Recent Advances in Indazole-Containing Derivatives: Synthesis and Biological Perspectives

Shu-Guang Zhang, Chao-Gen Liang and Wei-Hua Zhang

Abstract: Indazole-containing derivatives represent one of the most important heterocycles in drug molecules. Diversely substituted indazole derivatives bear a variety of functional groups and display versatile biological activities; hence, they have gained considerable attention in the field of medicinal chemistry. This review aims to summarize the recent advances in various methods for the synthesis of indazole derivatives. The current developments in the biological activities of indazole-based compounds are also presented.

Keywords: indazole; synthesis; biological activities

1. Introduction

The nitrogen-containing heterocycles are important building blocks for many bioactive natural products and commercially available drugs. As pharmacologically important scaffolds, they have attracted considerable attention from chemists [1]. Indazoles are one of the most important classes of nitrogen-containing heterocyclic compounds bearing a bicyclic ring structure made up of a pyrazole ring and a benzene ring. Indazole usually contains two tautomeric forms: 1H-indazole and 2H-indazole (Figure 1). Since 1H-indazole is more thermodynamically stable than 2H-indazole, it is the predominant tautomer [2].

![Figure 1. Indazole nucleus.](image)

Indazole derivatives scarcely occur in nature, but this particular nucleus in a variety of synthetic compounds possesses a wide range of pharmacological activities, such as anti-inflammatory, antiarrhythmic, antitumor, antifungal, antibacterial, and anti-HIV activities [3–8].

Diversely substituted indazole-containing compounds furnished with different functional groups represent significant pharmacological activities and serve as structural motifs in drug molecules. For example, niraparib 1 (Figure 2) has been widely used as an anticancer drug for the treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal, breast and prostate cancer [9]. Pazopanib 2 (Figure 2) is a tyrosine kinase inhibitor, which has been approved by the FDA for renal cell carcinoma [10]. Bendazac 3 and Benzydamine 4 are two commercially available anti-inflammatory drugs, which contain the 1H-indazole scaffold (Figure 2) [11].

In light of indazole scaffolds exhibiting a broad spectrum of pharmacological activities, numerous methods have been developed to construct of these heterocycles with better biological activities.
There are some excellent reviews, which have been published on the biological properties of this class of compounds [12–14]. This review serves as a comprehensive overview of recent literature that references the synthesis and biological activities of novel indazole-containing derivatives.

2. Synthesis Route for Indazole Derivatives

2.1. Synthesis of 1H-Indazole

The synthesis of 1H-indazoles 7 from aminohydrazone 6 with an intramolecular ligand-free palladium-catalyzed C-H amination reaction has been reported by Charette et al. [15]. Substituted aminohydrazones were easily prepared based on trifluoromethanesulfonic anhydride-mediated activation of tertiary amides 5, and the addition of nucleophilic hydrazides (Scheme 1). Chang et al. [16] treated diaryl and tert-butyl aryl ketone hydrazones 8 with iodine in the presence of potassium iodide and sodium acetate obtaining 1H-indazoles 9 via direct aryl C-H amination, as shown in Scheme 2. The synthesis of 1H-indazoles 11 from arylhydrazones 10 through direct aryl C-H amination using [bis-(trifluoroacetoxy)iodo]benzene (PIFA) as an oxidant was described by Zhang et al. (Scheme 3) [17]. The reaction displayed good functional group compatibility and provided the corresponding compounds in good yields. It is worth noting that both of the two following examples underwent a metal free catalyzed process.

![Figure 2. Chemical structure of indazole-containing drugs 1–4.](image_url)

**Scheme 1.** Synthesis of 1H-indazoles 7 from tertiary amides 5.

**Scheme 2.** Synthesis of 1H-indazoles 9 from hydrazones 8 via iodine-mediated aryl C-H amination.

**Scheme 3.** Synthesis of 1H-indazoles 11 from hydrazones 10 via PIFA-mediated aryl C-H amination.

Tang et al. [18] developed a protocol that realized the thermo-induced isomerization of o-haloaryl N-sulfonylhydrazones and Cu2O-mediated cyclization to obtain 1H-indazoles 13 (Scheme 4). Moreover, the reaction tolerated various functional groups. Wang et al. [19] disclosed a versatile approach for the synthesis of 1H-indazoles 15 via a cyclization of o-haloaryl N-sulfonylhydrazones 14.
using Cu(OAc)$_2$·H$_2$O as the catalyst, as can be seen in Scheme 5. Compared to Tang’s methods, this approach proceeded at lower temperatures with lower catalyst loading. As an example, Bunce et al. [20] recently explored an efficient route to substituted 1-aryl-1H-indazoles 17 (Scheme 6). This transformation involved the preparation of arylhydrazones, followed by deprotonation and nucleophilic aromatic substitution (SNAr) ring closure. Notably, treatment of bromoacetophenone and bromobenzaldehyde with ArNNH$_2$·HCl and 30 wt% of powdered 4 Å molecular sieves in the presence of CuI and K$_2$CO$_3$ also afforded the desired compounds in good yields.

![Scheme 4](image)

Scheme 4. Synthesis of 1H-indazoles 13 from o-haloaryl N-tosylhydrazones 12 catalyzed by Cu$_2$O.

![Scheme 5](image)

Scheme 5. Synthesis of 1H-indazoles 15 from o-haloaryl N-tosylhydrazones 14 catalyzed by Cu(OAc)$_2$·H$_2$O.

![Scheme 6](image)

Scheme 6. Synthesis of 1-aryl-5-nitro-1H-indazoles 17.

The synthesis of 1H-indazoles 20 from pyrazoles 18 and internal alkynes 19 via Pd(OAc)$_2$/P(tBu)$_3$:HBF$_4$ mediated oxidative benzannulation was achieved by Joo et al. (Scheme 7) [21]. Under the optimized conditions, the corresponding 1H-indazoles possessing different substituents on the benzene ring were constructed in moderate to good yields. Joo et al. [22] also disclosed another synthesis method for 1H-indazoles 24 using a sequence reaction, as shown in Scheme 8. They carried out the regioselective dialkenylation of pyrazoles 21 with electron-deficient alkenes 22 in the presence of Pd(OAc)$_2$ and Ag$_2$CO$_3$. A sequence involving thermal 6π-electrocyclization of dialkenyl pyrazoles and oxidation afforded the desired products.

![Scheme 7](image)

Scheme 7. Pd-catalyzed benzannulation of 4-bromopyrazoles 18 for synthesis of 1H-indazoles 20.

![Scheme 8](image)

Scheme 8. Strategies for dialkenylation of pyrazoles 21 and synthesis of 1H-indazoles 24.

Zhu et al. [23] present a simple and efficient strategy to afford 1H-indazoles 26 from readily available aldehyde phenylhydrazones 25 through Rh(III)-promoted double C-H activation and C-H/C-H cross coupling (Scheme 9). The reaction tolerated a range of functional groups and lead to the corresponding products in moderate to good yields.
Scheme 9. Synthesis of 1H-indazoles 26 from aldehyde hydrazones 25.

An efficient and general method to build up 1H-indazoles 29 by Cu(OAc)$_2$-mediated N-N bond formation using oxygen as the sole oxidant was reported by Chen et al. [24] (Scheme 10). Ketimine species as the key intermediates for this reaction were easily prepared from o-aminobenzonitriles 27 and organometallic reagents. The cyclization of ketamine 28 was performed by using Cu(OAc)$_2$ in the presence of oxygen efficiently converted the desired products in good to excellent yields.

Scheme 10. Synthesis of 1H-indazoles 29 from 2-aminobenzonitriles 27.

Li et al. [25] accomplished a rhodium and copper catalyzed C-H activation and C-N/N-N coupling of imidate esters or NH imines with nitrosobenzenes 31 to 1H-indazoles 32 (Scheme 11). In this transformation, the desired products were obtained under redox-neutral conditions in good yields. In the same year, they [26] observed that 1H-indazoles can be synthesized via rhodium-catalyzed amination using anthranil as an aminating reagent under both redox-neutral and oxidative conditions (Scheme 12). With this method, a series of bifunctional products were prepared in good to excellent yields. Both of these two examples involved expensive rhodium catalyst. To address this issue, they [27] explored a synergistic cobalt and copper catalytic system using a similar process to give 1H-indazoles 35 (Scheme 12). In this work, anthranil served as both an aminating reagent and organic oxidant. The reactions tolerated various functional groups and good yields were observed.

Scheme 11. Synthesis of 1H-indazoles 32 from nitrosobenzenes 31.

Scheme 12. Synthesis of 1H-indazoles 35 via Co(III)/Cu(II)-catalyzed C-H activation.

