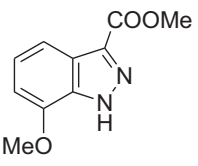
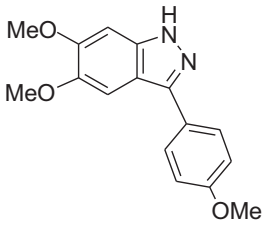
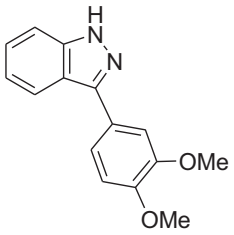
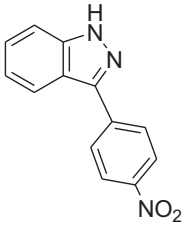
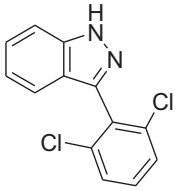
Sr. No	Product	Yield %	Sr. No.	Product	Yield %
01		87	03		45
02		84	04		65

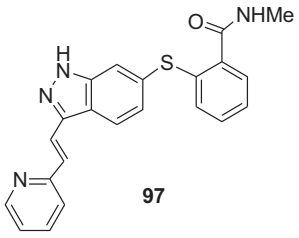
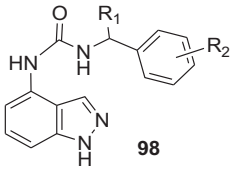
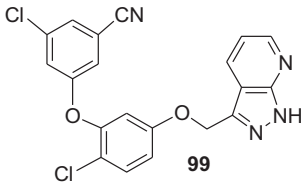
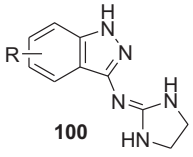
Table 2
Excellent yield were reported from the above Reaction Conditions.

Sr. No	Product	Yield %	Sr. No.	Product	Yield %
01		56	03		84
02		55	04		75

receptor 1 (MCHr1) antagonism. Several compounds that acted as MCHr1 antagonists were identified, and optimization afforded a compound with excellent binding affinity, good functional potency, and oral efficiency in a chronic model for weight loss in diet-induced obese mice [108] (Fig. 18).

Design, synthesis and insight into the structure–activity relationship of 1, 3-disubstituted indazoles (**41**) as novel HIF-1 inhibitors have been reported [109] (Fig. 19).

Table 3
Pharmaceutical drug molecule containing indazoles nucleus which have different medicinal activity.

Sr. No	Compounds	Activity	Published
01	 **97**	Axitinib	Ferrara N., [96]
02	 **98**	Chronic Pain	Kiril Lukin et al. [97]
03	 **99**	Antiretroviral	Robert Gomez et al. [98]
04	 **100**	Hypertensive	Franciszek Saczewski [99]

Anti-spermatogenic activity of 1-p-chlorobenzyl-*1H*-indazole-3-carboxylic acid (**42**) has led to the synthesis of a large number of *1H*-indazole-3-carboxylic acid derivatives [110] (Fig. 20).

The optimization of potency and selectivity for a 3-(indol-2-yl) indazole (**43**) class of Chek1 kinase inhibitors is described [111] (Fig. 21).

The 3-benzimidazol-2-yl-1H-indazole (**44**) scaffold was developed for our receptor tyrosine kinase (RTK) inhibitor program. In exploring the SAR of this series, subsets of these compounds were found to potently inhibit the enzyme c-ABL. The SAR of these compounds is described [112] (Fig. 22).

Corbera A. and Esteve, S.A. et al. [113] had reported some tetrahydro indazole (**45**) and fused pyrazole derivatives having pharmacological activity towards the sigma receptor, and their use in particular for the treatment of psychosis or pain (Fig. 23).

The [1,2] oxazolo[5,4-*e*] indazoles (**46**) show growth-inhibitor activity against human tumor cell lies generally at low micromolar concentrations are reported [114] (Fig. 24).

4.5. Drug design

Pan-Kinase Inhibitor Anthrapyrazolone is rationally used for designing of indazoles based potent Cell-Active Mps1 Kinase Inhibitors (**47**, **48**) [101] (Fig. 25).

The 5-aryl substituent of the oxazole core is identified as a potent inhibitor. The analogs show poor aqueous solubility. But *N*-acyloxymethyl analog has good activity like aqueous solubility and susceptibility to enzymatic hydrolysis (**49**, **50**) [115] (Fig. 26).

Members of this series of benzopyrazole analogs had demonstrated for better oral bioavailability (**51**–**53**) [116] (Fig. 27).

