Original Article

Indazole From Natural Resources And Biological Activity: A Review

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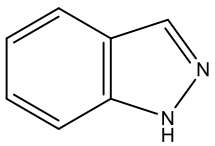
Abstract

Nitrogen-containing heterocycles are having a lot of significance due to their broad range of pharmacological and biological activity. Structure and reactivity of small molecules, macromolecules information is required in drug discovery and the ways in which molecules cooperate by means of both covalent and non-covalent recognition through signal transfer. They have significant role in the medicinal chemistry, polymers, industries, and agricultural sciences.

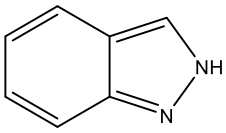
Key Words: Heterocyles, Indazole, Natural Resources, Biological activity

Introduction:

Heterocycles are broadly found in naturally occurring compounds and have immense importance in the design and discovery of new compounds for pharmaceutical applications. Among the numerous heterocycles, nitrogen containing heterocyclic skeleton show a key role in alkaloids chemistry. These alkaloid compounds are gaining a lot of importance and they have exhibit a broad spectrum of pharmacological and biological activities. There are two tautomeric forms for indazole, the 1H and 2H form.[1]



Benzenoid 1H-Indazole

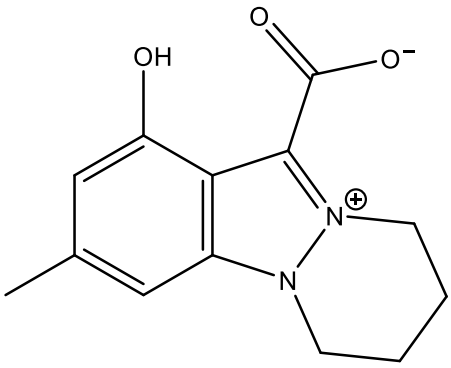


Quinnoid 2H-indazole

The indazole scaffold represents a capable pharmacophore, usually incorporated in a range of therapeutic drugs. Though indazole-containing drugs are normally marketed as the corresponding N-alkyl 1H- or 2H-indazole derivative, the capable synthesis and isolation of the desired N-1 or N-2 alkyl indazole region isomer can regularly be challenging and unfavourably affect product yield.[2]

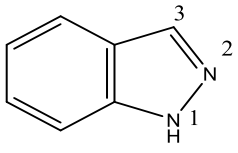
Indazole defined as a pyrazole ring fused with the benzene ring by the scientist Emil Fisher. It is generally studied due to its significant chemical and biological properties. Indazole is starting the azoles family containing carbon, hydrogen and nitrogen atoms. Indazole derivatives are pharmacologically significant as they form the primary structure of numerous drug molecules, like Benzydamine used as anti-inflammatory agent and Granisetron, $5HT_3$ receptor antagonist for anti-emetic in cancer chemotherapy. Two nitrogen atoms in indazole can be capable to functionalized with high selectivity at diverse positions.[3]

Indazoles are logically taking place alkaloids like Nigellidine, Nigellicine and Nigeglanine. Nigellicine was inaccessible from extensively spread plant Nigella sativa. Nigeglaninewas isolated from extracts of Nigella glandulifera. Only few of the alkaloids studied leading isolation show the presence of indazole ring system. The first element of this alkaloid family Nigellicine which is isolated in 1985 from the plant N. sativa an yearly flowering plant, native to Southwest Asia. The structure of nigellicine has an intramolecular hydrogen bond with the carboxylate oxygen atom and the hydroxyl group. The structure of nigellicine is a pseudo cross conjugated heterocyclic mesomericbetaine, which means that it is capable to be existing by dipolar canonical formula where both the positive and negative charge is delocalized in the structure.[3]

