INTERNATIONAL JOURNAL IN PHARMACEUTICAL SCIENCES

Journal Homepage: https://www.ijpsjournal.com

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Review Article

Synthetic Strategy And Pharmacological Approaches Of Benzopyrazole: A Review

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ARTICLE INFO

Received: 11 July 2023
Accepted: 13 July 2023
Published: 19 July 2023

Keywords:
Heterocyclic compounds, Indazole, Biological activity, Pharmacological uses

DOI:
10.5281/zenodo.8161568

ABSTRACT

Indazole-containing derivatives represent one of the most important heterocycles in drug molecules. The presence of two nitrogen sites located in adjacent positions in the molecular structure allows indazole, at low concentrations in mildly acid or basic media, to form 1H and 2H tautomers via acid-base interactions as well as symmetrical dimers by hydrogen bonding. Indazole is also known as 1H-Benzopyrazole, 2-Azaindole. Synonyms of indazoles are 1H-Indazole, 2H-indazole, Isoindazole1,2-Diazaindene and Benzopyrazole. The first compound known to contain the indazole ring system was indazole and its preparation, by heating o-hydrazinobenzoic acid was reported in 1880 by Fischer. Indazole itself was first prepared a few years later by Fischer and Kuzel. Since then, several approaches for the preparation of indazole and its derivatives have been developed. Indazole shows many biological activities like anti-cancer, anti-microbial, anti-tubercular, antioxidant, anti-platelet and neuroprotective activity. This review aims to summaries the recent method of synthesis of Indazole derivatives and advanced biological activity study of the Indazole derivatives.

INTRODUCTION

Heterocyclic compound, also called heterocycle, any of a major class of organic chemical compounds characterized by the fact that some or all of the atoms in their molecules are joined in rings containing at least one atom of an element other than carbon (C). The cyclic part (from Greek *kyklos*, meaning "circle") of heterocyclic indicates that at least one ring structure is present in such a compound, while the prefix hetero- (from Greek *heteros*, meaning "other" or "different") refers to the noncarbon atoms, or heteroatom, in the ring.

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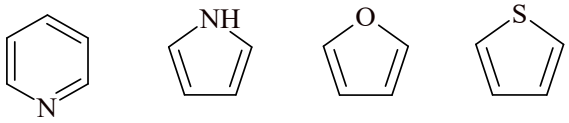
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



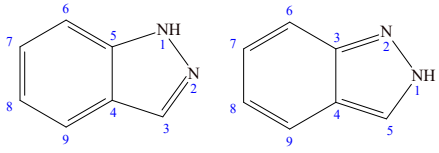
Pyridine 1H-Pyrrole Furan Thiophene

The most common heterocycles are those having five or six- member rings and containing heteroatom of nitrogen (N), oxygen (O), or sulphur (S). The best known of the simple heterocyclic compounds are pyridine, pyrrole, furan, and thiophene.[1]

HISTORY OF INDAZOLE:

Hermann Emil Louis Fischer was a German chemist and 1902 recipient of the Nobel Prize in Chemistry. In 1883, Indazole $C_7H_6N_2$, was obtained by E. Fischer by heating ortho-hydrazine cinnamic acid.

CHEMISTRY OF INDAZOLE:



1H-indazole 2H-indazole

Indazoles are heterocyclic aromatic organic compounds, in which pyrazole is fused with a benzene ring. The presence of two nitrogen sites located in adjacent positions in the molecular structure allows indazole, at low concentrations in mildly acid or basic media, to form 1H and 2H tautomers via acid-base interactions as well as symmetrical dimers by hydrogen bonding. Indazole is also known as 1H-Benzopyrazole, 2-Azaindole. Synonyms of indazoles are 1H-Indazole, 2H-indazole, Isoindazole1,2-Diazaindene and Benzopyrazole.[3-4]

The first compound known to contain the indazole ring system was indazole and its preparation, by heating o-hydrazinobenzoic acid was reported in 1880 by Fischer. Indazole itself was first prepared a few years later by Fischer and Kuzel. Since then, several approaches for the preparation of indazole and its derivatives have been developed. [5]

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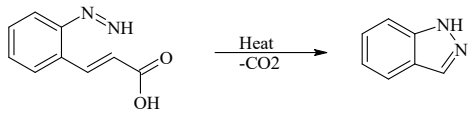
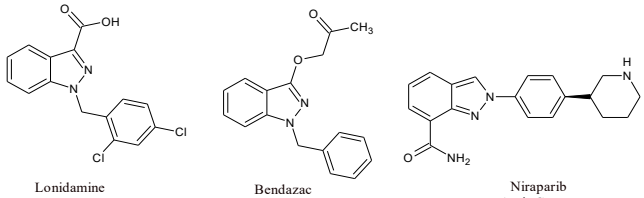


ortho-hydrazine-cinnamic acid 1H-indazole

Skeletal structuresfor the reaction of ortho-hydrazine-cinnamic acid at high temperature to give indazole with loss of carbon dioxide, by Emil Fischer.