Peng et al. [28] developed a strategy to access 3-aryl/alkyl-1H-indazoles 38 by a 1,3-dipolar cycloaddition reaction of α-diazomethylphosphonates 36 with o-(trimethylsilyl)phenyl triflate 37 in the presence of CsF (Scheme 13). In addition, this transformation provided moderate to excellent yields.
2.2. Synthesis of 2H-Indazole

Nazaré et al. [29] demonstrated an organophosphorus-mediated reductive cyclization and a subsequent N-N bond formation of substituted benzamidines 40 to construct 3-amino-2H-indazoles 41 (Scheme 14a). The substituted benzamidines 40 were synthesized from 2-nitrobenzonitriles 39 through a two-step sequence involving a trimethylaluminium-mediated conversion. The reaction showed good functional group tolerance and satisfactory yields could be obtained. Later, the same group [30] reported a one-pot, two-step approach to generate 2H-indazol-2-amines 44 via a reductive cyclization of substituted hydrazones precursors 43 in the presence of organophosphorus reagent (Scheme 14b). In this process, substituted hydrazones 43 were easily prepared from 2-nitrobenzaldehyde 42 and phenylhydrazine.

![Scheme 13. Synthesis of 1H-indazoles 38 from α-diazomethylphosphonates 36.](image)

Scheme 13. Synthesis of 1H-indazoles 38 from α-diazomethylphosphonates 36.

Radosevich et al. [31] developed a useful method to construct 2H-indazoles 46 from o-nitrobenzaldimines 45 improved by 1,2,2,3,4,4-hexamethylphosphetane (Scheme 15a). In their work, o-nitrobenzaldimines 45 underwent deoxygenative N-N bond forming cadogan heterocyclization to provide desired products 46 in the presence of 1,2,2,3,4,4-hexamethylphosphetane and hydrosilane terminal reductant. This approach showed good functional group compatibility. The proposed mechanism revealed that the reaction proceeded via catalytic PIII/PV=O redox cycling. According to the DFT calculation, (3 + 1) cheletropic addition between the phosphetane catalyst and nitroarene substrate was a turnover-limiting step. Recently, Nazaré et al. [32] reported a one-pot, two-step method to prepare 2H-indazoles 49 from 2-nitrobenzaldehydes 47 and amines 48 by domino imine condensation/reductive cyclization in the presence of organophosphorus reagent (Scheme 15b). Similar to Radosevich’s prior work, the organophosphorus agents generated in situ via a redox process from phospholen oxide with organosilanes. The protocol was carried out at 110 °C, tolerating various carboxylic acids, boronic esters, protected amines, phenols to give cyclization products in good yields. In the same year, Nazaré et al. [33] discovered a SnCl2·H2O mediated reductive cyclization to afford 3-perfluoroalkylated-2H-indazoles 54 from α-perfluoroalkylated benzylamine 53 (Scheme 16). This protocol involved the preparation of precursors 52 from 2-nitrobenzaldehydes 50 and anilines 51, followed by reductive cyclization.
Scheme 15. (a) Synthesis of 2H-indazoles 46 from o-nitrobenzaldimines 45 via 1,2,2,3,4,4-hexamethylphosphetane-mediated N-N bond formation (b) Synthesis of 2H-indazoles 46 from 2-nitrobenzaldehydes 47 and amines 48 by phospholene oxide with organosilanes-mediated N-N bond formation.

Scheme 16. Synthesis of 3-perfluoroalkylated-2H-indazoles 54.

Ellman et al. [34] reported a practical bench-top reaction for the synthesis of N-aryl-2H-indazoles 57 through Cp*Co(III)-promoted C-H bond functionalization/addition/cyclization cascades (Scheme 17). In this work, treatment of azobenzenes 55 and aldehydes 56 with [Cp*Co(C₅H₆)][B(C₆F₅)₄] and AcOH in 1,4-dioxane at 100 °C led to the corresponding products with moderate to excellent yields. This reaction tolerated a wide range of functional groups and was successfully carried out on a large scale. A similar approach was used by Wang et al. [35] for the synthesis of 2H-indazoles 57 via a re-catalyzed C-H transformation of azobenzenes 55 and aldehydes 56 (Scheme 17). It should be mentioned that this reaction is a good example of using isolabe cyclic Re¹-complex as the catalyst. Remarkably, mechanistic studies disclosed that the aldehyde-insertion step was irreversible in the catalytic cycle.

Scheme 17. Co(III) or Re-catalyzed synthesis of N-aryl-2H-indazoles 57 from azobenzenes 55 and aldehydes 56.

The cyclization of azobenzenes 58 with α-keto aldehydes 59 was also realized by Kim et al. [36] using rhodium (III) catalyst (Scheme 18a). This process provided an efficient method to synthesize 3-acylated-2H-indazoles 60 via functionalization of C (sp²)-H bond in moderate to high yields.
A tandem C-H activation/intramolecular annihilation reaction between azobenzenes 61 with sulfoxonium ylides 62 for the synthesis 3-acylated-2H-indazoles 63 was reported by the same group (Scheme 18b) [37]. In contrast to the reaction conditions in the previous work, Cu(OAc)$_2$ and CuCO$_3$Cu(OH)$_2$ were utilized instead of AgOAc. In this process, the target products were synthesized with a wide range of substrate scope in good yields.

![Scheme 18](image)

Scheme 18. (a) Rh-catalyzed synthesis of 2H-indazoles 60 from azobenzenes 58 and α-keto aldehydes 59 (b) Rh-catalyzed synthesis of 2H-indazoles 60 from azobenzenes 61 and sulfoxonium ylides 62.

Xi et al. [38] reported rhodium (III)-catalyzed C-H functionalization of azobenzenes 64 with acrylates 65 to furnish the corresponding 2H-indazoles 66 in the presence of Cu(OAc)$_2$ with good functional group tolerance and satisfying yields (Scheme 19). Notably, copper acetate played an important role for β-hydride elimination during the course of transformation.

![Scheme 19](image)

Scheme 19. Rh-catalyzed synthesis of 2H-indazoles 66 from azobenzenes 64 and acrylates 65.

You et al. [39] discovered a rhodium (III)-catalyzed tandem C-H alkylation/intramolecular decarboxylative cyclization that used azyo compounds 67 and diazoesters 68 for the synthesis of 3-acyl-2H-indazoles 69 (Scheme 20a). In this reaction, azyo compounds 67 reacted with diazoesters 68 under the catalysis of [Cp*RhCl]$_2$ in the presence of AgSbF$_6$ to furnish the corresponding 2H-indazoles products with a broad functional group tolerance. Another example regarding the application of similar strategy for the synthesis of 2H-indazoles 72 was disclosed by the same group (Scheme 20b) [40]. Under the modified catalytic system, azyo compounds 70 and alkynes 71 underwent C-H activation/cyclization cascades to provide 2H-indazoles 72 in good yields.

![Scheme 20](image)

Scheme 20. (a) Rh-catalyzed synthesis of 2H-indazoles 69 from azoxybenzenes 67 and diazoesters 68 (b) Rh-catalyzed synthesis of 2H-indazoles 72 from azyo 70 and alkynes 71.

Lin et al. [41] introduced a Cu/Pd cooperatively catalyzed tandem C-N and C-P bonds formation reaction of 2-alkynyl azobenzenes 73 and compounds 74 for the construction of 2H-indazoles 75
(Scheme 21). In this approach, the phosphorated 2H-indazoles were synthesized in moderate to good yields, displaying good functional groups tolerance.

![Scheme 21. Cu/Pd-catalyzed synthesis of 2H-indazoles 75 from 2-alkynyl-azobenzenes 73.](image)

Xi et al. [42] developed an efficient iodine-mediated synthesis of 2H-indazoles 77 from ortho-alkylazobenzenes 76 via benzyl C-H functionalization (Scheme 22). With this method, a variety of 2H-indazoles bearing various functional groups were prepared in moderate to good yields. Mechanism studies suggested iodine assisted hydrogen transfer from the benzylic position to nitrogen. DFT calculations revealed that it was a radical chain mechanism. Subsequently, the same group [43] expanded the scope of the substrates. Under similar reaction conditions, using CuI as oxidation promoter and oxygen as a terminal oxidant, ortho-alkylazobenzenes could be converted to corresponding products via C-H bond functionalization with high yields.

![Scheme 22. I$_2$-mediated synthesis of 2H-indazoles 77 from ortho-alkylazobenzenes 76.](image)

Cheng et al. [44] disclosed a copper-mediated method for the annulation of 2-(1-substituted vinyl) anilines 79 with aryl nitrosamines 80 for the synthesis of 2,3-aryl-2H-indazoles 80 (Scheme 23). The reaction took place at 130 °C with Cu(OAc)$_2$ as a catalyst, O$_2$ as an oxidant in DMSO, affording the desired products.

![Scheme 23. Copper-mediated synthesis of 2H-indazoles 80.](image)

3. Biological Applications of Indazole Derivatives

3.1. Antitumor Activity

Paul et al. [45,46] reported the synthesis of a series of (1R,2S)-2-(1H-indazol-6-yl)spiro[cyclopropane-1,3’-indolin]-2’-one derivatives based on previous biosisosteric scaffold and evaluated their possible potential against Polo-like kinase 4 (PLK4) (Figure 3). As a result, compounds 81a, 81b, and 81c were single-digit nanomolar PLK4 inhibitors. In particular, compound 81c (CFI-400945) was an effective inhibitor of HCT116 tumor growth in a mouse model of colon cancer and was identified as a novel clinical candidate for cancer therapy.