Microwave synthesis, characterization and bio-efficiency evaluation of novel chalcone based 6-carbethoxy-2-cyclohexen-1-one and 2H-indazol-3-ol derivatives has been reported (**54**, **55**) [117] (Fig. 28).

Convenient synthesis of novel N-(5-allyl-7,7-difluoro)-4,5,6,7-tetrahydro-2H-indazol-3-yl)-carboxymides has been studied (**56**, **57**) [118] (Fig. 29).

In this work, bioconjugates combine with acetylenic derivatives known to have anticancer activity and condensed anthraquinoid cycles, capable of intercalating DNA duplex (**58**–**60**) [119] (Fig. 30).

Base-catalyzed rearrangement of *2H*-indazoles 1-oxides, prepared by tandem carbon–carbon followed by nitrogen–nitrogen bond formations from easily accessible *N*-alkyl-2-nitro-*N*-(2-oxo-2-aryl-ethyl)-benzenesulfonamides using glycine, 2-nitrobenzenesulfonyl chlorides, and bromo ketones/acetates, yielded high purity quinazolines. After substitution of bromide with amine nucleophiles, acylation with carboxylic acid, and subsequent reduction of nitro group, the resulting precursors undergo cyclocondensation to quinazolinone derivatives (**61**) [120] (Fig. 31).

2, 4-Dianilino pyrimidines with a phenolic group at 4-position are potent inhibitors of Lck tyrosine kinase enzyme activity. But they have poor pharmacokinetic properties. Analogs where the 4-position was replaced by 4-amino (5-methyl-*1H*-indazole) had comparable enzyme potency and improved pharmacokinetic properties (**62**, **63**) [121] (Fig. 32).

Studies on substituted benzo[h]quinazolines, benzo [g]indazoles, pyrazoles, 2, 6-diarylpyridines as anti-tubercular agents has been done (**64**–**67**) [122] (Fig. 33).

4.6. Miscellaneous

The following indazole derivatives are biologically active but their reactivity has to be confirmed (Figs. 34–36).

5. Advantages

- The designing of small drug-like molecules with a unique structural framework is an indazole which has great importance for the pharmaceutical industry in order to speed up drug discovery.
- Indazole is a medicinally important heterocyclic moiety.
- Indazole nucleus is easily available in the nature in many alkaloids.
- Indazole derivatives has a prominent role in treatment of cancer
- The derivatives of indazoles exhibits antibacterial, anticancer, antionidants, anti-inflammatory, antidiabetic, antiviral, atniproliferative, antituberculosis, antispermetogenic activity, antipsychotic drugs etc.

6. Disadvantages

- Synthesize 1H-indazoles are suffering from several disadvantages, such as harsh reaction conditions, expensive starting materials, or carcinogenic reaction partners are used.
- Some synthesis indazoles have multistep are reported but this methodology not given very good results.

7. Conclusion

The biological and pharmaceutical properties of substituted indazoles find a wide range of application in novel drug designing. Indazole derivatives have great relevance in many field of heterocyclic chemistry and these reactions are excellent and have medicinal approach to their synthesis. Besides the developments of new reactions or improved conditions for the classical ones, future developments in this field will probably involve the application of indazole motifs strategies to target oriented synthesis. We hope this review will serve to stimulate research in this fascinating and very useful area for the synthesis of indazole derivatives.

Acknowledgments

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References

[1] Aaron D. Mills, Musa Z. Nazer, Makhluf J. haddadin, Mark J. Kurth, J. Org. Chem. 71 (2006) 2687–2689.
[2] Tianshui Zhang, Weiliang Bao, J. Org. Chem. 78 (2013) 1317–1322.
[3] Pan Li, Chunrui Wu, Jingjing Zhao, Donald C. Rogness, Feng Shi, J. Org. Chem. 77 (2012) 3149–3158.
[4] Christian Spiteri, Steve Keeling, John E. Moses, Org. Lett. 12 (2010) 3368–3371.
[5] Manian Rajesh Kumar, Ahbyeol Park, Sunwoo Lee, Org. Lett. 13 (2011) 3543–3545.
[6] J. Elguero, A.R. katritzky, O.V. Denisko, Adv. Heterocycl. Chem. 76 (2000) 157–323.
[7] C.T. Fatima, R. Helene, F.A. Ines, M. Joao, M. Curto, D.M. Teresa, Isabel Bento, Molecules 11 (2006) 867.
[8] Y.M. Liu, J.S. Yang, Q.U. Liu, Chem. Pharm. Bull. 52 (2004) 454–455.
[9] E. Abu-Irmaileh Barakat, U. Afifi Fatma, J. Ethnopharmacol. 89 (2003) 193–197.
[10] M. Eddouks, M. Maghrani, A. Lemhadri, M.L. Quahidi, H. Jouad, J. Ethnopharmacol. 82 (2002) 97–103.
[11] O. Said, K. Khali, S. Fulder, H. Azaizeh, J. Ethnopharmacol. 83 (2002) 251–265.
[12] A. Schmidt, L. Merkel, W. Eisfeld, Eur. J. Org. Chem. (2005) 2124–2130.
[13] R. Attaur, S. Malik, S.S. Hasan, M.I. Choudharry, C.Z. Ni, J. Clardy, Tetrahedron Lett. 36 (1995) 1993–1996.
[14] P.D. Lokhande, Abdul Raheem, S.T. Sabale, A.R. Chabukswar, S.C. Jagdale, Tetrahedron Lett. 48 (2007) 6890–6892.

