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Review Article

Recent Progress in Chemistry and Biology of Indazole and its Derivatives: A Brief Review

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Abstract

The biological and medicinal properties of indazoles have prompted enormous research aimed at developing synthetic routes to these heterocyles. This review focuses on the biological properties associated with this system, chemical reactions, functionalizations, and medicinal application of indazole nucleus. Moreover many useful drugs have emerged from the successful investigation carried out in this branch. Indazole ring system is not a common feature in nature but a large number of synthetically prepared compounds have shown desirable pharmacological properties, so efforts have been made in the last few decades to synthesize a different new and novel heterocyclic indazole compounds & its derivatives which were evaluated for various activity. Study of biological activity of substituted heterocyclic compounds represents a core area in the field of drug development and discovery.

This overview summarizes structures of pharmacologically interesting indazoles published during the last decade, as well as syntheses, reactions, and functionalizations.

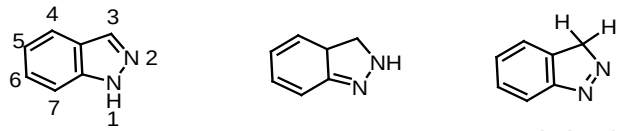
Keywords: Heterocycles; indazoles; Indazole tautomer biological activities

Introduction

Indazoles refers to isomeric chemical compounds with molecular formula $C_7H_6N_2$, having pyrazole ring condensed with the benzene ring. The indazole heterocycle is normally referred to as 1*H*-indazole, although it has two other potential tautomers 2*H*-indazole and 3*H*-indazole [1].

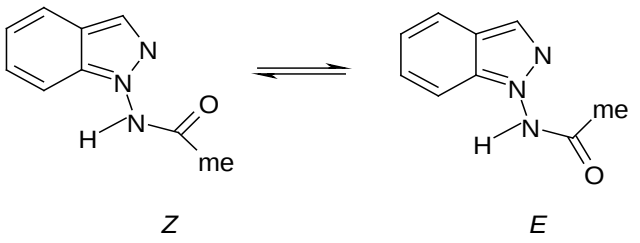
Three tautomeric forms of indazole can be discussed; the 1*H*-, 2*H*-, and 3*H*-form (Scheme 1). Tautomerisations of indazoles have been thoroughly investigated both from a theoretical and a synthetic view, and a review article summarizing the knowledge appeared in 2000 [2]. The tautomeric equilibrium between 1*H*- and 2H indazoles both in the ground state (S_0) and in the excited state (S_1) has been investigated by photophysical and thermochemical techniques, and have also been calculated. According to this study, the 1H tautomer is 2.3kcal mol–1 (9.63kcal/mol) more stable than the 2H tautomer, regardless of the ground state or excited state, and this trend is not reversed by solvent effects from water or formic acid. Correspondingly, 1-methylindazole is 3.2 kcalmol–1 (13.40 kcal/mol) more stable than 2-methylindazole [3]. The MP2/6-31G* level of theory predicts an energy difference of 3.6 kcal/mol (15.1kcal/mol), which is characterized also by ΔG0 298.15 = 4.1 kcal/mol (17.2kcal/mol), when thermal energy correction and entropy effects are taken into account [4]. Calculations on the tautomerism of substituted indazoles lead to similar results in the gas-phase [5] as well as in water [6]. AM1/B3LYP calculations, however, predict also some candidates of substituted and annulated indazoles which are more stable as 2*H*-tautomers [7]. The two tautomeric forms can be identified in solid-state substances by NMR-NQR spectroscopy [8]. In addition, theoretical ^{13}C NMR studies have been carried out [9], as well as 1H, 13C and 15N NMR studies on indazoles in solution and in the solid state [10]. Only few examples of 3Hindazoles are known, which carry alkyl or aryl groups on the five-membered ring [1]. Indazol-3-ones, which can be regarded as 3*H*-indazole derivatives, however, are well-documented. Some interest has also been focused on conformers of indazole derivatives. Thus, similar to 1-(formylamino)indazole, 1-(acetylamino)indazole (1) exists as an equimolar mixture of E- and Z-conformers in CDCl3 solution, as evidenced by 1H NMR spectroscopy (Scheme 2) [11].

NOESY NMR spectroscopy reveals that the imine 2 (Scheme 3) exists in form A in $CDCl_3$ and in form B with disrupted hydrogen bond in [D6] DMSO. 13C and 15NCPMAS NMR studies show that in



1*H*-indazole 1a | **2*H*-indazole** 1b | **3*H*-indazole** 1c

Scheme 1: Structures of various indazole nucleus.



Z *E*

Scheme 2: Conformers.

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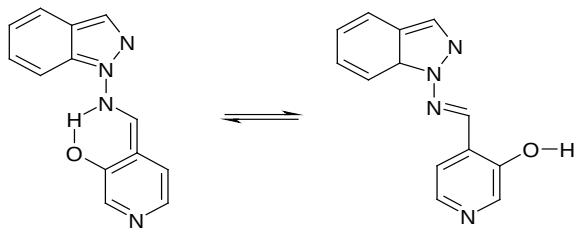
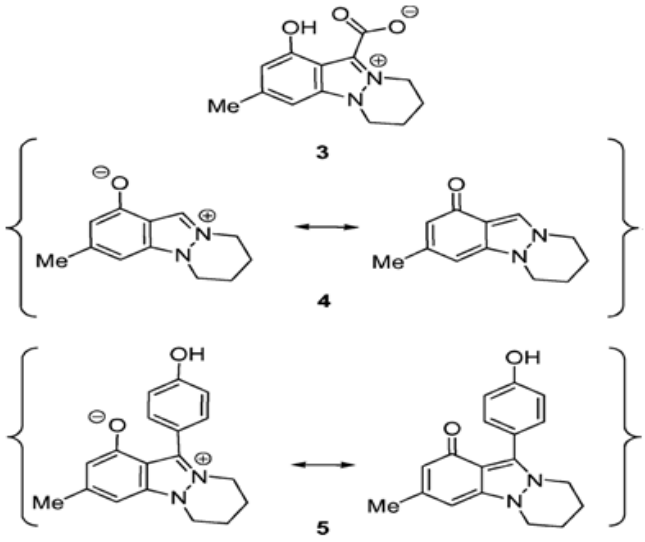


Scheme 3: Conformers and hydrogen bonds.



Scheme 4: The indazole alkaloids Nigellicine, Nigeglanine and Nigellidine.

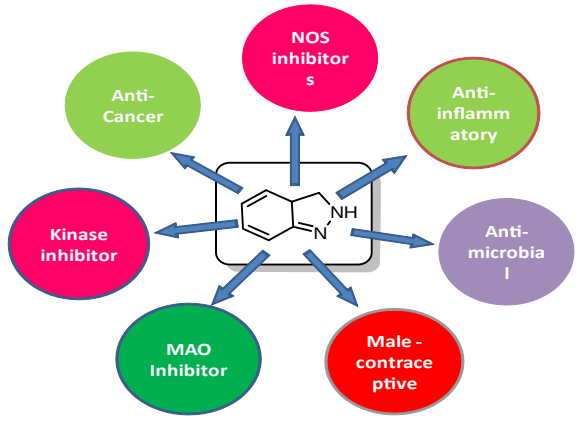


Figure 1: Graphical representation of Pharmacological activities of indazoles moiety.

the solid state no hydrogen bonds exist, so that rotamer B is detected [12].

Two concomitant polymorphs of 3-phenyl-1*H*-indazole were examined by X-ray crystallography and their NMR properties were measured [13].

Indazoles as Natural Products

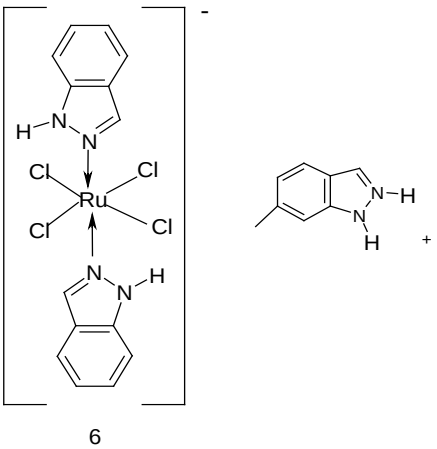
Indazoles are rare in Nature.[14] To date, only three natural products possessing the indazole ring have been isolated: Nigellicine (3), Nigeglanine (4), and Nigellidine (5) (Scheme 4) (Figure 1). The alkaloid Nigellicine (3), a 6,7,8,9-tetrahydropyridazino[1,2-*a*] indazolium-11-carboxylate, was isolated as yellow crystals from the widely distributed herbaceous plant *Nigella sativa L.* [*Ranunculaceae*; *black cumin* (engl.), *Schwarzkümmel* (name in German)] which is an annual flowering plant, native to southwest Asia [15]. The structure was determined by an X-ray crystal structure analysis. An intramolecular hydrogen bond was found between the carboxylate oxygen atom and the hydroxy group. Nigellicine (3) belongs to the class of heterocyclic mesomeric betaines (MB), as it can exclusively be represented by dipolar canonical formulae in which both the positive and negative charge are delocalized in a common π-electron system. More precise, Nigellicine is a pseudo-cross-conjugated heterocyclic mesomeric betaine (PCCMB). The biological, physical, and chemical consequences of the distinct types of conjugation have been surveyed recently [16]. The alkaloid Nigeglanine (4) was isolated from extracts of *Nigella gland-ulifera* [17]. *Nigeglanine* (4) and Nigellidine (5) *(Nigella sativa*) [18] can be represented by zwitter ionic as well as by neutral canonical formulae (Scheme 4), thus setting them apart from mesomeric betaines (Table 1).