Wang et al. [47] described the synthesis of novel 1H-indazole derivatives based on systematic optimization of both the piperidine and 2,6-difluorophenyl moieties of 3-(pyrazin-2-yl)-1H-indazole as potential inhibitors of pan-Pim kinases (Figure 4). The vitro assay study revealed that among the synthesized and tested compounds, 82a possessed the strongest activity against Pim-1, Pim-2 and Pim-3 with IC$_{50}$ values of 0.4, 1.1 and 0.4 nM, respectively. Meanwhile, compound 82a showed moderate cellular potency in KMS-12 BM cell assays with an IC$_{50}$ value of 1400 nM.
Wang et al. [49] designed and synthesized a novel series of azaindazole derivatives, which were identified as one of the lead compounds in the series. They also found that compound 83 possessed potent antiproliferative activity against the MM1.S multiple myeloma cell line with IC₅₀ value of 0.64 μM (Figure 5).

Wang et al. [49] designed and synthesized a novel series of azaindazole derivatives, which were tested as inhibitors of pan-Pim Kinases. It was found that compounds 84 possessed the strongest activity against Pim-1, Pim-2 and Pim-3 with Kᵢ values of 0.03, 0.11 and 0.02 nM, respectively (Figure 6). In particular, 84 was relatively impotent in a two-point hERG patch clamp assay, exhibiting moderate 37% Pim inhibition at 1 μM and 49% Pim inhibition at 10 μM.
Indazole-based series of selective estrogen receptor degraders (SERDs) were reported by Govek et al. [50]. A structure-activity relationship study of synthesized derivatives based on compound 85 (Figure 7) revealed that when replacing the ethyl with cyclobutyl group, the corresponding analogs displayed enhanced potency. However, incorporating larger substituents on para-position of the upper aryl ring, such as CF3, the corresponding compounds showed improved degradation efficacy. They also discovered that by tempering the polarity of lipophilic acids and incorporation of the 3-fluoroindazole motifs, oral bioavailability could be increased. Ultimately, compounds 86 and 87, which were identified by exploration of ER degradation and antagonism in vitro followed by in vivo antagonism and culminating in oral exposure, could induce tumor regression in a tamoxifen-resistant breast cancer xenograft.

The same year, Smith et al. [51] identified a series of 1H-indazole derivatives as orally bioavailable estrogen receptor degraders (SERDs) based on SAR studies on a triphenylalkene scaffold (Figure 8). Among the optimized compounds, 88 was the most efficient degrader of the ER-α with an IC50 value of 0.7 nM (Figure 8). Furthermore, 88 exhibited good bioavailability across species and displayed robust activity in tamoxifen-sensitive and tamoxifen-resistant xenograft models of breast cancer.

Wang et al. [52] synthesized a series of 1H-indazol-3-amine derivatives and evaluated their activity against Bcr-Abl wild type as well as T315I mutant. Among these compounds, 89 and 90 appeared to be the most potent Bcr-Abl inhibitors (Figure 9). In particular, compound 89 served as a promising inhibitor, which exhibited comparable potency with that of Imatinib and inhibited Bcr-AblWT, Bcr-AblT315I and K562 leukemia cancer cells with IC50 values of 0.014, 0.45 and 6.50 μM, respectively. The docking studies indicated that compound 89 bound to Bcr-AblWT in a similar manner as imatinib.

A novel series of 3-(pyrrolopyridin-2-yl)indazole derivatives were synthesized and evaluated for their anti-proliferative effects on five human cancer cell lines (HL60, KB, SMMC-7721, HCT116, and A549) by Hu et al. [53]. The study revealed that all of the synthesized compounds exhibited vigorous potency against HL60 cell line with IC50 values ranging from single digital nanomolar to
micromolar level. Among them, compound 93 was identified to be the most potent inhibitor, with IC$_{50}$ values of 8.3 nM and 1.3 nM against HL60 and HCT116 cell lines, respectively (Figure 10). Furthermore, results of the inhibitory activities against a panel of kinases demonstrated that compounds 91, 92 and 93 could selectively inhibit CHK1, CDK2, MEK1, GSK3β, BRAF, IKKβ and PKC.

![Figure 10. Chemical structures of 3-(pyrrolopyridin-2-yl)indazole derivatives 91, 92 and 93.](image)

Pauls et al. [54] synthesized a new set of 3-(4-(heterocyclyl)phenyl)-1H-indazole-5-carboxamides derivatives, which were tested as inhibitors of tyrosine threonine kinase (TTK). It was found that compounds 94, 95 (designated CFI-401870) and 96 were single-digit nanomolar TTK inhibitors, with acceptable off-target activity and good oral bioavailability in rodents (Figure 11). In particular, compound 95 served as the most efficacious of the shortlisted compounds in an HCT116 tumor xenograft model, which also could inhibit the growth of a broad panel of human cancer cell lines including breast, ovarian, colon, prostate, lung and melanoma cell lines.

![Figure 11. Chemical structures of 3-(4-(heterocyclyl)phenyl)-1H-indazole-5-carboxamides derivatives 94, 95 and 96.](image)

Qu et al. [55] performed anticancer activities screening assays as well as cancer growth inhibitory studies on previously synthesized N-(4-(1-(4-chlorineindazole))phenyl)-N-(4-chloro-3-tri fluoromethyl phenyl) urea 97 (Figure 12). The results indicated that compound 97 could be a multi-kinases inhibitor targeting c-Kit, PDGFRβ and FLT3 with K$_{d}$ values at 68.5 ± 9.5 nM, 140 ± 0 nM and 375 ± 15.3 nM, respectively. Compound 97 also possessed strong inhibition activities against 12 human cancer cells with IC$_{50}$ values ranging from 1.12 to 6.84 μM. Especially, it exhibited strong inhibition on SK-MEL-3, NB-4, and SK-MEL-31 with IC$_{50}$ values at 1.12 ± 0.06 μM, 1.34 ± 0.20 μM, and 1.77 ± 0.06 μM, respectively. Meanwhile, compound 97 effectively delayed the growth of cancer xenografts and safety to mice [56].

![Figure 12. Chemical structure of N-(4-(1-(4-chlorineindazole))phenyl)-N-(4-chloro-3-trifluoro-methyl phenyl) urea 97.](image)

Li et al. [57] designed and synthesized a novel series of 1H-indazol-3-amine scaffold derivatives by utilizing scaffold hopping and molecular hybridization strategies aiming to develop potent FGFR inhibitors. The authors carried out an evaluation of their inhibitory activity against FGFR1. It was found that 6-(3-methoxyphenyl)-1H-indazol-3-amine derivative 98 was a promising FGFR1 inhibitor, exhibited good enzymatic inhibition (IC$_{50}$ = 15.0 nM) and modest anti-proliferative activity.
(IC₅₀ = 642.1 nM) (Figure 13). Further structural optimization revealed that compound 99 was identified as the most potent FGFR1 inhibitor with the best enzyme inhibitory (IC₅₀ = 2.9 nM) and cellular activity (IC₅₀ = 40.5 nM). The SAR studies revealed that N-ethylpiperazine group was important for enzyme inhibitory and cellular activity.

Figure 13. Chemical structures of 1H-indazol-3-amine derivatives 98 and 99.

As a continuation of their research to improve the cellular activity of hit compound 100 bearing an indazole scaffold, a series of new compounds harnessing fluorine substituents were designed, synthesized and evaluated as inhibitors of the above enzyme by Li et al. [58]. Among them, compound 100 containing 2,6-difluoro-3-methoxyphenyl group, possessed the most enzymatic and antiproliferative activities (FGFR1: IC₅₀ value less than 4.1 nM, FGFR2: IC₅₀ = 2.0 ± 0.8 nM, KG1 cell lines: IC₅₀ = 25.3 ± 4.6 nM, SNU16 cell lines: IC₅₀ = 77.4 ± 6.2 nM) (Figure 14).

Figure 14. Chemical structure of 1H-indazol-3-amine derivative 100.

Zhao et al. [59] disclosed novel 6-(2,6-dichloro-3,5-dimethoxyphenyl)-4-substituted-1H-indazole derivatives and assessed their potency as tyrosine kinase fibroblast growth factor receptor (FGFR) inhibitors for cancer therapy. The results indicated that compound 101 was a potent FGFR1 inhibitor, with good enzymatic inhibition (IC₅₀ = 69.1 ± 19.8 nM) (Figure 15). According to the obtained structure activity relationship, the authors further designed and synthesized a new series of derivatives. 6-(2,6-Dichloro-3,5-dimethoxyphenyl)-N-(3-(4-methylpiperazin-1-yl)phenyl)-1H-indazole-4-carboxamide (102) exhibited the most potent FGFR1 inhibitory activity in the enzymatic assay (IC₅₀ = 30.2 ± 1.9 nM).

Figure 15. Chemical structures of 6-(2,6-dichloro-3,5-dimethoxyphenyl)-4-substituted-1H-indazole derivatives 101 and 102.