[15] Yoshiyuki Hari, Yoshimichi Shoji, Toyohiko Aoyama, Tetrahedron Lett. 46 (2005) 3771.
[16] Kirill Lukin, Margaret C. Hsu, Dilinie Fernando, M. Robert Leanna, J. Org. Chem. 71 (2006) 8166–8172.
[17] S. Caron, E. Vazaqnez, Synthesis (1999) 588.
[18] Digambar D. Gaikwad, Rajendra P. Pawar, J. Iran. Chem. Res. 3 (2010) 191–194.
[19] Sunita S. Shinde, Satish U. Deshmukh, Rjendra P. Pawar, Rajendra p. Marathe, Rajesh B. Nawale, Digambar D. Gaikwad, Der Chem. Sin. 1 (2010) 29–34.
[20] Digambar D. Gaikwad, Syed Abed, Rajendra P. Pawar, Int. J. ChemTech Res. 1 (2009) 442–445.
[21] Miklos Nyeges, Andrea Viranyi, Weimin Zhang, Paul W. Groundwater, Gabor Blasko, Laszlo Toke, Tetrahedron 60 (2004) 9937.
[22] Rob C. Wheeler, Emma Baxter, Ian B. Campbell, Simon J.F. Macdonald, Am. Chem. Soc. 15 (3) (2011) 565–569.
[23] D. Ramesh, B. Sreenivasulu, Indian J. Het. Chem. 13 (2003) 163–164.
[24] Chan Sik Cho, Dong kwon Lim, Nam Ho Heo, Tae Jeong Kim, Sang Chul Shim, Chem. Commun. (2004) 104.
[25] J. Lee, H. Choi, K.H. Kim, S. Jeong, J.W. Park, C.S. Baek, S.H. Lee, Bioorg. Med. Chem. Lett. 18 (2008) 2292.
[26] C.M. Counceller, C.C. Eichman, B.C. Wray, J.P. Stambuli, Org. Lett. 10 (2008) 1021.
[27] Klyofumi Inamoto, Mika Katsuno, Takashi Yoshino, Yukari Aral, Kou Hiroya, Takao Sakamoto, Tetrahedron 63 (2007) 2695.
[28] Han-Jun Liu, Shiang-Fu Hung, Chuan-Lin Chen, Mei-Huey Lin, Tetrahedron 69 (2013) 3907–3912.
[29] S. Peruncheralathan, T.A. Khan, H. Ila, H. Junjappa, Tetrahedron 60 (2004) 3457–3464.
[30] Yoshiyuki Hari, Ryosuke Sone, Toyohiko Aoyama, Org. Biomol. Chem. 7 (2009) 2804–2808.
[31] X. Xiong, Y. Jiang, D. Ma, Org. Lett. 14 (2012) 2552–2555.
[32] B.C. Wray, J.P. Stambuli, Org. Lett. 12 (2010) 4576–4579.
[33] V. Lefebvre, T. Cailly, F. Fabis, S. Rault, J. Org. Chem. 75 (2010) 2730–2732.
[34] Thomé, Claire Besson, Tillmann Kleine, Carsten Bolm, Angew. Chem. 52 (2013) 7509–7513.
[35] Jung-Hui Sun, Christopher A. Teleha, Jia-Sheng Yan, James D. Rodgers, David A. Nugiel, J. Org. Chem. 62 (1997) 5627–5629.
[36] Fredrik Lehmann, Tobias Koolmeister, Luke R. Odell, Martin Scobie, Org. Lett. 11 (2009) 5078–5081.
[37] I. Magano, M. Waldo, D. Greene, E. Nord, Org. Process Res. Dev. 12 (2008) 877.
[38] F. Crestey, V. Collot, S. Stiebing, J.-F. Lohier, J. Sopkova-de Oliveira Santos, S. Rault, Tetrahedron Lett. 48 (2007) 2457.
[39] Tuula Kylmala, Antti Hamalainen, Noora Kuuloja, Jan Tois, Robert Franzén, Tetrahedron 66 (2010) 8854–8861.