Biologically Active Indazole Derivatives

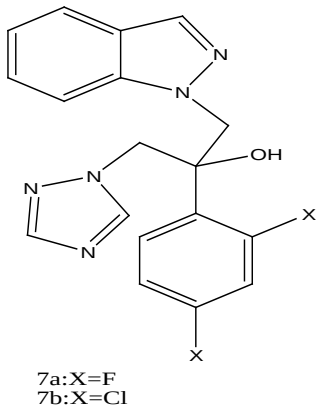
The indazole ring system is of great current interest as partial structure of biologically active compounds. Some aspects of pharmacological properties of indazoles have been reviewed in 2005 [19]. As the molecular shape and electrostatic distribution play a crucial role in enzyme and receptor recognition and contribute extensively to binding affinity, a study on electroforms of molecules, including indazole, have been presented in order to help drug discovery [20]. Unsubstituted indazole was used as ligand in metal complexes. Thus, tumor-inhibiting [21,22], and redox-active antineoplastic ruthenium complexes with indazole have been reported and a correlation between *in vitro* potency and reduction potential was examined [23]. An example is the water-soluble anionic complex 6 with *trans*-standing indazoles, in which bonding with the metal is achieved via N(2) (Scheme 5) [24].

Monosubstituted Indazoles

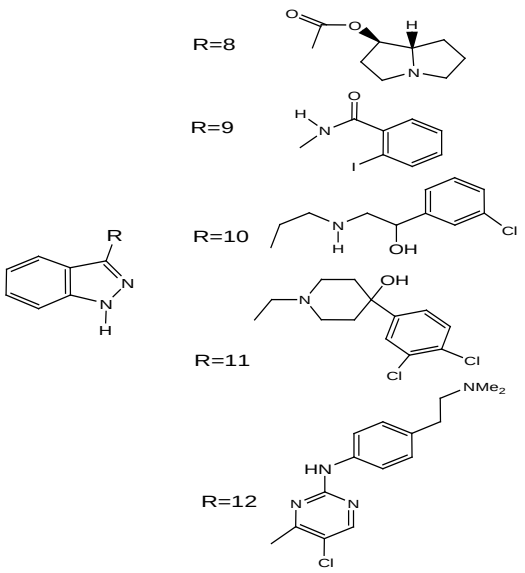
To the best of our knowledge, relatively few examples of N(1)-



Scheme 5: Unsubstituted indazole as ligand.



Scheme 6: An N(1)-monosubstituted indazole as biologically interesting compound.

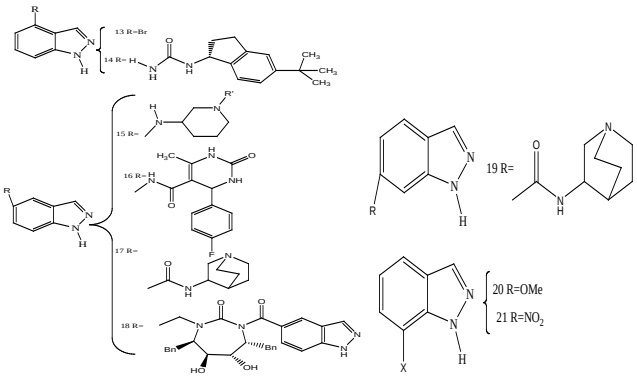


Scheme 7: C(3)-substituted indazoles.

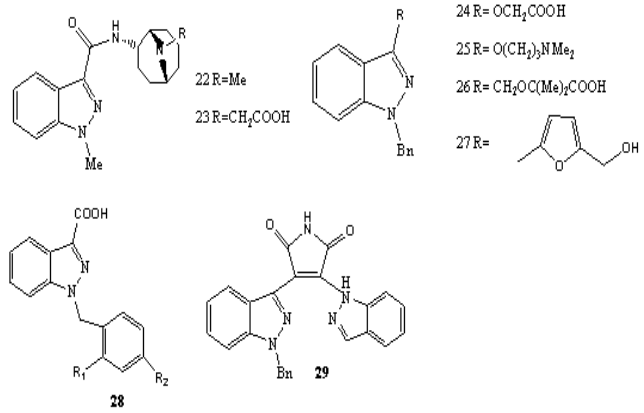
monosubstituted indazoles were published as biologically interesting compounds during the last decade. As examples, the indazoles 7a,b were screened for antifungal activities as fluconazole analogues (Scheme 6) [25].

By contrast, several series of C (3)-monosubstituted indazoles were described as biologically interesting compounds (Scheme 7). Thus, 8 were tested as 5-HT4 receptor agonist [26]. The iodobenzamide derivative 9 shows antifungal activities [27] and derivatives such as 10 were examined in search of β3-adrenergic receptor agonists as potential drugs for the treatment of type II diabetes [28]. Indazole 11 is interesting as analogue of an dopamine D2 receptor antagonist [29], while 12 was tested as inhibitor of VEGFR-2 and cyclin dependent kinase 1 (CDK1) [30].

Introduction of bromine at C(4) provides compound 13 which is almost as potent as the reference compound 7-nitroindazole as inhibitor of neuronal nitric oxide synthase, and 4-nitroindazole also proved to be a potent inhibitor of NOS activity (Scheme 8) [31]. ABT-102 14 has been identified as potent vanilloid receptor (VR1)



Scheme 8: C(4)-, C(5)-, C(6)-, and C(7)-substituted indazoles.



Scheme 9: N(1)–C(3)-disubstituted indazoles.

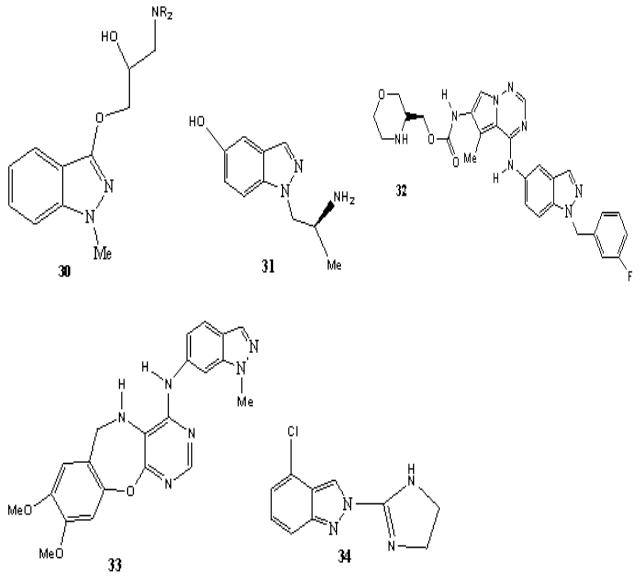
antagonist and is currently undergoing advanced clinical development for the treatment of chronic pain [32]. 3-Aminopiperidinyl-substituted indazoles 15 with R«' substituents varying from *n*-propyl to 3-methylfuryl represent C(5)-mono substituted indazoles with potential biological activities as they were tested as Rho kinase inhibitors [33]. More examples are the selective Rho-kinase inhibitor 16 [34], the A7 nicotinic acetylcholine receptor agonist 17 [35], and the anti-HIV protease inhibitor18 [36]. No effect of 5- and 6-nitroindazole nucleosides of D-pinitol as antitumor agents, however, was found [37]. A series of substituted 6-anilinoindazoles as inhibitors of c-Jun *N*- terminal kinase-3 was recently described [38]. The latter mentioned compounds are examples for C(6)-monosubstituted indazoles of pharmacolocical interest, only few examples of this group are described [39]. Two additional examples are TAS-3–124 [46] and 19 [36]. Biologically interesting indazoles substituted at C(7) are represented by 20 and 21. 7-Methoxyindazole (20) [40] as well as 7-nitroindazole (21) [41–43], are nitric oxide synthase inhibitors. The latter mentioned (7- NI 21) and related indazoles were also shown to exhibit antinociceptive and cardiovascular effects [44]. Several substituted indazoles and potential analogues of 7-NI have been reported [39,45] from which 7-methoxyindazole proved to be the most active compound in *in vitro* enzymatic assays of nNOS activity [46]. *N*-(7-Indazolyl)benzenesulfonamide derivatives were prepared and investigated as cell cycle inhibitors [47].

Disubstituted Indazoles

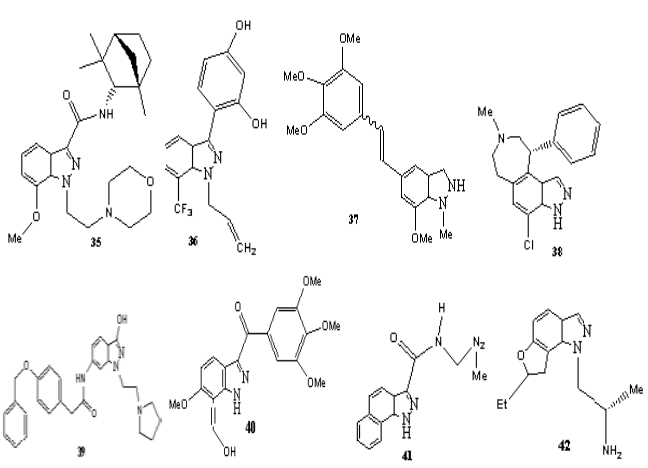
Numerous examples of N(1)–C(3)-disubstituted indazoles showing pharmacologically interesting properties have been published (Scheme 9). The selective 5-HT3 receptor antagonist Granisetron (22) has been used clinically to prevent nausea and emesis induced by cancer chemotherapeutic agents [48]. Gastrointestinal prokinetic and dopamine D2 receptor antagonists were observed with derivatives such as 23 [49]. A series of N(1)-benzyl-substituted indazoles is represented by 24–27. Bendazac (24), a topical anti-inflammatory agent, impedes effects associated with lens opacification and photochemical modes of action have been suggested [50]. Benzydamine (25) is a widely applied locally-acting nonsteroidal anti-inflammatory drug with local anaesthetic and analgesic properties. Bindarit (26) as well as Bendazac showed a selective inhibition of protein denaturation. The indazole derivative YC-1 (27) has been reported as activator of the physiological receptor for nitric oxide, sGC, which is a signalling molecule in the cardiovascular and central nervous system. YC-1 displays also some other biological activities such as inhibition of endothelial cell functions induced by angiogenic factors *in vitro* and angiogenesis *in vivo* [51]. It also effects cGMP metabolism by inhibiting the activity of phosphodiesterase isoforms 1–5 [52]. The corresponding 2-benzyl isomer showed no activity [53]. Syntheses of YC-1 analogues [54] as well as of structural variationsin search for new antithrombotics [55] have been reported.