Indazole nuclei are present in naturally occurring alkaloids and biologically active molecules. Nigellidine is a natural product containing an indazole nucleus, isolated from nigella sativa, which is used for the treatment of various diseases. Commonly believed to have carminative, stimulatory, and diaphoretic properties. Indazole-based heterocycles like indazole pyrimidines and their derivatives are found to have a wide range of activities. Earlier findings on indazole derivatives are specifically known to be active as protein kinase inhibitors, cancer cell proliferative disorders, Alzheimer's disease, viral infections, autoimmune diseases, and neurodegenerative disorders [6]

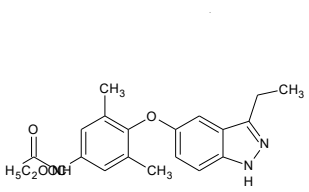
Marketed medicinal compounds containing indazole moiety:



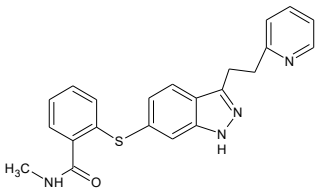
Lonidamine Anti-tumer

Bendazac Anti- inflammatory

Niraparib Anti- Cancer



Thyromimetics
In Fat Reduction and Tachycardia



Axitinib
In Renal cell Carcinoma

PYSICOCHEMICAL PROPERTIES OF INDAZOLE: [7]

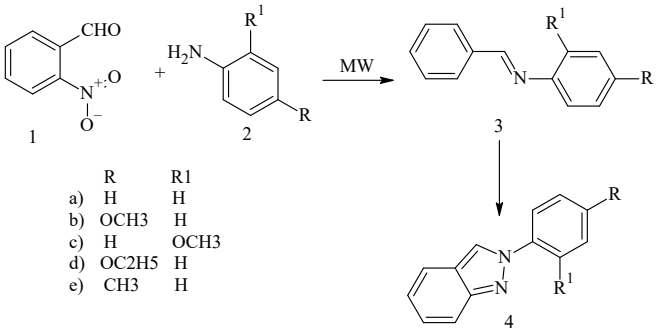
Molecular Formula:	C7H6N2
Formula Weight:	118.13594
Composition:	C (71.17%) H (5.12%) N (23.71%)
Molar Refractivity:	36.61 ± 0.3 cm3
Molar Volume:	95.0 ± 3.0 cm3
Parachor:	264.8 ± 4.0 cm3
Index of Refraction:	1.696 ± 0.02
Surface Tension:	60.1 ± 3.0 dyne/cm
Density:	1.242 ± 0.06 g/cm3
Dielectric Constant:	Not available
Polarizability:	14.51 ± 0.5 10-24cm3
RDBE:	6
Monoisotopic Mass:	118.053098 Da
Nominal Mass:	118 Da
Average Mass:	118.1359 Da
M+:	118.05255 Da
M-:	118.053647 Da
[M+H]+:	119.060375 Da
[M+H]-:	119.061472 Da
[M-H]+:	117.044725 Da
[M-H]-:	117.045822 Da

Table No.1: Physicochemical Properties of Indazole.

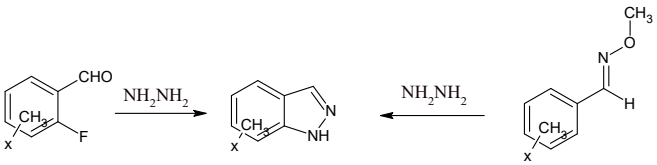
METHODOLOGY FOR SYNTHESIS OF INDAZOLE:

Deepu J. V. et al were reported that a mixture of equivalent amounts of 2-nitrobenzaldehyde (1a) and aniline is treated and an excess of triethyl phosphite was irradiated with microwaves for 10 min. For the first 2 min the power level was kept low (about 200 W), so that the temperature of the mixture was kept below 70^0C; then the temperature was allowed to rise to 150^0C by increasing the power to about 400 W (it should be noted that these parameters will depend on the particular microwave oven in use).