[40] Takehiko Kawakami, Koji Uehata, Hitomi Suzuki, Org. Lett. 2 (2000) 413–415.
[41] Yajing Lian, Robert G. Bergman, Luke D. Lavis, Jonathan A. . Ellman, J. Am. Chem. Soc. 135 (2013) 7122–7125.
[42] Da-Gang Yu, Mamta Suri, Frank Glorius, J. Am. Chem. Soc. 135 (2013) 8802–8805.
[43] Antonio Palumbo Piccionello, Andrea Pace, Ivana Pibiri, Silvestre Buscemi, Nicolò Vivona, Tetrahedron 62 (2006) 8792–8797.
[44] P. Schumann, V. Collot, Y. Hommet, W. Gsell, F. Dauphin, J. Sopkova, E.T. Mackenzie, D. Duval, M. Boulouard, S. Rault, Bioorg. Med. Chem. Lett. 11 (2001) 153.
[45] D. Zhang, D. Kohlman, J. Krushinki, S. Liang, B.P. Ying, J.E. Relly, S.R. Dinn, D.B. Wainscot, S. Nutter, W. Gough, D.L.G. Nelson, J.M. Schaus, Y.C. Xu, Bioorg. Med. Chem. Lett. 14 (2004) 6011.
[46] Paola L. Lucero, Walter J. Peláez, Zsuzsanna Riedl, Gyorgy Hajos, Elizabeth L. Moyano, Gloria I. Yranzo, Tetrahedron 68 (2012) 1299–1305.
[47] V. Leroy, G.E. Lee, J. Lin, S.H. Herman, T.B. Lee, Org. Process Res. Dev. 5 (2001) 179.
[48] P. Li, C. Wu, J. Zhao, D.C. Rogness, F. Shi, J. Org. Chem. 77 (2012) 3127–3133.
[49] Vincent Leroy, George E. Lee, Jiang Lin, Sandra H. Herman, Thomas B. Lee, Org. Process Res. Dev. 5 (2001) 179–183.
[50] Z. Liu, F. Shi, P.D.G. Martinze, C. Raminelli, R.C. Larock, J. Org. Chem. 73 (2008) 219–226.
[51] P. Li, J. Zhao, C. Wu, R.C. Larock, F. Shi, Org. Lett. 13 (2011) 3340–3343.
[52] Jens Maes, Tom R.M. Rauws, Bert U.W. Maes, Eur. J. Med. Chem. 19 (2013) 9137–9141.
[53] Kiyofumi Inamoto, Mika Katsuno, Takashi Yoshino, Yukari Arai, Kou Hiroya, Takao Sakamoto, Tetrahedron 63 (2007) 2695–2711.
[54] Chittari Pabba, Hong-Jun Wang, Susan R. Mulligan, Zhen-Jia Chen, Todd M. Stark, Brian T. Gregg, Tetrahedron Lett. 46 (2005) 7553–7557.
[55] (a) T.J. Watson, T.A. Ayers, N. Shah, D. Wenstrup, M. Webster, D. Freund, Org. Process Res. Dev. 7 (2003) 521;
(b) C. Pabba, H.-J. Wang, S.R. Mulligan, Z.-J. Chen, T.M. Stark, B.T. Gregg, Tetrahedron Lett. 46 (46) (2005) 7553.
[56] D. Bauer, D.A. Whittington, A. Coxon, J. Bready, S.P. Harriman, V.F. Patel, A. Polverino, J.-C. harmange, Bioorg. Med. Chem. Lett. 18 (2008) 4844.
[57] D.H. Vyas, S.D. Tala, J.D. Akbari, M.F. Dhaduk, H.S. Joshi, Indian J. Chem. 44B (2009) 1405–1410.
[58] A. Correa, I. Tellitu, E. Dominguez, San Martin, Org. Chem. 55 (2006) 4724.
[59] M.R. Kumar, A. Park, N. Park, S. Lee, Org. Lett. 13 (2011) 3542–3545.
[60] Ornelio Rosati, Massimo Curini, Maria Carla Marcotullio, Antonio Macchiarulo, Marina Perfume, Laura Mattioli, Francesco Rismondo, Giancarlo Cravotto, Bioorg. Med. Chem. 15 (2007) 3463.