Indazol-3-carboxylic acid derivatives such as 28 compromises non-hormonal and non-steroidal, antispermatogenic agents and found interest in male contraception [56]. It was found that the presence of substituted benzyl groups at N(1) are essential for this specific activity, and so are halogen or methyl groups as R1. The activity increases when two substituents are present in *o*- and *p*-position (R1= R2 = Cl; or R1 = Me, R2 = Cl). AF 1311 (R1 = R2 = H) displays no anti-spermatogenic activity, but is able to reduce protein denaturation. By contrast, in Lonidamine (R1 = R2 = Cl) this property is decreased. The corresponding indazole- 3-carbohydrazide (R1 = R2 = Cl, AF2364) and 3- acrylic acid (R1 = R2 = Cl; AF 2785) showed anti-spermatogenic effects [57]. (Indolyl-indazolyl)maleinimides 29 with a broad variety of substituents Ar (vinyl, Ph, 2-thiazolyl, 2- naphthyl, 3-quinolyl etc.) and X (Me2N, morpholinyl etc.) were tested as inhibitors of protein kinase C-β [58].

N(1)–C(X)-Substituted indazoles (X ≠ 3) are represented by the structures 30–33 (Scheme 10). Indazoles such as 30 exhibit antiarrhythmic, local anaesthetic and analgesic activities, [59] where as 31 was identified as a periphally acting potent 5-HT2 receptor agonist [60]. BMS-599626 (32) [61] is in clinical development as EGFR and HER2 protein tyrosine kinase inhibitor. Structural optimizations have been reported [62]. Compound 33 was reported as inhibitor of epidermal growth factor receptor tyrosine kinase [63]. Syntheses as well as I2/α2-adrenoceptor binding profiles of a series of 2-(4,5-dihydroimidazol-2-yl)indazoles (indazim) such as 34 have been described [64]. These receptors are involved in several diseases such as psychiatric disorders, Parkinson's and Alzheimers's diseases and Huntington's chorea. Compound 34 is a typical N(2)–C(4)-disubstituted indazole.



Scheme 10: N(1)–C(X)-disubstituted [X ≠ 3] indazoles 40–43 and the N(2)–C(4)-disubstituted indazole 44.



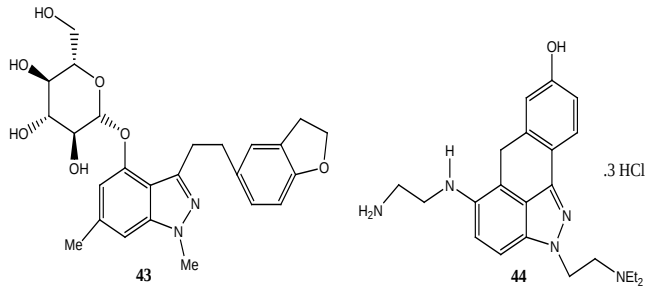
Scheme 11: Biologically active trisubstituted indazoles.

Trisubstituted Indazoles

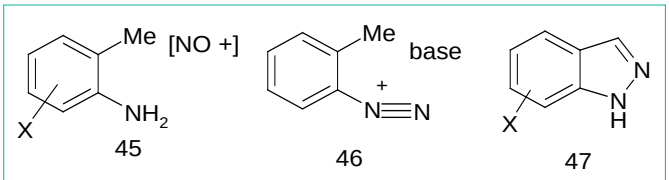
Some trisubstituted indazoles have also been described as biologically active compounds (Scheme 11). Novel Combretastatin analogues endowed with antitumor activity [65] belong to this class of compounds. In addition, a series of indazoles such as 35 was rationally designed and synthesized as cannabinoid ligands (Scheme 16) [66]. The dopamine D1/D5 receptor antagonist 37, indazole 38 (a phenol bioisosteric analogue of benzazepine derivatives [67]), the orally efficacious melanin-concentrating hormone receptor 1 antagonist 39 (treatment of obesity [68]) and the indazole 40 (binds specifically to the colchicines binding site and inhibits tubulin polymerization *in vitro* [69]) are examples for active trisubstituted indazoles. In addition, 41 and related systems are potential DNA-intercalators and demonstrated significant antiproliferative activities [70]. The furoindazole YM348 (42) was identified as a new and potent 5-HT2c receptor agonist, which is one of the serotonine receptors [71].

Tetrasubstituted Indazoles

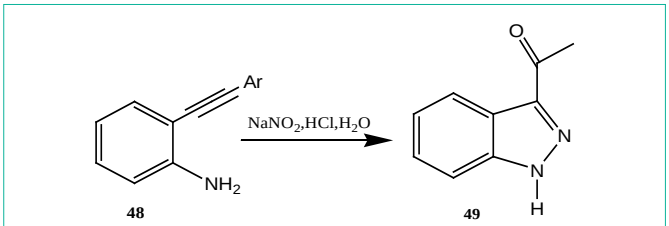
The N(1)–C(3)–C(4)–C(6)-tetrasubstituted indazole 43 is



Scheme 12: Tetrasubstituted indazoles.



Scheme 13: General routes to indazoles I.



Scheme 14:

interesting as sodium glucose co-transporter 2 inhibitor (Scheme 12) [72]. A number of benzothiopyrano-indazoles such as 44 demonstrate significant antitumor activities. A promising example is CL-958 which is in clinical evaluation for prostate cancer treatment. In this context, aza-bioisosters of CL-958 were prepared [73].

Routes for the Syntheses of 1H-Indazoles

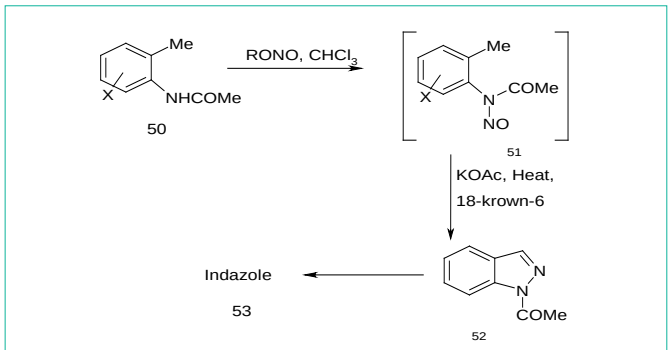
Reactions from hydrazines, hydrazones, azo, and diazo compounds

By means of intermolecular coupling of diazo groups with *o*-methyl groups: A general route to indazoles is the intermolecular coupling of diazo groups with *o*-methyl groups (Scheme 13).

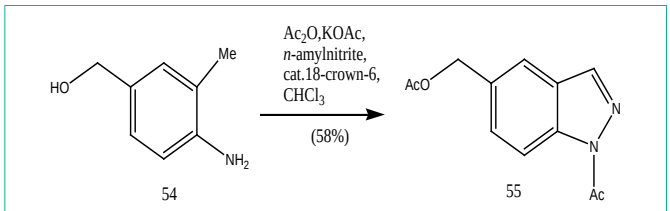
Some applications of this procedure were described recently [68,74,75]. It was also shown that *o*-alkynylanilines such as 48 can be diazotized to give indazoles 49 (Scheme 14) [69,76] and some studies were presented to elucidate the mechanisms leading to five-membered (pyrazole) or six membered (pyridazine) partial structures [77]. A similar reaction leading to 1*H*-naphtho[2,3-*g*]indazole-6,11-diones was described before [78].

By means of nitrozation of *N*-acetyl derivatives (Jacobsen modification): Another general route to indazoles is the nitrozation of *N*-acetyl derivatives (Jacobsen modification) (Scheme 15).

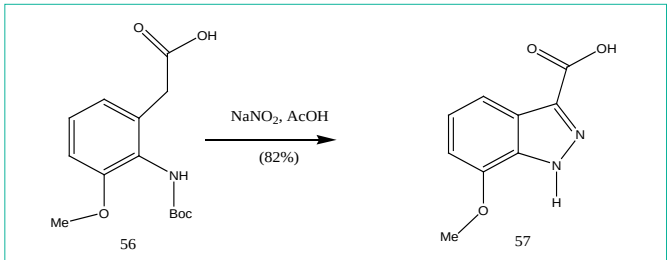
Thus, acetic anhydride preforms the diacetate of 54, which yields the indazole 55 on treatment with *n*-amyl nitrite under phase-transfer conditions (Scheme 16) [36].



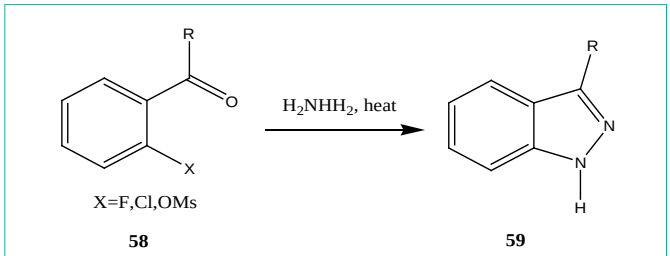
Scheme 15: General routes to indazoles II.



Scheme 16:



Scheme 17:



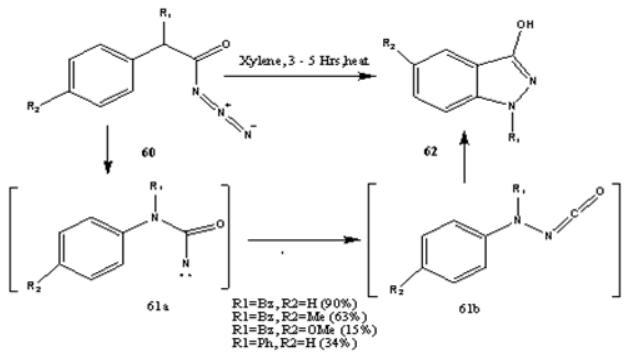
Scheme 18: General routes to indazoles III.

By means of cyclization of NH Boc-protected methoxyaniline: A related procedure was described recently. Thus, the NH Boc-protected methoxyaniline 56 cyclized to indazole 57 (Scheme 17) [66].

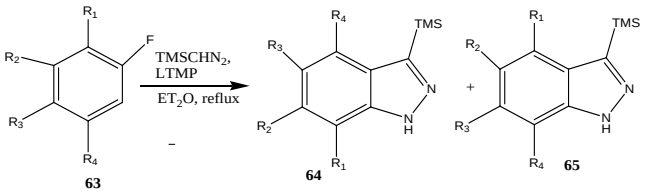
By means of condensation of *o*-substituted benzaldehyde with hydrazine: The condensation of *o*-substituted benzaldehydes with hydrazine is an alternative common synthetic route for the preparation of indazoles (Scheme 18).