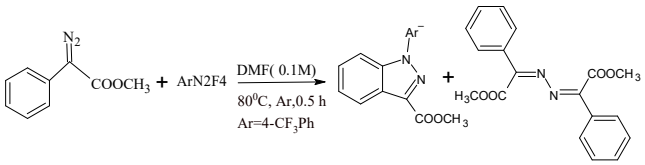
The initial 2 min are the first stage that involves the formation of the Schiff base (3a), in the second stage cyclization to indazole (4a) occurs as the temperature is raised to about 150^0C.[8]



Kirill Lukin et al were reported the reaction of *o*-fluorobenzaldehydes and their *O*-methyloximes with hydrazine has been developed as a new practical synthesis of indazoles. [9]



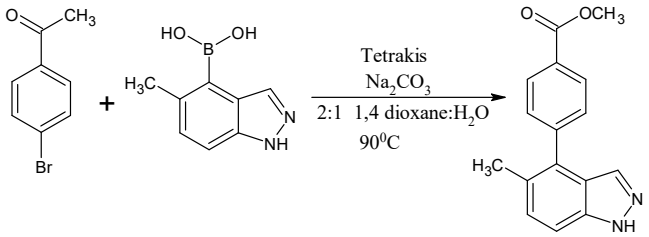
XumingLi et al were reported that it is the reaction between diazo compound and diazonium salt. The reaction was conducted at 80 °C under Ar (4-CF3Ph), and DMF as solvent, giving the desired indazolein78% yield.[10]



Nandish Talpada et al were reported synthetic route of indazole derivatives.

500 mg methyl 4-bromobenzoate and 615 mg boronic acid dissolve in 2:1 ratio (12 ml) 1, 4 dioxane + water. After one hour dropwise add 740 mg saturated Na_2CO_3 solution with constant stirring. Then add 269 mg Tetrakis catalyst get 90ºC temperature. TLC performed in 30% E.A-Haxene. Work Up (Ethyl-Water): Organic layer taken and Brian solution was added in this layer and again separates the upper organic layer. After

that sodium sulphate was added and then concentrates on Rotavapor. [11]



BIOLOGICAL ACTIVITY OF INDAZOLE:

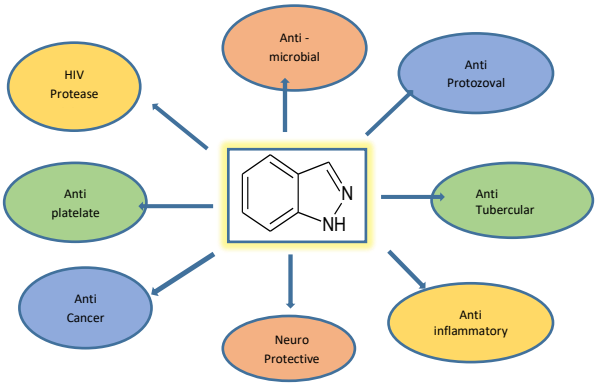
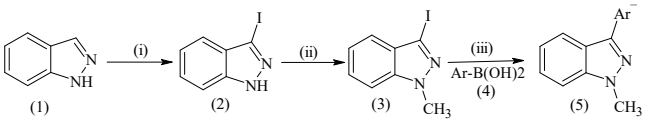


Fig. 1: Pharmacological properties of derivatives with indazole scaffold

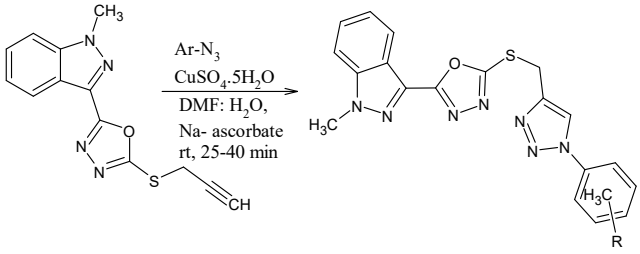
Antimicrobial activity:

Bollikolla et al were reported the construction of various N-methyl-3aryl-indazole derivatives using the below Scheme and the structures of the obtained indazoles, were confirmed by physical parameters like melting point and spectral data and he also report the antimicrobial activities of some N-methyl-3-arylindazoles.[12]



Reagent and Condition:
(i) KOH,I2, DMF, 25°C, 2 h, 79%
(ii) MeI,KOH, acetone, 0°C, Overnight, 60-75%
(iii) Pd(PPh3)4,NaHCO3, DMF, 80°C,Overnight, 60-75%.

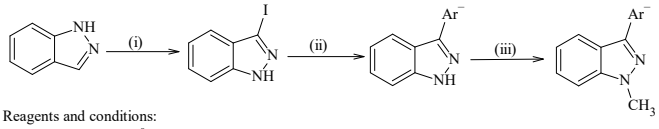
Ananda Kumar Dunga et al were reported synthesis of indazole tethered 1, 2, 3-triazole-1, 3, 4-oxadiazole hybrids which shows antimicrobial activity. They used the synthetic strategy shown in scheme. Their research state that the compound having –F, –Cl, –OH groups at 2-, 4-position of phenyl ring exhibited higher activity than standard drugs (Ampicillin and Fluconazole) and compound bearing para fluoro, orthochloro and para hydroxy groups showed good activity against *B. subtilis.*[13]



Anti-cancer activity:

Jagan Mohana Rao Saketi et al were reported the synthesis of a series of 3-aryl-1H-indazoles and N-methyl-3H-indazoles by below scheme by using simple reagents. All the synthesized indazoles were screened for their in vitro anti-cancer activities against the cell lines HCT-116 and MDA-MB-231. The results of the cytotoxic studies of the tested compounds reveal that compound Containing -F at para position of phenyl group exhibited significant inhibitory effect on the two tested cancer cell lines amongst all the compounds synthesized.