Liu et al. [60] reported that the synthesis of pyridin-3-amine derivatives served as multi-targeted protein kinase inhibitors for the treatment of non-small cell lung cancer (NSCLC). First, they discovered compound 103 via in silico screening against fibroblast growth factor receptors (FGFR) and this was sequentially validated by in vitro experiments (IC₅₀ value of 3.8 ± 0.5 μM against FGFR1). Aiming to improve the inhibition potency of compound 103 against FGFR1, the authors carried
out a structure-based structural optimization, and then explored further to afford novel FGFR inhibitors (Figure 16). Among them, compound 104 displayed attractive inhibitory activity against FGFR1, 2 and 3 with IC\textsubscript{50} values of 18.0, 1.6 and 27.5 nM, respectively. Notably, compound 104 also exhibited nanomolar level inhibition against several other NSCLC-related oncogenes kinases, such as RET, EGFR, EGFR/T790M/L858R, DDR2, and ALK. Significant antitumor activity (TGI = 66.1\%) of compound 104 in FGFR-driven NCI-H1581 xenografts with good PK profiles was observed in vivo pharmacology evaluations.

![Figure 16. Chemical structures of pyridin-3-amine derivatives 103 and 104.](image)

Duan et al. [61] reported the synthesis of novel 3-(5'-Substituted)-Benzimidazole-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazole derivatives and evaluated for Fibroblast growth factor receptors (FGFRs) inhibitory activities. Among them, compound 105 was identified as a potent pan-FGFR inhibitor (FGFR1-4 IC\textsubscript{50} values of 0.9, 2.0, 2.0, and 6.1 nM, respectively) (Figure 17). Moreover, compound 105 provided nearly complete inhibition of tumor growth (96.9\% TGI) in NCI-H1581 (FGFR1-amplified) xenograft mice model at the dose of 10 mg/kg/qd via oral administration.

![Figure 17. Chemical structure of 3-(5'-Substituted)-Benzimidazole-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazole derivative 105.](image)

Fishwick et al. [62] discovered a novel series of 1H-indazole-based derivatives for the inhibition of Fibroblast growth factor receptors (FGFRs) kinases using fragment-led de novo design. Biological evaluation indicated that these 1H-indazole-based derivatives inhibited FGFR1-3 in the range of 0.8–90 \( \mu \text{M} \) with excellent ligand (LE) efficiencies of 0.30–0.48. Among them, compound 106 was identified as the most active inhibitor (FGFR1-3 IC\textsubscript{50} values of 2.0 ± 0.4, 0.8 ± 0.3 and 4.5 ± 1.6 \( \mu \text{M} \), respectively) (Figure 18).

![Figure 18. Chemical structure of 1H-indazole derivative 106.](image)

Rauh et al. [63] described a structure-based approach, rationalized by subsequent computational analysis of conformational ligand ensembles in solution, to design 1H-indazole analogues as irreversible and mutant-selective EGFR inhibitors based on systematic optimization of 80 NSCLC cell lines against approximately 1500 compounds. The in vitro assay study revealed that among the
synthesized and tested compounds, 107 was the most active compound against the L858R/T790M double mutant of EGFR with IC\textsubscript{50} values of 0.07 \( \mu \)M. Meanwhile, 107 exhibited moderate effects on the activating and drug resistant cell lines HCC827 and H1975 (GI\textsubscript{50} = 2.5 \( \mu \)M and 9.8 \( \mu \)M, respectively) (Figure 19).

![Figure 19. Chemical structure of 1H-indazole derivative 107.](image)

A series of 1H-indazole derivatives were synthesized using structure-guided drug design from lead compound 108 by Liu et al. [64] and evaluated for their epidermal growth factor receptor (EGFR) kinase activity. The results indicated that compound 109 displayed strong potencies against EGFR T790M and EGFR kinases with IC\textsubscript{50} values of 5.3 and 8.3 nM, respectively (Figure 20). In particular, compound 109 displayed strong antiproliferative effects against EGFR mutant-driven non-small cell lung cancer (NSCLC) cell lines such as H1975, PC9, HCC827, and H3255 without obvious toxicity.

![Figure 20. Chemical structures of 1H-indazole derivatives 108 and 109.](image)

Hah et al. [65] reported the synthesis of novel 3-carboxamido-2H-indazole-6-arylamide derivatives as selective CRAF inhibitors. The compounds were evaluated for antiproliferative activity against the WM3629 melanoma cell line. Results revealed that most of the compounds displayed potent antiproliferative activity against the WM3629 melanoma cell line. In particular, compounds 110 and 111 exhibited superior selectivity (Figure 21). Compound 110 was found to be the most promising inhibitor against the WM3629 melanoma cell line with IC\textsubscript{50} value of 38.6 nM, which also showed enzymatic activities against wild-type BRAF and BRAF (V599E) kinase with IC\textsubscript{50} values of 9.45 and 7.82 \( \mu \)M, respectively.

![Figure 21. Chemical structures of 3-carboxamido-2H-indazole-6-arylamide derivatives 110 and 111.](image)

Schiemann et al. [66] synthesized a series of 3-benzylindazoles analogues based on a high-throughput screening (HTS) campaign sampling the Merck compound collection, which were tested as potent and selective CDK8 inhibitors with high affinity to CDK19. Medicinal chemistry optimization allowed them to identify inhibitors with improved potency, physicochemical properties and oral pharmacokinetics. Compound 112 displayed promising selectivity against CDK8 with IC\textsubscript{50} value of 53 nM (Figure 22).
Czodrowski et al. [67] described a series of imidazo-thiadiazole derivatives as CDK8 inhibitors based on a Forster resonance energy transfer (FRET)-based Lanthascreen binding competition assay. In several optimization cycles, compounds 113 displayed excellent kinase selectivity (CDK8 IC\textsubscript{50} = 2.6 nM), biochemical and cellular potency, microsomal stability (Figure 23). In particular, compound 113 demonstrated reduction of tumor growth rates of established human SW620 colorectal carcinoma xenografts using two different oral dosing schedules.

Mallinger et al. [68] disclosed a novel series of 1H-indazole derivatives and the application of physicochemical property analyses to successfully reduce in vivo metabolic clearance, minimize transporter-mediated biliary elimination while maintaining acceptable aqueous solubility. The results indicated that compound 114 was a potent selective, and orally bioavailable inhibitor of CDK8 (IC\textsubscript{50} = 2.3 ± 0.8 nM) with equipotent affinity for CDK19 (IC\textsubscript{50} = 2.6 ± 0.4 nM) (Figure 24). According to the assay results, compound 114 afforded the optimal compromise of in vitro biochemical, pharmacokinetic, and physicochemical properties and was suitable for progression to animal models of cancer.

A series of 1H-indazole amide derivatives were synthesized using structure-guided and knowledge-based design from lead compound 115 by Cao et al. [69] and evaluated for their extracellular signal-regulated kinase1/2 (ERK1/2) activity. The results indicated that most advanced compounds 116, 117 and 118 showed both very good enzymatic and cellular activity toward ERK1/2 and HT29 cell lines with IC\textsubscript{50} values ranging between 9.3 ± 3.2–25.8 ± 2.3 nM, 0.9 ± 0.1–6.1 ± 1.1 μM, respectively (Figure 25).

Babu Boga et al. [70] developed a series of novel 3(S)-thiomethyl pyrrolidine-1H-indazole derivatives aiming to identify new and safe compounds as ERK inhibitors for treatment of cancer. Among all the tested compounds, compound 119 displayed excellent potency, high ERK 1/2 selectivity and dual mechanisms of action inhibition (IC\textsubscript{50} = 20 and 7 nM, respectively) (Figure 26). Additionally, the detailed pharmacological and clinical evaluation demonstrated that compound 119 was well tolerated up to 400 mg twice daily and exhibited antitumor activity in patients with BRAFV600-mutant melanoma.
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Hsieh et al.

Manna et al. 

Manna et al. [72] described the synthesis of a series of 3-substituted 1H-indazoles which were investigated for their IDO1 enzyme inhibition efficiencies. The studies revealed that, among the synthesized and tested derivatives, 121 and 122 possessed the most potent inhibitory activity with IC50 values of 720 and 770 nM, respectively (Figure 28). According to SAR studies, the presence of 1H-indazole ring and suitably substituted carbohydrazide moiety at the C3 position of the indazole ring played a crucial role for their strong inhibitory activities in vitro.
Hsieh et al. [73] described the synthesis of indazole-based derivatives by utilizing in silico fragment-based approach and knowledge-based drug design and evaluated them for Aurora kinase activity. The study revealed that, among the optimized derivatives, compounds 123 (dual Aurora A and B), 124 (Aurora B selective) and 125 (Aurora A selective) provided subtype-type kinase selectivity (Figure 29). Furthermore, compounds 123 appeared to be the most potent dual Aurora A and B inhibitor (IC_{50} = 0.026, 0.015 μM, respectively). Docking analysis revealed that compound 123 formed hydrogen bonds with particular targeting residues Glu211, Ala213, Lys141, Thr217 and Arg220 in Aurora kinase binding pocket.

Menichincheri et al. [74] used 3-amino-5-substituted indazole 126 as a promising starting point for further investigation and obtained novel 3-aminoindazole derivatives. The synthesized compounds were tested for their enzyme inhibition and antiproliferative activities. Results revealed that compound 127 (entrectinib) showed highest activity against anaplastic lymphoma kinase (ALK) with an IC_{50} value of 12 nM (Figure 30). Moreover, compound 127 caused potent inhibition of the closely related tyrosine kinases ROS1 and TRKs with nanomolar activity and it was recently used in phase I/II clinical trial for the treatment of patients affected by ALK-, ROS1- and TRK-dependent tumors [75,76].