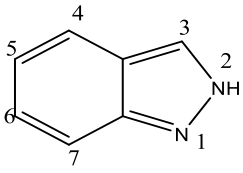


Nigellicine

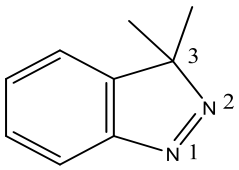
Indazoles refers to isomeric chemical compounds by molecular formula $C_7 H_6 N_2$ have pyrazole ring compressed with the benzene ring. The indazole heterocycle is usually referred to as 1H-indazole, though it has two previous potential tautomers 2H-indazole and 3H-indazole. The tautomeric stability between 1H- and 2H indazoles equally in the ground position (S0) and in the excited state (S1) has been investigate by photophysical and thermochemical techniques. Indazole ring system is not a common attribute in nature but a large number of unnaturally prepared compounds have shown attractive pharmacological properties, so efforts have been complete in the last few decades to produce a different new and novel heterocyclic indazole compounds.[4] Heterocyclic are create in many natural products and biologically active compounds. Nitrogen-containing heterocycles are having a lot of significance due to their broad range of pharmacological and biological activity. Structure and reactivity of small molecules, macromolecules information is required in drug discovery and the ways in which molecules cooperate by means of both covalent and non-covalent recognition through signal transfer. Indazoles are heterocyclic molecules, structurally pyrazole attach to benzene ring. Structurally Indazole has 10 π electrons, two nitrogen atoms existing in five-membered rings. Due to π electrons delocalization, it exhibits 3 tautomeric forms, i.e., 1H-Indazole, 2H-Indazoles, 3H-Indaoles. It acts as pyridine as well as pyrrole dual activities. Indazole is generally measured as 1H-Indazole, the other two are potential tautomers.[5]



1H-Indazole



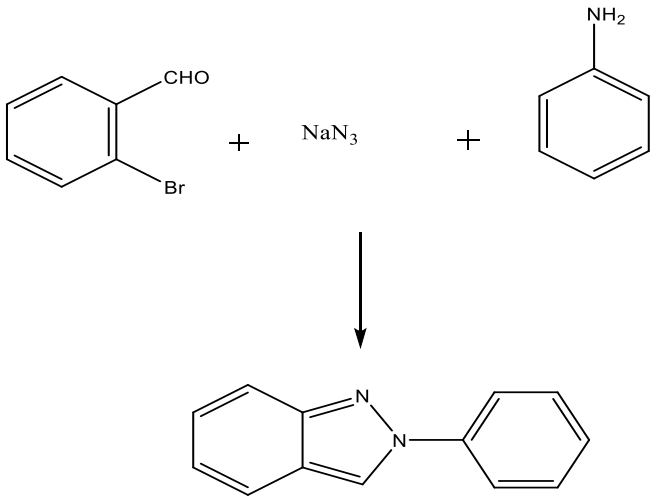
2H-Indazole



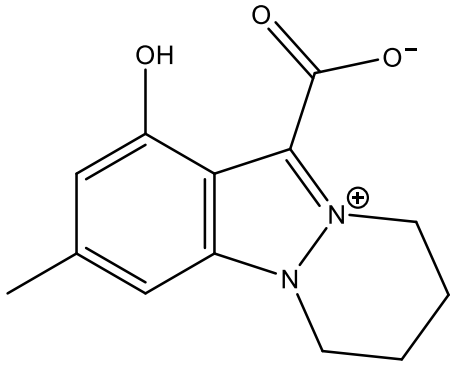
3H-Indazole

Review of Literature:

Chaudhari et al 2019 synthesized bicyclic pyrazole bearing heterocyclic compounds 2H-Indazole unit has been reorganized by a "privileged structure" and was an important pharmacophore in medicinal chemistry. Indazoles was rare in nature and to date only three natural products possessed the indazole ring has been isolated are Nigellicine, Nigeglanine and Nigellidine.

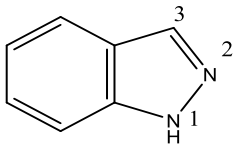


Keating et.al 2021 represented a promising pharmacophore, commonly incorporated in a variety of therapeutic drugs. Although indazole-containing drugs were frequently marketed as the corresponding N-alkyl 1H- or 2H-indazole derivative, the efficient synthesis and isolation of the desired N-1 or N-2 alkyl indazole regioisomer could often be challenging and adversely affect product yield. Thus, as part of a broader studied focusing on the synthesis of bioactive indazole derivatives.