By means of rearrangement reactions

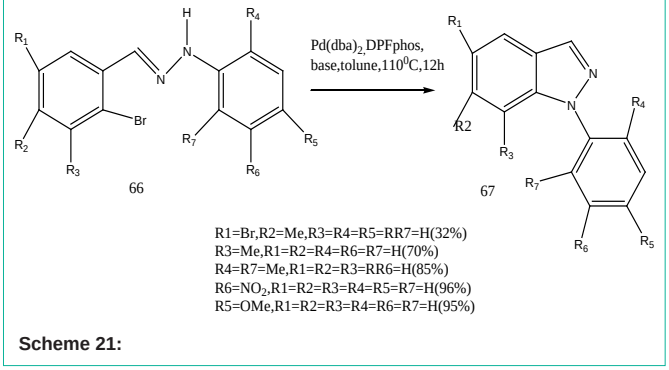
Diphenylcarbamoyl azide 60 underwent a rearrangement to indazole 62 [79,80]. The mechanism is depicted in Scheme 19.



Scheme 19:



Scheme 20:



Scheme 21:

By means of cycloaddition reactions

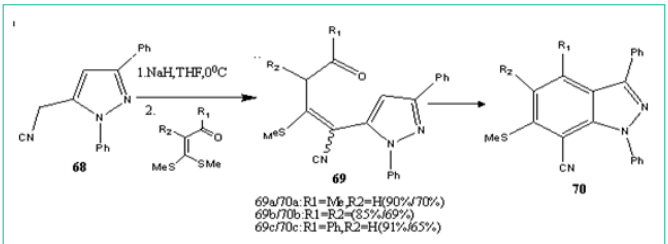
The aryne mechanism was observed on [3+2] cycloaddition starting from fluorobenzenes 63 and trimethylsilyldiazomethane in a basic medium [81]. In some cases, regioisomers 64 and 65 were obtained (Scheme 20).

By means of metal-organic syntheses

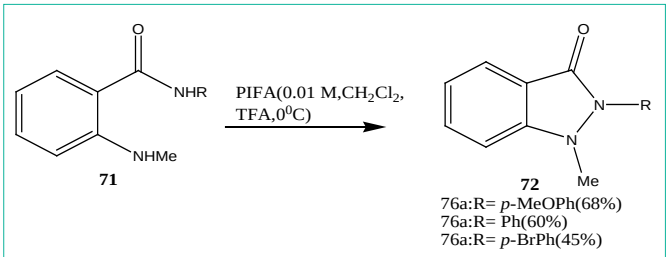
A broad variety of substituted indazoles was prepared starting from 2-bromobenzaldehydes and arylhydrazines by palladium catalysis [82]. Phosphorous-chelating ligands such as 1,1_-bis(diphenylphosphanyl) ferrocene and 1,3-bis(diphenylphosphanyl) propane along with sodium *tert*-butox ide were used. A broad variety of substituted indazoles 67 were prepared via palladium-catalyzed intramolecular mination of aryl halides 66 (Scheme 21) [83,84].

Syntheses starting from pyrazoles

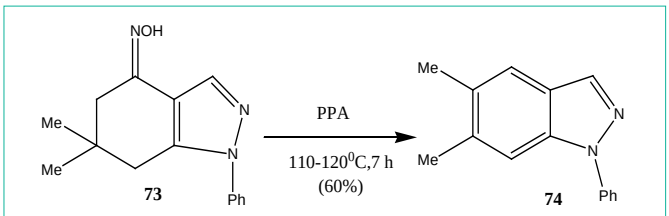
A two-step [3+2] annulation of 1,3-diphenyl-5-cyanomethylpyrazole 68 with α-oxoketenes dithioacetals afforded



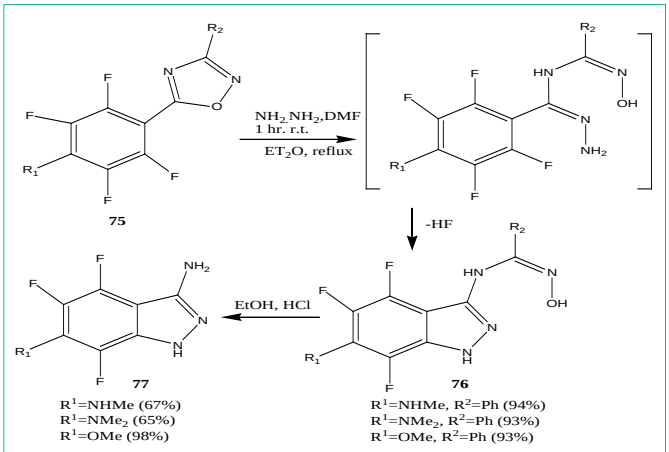
Scheme 22:



Scheme 23:



Scheme 24:

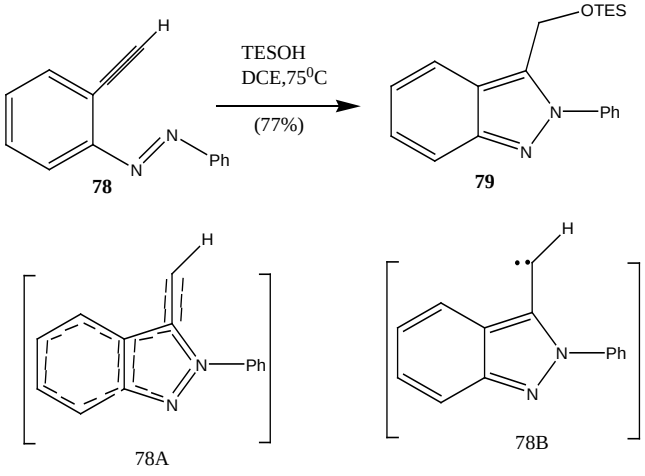


Scheme 25:

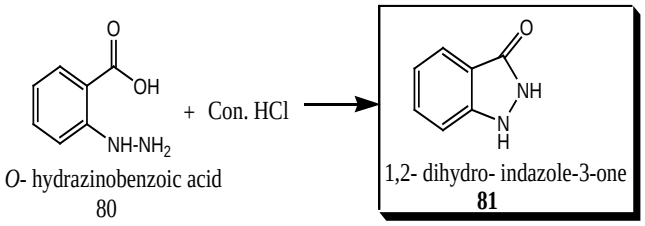
functionalized indazoles 70 with high regioselectivity (Scheme 22) [85].

By means of oxidative N–N coupling reactions

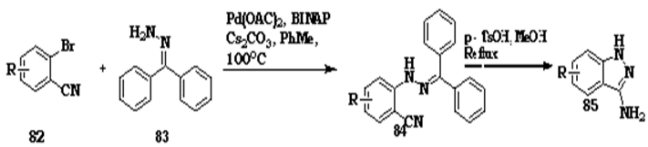
Most syntheses of indazoles involve the formation of the pyrazole moiety. A suitable method is the oxidation of anthranilic acid amides 71 with iodine reagents such as the hypervalent iodine reagent phenyliodine(III) bis(trifluoroacetate) (PIFA) to 1,2-disubstituted indazolones 72 [86]. The key cyclization step embraces the PIFA-mediated formation of an *N*-acylnitrenium intermediate (Scheme 23).



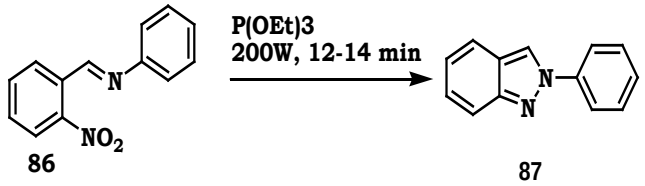
Scheme 26:



Scheme 27:



Scheme 28:



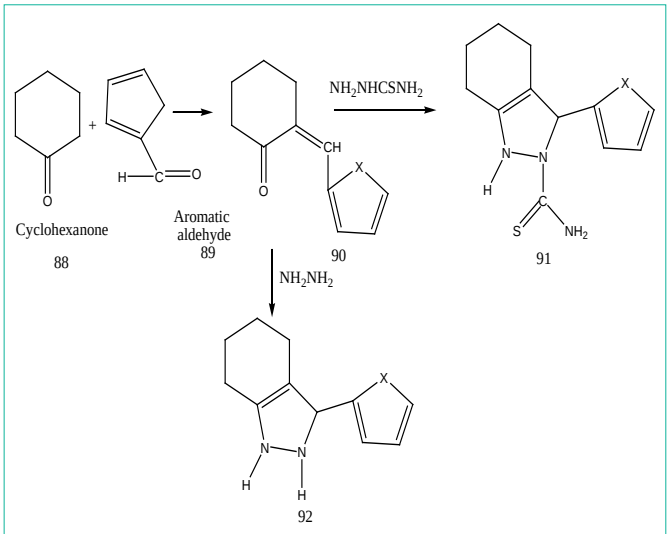
Scheme 29:

By means of carbocycle aromatization

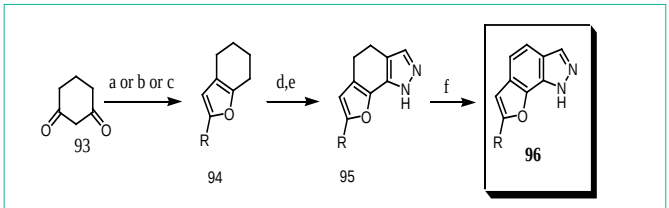
Aromatization of 4-hydroxyimino-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydroindazole (73) to 74 was accomplished by heating in PPA. The proposed mechanism proceeds via the formation of an iminium cation, followed by subsequent hydride and methyl migration, and final oxidation to indazole 74 (Scheme 24) [87].