[61] Belem Avila, Mohammad H. El-Dakdouki, Musa Z. Nazer, Jason G. Harrison, Dean J. Tantillo, Makhluf J. Haddadin, Mark J. Kurth, Tetrahedron Lett. 53 (2012) 6475–6478.
[62] A. Gerpe, O.E. Piro, H. Cerecetto, M. Gonzalez, J. Mol. Struct. 98 (2007) 871.
[63] Fang Sun, Xian Feng, Xuan Zhao, Zhi-Bin Huang, Da-Qing Shi, Tetrahedron 68 (2012) 3851–3855.
[64] Abutariq Taher, Sweta Ladwa, Srinath Thirumalai Rajan, George W. Weaver, Tetrahedron Lett. 41 (2000) 9893–9897.
[65] Aaron D. Mills, Musa Z. Nazer, Makhluf J. Haddadin, Mark J. Kurth, J. Org. Chem. 71 (2006) 2687–2689.
[66] Jeffrey D. Butler, Danielle M. Solano, Lori I. Robins, Makhluf J. Haddadin, Mark J. Kurth, J. Org. Chem. 73 (2008) 234–240.
[67] Gil Hwan Ahn, Jung June Lee, Young Moo Jun, Byung Min Lee, Byeong Hyo Kim, Org. Biomol. Chem. 5 (2007) 2472–2485.
[68] Jiantao Hu, Yongfeng Cheng, Yiqing Yang, Yu Rao, Chem. Commun. 47 (2011) 10133–10135.
[69] C. Wu, Y. Fang, R.C. Larock, F. Shi, Org. Lett. 12 (2010) 2171–2173.
[70] M.V. Peters, R.S. Stoll, R. Goddard, G. Buth, S. Hecht, J. Org. Chem. 71 (2006) 7840.
[71] K.Y. Lee, S. Gowrisankar, J.N. Kim, Tetrahedron Lett. 46 (2005) 5387.
[72] Benjamin Haag, Zhihua Peng, Paul Knochel, Org. Lett. 11 (2009) 4270–4273.
[73] J.J. Song, N.K. Yee, Org. Lett. 2 (2000) 519.
[74] Deepu John Varughese, Maghar S. Manhas, Ajay K. Bose, Tetrahedron Lett. 47 (2006) 6795–6797.
[75] A. Gerpe, G. Aguirre, L. Boaini, H. Cerecetto, M. Gonzales, C. Olea Azar, C. Rigol, J.D. Maya, A. Morello, O.E. Piro, V.J. Aran, A. Azqueta, A. Lopez De Cerain, A. Monge, M.A. Rojas, G. Yaluff, Bioorg. Med. Chem. 14 (2006) 3467.
[76] M. Akazome, T. Kondo, Y. Watanabe, J. Org. Chem. 59 (1994) 3375.
[77] Sudhakar Reddy Baddam, N. Uday Kumar, A. Panasa Reddy, Rakeshwar Bandichhor, Tetrahedron Lett. 54 (2013) 1661–1663.
[78] Najat Abbassi, Hakima Chicha, El Mostapha Rakib, Abdellah Hannioui, Mdaghri Alaoui, Abdelouahed Hajjaji, Detlef Geffken, Cinzia Aiello, Rosaria Gangemi, Camillo Rosano, Maurizio Viale, Eur. J. Med. Chem. 57 (2012) 240–249.
[79] Laurent Gavara, Fabrice Anizon, Pascale Moreau, Tetrahedron 67 (2011) 7330–7335.
[80] Mengchun Ye, Andrew J.F. Edmunds, James A. Morris, David Sale, Yejia Zhang, Chem. Sci. 4 (2013) 2374–2379.
[81] Haresh Sivaram, Ramasamy Jothibasu, Han Vinh Huynh, Organometallics 31 (2012) 1195–1203.
[82] Laura Marsili, Alessandro Palmieri, Marino Petrini, Org. Biomol. Chem. 8 (2010) 706–712.