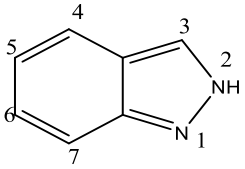


Nigellicine

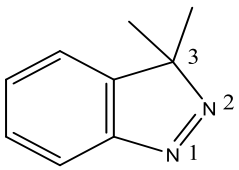
Singh et al 2016 focused on the biological properties associated with this system, chemical reactions, functionalizations, and medicinal application of indazole nucleus. Moreover many useful drugs have emerged from the successful investigation carried out in this branch. Indazole ring system was not 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.



1H-Indazole



2H-Indazole

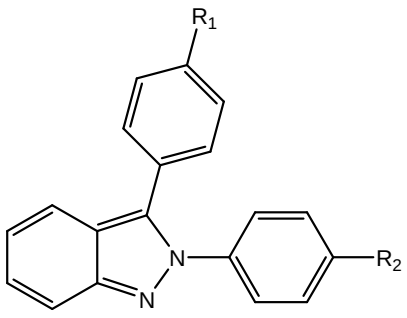


3H-Indazole

Gaikwad et al 2022 studied the silico design, synthesis and biological evaluation of novel effective phenyl, indole, 3, 4-dimethyl substituted 4, 5, 6, 7- tetrahydro-1H-indazole derivatives. The novel multi- substituted indazole derivatives (5A-5J) were synthesized from the treatment of hydrazine hydrates in MeOH/H+ with multi substituted cylohexanone derivatives (4a-4j). The final scaffold was characterized with the help of spectroscopic data such as IR, 1H NMR, 13C NMR, and mass spectra. The compound 5A, 5D, and 5F shows excellent antibacterial activity and the compounds 5B, 5C, 5H 5I and 5J exhibited moderate antibacterial activity against the S. aureus, Bacillus subtilis and E. coli. Finally, the molecular docking studies show that the compound 5D and 5F scaffolds display excellent bonding mode of interactions with the active site of DNA gyrase 1KZN enzyme.

Zhang et al 2018 synthesized 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 summarized 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.

Pérez-Villanueva et al., 2017 synthesised a new set of 2H-indazole derivatives and screened lied activities against selected intestinal and vaginal pathogens, including the protozoa Giardia intestinalis, Entamoeba histolytica, Trichomonas vaginalis; the bacteria Escherichia coli and Salmonella enterica serovar Typhi; and the yeasts Candida albicans and Candida glabrata. Biological evaluations revealed that most of the synthesized compounds showed more potent antiprotozoal activity than metronidazole.



Buchwald et al 2022 synthesized highly enantioselective synthesis of indazoles with a C3-quaternary chiral center using CuH catalysis. C3-substituted 1H-indazoles were useful and important substructures in many pharmaceuticals. Methods for direct C3-functionalization of indazoles are relatively rare, compared to reactions developed for the more nucleophilic N1 and N2 positions. They reported a highly C3-selective allylation reaction of 1H-N-(benzoyloxy) indazoles using CuH catalysis. A variety of C3-allyl 1H-indazoles with quaternary stereocenters were efficiently prepared with high levels of enantioselectivity. Density functional theory (DFT) calculations were performed to explain the reactivity differences between indazole and indole electrophiles.

Kim et al (2021) synthesized 1H-indazoles via Silver (I)-mediated Intramolecular Oxidative C−H Bond amination. Indazole and its derivatives were ubiquitously found in a broad spectrum of biological and pharmaceutical applications. In particular, as a surrogate of indole that was a central motif in natural and synthetic pharmacophores, indazole still has extensive space of derivatization to expand a new chemical territory for the acquisition of patents. Indeed, indazole moiety was found in a variety of FDA-approved drugs such as Granisetron (5-HT3 antagonist) as an antiemetic drug and Lonidamine (antiglycolytic drug) for brain tumor treatment. In addition, indazoles are also found as a core structure in tyrosine kinase inhibitors such as Axitinib, Pazopanib, and Entrectinib for renal cell carcinoma treatment 3c, d or for ROS-1 positive, metastatic nonsmall cell lung cancer.

Conclusion

Heterocycles have an immense importance in the design and discovery of new compounds for pharmaceutical applications. Heterocycles, nitrogen containing heterocyclic skeleton show a key role in alkaloids chemistry. These alkaloid compounds are gaining a lot of importance and they have exhibit a broad spectrum of pharmacological and biological activities. They have gained considerable attention in the field of medicinal chemistry and 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.

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