By means of nucleophilic ring transformation

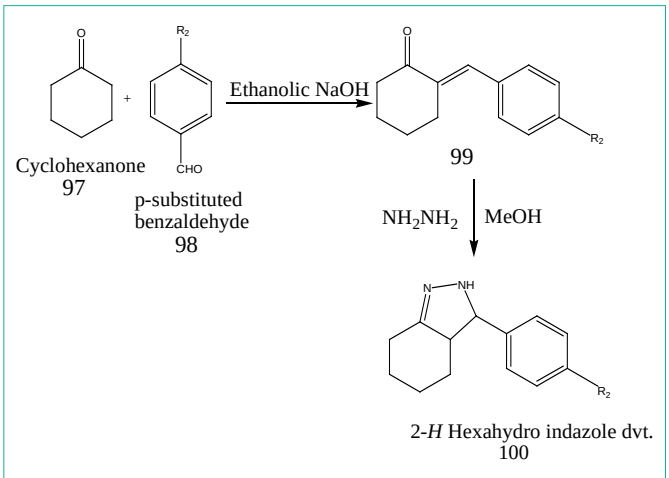
A series of fluorinated indazoles 76 and 77 (Scheme 25) was synthesized by an ANRORC-type rearrangement of 5-tetrafluorophenyl-1,2,4-oxadiazoles 75 with hydrazine [88].



Scheme 30:



Scheme 31:

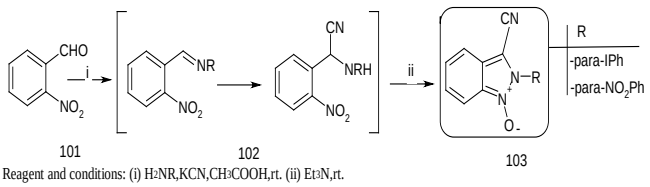


Scheme 32:

Routes for the Syntheses of 2H-Indazoles

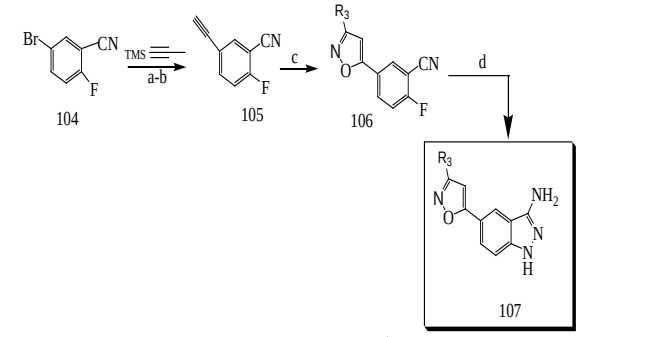
By coarctate reactions

Coarctate[89] cyclizations are defined by the presence of a coarctate atom where two bonds are being broken and two are being made and that bond breaking and making do not occur in a cyclic array, thus setting them apart from pericyclic reactions. Analogous disconnections in coarctate reactions are termed pseudocoarctate. A coarctate mechanism formed 2-phenylisoindazoles 79 from



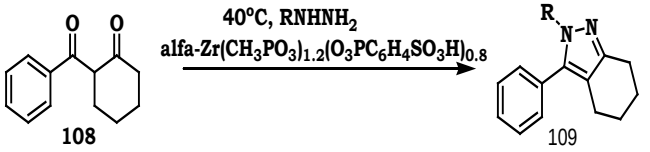
Reagent and conditions: (i) H_2NR,KCN,CH_3COOH,rt. (ii) Et_3N,rt.

Scheme 33:



Reagents and conditions: (a) CuI, $(Ph_3)_2Cl_2Pd$, DMF, Et_3N, 95° C, 24 h, 93%; (b) TBAF, THF, 55%; (c) R_3CHO, NH_2OH_1 HCl, 6 N NaOH, chloramine-T_1 $_3H_2O$, $CuSO_4$, Cu wire, t-BuOH, H_2O, 50° C, 33–69%; (d) NH_2NH_2, EtOH, 70° C, 24 h, 53–78%

Scheme 34:



Scheme 35:

(2-ethynylphenyl) phenyldiazenes 78 (Scheme 26-42); the intermediary carbene 78B was formed under neutral conditions via transition state 78A at moderate temperatures [90]. The free carbene could also be trapped as a [2+1] cycloadduct with 2,3-dimethyl-2-butene.

Different Scheme of Synthesis of Indazoles and Its Derivatives

Synthesis of Schiff's bases of Indazole 3-one derivatives using O-hydrozinobenzoic acid [91]

P. Muthumani et al synthesized and evaluated of some novel schiff's bases of Indazole 3-one derivatives [81].

Bromobenzonitrile mediated synthesis of 3-aminoindazole

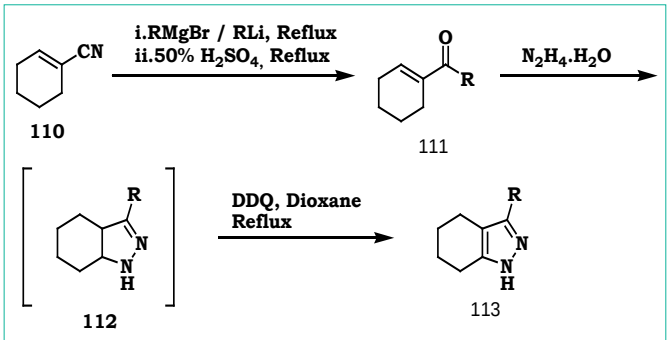
Frederic Fabis et al. reported synthesis of 3-amionoindazole from 2- bromobenzonitriles [92].

Microwave assisted synthesis of indazole

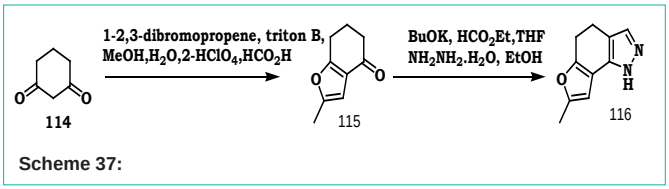
Scheme 7 Imine was mixed with triethylphosphite and irradiated with microwave irradiation to give the corresponding indazoles. Evelyn Cuevas Creencia et al [93].

Hydrazine and their derivative mediated synthesis of Indazoles [94]

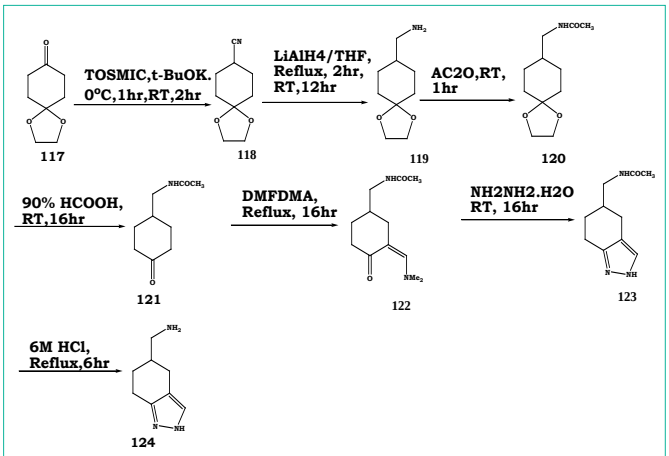
Nesrin Gokhan-Kelekci et al synthesized 2-thiocarbamoyl-



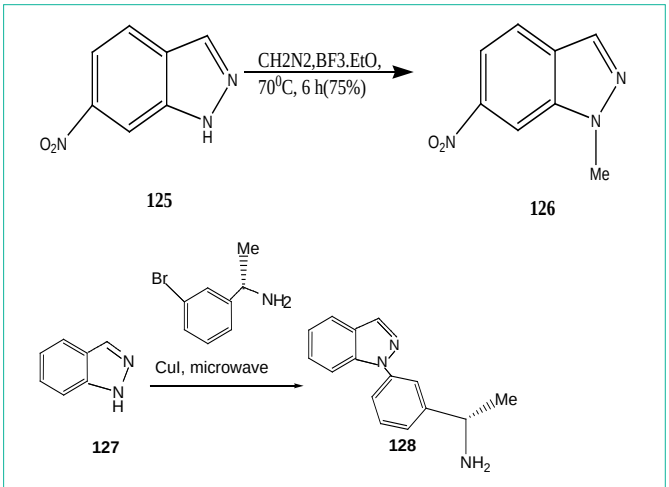
Scheme 36:



Scheme 37:

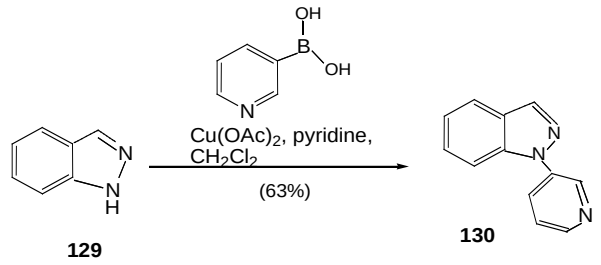


Scheme 38:



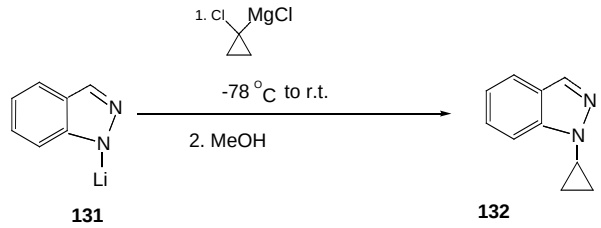
Scheme 39:

2,3,4,5,6,7-hexahydro-1*H*-indazole derivatives by using arylidenecyclohexanones 88 as a starting material.



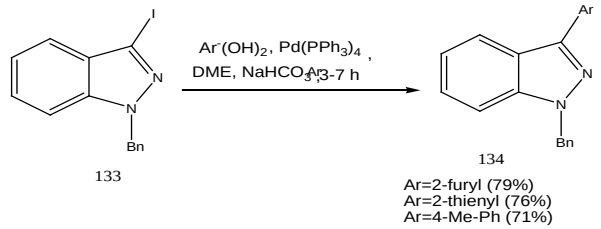
129 130

Scheme 40:



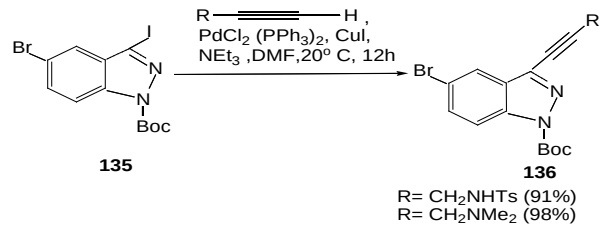
131 132

Scheme 41:



133 134

Scheme 42:



135 136

Scheme 43:

Synthesis of furan-fused indazole using 1,3-Cyclohexanedione [95]

Itsuro Shimada et al synthesized furan-fused indazole. 1,3-Cyclohexanedione [93] was reacted with chloroacetaldehyde to give 6,7-dihydrobenzofuran- 4(5H).