Rauh et al. [77] reported the synthesis of novel selective indazole-based derivatives as potential inhibitors of mutated drug resistant EGFR-L858R/T790M and covalently alkylate Cys797. The assay resulted in a promising compound 128 (Figure 31), which displayed inhibitory activity against
H1975 and HCC827 cell lines with the EC₅₀ values of 191 nM and 22 nM, respectively, while sparing the wild type with a EC₅₀ value of 3103 nM in A431 cells.

![Figure 31. Chemical structure of indazole-based EGFR inhibitor 128.](image1)

Vankayalapati et al. [78] prepared a novel class of 1H-benzo[d]imidazol-2-yl)-1H-indazol derivatives as phosphoinositide-dependent kinase-1 (PDK1) inhibitors based on a fragment-based, structure-assisted approach. The preliminary biological results led to the identification of the two most active compounds, namely compounds 129 and 130 (Figure 32). These lead compounds exhibited potent PDK1 activity with IC₅₀ values of 80 and 90 nM, respectively.

![Figure 32. Chemical structures of 1H-benzo[d]imidazol-2-yl)-1H-indazol derivatives 129 and 130.](image2)

Recently, Zhang et al. [79] developed a novel series of pazopanib hybrids as polypharmacological antitumor agents based on the crosstalk between histone deacetylases (HDACs) and vascular endothelial growth factor (VEGF) pathway. Among these compounds, ortho-aminoanilide based compound 131 and pazopanib-based hydroxamic acid 132 were identified as the most potent histone deacetylases (HDACs) inhibitors with IC₅₀ values of 4.6 and 0.0033 μM, respectively (Figure 33). It is worth noting that compound 131 exhibited more potent antiproliferative activity against HT-29 than both SAHA and MS-275, while compound 132 was slightly more potent than MS-275. Furthermore, compounds 131 and 132 displayed comparable vascular endothelial growth factor receptor (VEGFR) signaling pathway potencies to pazopanib with IC₅₀ values of 37 and 46 nM, respectively. Additionally, compound 131 possessed desirable pharmacokinetic profiles with oral bioavailability of 72% in SD rats and considerable in vivo antitumor efficacy in a human colorectal adenocarcinoma (HT-29) xenograft model [80].

![Figure 33. Chemical structures of 2H-indazole derivatives 131 and 132.](image3)
Zhang et al. [81] designed and prepared three classes of multi-target inhibitors based on the extensive sequence homology along the kinase domain of angiogenic RTKs. Biological evaluation indicated that these multi-target inhibitors exhibited considerable potential as novel anti-angiogenic and anticancer agents. Among them, compound 133 showed the most potent multi-target RTKs inhibitors with IC\textsubscript{50} values of 3.45 nM (VEGFR-2), 2.13 nM (Tie-2), and 4.71 nM (EphB4), respectively (Figure 34). Additionally, compound 133 also showed inhibition on the viability of human umbilical vein endothelial cells and antiproliferation against a broad spectrum of cancer cells.

Abouzid et al. [82] reported the synthesis of three series of novel indazole-pyrimidine based derivatives based on the development of derivatives of pazopanib 134 (VEGFR-2 IC\textsubscript{50} = 30 nM) (Figure 35). The synthesized compounds were tested for their VEGFR-2 kinase inhibitory activity and selected compounds were evaluated for their inhibitory activity against the NCI-60 cancer cell line. Among the tested derivatives, compound 135 showed the highest potency inhibitory activity against VEGFR-2 with the IC\textsubscript{50} value of 24.5 nM and cellular anti-angiogenic activity against the human umbilical vein endothelial cells (HUVEC) cell line with the IC\textsubscript{50} value of 1.37 μM. In addition, compound 136 exerted nanomolar GI\textsubscript{50} values against several cell lines: CCRF-CEM (901 nM), MOLT-4 (525 nM) and CAKI-1 (992 nM). Compound 137 showed one-digit micromolar activity against the whole panel of cell lines ranging from 1.55 μM to 7.4 μM.

Dong et al. [83] prepared a novel series of 1H-indazole derivatives and investigated against VEGFR-2 kinase inhibitory activities and anti-proliferative activities in vitro. Biological activity results indicated that most of the nascent compounds under investigation exhibited significant VEGFR-2 kinase inhibitory activity. Among them, 138, 139, 140, and 141 exhibited more potent inhibitory activities and favorable anti-proliferative activities at the concentration of 10 μM with IC\textsubscript{50} values of 5.03 μM (SD = 1.13, n = 3), 5.73 μM (SD = 1.30, n = 3), 2.18 μM (SD = 1.43, n = 3), and 2.15 μM (SD = 1.46, n = 3), respectively (Figure 36).

Arifuddin et al. [84] reported a novel series of sulfocoumarin/coumarin/4-sulfamoylphenyl bearing indazole-3-carboxamide hybrids. The synthesized compounds were evaluated in vitro as inhibitors against four relevant human carbonic anhydrases (hCAs), comprising the cytosolic and
ubiquitous isozymes hCA I and II as well as the transmembrane hCA IX and hCA XII. Among them, compounds 142a, 142b and 142c potentially inhibited tumor associated, hypoxia induced isoforms hCA IX with k values 1.8, 2.3, and 2.0 nM, respectively (Figure 37).

![Figure 36. Chemical structures of 1H-indazole derivatives 138–141.](image)

![Figure 37. Chemical structures of indazole-3-carboxamide derivatives 142a–c.](image)

Jin et al. [85] report SAR studies that focus on modifications to various regions of the enhancer of zeste homologue 2/1 (EZH2/1) inhibitor UNC1999 (143) to investigate the impact of the structural changes on EZH2 and EZH1 inhibition and selectivity (Figure 38). The SAR studies demonstrated that the two methyl groups at the 4 and 6 positions of the pyridone ring showed the importance of inhibiting these two enzymes, especially EZH2. In addition, the indazole ring was the best among the heterocyclic rings and various substituents at the N-1 position of this ring system had stronger effects on EZH1 potency than EZH2 potency.

![Figure 38. Chemical structure of 1H-indazole derivative 143.](image)
Di Lello et al. [86] adopted fragment-based lead discovery (FBLD) by NMR combined with virtual screening and re-mining of biochemical high-throughput screening (HTS) hits led to the discovery of a series of ligands that bind in the “palm” region of the catalytic domain of ubiquitin specific protease 7 (USP7) and inhibit its catalytic activity. These ligands were then optimized by structure-based design to yield cell-active molecules with reasonable physical properties. Among them, compound 144 and 145 displayed the most promising activity against USP7 with IC₅₀ values of 0.75 and 0.61 μM, respectively (Figure 39). MDM2 MSD cell-based assay results showed that compound 145 was the most potent analog with an EC₅₀ value of 0.30 μM. Furthermore, compound 145 decreased cell viability via both apoptosis and cell cycle arrest.

![Chemical structures of 1H-indazole derivatives 144 and 145.](image)

Roush et al. [87] using an in silico HTS campaign utilizing a published X-ray structure of ULK1 and the electronic coordinates of an in-house chemical library, identified compound 146 as a moderately active Unc-51-like kinase 1 (ULK1) inhibitor (IC₅₀ = 22.4 μM). Further optimization of compound 146 using structure-guided rational drug design then resulted in significantly more potent ULK1 inhibitors. Among them, compounds 147 and 148 exhibited strong inhibition on ULK1 with IC₅₀ values of 11 and 45 nM, respectively (Figure 40). SAR efforts confirmed that 3-aminocyclohexane substituent played a crucial role in ULK1 inhibition.

![Chemical structures of 1H-indazole derivatives 146–148.](image)

### 3.2. Antimicrobial Activity

Qin et al. [88] described the synthesis of a novel series of aromatic carboxylic acid amides containing 1H-indazole moiety based on a bioisosterism approach and evaluation of their activities against six phytopathogenic fungi by an in vitro mycelia growth inhibition assay. The preliminary biological results demonstrated that all of the target molecules displayed moderate to good activity against the six kinds of fungi. Among them, compounds 149 and 150 exhibited higher inhibition activity than others (Figure 41). In particular, N-[(2-(1H-indazol-1-yl)phenyl)-2-(trifluoromethyl)-benzamide (150) exhibited the highest antifungal activity against *Pythium aphanidermatum* (EC₅₀ = 16.75 μg/mL) and *Rhizoctonia solani* (EC₅₀ = 19.19 μg/mL), respectively. The molecular docking studies indicated that the fluorine and the carbonyl oxygen atom of 150 formed hydrogen bonds with the hydroxyl hydrogens of TYR58 and TRP173.
Ma et al. [89] developed a series of novel 4-bromo-1H-indazole derivatives aiming to identify new and safe compounds as filamentous temperature-sensitive protein Z (FtsZ) inhibitors. The authors performed an evaluation of their antibacterial activity and cell inhibitory activity against various phenotypes of Gram-positive and Gram-negative bacteria. Among all the tested compounds, compounds 152 and 153 exhibited more potent activity than 3-methoxybenzamide (3-MBA) against penicillin-resistant staphylococcus aureus (Figure 42). Particularly, compound 151 presented the best activity with an MIC value of 4mg/mL against S. pyogenes PS in the tested compounds.