[83] James M. Salovich, Craig W. Lindsley, Corey R. Hopkins, Tetrahedron Lett. 51 (2010) 3796–3799.
[84] R. Atta-ur, S. Malik, S.S. Hasan, M.I. Choudhary, C.Z. Ni, Clardy, Tetrahedron Lett. 36 (1995) 1993–1996.
[85] H. Cerecetto, A. Gerpe, M. Gonzalez, V.J. Aran, Ocariz C. Ochoa de, Mini Rev. Med. Chem. 5 (2005) 869–878.
[86] Ayano Takeuchi, Makihito Hori, Shinichi Sato, Hyun Seung Ban, Takahir Kuchimaru, Shinae Kizaka-Kondoh, Takao Yamori, Hiroyuki Nakamura, Med. Chem. Commun. 3 (2012) 1455–1461.
[87] S. Brian, R.K. Brown, J.P. Richard, D. Stanley, R.K. John, K.J. Tammie, M.H. Steven, A.M. Heath, R.B. Bruce, P.S. Prisca Honore, R.B.M. Puttfarcken, C.M. Kennan, R.F. Connie, L. Chih-Hung, Bioorg. Med. Chem. Lett. 20 (2010) 3291–3294.
[88] S. Di Cosimo, G. Ferretti, P. Papaldo, P. Carlini, A. Fabi, F. Cognetti, Drugs Today Barc. 39 (2003) 157–174.
[89] K.W. Locke, R.W. Dunn, J.W. Hubbard, C.L. Vanselous, M. Cornfeldt, F. Stuart, J.T. Strupczewski, Studies on the synthesis and rearrangement of indazolylpyridinium, Drug Dev. Res. 19 (1990) 239–256.
[90] S.S. Matthew, J.S. Mitchell, Org. Biomol. Chem. 2 (2004) 2551–2554.
[91] P.I. Hesketh, D.R. Gandara, J. Natl. Cancer Inst. 83 (45) (1991) 613–620.
[92] M. Nakane, Clin. Chem. Lab. Med. 41 (2003) 865–870.
[93] A.J. Souers, J. Gao, M. Brune, F. Bush, D. Wodka, A. Vasudevan, A.S. Judd, M. Mulhern, S. Brodjian, B. Dayton, R. Shapiro, L.E. Hernandez, K.C. Marsh, H.L. Sham, C.A. Collins, P.R. Kym, J. Med. Chem. 48 (2005) 1318–1321.
[94] Mona Patel, James D. Rodgers, Robert J. McHugh Jr., Barry L. Johnson, Beverly C. Cordova, Ronald M. Klabe, Lee T. Bacheler, Susan Erickson-Viitanen, Soo S. Ko, Bioorg. Med. Chem. Lett. 9 (1999) 3217–3220.
[95] C. Dell'Erba, M. Novi, G. Petrillo, C. Tavani, Tetrahedron 48 (1992) 325.
[96] N. Ferrara, Oncologist 9 (Suppl. 1) (2004) 2–10.
[97] Kirill Lukin, Margaret C. Hsu, Gilles Chambournier, Brian Kotecki, C.J. Venkatramani, M. Robert Leanna, Org. Process Res. Dev. 11 (2007) 578–584.
[98] Robert Gomez, Samson J. Jolly, Theresa Williams, Joseph P. Vacca, Maricel Torrent, Georgia McGaughey, Ming-Tain Lai, Peter Felock, Vandna Munshi, Daniel DiStefano, Jessica Flynn, Mike Miller, Youwei Yan, John Reid, Rosa Sanchez, Yuexia Liang, Brenda Paton, Bang-Lin Wan, Neville Anthony, J. Med. Chem. 54 (2011) 7920–7933.
[99] Franciszek Sączewski, Anita Kornicka, Alan L. Hudson, Shayna Laird, Mika Scheinin, Jonne M. Laurila, Apolonia Rybczyńska, Konrad Boblewski, Artur Lehmann, Maria Gdaniec, Bioorg. Med. Chem. 19 (2011) 321–329.