Synthesis of hexahydro-2-*H*-indazoles derivatives [96]

Maninder Minu et al synthesized and evaluated new 2,3-disubstituted-3,3a,4,5,6,7-hexahydro-2*H*-indazoles. Synthesis of substituted benzylidenecyclohexanones (100) by the reaction of cyclohexanone (97) with p-substituted benzaldehydes (98) in the presence of ethanolic sodium hydroxide. Benzylidenecyclohexanones, on heating with hydrazine hydrate resulted in the formation of 100.

Synthesis of indazole N-oxide derivatives [97]

Alejandra Gerpe et al has been synthesized a series of indazole N-oxide derivatives and the synthesized are studied for their antichagasic and leishmanocidal properties.

Treatment with sodium cyanide converts the Schiff base to it's a aminonitrile derivatives (102), which in turn undergo basic cyclization and forms indazole N-oxide derivatives (103). The cyclization occurs under extremely mild condition and indazole N1-oxide yield depends on the reaction solvent, being acetic acid the best condition.

Synthesis of 5-substituted indazoles [98]

Irini Akritopoulou-Zanze et al synthesized and evaluated 5-substituted indazoles as kinase inhibitors. 5-substituted-3-amino indazoles (107) could be prepared by Sonogashira coupling of trimethylsilylacetylene with commercially available 2-fluoro-5-iodobenzonitrile. Deprotected intermediate was subjected to cycloaddition reactions, followed by treatment with hydrazine to afford the final 5- substituted indazoles products (107).

Synthesis of tetrahydro-2*H*-indazoles from 2-benzoylcyclohexanone [99]

Ornelio Rosati et al. reported synthesis of 2,3-diaryl-4,5,6,7-tetrahydro-2*H*-indazoles from 2-benzoylcyclohexanone and substituted hydrazine in the presence of α-Zr(CH_3PO_3)1.2($O_3PC_6H_4SO_3H$)0.8.

Synthesis of indazole derivatives from 1-cyanocyclohexene [100]

Synthesis of indazole derivatives from 1- cyanocyclohexene was reported by Jan Bergman et al.

Synthesis of 2-(1*H*-furo[2,3-g]indazol-1-yl) ethylamine derivatives from 1,3-Cyclohexadione [101]

Itsuro Shimada et al. reported synthesis of series of substituted 2-(1*H*-furo[2,3-g]indazol-1-yl) ethylamine derivatives from 1,3-Cyclohexadione.

Synthesis of tetrahydroindazole from novel enamino ketone [102]

Synthesis of tetrahydroindazole was reported by Danijel Kikelj et al. from novel enamino ketone as the key intermediate.

Chemical Reactions of Indazoles and Its Derivatives

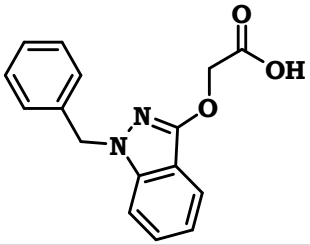
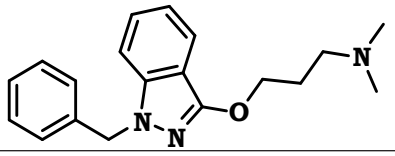
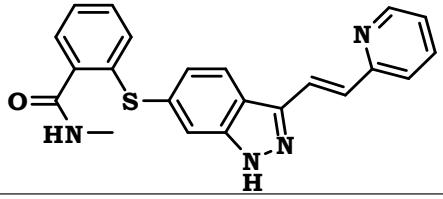
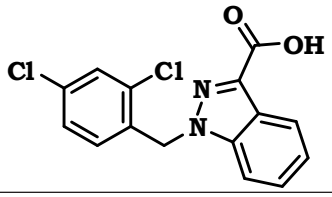
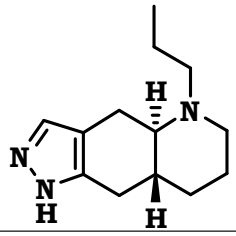
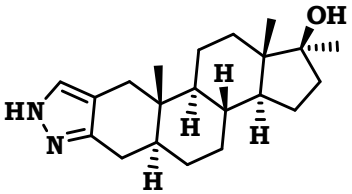
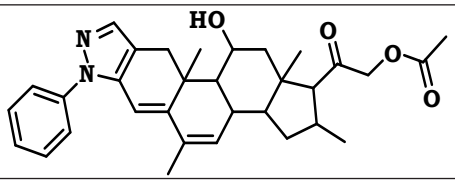
Alkylations and Arylations of N(1) and N(2)

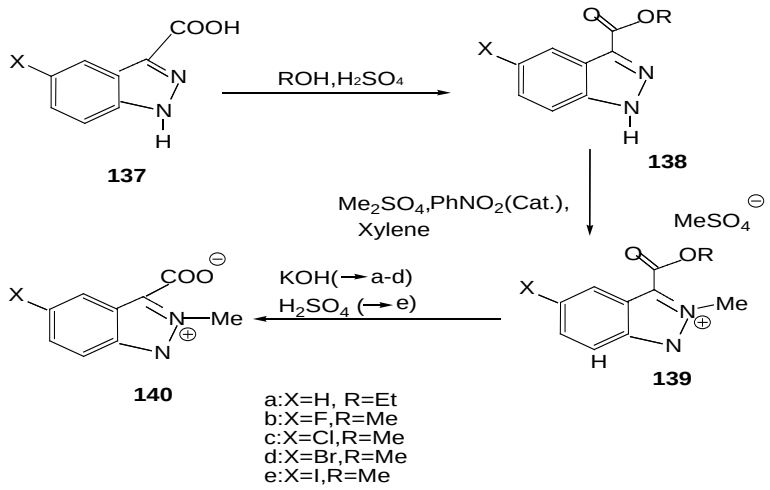
Indazoles are alkylated or acylated at N(1), N(2), or at both positions depending on the reaction conditions [49,103–107]. For example, Reaction of 1-lithioindazole 131 with cyclopropylmagnesium derivatives yields indazoles 132 which are cyclopropanylated at N(1) (Scheme 41) [108].

Functionalizations of C(3) position in indazoles

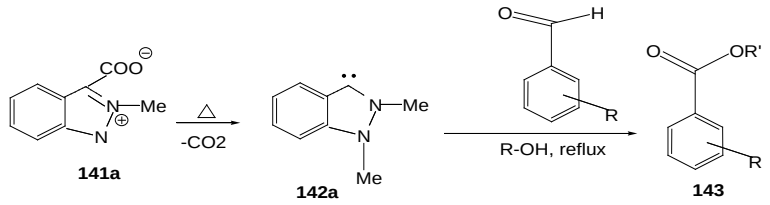
In view of the large number of biologically active indazoles substituted at C(3), functionalizations of this position are of great current interest. In this context, Heck [109] as well as Suzuki-type cross-couplings of 3-iodoindazoles has been described. As example for the latter mentioned procedure, 133 reacts with aryl- and hetarylboronic acids to give 3-arylated indazoles 134 (Scheme 42) [110].

Table 1: Chemical name, structure, IUPAC name and uses of some important indazole derivatives.

Chemical name	Structure	IUPAC name	Uses
Benzdac		(1-Benzyl-1H-indazole-3yloxy)-acetic acid	Anti-cataract, Anti-inflammatory
Benzylamine		[3-(1-Benzyl-1H-indazol-3-yloxy)-propyl]-dimethyl-amine	Anti-inflammatory
Axitinib		N-Methyl-2-[3-(2-pyridin-2-yl-ethyl)-1H-indazol-6-ylsulfanyl]-benzamide	Anti-cancer
Lonidamine		1-(2,4-dichlorobenzyl)-1H-indazole-3-carboxylic acid	Anti-cancer
Quiniprole		(4aR,8aR)-5-propyl-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-9] quinoline	D_2 and D_3 receptor agonist
Stanozolol		(1S,3aS,3bR,5aS,10aS,10bS,12aS)-1,10a,12a-trimethyl-1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a-hexadecahydrocyclopenta [5,6] naptho[1,2-F] indazole-1-ol	Anabolic steroids
Cortivazol		(11β,16α)-21-(Acetyloxy)-11,17-dihydroxy-6,16-dimethyl-2'-phenyl-*2'H*-pregna-2,4,6-trieno[3,2-c]pyrazol-20-one	Anabolic steroids

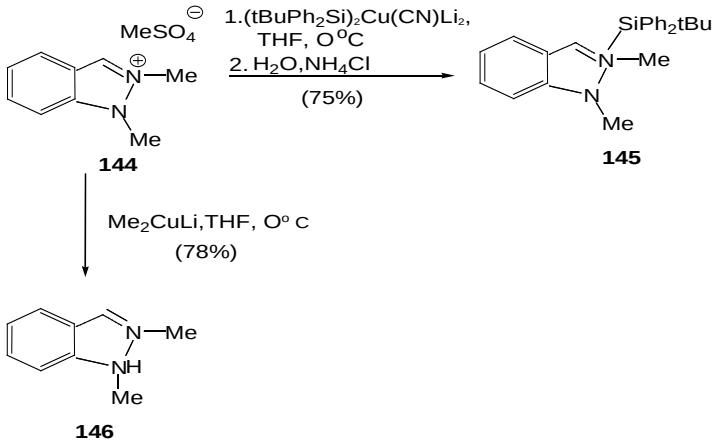


Scheme 44: Synthesis of pseudo-cross-conjugated heterocyclic mesomeric betaines (PCCMB) of indazole.