A new set of 2H-indazole derivatives were studied for their activities against selected intestinal and vaginal pathogens, including the protozoa Giardia intestinalis, Entamoeba histolytica, and Trichomonas vaginalis; the bacteria Escherichia coli and Salmonella enterica serovar Typhi; and the yeasts Candida albicans and Candida glabrata by Pérez-Villanueva et al. [90]. Biological evaluations revealed that most of the synthesized compounds showed more potent antiprotozoal activity than metronidazole. Furthermore, compounds 154 and 155 inhibited in vitro growth of C. albicans and C. glabrata with the same minimum inhibitory concentration (MIC) (Figure 43). In addition, compounds 154, 155, 156, and 157 were identified as anti-inflammatory agents and displayed in vitro inhibitory activity against COX-2 (36–50%, at 10 μM).

3.3. Anti-Diabetic Agents

A novel series of indazole-based compounds were designed and synthesized by Lin et al. [91] as glucagon receptor antagonists (GRAs) for treatment of type 2 diabetes mellitus. Among them, compound 158 was identified to be orally active in blunting glucagon induced glucose excursion in an acute glucagon challenge model in glucagon receptor humanized (hGCCR) mice at 1, 3 and 10 mg/kg (mpk), and significantly lowered acute glucose levels in hGCCR ob/ob mice at 3 mpk dose (Figure 44).
Structure-activity relationship (SAR) studies revealed that aryl groups on the C3 and C6 positions of the indazole core were crucial for inhibitory activities.

![Image of chemical structure](image1)

**Figure 44.** Chemical structure of 1H-indazole derivative 158.

Cheruvallath et al. [92] discovered a novel class of 1,4-disubstituted indazole derivatives as the potent Glucokinase activators using scaffold morphing and structure guided medicinal chemistry approach. The anti-diabetic oral glucose tolerance test (OGTT) demonstrated that compound 159 exhibited promising hERG (human Ether-a-go-go Related Gene) inhibitory activity with EC50 values of 0.08 μM (Figure 45). It was further established that compound 159 combined the best balance of GK activation and in vitro DMPK properties.

![Image of chemical structure](image2)

**Figure 45.** Chemical structure of 1,4-disubstituted-1H-indazole derivative 159.

McCoul et al. [93] identified an indazole-6-phenylcyclopropylcarboxylic acid series of GPR120 agonists and (S,S)-cyclopropylcarboxylic acid series of GPR40 agonists. Among them, compounds 160 and 161 exhibited potent GPR120 inhibition activity with EC50 values of 0.74 and 0.36 μM, respectively (Figure 46). Furthermore, compounds 160 and 161 were progressed to in vivo studies and demonstrated significant reduction in blood glucose excursion in response to a glucose challenge. Taking all these data together, the two compounds were excellent in vivo for exploring the agonist pharmacology of the GPR120.

![Images of chemical structures](image3)

**Figure 46.** Chemical structures of 1H-indazole derivatives 160 and 161.

### 3.4. Anti-Inflammatory Activity

Hemmerling et al. [94] adopted a structure-based design approach to obtain a novel class of indazole ether based molecular scaffolds and evaluated their glucocorticoid receptor (GR) modulate activities. The results indicated that several examples displayed efficacy in a cellular transrepression assay at picomolar concentrations. Additionally, compound 162, 163a, 163b and 163c were investigated in the SCW rat PD model where in vitro potency translated well into in vivo efficacy (Figure 47), which showed that they were potential GR modulators for treatment of inflammatory diseases.
Jones et al. [95] discovered a series of novel 1H-indazoles analogues as selective pan-Janus kinase (JAK) inhibitors with a type 1.5 binding mode by means of structure-based computational method. After optimizing the synthesized compounds for potency and increased duration of action commensurate with inhaled or topical delivery, the authors identified a potent inhibitor 164 (PF-06263276) (Figure 48), which displayed good cellular JAK inhibitory activities and was potentially well suited for use as an inhaled or topical therapy to treat inflammatory diseases.

Casillas et al. [96] identified and characterized 6-(tert-Butylsulfonyl)-N-(5-fluoro-1H-indazol-3-yl)quinolin-4-amine (165) as a potent and highly selective inhibitor of RIP2 kinase (IC\(_{50}\) = 5 nM) for the treatment of chronic inflammatory diseases (Figure 49). Compound 165 potently and dose dependently inhibited MDP stimulated tumor necrosis factor-alpha (TNFα) production with an IC\(_{50}\) = 8 nM. Compound 165 also inhibited the increase in serum levels of KC following administration of the NOD1 ligand, FK156 in mice with a single oral dose of 10 mg/kg. Moreover, in human biopsy assay, 165 significantly inhibited both TNFα and IL-6 production in a concentration-dependent fashion in both Crohn’s disease (CD) and ulcerative colitis (UC) samples.

Hemmerling et al. [97] developed a class of potent, nonsteroidal, selective indazole ether-based glucocorticoid receptor modulators (SGRMs) for the treatment of airway inflammation. The authors developed a soft-drug strategy to deliver the first inhaled candidate 166, which potently inhibited a Sephadex-induced lung edema in a dose-dependent manner with an ED\(_{50}\) value of 1.2 μg/kg (Figure 50). Further optimization of the inhaled drug properties provided a second, equally potent, candidate 167, which achieved the requisite low solubility profile but retained the potency of compound 166 and demonstrated a robust local anti-inflammatory effect in rat lung airways at the same dose.
Pryde et al. [98] reported a series of novel 1H-indazole derivatives as transient receptor potential ankyrin-repeat 1 (TRPA1) antagonists. The authors investigated the derivatives’ physical properties and in vitro drug metabolism and pharmacokinetics (DMPK) profiles. Compounds 168 and 169 showed significant activity against hTRPA1 with IC\textsubscript{50} values of 20 and 686 nM, respectively, when administered either systemically or topically (Figure 51). Furthermore, the computational docking model proposed that compound 169 bounded in the S5 region of TRPA1 channel.

Hamblin et al. [99] synthesized a novel series of 4,6-disubstituted-1H-indazole derivatives as selective phosphoinositide 3-kinase delta (PI3K\(\delta\)) inhibitors for the treatment of respiratory disease. The authors discovered compounds 170 and 171 via a structure-based design approach (Figure 52). Compounds 170 and 171 were both highly selective against PI3K\(\delta\) with \(pK_i\) values of 9.9 and 10.1, respectively. Moreover, in the brown Norway rat acute OVA model of Th2 driven inflammation in the lungs of rats, compounds 170 and 171 were shown to protect against eosinophil recruitment with ED\textsubscript{50} of 67 and 35 \(\mu\)g/kg, respectively.

Henley et al. [100] described a novel, potent, and selective series of 4,6-disubstituted-1H-indazole derivatives and subsequent exploration of the structure-activity relationship led to the discovery of phosphoinositide 3-kinase delta (PI3K\(\delta\)) inhibitor for the treatment of inflammatory diseases. Among them, compound 172 showed significant PI3K\(\delta\) activity (\(pIC_{50} = 7.0\)), specifically against the other PI3K isoforms (\(\alpha\) \(pIC_{50} = 5.0\), \(\beta\) \(pIC_{50} = 5.2\), \(\gamma\) \(pIC_{50} = 5.2\)) (Figure 53).
Ellman et al. [101] prepared and evaluated a novel series of N-alkylated indazole chloroacetamidine derivatives as potential protein arginine deiminase 4 (PAD4) inhibitors. Derivatization around the indazole ring with chloro substituents then led to the identification of trichloroindazole compound 173 with high inhibitory activity against PDAs ($k_{\text{inact}}/K_i$ values: PDA1, 20 ± 5; PDA2, 940 ± 240; PDA3, 5100 ± 400, 5,4000 ± 3000) (Figure 54). Furthermore, compound 173 inhibited PAD4-mediated H4 citrullination at low micromole concentrations.

Ripa et al. [102] designed a novel series of 1H-indazole derivatives as potent glucocorticoid receptor (GR) modulators and conducted transactivation (TA) and transrepression (TR) assays. Based on the assays results, the compounds were further evaluated in functional assays measuring inhibition of lipopolysaccharide (LPS) induced tumor necrosis factor (TNF) α release in whole blood, upregulation of tyrosine aminotransferase (TAT) in primary hepatocytes, and downregulation of osteoprotegerin (OPG) in human fetal osteoblasts (hFOB). The experimental data ultimately lead to the discovery of compound 174, which displayed excellent inhibitory activity against GR with IC$_{50}$ value of 3.8 nM (Figure 55). In addition, compound 174 exhibited excellent efficacy in the streptococcal cell wall (SCW) reactivation model of joint inflammation.