[100] H. Kawakubo, T. Sone, K. Wakigawa, T. Narita, Yakugaki Zasshi 107 (1987) 28–36.
[101] S. Metz , M. Clare, J. Crich, T. Hagen, G.J. Hanson, H. Huang, S.J. Houdek, M.A. Stealey, M.L. Vazquez, R.M. Weier, X. Xu, EP 1427706 B1 (2004).
[102] Li-Jiau Huang, Mei-Ling Shih, Hua-Sin Chen, Shiow-Lin Pan, Che-Ming Teng, Fang-Yu Lee, Sheng-Chu Kuo, Bioorg. Med. Chem. 14 (2006) 528–536.
[103] Mei Bai, Grant Carr, Russell J. DeOrazio, Thomas D. Friedrich, Svetlana Dobritsa, Kevin Fitzpatrick, Peter R. Guzzo, Douglas B. Kitchen, Michael A. Lynch, Denise Peace, Mohammed Sajad, Alexander Usyatinsky, Mark A. Wolf, Bioorg. Med. Chem. Lett. 20 (2010) 3017–3020.
[104] P. Salvatore, R. Demetrio, P. Fabiana, C. Giovanni, M. Benedetta, D. Giuseppe, Maria, R. Valeria, G.C. Maria, B. Gabriella, M. Fiorella, ARKIVOC 10 (2010) 163–177.
[105] Matthew D. Surman, Emily E. Freeman, James F. Grabowski, Mark Hadden, Alan J. Henderson, Guowei Jiang, Xiaowu (May) Jiang, Michele Luche, Yuri Khmelnitsky, Steven Vickers, Jean Viggers, Sharon Cheetham, Peter R. Guzzo, Bioorg. Med. Chem. Lett. 20 (2010) 7015–7019.
[106] M.T. Maninder, R.W. Sharad, S.A. Shyam, N. Balasubramanian, Synthesis, antimicrobial activity and QSAR studies of new 2,3-disubstituted-3,3a,4,5,6,7-hexahydro-2H-indazoles, Bioorg. Med. Chem. Lett. 19 (2009) 2960–2964.
[107] Yonghan Hu, Derek Cole, Rajiah Aldrin Denny, David R. Anderson, Manus Ipek, Yike Ni, Xiaolun Wang, Suvit Thaisrivongs, Timothy Chamberlain, J. Perry Hall, Julie Liu, Michael Luong, Lih-Ling Lin, Jean-Baptiste Telliez, Ariamala Gopalsam, Bioorg. Med. Chem. Lett. 2 (2011) 4758–4761.
[108] Andrew J. Souers, Ju Gao, Dariusz Wodka, Andrew S. Judd, Mathew M. Mulhern, James J. Napier, Michael E. Brune, Eugene N. Bush, Sevan J. Brodjian, Brian D. Dayton, Robin Shapiro, Lisa E. Hernandez, Kennan C. Marsh, Hing L. Sham, Christine A. Collins, Philip R. Kym, Bioorg. Med. Chem. Lett. 15 (2005) 2752–2757.
[109] Hongchan An, Nam-Jung Kim, Jong-Wha Jung, Hannah Jang, Jong-Wan Park, Young-Ger Suh, Bioorg. Med. Chem. Lett. 21 (2011) 6297–6300.
[110] A. Caputo, B. Silvestrini, Lonidamine, a new approach to cancer therapy, Oncology 41 (1984) 2–6.
[111] Mark J. Kurth, Marilyn M. Olmstead, Makhluf J. Haddadin, J. Org. Chem. 70 (2005) 1060–1062.
[112] Christopher M. McBride, Paul A. Renhowe, Thomas G. Gesner, Johanna M. Jansen, Julie Lin, Sylvia Ma, Yasheen Zhou, Cynthia M. Shafer, Bioorg. Med. Chem. Lett. 16 (2006) 3789–3792.
[113] A. Corbera, S.A. Esteve, EP.1634873 Al. (2006).
[114] Paola Barraja, Virginia Spanò, Daniele Giallombardo, Patrizia Diana, Alessandra Montalbano, Anna Carbone, Barbara Parrino, Girolamo Cirrincione, Tetrahedron 69 (2013) 6474–6477.
[115] Se-Ho Kim, Benjamin Markovitz, Richard Trovato, Brett R. Murphy, Harry Austin, Adam J. Willardsen, Vijay Baichwal, Scott Morham, Ashok Bajji, Bioorg. Med. Chem. Lett. 23 (2013) 2888–2892.
[116] Olaf Kinzel, Daniela Fattori, Ester Muraglia, Paola Gallinari, Maria Chiara Nardi, Chantal Paolini, Giuseppe Roscilli, Carlo Toniatti, Odalys Gonzalez Paz, Ralph Laufer, Armin Lahm, Anna Tramontano, Riccardo Cortese, Raffaele De Francesco, Gennaro Ciliberto, Uwe Koch, J. Med. Chem. 49 (2006) 5404–5407.
[117] N.A. Shakil, Manish K. Singh, M. Sathiyendiran, J. Kumar, Jasdeep C. Padaria, Eur. J. Med. Chem. 59 (2013) 120–131.
[118] Chigalli N. Revanna, Goravanahalli M. Raghavendra, Kebbahalli N. Nandeesh, Doddamedur G. Bhadregowda, Kanchugarakoppal S. Rangappa, Kempegowda Mantelingu, Tetrahedron Lett. 54 (2013) 5224–5226.
[119] A.A. Stepanov, L.M. Gornostaev, S.F. Vasilevsky, E.V. Arnold, V.I. Mamatyuk, D.S. Fadeev, B. Gold, I.V. Alabugin, J. Org. Chem. 76 (2011) 8737–8748.
[120] Sona Krupkova, Greg A. Slough, Viktor Krchnak, J. Org. Chem. 75 (2010) 4562–4566.
[121] Paul Bamborough, Richard M. Angell, Inder Bhamra, David Brown, James Bull, John A. Christopher, Anthony W.J. Cooper, Lynsey H. Fazal, Ilaria Giordano, Lucy Hind, Vipulkumar K. Patel, Lisa E. Ranshaw, Martin J. Sims, Philip A. Skone, Kathryn J. Smith, Emma Vickerstaff, Melanie Washington, Bioorg. Med. Chem. Lett. 17 (2007) 4363–4368.
[122] Hardesh K. Maurya, Ruby Verma, Saba Alam, Shweta Pandey, Vinay Pathak, Sandeep Sharma, Kishore K. Srivastava, Arvind S. Negi, Atul Gupta, Bioorg. Med. Chem. Lett. 23 (2013) 5844–5849.