143	R	R'	
a	H	Et	49%
b	4-Et	Et	51%
c	4-OMe	Et	69%
d	2,4-Cl_2	Et	22%
e	2-Me	Et	33%
f	4-NMe_2	Et	80%
g	4-NMe_2	nPr	93%
h	4-NMe_2	nBu	47%
i	4-NMe_2	iPr	49%

Scheme 45:



Scheme 46:

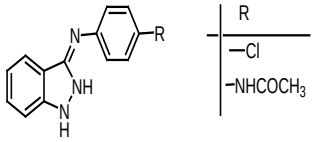
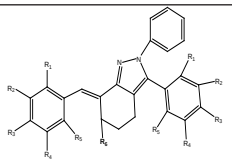
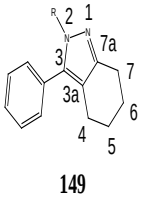
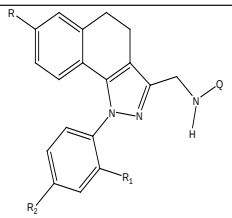
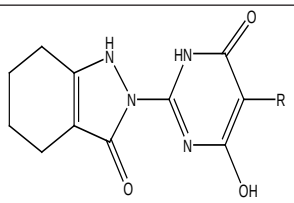
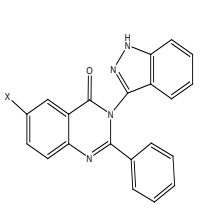
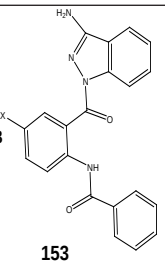
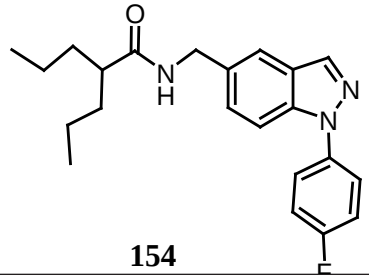
Sonogashira reactions for acetylenizations of C(3) of the starting material 135 were also described. The reaction products 136 undergo an additional Sonogashira coupling to afford bis-acetylene-substituted indazoles (Scheme 43) [111,112].

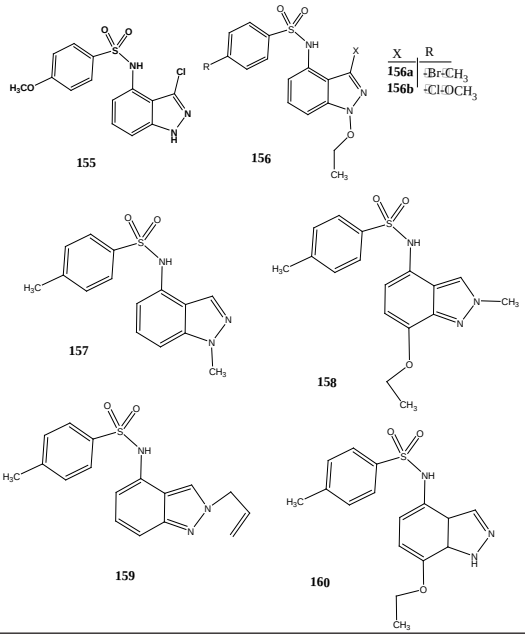
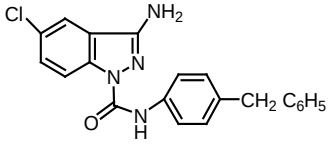
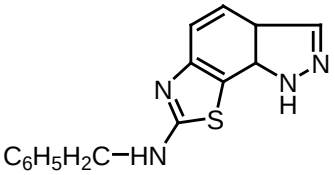
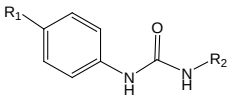
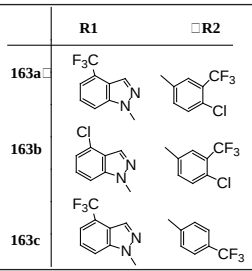
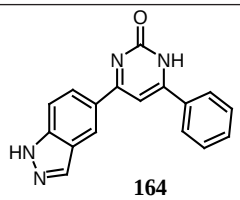
N-Heterocyclic Carbenes of Indazole

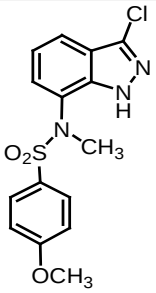
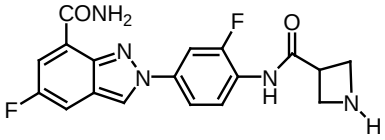
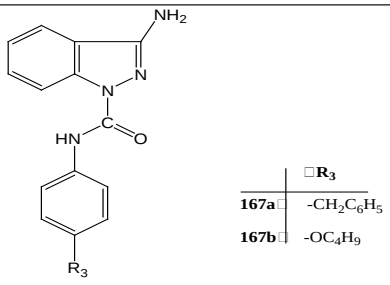
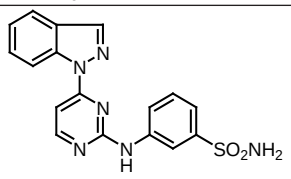
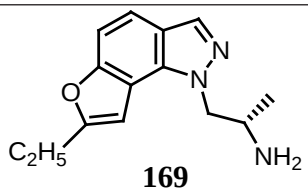
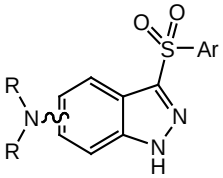
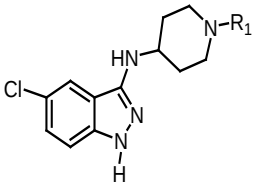
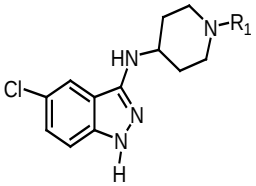
Trapping reactions

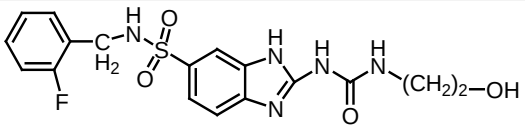
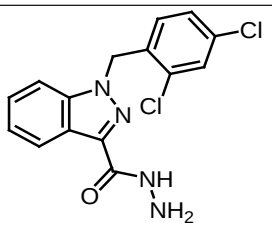
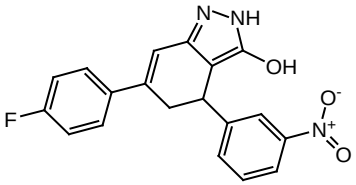
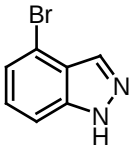
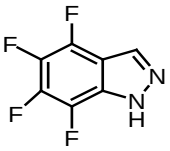
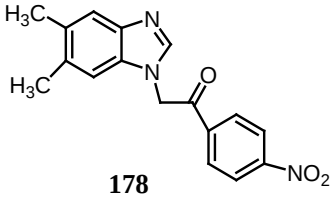
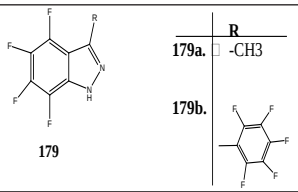
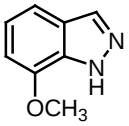
N-Heterocyclic carbenes of indazole are accessible by extrusion

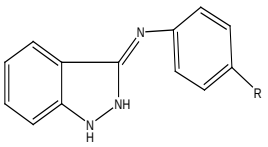
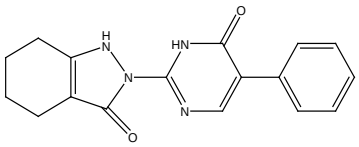
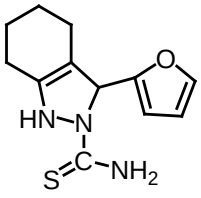
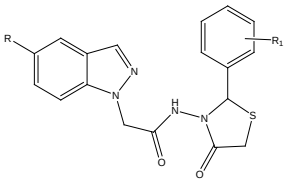
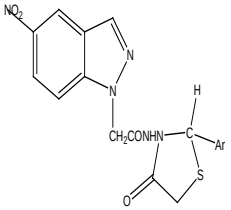
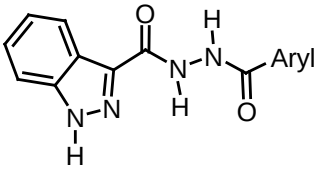
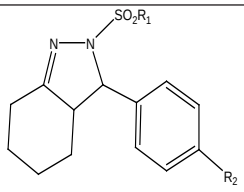
Table 2: Pharmacological activities of Indazole and its derivatives.

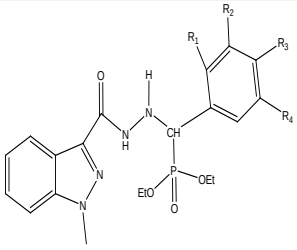
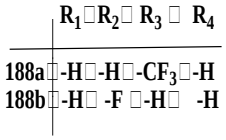
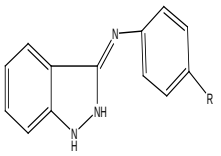
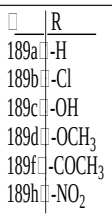
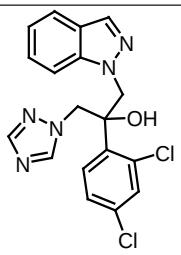
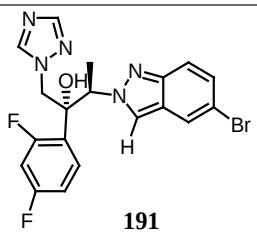
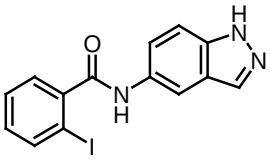
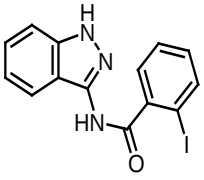
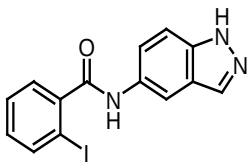
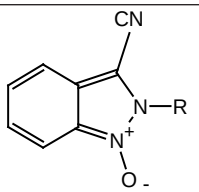
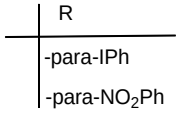
Sl. No.	Pharmacological Activity	Indazole derivatives	Structures	Reference
1.	Anti-inflammatory activity.	Novel Schiff's bases of Indazolone derivatives.	 **147**	P. Muthumani et al [117],[91]
		7-Benzylidene-2, 3-diphenyl-4, 5, 6, 7-tetrahydro-2*H*-indazole derivatives.	 **148** R_6=H, R_6=Me 148a -Cl -OMe -OMe -H -Cl 148b -H -H $-CF_3$ -H -H 148c -OMe -H -H -H -OMe 148d -Cl -OMe -OMe -H -Cl 148e -H -H $-CF_3$ -H -H	Richa Kaur Bhatia et al [118]
		2,3-disubstituted tetrahydro-2*H*-indazols	 **149** **149a.** 2-Hydrazino-4-(trifluromethyl)pyrimidine **149b.** 4-(Trifluromethyl)phenylhydrazine	Ornelio Rosati et al [90]
		4,5-dihydro-1*H*-benzo[g] indazole-3-carboxamides	 **150** 150a -Cl -Cl -Cl 150b -CH3 -Cl -Cl	Gabriele Murineddu et. Al [119]
		l-(pyrimidin-2-yl)-3-pyrazolin-5-ones and 2-(pyrimidin-2-yl)-1,2,4,5,6,7-hexahydro-3*H* indazol-3-ones.	 **151** **151a** $-C_4H_9$-n **151b** $-C_6H_6$	El-Sayed A.M. Badawey & Ibrahim M. El-Ashmawey [120]
		N-methyl and N-ethyl substitutions	 **152** **152a,531a** -H **152b,153b** $-CH_3$ **152c,153 c** -Cl **152d,153d** -Br  **153**	Demetrio Raffa et al [121]
2.	**Anti-cancer activity**	N-[(1-aryl-1*H*-indazol-5 yl) methyl]amide	 **154**	Gabriella Dessole et al [122]