3.5. Treatment of Parkinson’s Disease

cis-2,6-Dimethyl-4-(6-(5-(1-methylcyclopropoxy)-1H-indazol-3-yl)pyrimidin-4-yl)morpholine (MLi-2) 178 is a structurally novel, highly potent drug-like compound developed by Merck [103,104] as a selective Leucine-Rich Repeat Kinase 2 (LRRK2) inhibitor for treatment of Parkinson’s disease (PD). MLi-2 has exhibited exceptional potency inhibitory activity against purified LRRK2 kinase with IC$_{50}$ value of 0.76 nM in vitro. Additionally, in an evaluation performed in dephosphorylation of pSer935 LRRK2 and radioligand competition binding assays, compound 175 provided IC$_{50}$ values of 1.4, 3.4 nM, respectively (Figure 56). Moreover, target engagement was confirmed through a dose-dependent reduction in the ratio of pS935 LRRK2 to total LRRK2 in the brains of rats after oral
dosing with compound 175. These data demonstrate the emergence of compound 175 as a key tool in the understanding of LRRK2 function and it possible suitability as a potent, highly selective, orally available compound to explore the LRRK2 inhibitor for treatment of Parkinson’s disease (PD).

![Chemical structure of 1H-indazole derivative 175 as LRRK2 inhibitor.](image)

Tzvetkov et al. [105] reported the synthesis of a class of N-alkyl-substituted indazole-5-carboxamide derivatives and optimized their Monoamine oxidases inhibitory activities to develop potential drug and radioligand candidates for the treatment of Parkinson’s disease (PD) and other neurological disorders. Some analogues showed promising inhibitory activities with nanomolar potency towards MAO-B and were moderately active against the MAO-A enzyme, respectively. The most promising derivatives among the tested compounds were 176 (IC\(_{50}\) hMAO-B 0.662 nM) and 177 (IC\(_{50}\) hMAO-B 8.08 nM, IC\(_{50}\) hMAO-A 0.56 µM) (Figure 57). The following studies confirmed that compounds 176 and 177 established binding interactions with hMAO-B via the carbonyl group of the carboxamide linkage and the N1 or N2 nitrogen of the indazole moiety.

![Chemical structures of N-alkylated indazole-5-carboxamide derivatives 176 and 177.](image)

### 3.6. Treatment of Anemia of Chronic Disease

Fukuda et al. [106] reported a novel series of indazole derivatives as lead structures for potent hepcidin production inhibitors for treatment of anemia of chronic disease (ACD). The authors identified a 5-substituted indazole compound 178 through the screening of their compound library as a hepcidin production inhibitor, which showed weak activity in vitro (IC\(_{50}\) = 3.1 µM) (Figure 58). They adopted 178 as the leading compound and introduced a para-hydroxyphenyl group at the 6-position and [2-(morpholin-4-yl)ethoxy]benzamide group at the 3-position led to a potent hepcidin production inhibitor 179 (IC\(_{50}\) = 0.13 µM). Moreover, compound 179 exhibited serum hepcidin lowering effects in a mouse IL-6 induced acute inflammatory model.

![Chemical structures of 1H-indazole analogues 178 and 179.](image)
As a continuation of their research on the development of hepcidin production inhibitors for treating anemia of chronic disease (ACD), a series of new 4,6-disubstituted indazole compounds were designed, synthesized and evaluated as inhibitors of the above enzyme by Fukuda et al. [107]. Indazole derivative 180 was used as the leading compound to obtain a class of 4,6-disubstituted indazole analogues [108]. The optimization study revealed that compound 181 (DS28120313) appeared to be the most potent and bioavailable hepcidin production inhibitor with an IC\textsubscript{50} value of 0.093 \(\mu\text{M}\) (Figure 59). Furthermore, compound 181 exhibited serum hepcidin-lowering effects in an interleukin-6-induced acute inflammatory mouse model.

![Chemical structures of 4,6-disubstituted indazole analogues 180 and 181.](image)

**Figure 59.** Chemical structures of 4,6-disubstituted indazole analogues 180 and 181.

### 3.7. Others Activitives

Hoyt et al. [109] reported the discovery and hit-to-lead optimization of a series of novel indazole derivatives with the aim of developing new CYP11B2 inhibitors for treating hypertension. Among the optimized compounds, 182 displayed high selectivity and the most potent inhibition of CYP11B2 with an IC\textsubscript{50} value of 2.2 \(n\text{M}\) (Figure 60). It should also be mentioned that compound 182 showed lead-like physical and pharmacokinetic properties.

![Chemical structure of 1H-indazole derivative 182.](image)

**Figure 60.** Chemical structure of 1H-indazole derivative 182.

Furlotti et al. [110] reported the discovery and optimization of a series of novel 3,4-dihydropyrazino[1,2-\(b\)]indazol-1(2\(H\))-one derivatives with the aim of developing new 5-hydroxytryptamine receptor 2A (5-HT\textsubscript{2A}) inhibitors for the treatment of hypertension. Among the optimized compounds, 183 displayed high selectivity and the most potent inhibition of 5-HT\textsubscript{2A} with IC\textsubscript{50} value of 18 \(n\text{M}\) (Figure 61). It should be mentioned that compound 183 showed clear ocular hypotensive action, superior in magnitude for the whole course of the experiment.

![Chemical structure of 3,4-dihydropyrazino[1,2-\(b\)]indazol-1(2\(H\))-one derivative 183.](image)

**Figure 61.** Chemical structure of 3,4-dihydropyrazino[1,2-\(b\)]indazol-1(2\(H\))-one derivative 183.
Atobe et al. [111] reported a series of indazole derivatives as potent Sirt 1 activators by means of high-throughput screening. The design of the series was based on compound 184, which bears 3-quinoly groups exhibiting potent Sirt 1 activating activity (EC$_{50}$ = 1.49 µM) (Figure 62). Among these compounds, compound 185 appeared to show the best Sirt 1 activity (EC$_{50}$ = 0.40 µM) and it also showed osteogenesis activity in a cell assay. The results confirmed that Sirt 1 activators were potential candidates for the treatment of osteoporosis.

![Figure 62. Chemical structures of 1H-indazole derivatives 184 and 185.](image)

Igawa et al. [112] reported the synthesis of a novel series 1-(2H-indazole-5-yl)pyridin-2(1H)-one hybrids and investigated the potencies of the melanin-concentrating hormone receptor 1 (MCHR1). During the optimization, compound 186 showed binding affinity with MCHR1 (hMCHR1: IC$_{50}$ = 35 nM) in the Ames test (Figure 63). Based on a putative intercalation of 186 with DNA, the authors introduced a cyclopropyl group on the indazole ring to decrease planarity, which led to the discovery of compound 187 without mutagenicity in TA1537. In particular, compound 187 exerted significant body weight reduction in diet-induced obese F344 rats and was expected to be a novel antiobesity agent based on MCHR1 antagonistic activity.

![Figure 63. Chemical structures of 1-(2H-indazole-5-yl)pyridin-2(1H)-one derivatives 186 and 187.](image)

Xie et al. [113] disclosed a series of new N-substituted prolinamido indazoles as potent Rho kinase (ROCK) inhibitors. The design of the series was based on the previously reported [114] compound 5-nitro-1H-indazole-3-carbonitrile 188, which possess an IC$_{50}$ value of 6.7 µM against ROCK I. The lead optimization, resulted in the discovery of the most promising analogues 189 (IC$_{50}$ = 0.27 µM) and 190 (IC$_{50}$ = 0.17 µM), among other active analogues (Figure 64). Moreover, compounds 189 and 190 displayed comparable vasorelaxant activity (vasorelaxant activity in rat aortic rings in both the high-potassium models with EC$_{50}$ values of 4.00 and 3.47 µM, respectively; in norepinephrine models with EC$_{50}$ values of 5.62 and 4.07 µM, respectively) to the approved drug fasudil (vasorelaxant activity in rat aortic rings in both the high-potassium and norepinephrine models with EC$_{50}$ values of 5.47 and 4.65 µM, respectively) in rat aortic rings. The structure-activity relationship (SAR) demonstrated that the target compounds containing a β-proline moiety had improved activity against ROCK I relative to analogues bearing an α-proline moiety, and the target compounds bearing a benzyl substituent showed better inhibitory activity than those with a benzoyl substituent.

![Figure 64. Chemical structures of N-substituted prolinamido indazole derivatives 188, 189 and 190.](image)
Wada et al. [115] prepared a novel series of 1H-indazole derivatives and evaluated their biological activity and cardiovascular safety profile as human β3-adrenergic receptor (AR) agonists. Derivative 191 was identified as the initial hit compound, which exhibited significant β3-AR agonistic activity (EC50 = 21 nM), it also exhibited agonistic activity at the α1A-AR (EC50 = 219 nM, selectivity: α1A/β3 = 10-fold) (Figure 65). After systemic optimization, the authors developed the compound 192, which possessed potent β3-AR agonistic activity (EC50 = 13 nM) and high selectivity (α1A/β3 = >769-fold). Compound 192 was also inactive towards β1 and β2-ARs and showed dose dependent β3-AR mediated relaxation of marmoset urinary bladder smooth muscle.