Further reading

[123] Ananda Thangadurai, Maninder Minu, Sharad Wakode, Shyam Agrawal, Balasubramanian Narasimhan, Med. Chem. Res. 21 (2012) 1509–1523.
[124] Sunil U. Tekale, Vivekanand B. Jadhav, Vijay P. Pagore, Sushma S. Kauthale, Digambar D. Gaikwad, Rajendra P. Pawar, Mini Rev. Org. Chem. 10 (2013) 281–301.
[125] N.A. Ali, B.A. Dar, V. Pradhan, M. Farooqui, Mini Rev. Med. Chem. 13 (2013) 792–800.
[126] Andre Guingant, AtlanChim Pharma (2008) 1–12.
[127] Chengjie Li, Tianyi Zhang, Zhe Zeng, Xiujun Liu, Yunfeng Zhao, Bao Zhang, Yaqing Feng, Org. Lett. 14 (2012) 479–481.
[128] F. Rodrigues de Sa Alves, E.J. Barreiro, C.A.M. Fraga, Mini Rev. Med. Chem. 9 (2009) 782–793.
[129] E. Abele, R. Abele, O. Dzenitis, E. Lukevics, Chem. Heterocycle. Compd. 39 (2003) 3–35.
[130] S. Bhattacharya, P. Chaudhuri, Curr. Med. Chem. 15 (2008) 1762–1777.
[131] M. Alamgir, D.S.C. Back, N. Kumar, Top. Heterocycl. Chem. 9 (2007) 87–118.
[132] M. Boiani, M. Gonzalez, Mini Rev. Med. Chem. 5 (2005) 409–424.
[133] Y.M. Liu, J.S. Yang, Q.H. Liu, Chem. Pharm. Bull. 52 (2004) 454–455.
[134] Mark E. Fraley, Justin T. Steen, Edward J. Brnardic, Kenneth L. Arrington, Keith L. Spencer, Barbara A. Hanney, Yuntae Kim, George D. Hartman, Steven M. Stirdivant, Bob A. Drakas, Keith Rickert, Eileen S. Walsh, Kelly Hamilton, Carolyn A. Buser, James Hardwick, Weikang Tao, Stephen C. Beck, Xianzhi Mao, Robert B. Lobell, Laura Sepp-Lorenzino, Bioorg. Med. Chem. Lett. 16 (2006) 6049–6053.
[135] Nicolas Isambert, Maria Del Mar Sanchez Duque, Jean Christophe Plaquevent, Yves Genisson, Jean Rodriguez, Thierry Constantieux, Chem. Soc. Rev. 40 (2011) 1347–1357.
[136] Sebastian Brauch, Sander S. Van Berkel, Bernhard Westermann, Chem. Soc. Rev. 42 (2013) 4948–4962.
[137] Veronica Estevez, Mercedes Villacampa, Carlos Menendez, Chem. Soc. Rev. 39 (2010) 4402–4421.
[138] Zhor El. Asri, Yves Genisson, Frederic Guillen, Olivier Basle, Nicolas Isambert, Maria Del Mar Sanchez Duque, Sonia Ladeira, Jean Rodriguez, Thierry Constantieux, Jean Christophe Plaquevent, Green Chem. 13 (2011) 2549–2552.
[139] M.J. Haddadin, W.E. Conrad, M.J. Kurth, Mini Rev. Med. Chem. 12 (2012) 1293.