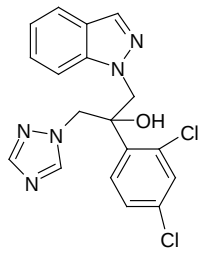
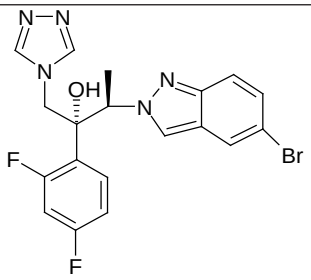
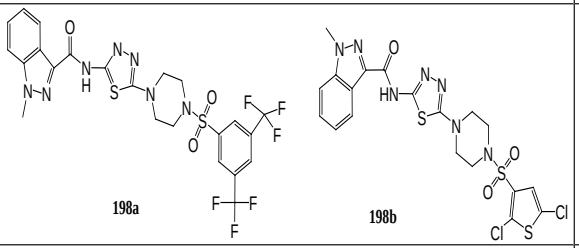
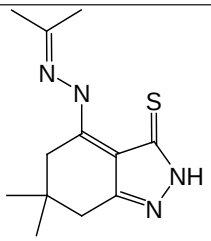
		N-(6(4)-indazolyl) benzenesulfonamides and 7-ethoxy-N-(6(4)-indazolyl) benzenesulfonamides.	 155 156 157 158 159 160	Najat Abbassi et al [123]
		N-phenyl-1H-indazole-1-carboxamides	 161	Benedetta Maggio et al [124]
		2-alkylamino- and 2-alkylthiothiazolo[5,4-e]- and -[4,5-g]indazoles	 162	Manas Chakrabarty et al [125]
		Diarylureas	 163 	Cui-rong Zhao et al [126]
		4-(4-hydroxyphenyl)-6-phenylpyrimidin-2(1*H*)-ones	 164	Cynthia M. Shafer et al [127]

		N-(7-indazolyl) benzenesulfonamide	 **165**	L. Bouissane et al [128]
		2-phenyl-2*H*-indazole-7-carboxamides	 **166**	Rita Scarpelli et al [129]
		3-amino-N-phenyl-1*H*-indazole-1-carboxamides	 **167**	Demetrio Raffa et al [121]
		N-phenyl-imidazo[4,5-b] pyridin-2-amines, 4-indazolyl-N-phenylpyrimidin-2-amines and N-phenyl-4-pyrazolo[3,4-b] pyridin-pyrimidin-2-amines	 **168**	Pawel M. Lukasik et al [130]
3.	**5-HT$_{2c}$ receptor agonists**	Novel indazole derivatives	 **169**	Itsuro Shimada et al [131]
4.	**5-HT$_6$ antagonists**	3-sulfonylindazole	 170	Kevin G. Liu et al [132]
5.	**Orally efficacious melanin concentrating hormone receptor-1 antagonists**	3-amino indazole melanin concentrating hormone	 **171**  **172**	Anil Vasudevan et al [133]

6.	**Male Contraceptive**	Series of benzoimidazole, benzothiazole, pyrazole, and indazole derivatives.	 **173**	Qianqian Chen et al [134]
		1-(2,4-dichlorobenzyl)-1*H*-indazole-3-carbohydrazide	 174	C. Yan Cheng et al [135]
7.	**Anti-oxidant activity**	6-carbethoxy-2-cyclohexen-1-one and 2*H*-indazol-3-ol derivatives	 **175**	N.A. Shakil et al [136]
8.	**Nitric Oxide Synthase (NOS) inhibitors**	Halo-1-*H*-indazoles	 **176**	Valérie Collot et al [137]
		Fluoro indazoles	 **177**	Rosa M. Claramunt et al [138]
		Substituted imidazoles or other mono or bicyclic nitrogen-containing heterocycles	 **178**	Loredana Salerno et al [139]
		NOS inhibitors	 179	Rosa M. Claramunt et al [140]
		Methoxyindazoles	 **180**	Pascale Schumann et al [141]

9.	**Analgesic activity**	Schiff's bases of Indazolone	 **181**	P. Muthumani et al [91]
		1 (pyrimidin-2-yl)-3-pyrazolin-5-ones and 2-(pyrimidin-2-yl)-1,2,4,5,6,7-hexahydro-3*H*-indazol-3-ones.	 182	El-Sayed A.M. Badawey, Ibrahim M. El-Ashmawey [142]
10.	**Monoamine Oxidase Inhibitors**	2-thiocarbamoyl-2,3,4,5,6,7-hexahydro-1*H*-indazole and 2-substituted thiocarbamoyl-3,3a,4,5,6,7-hexahydro-2*H*-indazoles	 **183**	Nesrin Gokhan-Kelekci et al [94]
11.	**Antimicrobial activity**	N-[(4-oxo-2-substituted aryl-1, 3-thiazolidine) –acetamidyl]-5-substituted indazoles	 184	Chirag Parekh et al [143]
		N-[(4-oxo-2-substituted aryl-1, 3-thiazolidine)-acetamidyl]-5-nitroindazoles	 **185**	Apoorva Upadhya et al [144]
		N'-(1*H*-indazole-3-carbonyl)-hydrazide derivatives	 **186**	T. Chandrasekhar [145]
		2,3-disubstituted-3,3a,4,5,6,7-hexahydro-2*H*-indazole derivatives	 187	Maninder Minu et al [146]

		α-aminophosphonates containing Indazole	 188 	Nasir ali Shafakat Ali et al [147]
		Schiff's bases of Indazolone	 189 	P. Muthumani et al [91]
		Series of fluconazole analogues	 190	N. Lebouvier et al [148]
		(2R,3R)-2-(2,4-difluorophenyl)-3-(substituted indazol-1-yl)-1-(1*H*-1,2,4- triazol-1-yl) butan-2-ol	 **191**	Joon Seok Park et al [149]
		Chalcone based 6-carbethoxy-2-cyclohexen-1-one and 2*H*-indazol-3-ol derivatives	 **192**	N.A. Shakil et al [136]
		N-(1-Phenyl-4-carbetoxypyrazol-5-yl)-, *N*-(indazol-3-yl)- and *N*-(indazol-5-yl)-2-iodobenzamides	 193  194	Demetrio Raffa et al [150]
12.	**Anti-Protozoal activity**	Indazole N-oxide derivatives	  195	Alejandra Gerpe et al [151]

13.	**Anti-Fungal activity**			Nicolas Lebouvier et al [150]
		(2R, 3R)-2-(2,4-difluorophenyl)-3-(substituted indazol-1-yl)-1-(1H-1,2,4- triazol-1-yl) butan-2-ol		Joon Seok Park et al [149]
14.	**Anticonvulsant Activity**	Indazole substituted-1,3,4-thiadiazole	 198a 198b	Kikkeri P. et al [152]
15.	**Immunomodulatory**	[2-(arylamino)-4,4-dimethyl-6-oxo-cyclohex-1-ene] carbodithioates and 6,6-dimethyl-4-(2-(propan-2-ylidene)hydrazinyl)-6,7-dihydro-2H-indazole-3(5H)-thione	 **199**	El Sayed H. El Ashry et al [120]

of heterocumulenes from pseudo-cross-conjugated heterocyclic mesomeric betaines (PCCMB). Indazolium-3- carboxylates are examples for those systems (Scheme 44). They were prepared starting from the indazole-3-carboxylic acids 137 which were first converted into the esters 138, then methylated to indazolium salts 139 with dimethyl sulfate in the presence of catalytic amounts of nitrobenzene, and finally saponified (140) [113,114].

Redox reactions of indazoles

Redox esterifications of aldehydes to the benzoates 143 were found on generation of NHC 142a in the presence of aromatic aldehydes and alcohols (Scheme 43) [115].

Indazolium Salts

Lithium bis(silyl)cuprates react with indazolium salt 144 to give 3-silylindazolines such as 145 (Scheme 45). Variation of the cuprate results in reductive ring opening leading to benzo-β-enaminoimines such as 146, or mixtures of both [116].

Pharmacological Activities of Indazole and Its Derivatives

See Table 2.

Conclusion

The above literature survey indicate that indazole and its derivatives have pivot role in the medicinal chemistry, as most of the essential drugs are having these heterocycles in their compositions. Indazole is an important heterocyclic system which has great significance in pharmaceutical industry as well as being a useful synthon for the synthesis of many bridgehead heterocycles. This review describes new strategies and the development of novel concepts along with conventional methods to synthesize a wide variety of substituted indazoles. The large number of biologically active indazoles substituted at C(3), functionalizations of this position are of great current interest. In this context, Heck as well as Suzuki-type cross-couplings of 3-iodoindazoles has been described in review, multi-component synthesis and ring transformations provide useful synthetic routes to unsubstituted, monosubstituted, disubstitued, trisustituted & tetrasustituted indazole derivatives. By means of cycloaddition reactions regioisomers have formed.

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