![Figure 65. Chemical structures of 1H-indazole derivatives 191 and 192.](image)

As a continuation of their research on the development of selective β3-adrenergic receptor (β3-AR) agonist, a series of new 1H-indazole compounds were designed, synthesized and evaluated as inhibitors of β3-AR agonist by Wada et al. [116]. Indazole derivative 192 was used as the leading compound to obtain a class of 1H-indazole analogues. The optimization study revealed that, compound 193 appeared to be the most potent β3-AR agonist with EC50 value of 18 nM (Figure 66). Additionally, compound 193 showed dose-dependent β3-AR-mediated responses in marmoset urinary bladder smooth muscle, had a desirable metabolic stability and pharmacokinetic profile, and did not obviously affect heart rate or mean blood pressure when administered intravenously (3 mg/kg) to anesthetized rats.

![Figure 66. Chemical structure of 1H-indazole derivative 193.](image)

Smith et al. [117] reported a series of 4-aminocinnoline-3-carboxamide derivatives as Bruton’s tyrosine kinase (Btk) inhibitors based on a fragment-based screening approach. Compound 194 was identified through this process, which exhibited excellent inhibitory activity against Btk with IC50 value of 4.0 ± 0.3 nM (Figure 67). Moreover, compound 194 reduced paw swelling in a rat model of collagen induced arthritis.

![Figure 67. Chemical structure of 1H-indazole derivative 194.](image)
Frost et al. [118] disclosed two series of indazole analogs that exhibited activity at Na<sub>v</sub>1.7. The 4-substituted indazole series exhibited good to moderate activity at Na<sub>v</sub>1.7. Furthermore, this series demonstrated improved pharmacokinetic profiles with good rat bioavailabilities and half-lives. Among them, (S)-3-fluoropyrrolidine 195 exhibited good activity at Na<sub>v</sub>1.7 (FRET IC<sub>50</sub> = 0.37 μM, EP IC<sub>50</sub> = 0.48 μM; manual EP IC<sub>50</sub> = 0.57 μM), good selectivity versus Na<sub>v</sub>1.5 (>33 μM) and good pharmacokinetic properties (F = 83%; t<sub>1/2</sub> = 1.7 h) (Figure 68). Compound 196 demonstrated moderate activity at Na<sub>v</sub>1.7 in the fluorescence resonance energy transfer (FRET) assay (FRET IC<sub>50</sub> = 3.9 μM), excellent metabolic stability and good PK properties, but no activity at Na<sub>v</sub>1.5. In addition, compound 196 exhibited good activity in the acute rat mono-iiodoacetate-induced osteoarthritis model at 10 and 30 mg/kg (EC<sub>50</sub> = 2.5 μg/mL).

**Figure 68.** Chemical structures of 4-substituted-1H-indazole derivatives 195 and 196.

Utilizing a hybrid approach, Larsen et al. [119] prepared a novel series of 1H-indazole derivatives as potent and selective G protein-coupled receptor kinase 2 (GRK2) inhibitors. Among them, compound 197 was the most selective compound, which had an IC<sub>50</sub> for GRK2 of 130 nM and no detectable inhibition of Rho-associated coiled-coil kinase 1 (ROCK1) (Figure 69). Co-crystal structures revealed that compound 197 binded snugly in the hydrophobic subsite of GRK2 with one methoxy group packing deep in the pocket.

**Figure 69.** Chemical structure of 1H-indazole derivative 197.

Lorthiois et al. [120] reported the synthesis of a novel series 1H-indazole hybrids and investigated their potencies of factor D (FD). During the optimization, compound 198 showed more potent inhibitory activity against FD with an IC<sub>50</sub> value of 0.006 μM in the in vitro membrane attack complex (MAC) deposition assay (Figure 70). Moreover, compound 198 displayed an excellent oral pharmacokinetic (PK) profile in Sprague–Dawley rats and, following an oral dose (10 mg/kg) in Brown Norway rats, demonstrated a good distribution and sustained exposure in ocular tissues including the neural retina and the posterior eye cup (PEC), which comprises the sclera, retinal pigmented epithelium, and choroid.
Read et al. [121] described the synthesis of a series of 2H-indazoles which were investigated for their trypanosoma brucei N-myristoyltransferase (NMT) inhibition efficiencies. The studies revealed that, among the synthesized and tested derivatives, 199 possessed the most potent inhibitory activity with IC50 values of 0.006 μM (Figure 71). In addition, compound 199 had good potency against the T. brucei parasite (EC50 = 5 nM), good microsomal stability (Cli = 2.9 mL/min/g), good selectivity ("S" = 47), good oral exposure, and good in vivo tolerability.

![Figure 70](image1.png)

**Figure 70.** Chemical structure of 1H-indazole derivative 198.

![Figure 71](image2.png)

**Figure 71.** Chemical structure of 2H-indazole derivative 199.

### 4. Conclusions

Indazole and its analogues are important scaffolds with a broad range of pharmacological activities. There has been an escalating interest in the development of compounds bearing indazole moiety against different kinds of diseases. Various bioactive moieties can easily be incorporated into indazole derivatives and a great amount of effort has been dedicated to the exploration of medicinal approaches for their preparation and evaluation of their biological activities. The present review not only updates recent developments in new reactions for the synthesis of indazole derivatives and their application in the medicinal field but also encourages medicinal chemists to further explore novel indazoles as potential drug candidates for useful therapeutics.

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**Abbreviations**

- ACD: Anemia of chronic disease
- ALK: Anaplastic lymphoma kinase
- AR: Adrenergic receptor
- Bcr-Abl: Break point cluster-Abelson
- Btk: Bruton’s tyrosine kinase
- CD: Crohn’s disease
- CDK: Cyclin-dependent kinase
- CHK: Checkpoint kinase
- DCE: 1,2-Dichloroethane
- DDQ: 2,3-Dicyano-5,6-dichlorobenzoquinone
| Acronym | Full Form |
|---------|-----------|
| DFT     | Density functional theory |
| DMPK    | Drug metabolism and pharmacokinetics |
| DMPU    | 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone |
| DMSO    | Dimethyl sulfoxide |
| EGFR    | Epidermal growth factor receptor |
| ER      | Endoplasmic reticulum |
| ERK     | Extracellular signal-regulated kinase |
| EZH     | Enhancer of zeste homologue |
| FBLD    | Fragment-based lead discovery |
| FDA     | Food and drug administration |
| FGFR    | Fibroblast growth factor receptor |
| FRET    | Forster resonance energy transfer |
| FLT3    | Fms-like tyrosine kinase 3 |
| FtsZ    | Filamentous temperature-sensitive protein Z |
| GK      | Glucokinase |
| GPR     | G-protein coupled receptor |
| GR      | Glucocorticoid receptor |
| GRAs    | Glucagon receptor antagonists |
| GRK     | G protein-coupled receptor kinase |
| GSK3β   | Glycogen synthase kinase 3 betas |
| hCAs    | Human carbonic anhydrases |
| HDACs   | Histone deacetylases |
| hEGR    | Human ether-a-go-go related gene |
| hFOB    | Human fetal osteoblasts |
| HFIP    | Hexafluorisopropanol |
| HT      | Hydroxytryptamine |
| HTS     | High-throughput screening |
| HUVEC   | Human umbilical vein endothelial cells |
| IDO     | Indoleamine-pyrrole 2,3-dioxygenase |
| IKKβ    | Inhibitor of nuclear factor kappa-B kinase betan |
| JAK     | Janus kinase |
| LE      | Excellent ligand |
| LPS     | Lipopolysaccharide |
| LRRK    | Leucine-rich repeat kinase |
| MA      | Molecular sieves |
| MAC     | Membrane attack complex |
| MBA     | Methoxybenzamide |
| MCHR    | Melanin-concentrating hormone receptor |
| MIC     | Minimum inhibitory concentration |
| NMT     | N-myristoyltransferase |
| NMR     | Nuclear magnetic resonance |
| NOD     | Nucleotide-binding oligomerization domain-containing protein |
| NSCLC   | Non-small cell lung cancer |
| OGTT    | Oral glucose tolerance test |
| OPG     | Osteoprotegerin |
| PAD     | Protein arginine deiminase |
| PD      | Pharmacodynamic |
| PDGFRβ  | Platelet-derived growth factor receptor betan |
| PDK     | Phosphoinositide-dependent kinase |
| PEC     | Posterior eye cup |
| P3Kδ    | Phosphoinositide 3-kinase deltae |
| PIFA    | [Bis-(trifluoroacetoxy)iodo]benzene |
| PK      | Pharmacokinetic |
| PKC     | Protein kinase C |
PLK4 Polol-like kinase 4
RET Rearranged during transfection
RIP Receptor-interacting protein
ROCK Rho-associated coiled-coil kinase
SAHA Suberoylanilide hydroxamic acid
SAR Structure-activity relationship
SCW Streptococcal cell wall
SEDRs Selective estrogen receptor degraders
SGRM Selective glucocorticoid receptor modulators
SNAr Nucleophilic aromatic substitution
TA Transactivation
TAT Tyrosine aminotransferase
TGI Tumor growth inhibition
TNFα Tumor necrosis factor-αs
TTK Tyrosine threonine kinase
TR Transrepression
TRPA Transient receptor potential ankyrin-repeat
UC Ulcerative colitis
ULK Unc-51-like kinase
USP Ubiquitin specific protease
VEGFR Vascular endothelial growth factor receptor

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