



## Mini-review

## Synthesis of indazole motifs and their medicinal importance: An overview



Digambar D. Gaikwad<sup>a,\*</sup>, Archana D. Chapolikar<sup>a</sup>, Chandrashekhar G. Devkate<sup>a</sup>, Khandu D. Warad<sup>a</sup>, Amit P. Tayade<sup>a</sup>, Rajendra P. Pawar<sup>b</sup>, Abraham J. Domb<sup>c</sup>

<sup>a</sup> Dept. of Chemistry, Govt. College of Arts & Science, Aurangabad 431001, India

<sup>b</sup> Dept. of Chemistry, Deogiri College, Aurangabad 431001, India

<sup>c</sup> School of Pharmacy, Department of Medicine, The Hebrew University of Jerusalem, Jerusalem 91120, Israel

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## ABSTRACT

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

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## 1. Introduction

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

Indazole derivatives are pharmacologically important as they form the basic structure of several drug molecules, such as Grani-setron, 5HT<sub>3</sub> receptor antagonist used as an anti-emetic in cancer chemotherapy and Benzydamine an anti-inflammatory agent. The indazole ring has two nitrogen atoms and can be functionalized with high selectivity at different positions. Planarity of the indazole ring, side chain length and fictionalizations at different positions

can afford an enormous number of indazole derivatives, providing new molecules with biological and therapeutic properties.

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

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

\* Corresponding author.

E-mail address: [gaikwad\\_dd@yahoo.com](mailto:gaikwad_dd@yahoo.com) (D.D. Gaikwad).

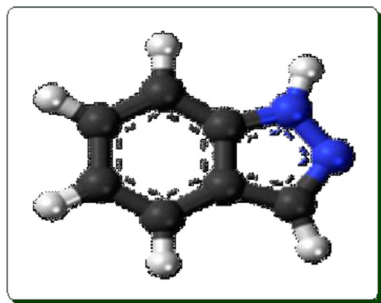
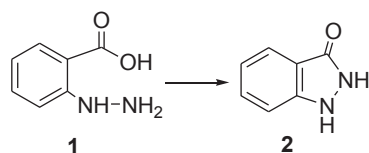


Fig. 1. Naturally accruing indazole nucleus.



### First reported synthesis of indazolone

Fig. 2. Naturally accruing indazole nucleus.

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

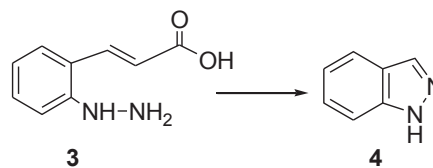
Most of the studies on indazole have been carried out by Karl Von Auwers during 1920s. His work and recent studies on indazole nucleus are reviewed in the following sections.

## 2. Tautomerism of indazoles

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

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

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



### First reported synthesis of indazole

Fig. 3. Naturally accruing indazole nucleus.



### Annular prototropic tautomerism of indazole

Fig. 4. Naturally accruing indazole nucleus.

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

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

## 3. Indazoles as natural products

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

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

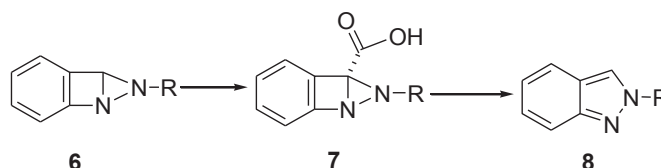


Fig. 5. Naturally accruing indazole nucleus.

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