Compounds containing pyridine ring and –OH group at para position of phenyl group also exhibited good cytotoxic activity. Most of the compounds are active against human colon carcinoma cell line (HCT-116) and human breast cancer cell line (MDA-MB-231). N,N-dimethylamide group at para position of the phenyl ring exhibited good anti-cancer activity. Presence of electron withdrawing fluoro substitution at 4th position of the phenyl ring is responsible for its superior anti-cancer activity. [14]



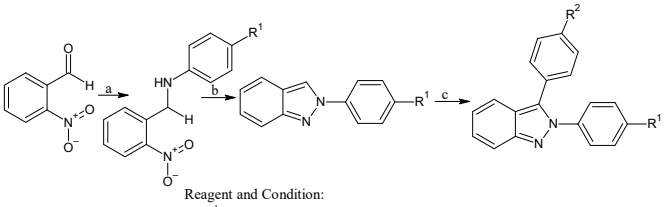
Reagents and conditions:
(i) KOH, I2, DMF, 25^{0}C, 2 h, 77%,
(ii) Ar-B(OH)2, Pd(PPh3)4, NaHCO3,DMF, 80^{0}C, 8-12 h, 55-70%,
(iii) MeI, KOH, acetone, 0^{0}C, 10—12 h, 58%—75%

Synthetic route for N-methyl-3-aryl indazoles.

Anti-inflammatory activity

Jaime Pérez-Villanueva et al were reported the synthesis of some2,3-diphenyl-2H-indazole derivatives which were evaluated in silico and in

vitro against human cyclooxygenase-2 (COX-2). The results showed that compounds containing –$COOCH_3$, SO_2CH_3 functional group at R^1 and –H atom at R^2display in vitro inhibitory activities against COX-2, whereas docking calculations suggest a similar binding mode as compared to rofecoxib, the crystallographic reference.[15]



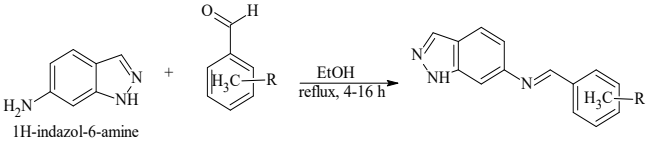
Reagent and Condition:
a:- $R^1C_6H_4NH_2$,EtOH,Reflux
b:- P(OEt), 150^{0}C
C:- $R^2C_6H_4I$ or $R^2C_6H_4Br$, Pd(dppf)Cl_2.DCM (5%mol)PPh_3(10%mol)
Ag_2CO_3,H_2O, 50^{0}C

Antidiabetic activity

Shahbaz Shamim et al were reported the synthesis of Schiff bases of indazole by treating 6-amino indazole with substituted aldehyde in ethanol as solvent under reflux condition as shown in scheme. Reaction time varied with differently substituted benzaldehydes and taken 4-16 h for complete condensation. Reaction between free amino groups of 6-amino indazole with carbonyl group of aldehyde proceeds without any catalyst. Compounds were afforded in good yields 70-85%.

Hydroxyl group containing compounds exhibited potent inhibitory activity as compared to the standard acarbose. Dihydroxy substituted compound was most potent.

2′,3′,4′-Trihydroxy substituted compound exhibited many fold increased and potent activity than the standard acarbose which shows that more the number of hydroxy more chances of hydrogen bonding interactions to the active site of enzyme. Hydroxyl group with halogen demonstrated promising *α*-glucosidase inhibitory activity.[16]

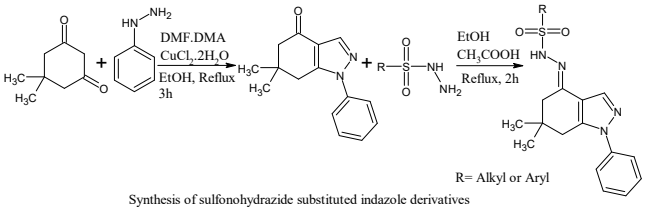


1H-indazol-6-amine

Scheme: Synthesis of indazole Schiff bases in ethanol under reflux.
R is representingdifferent substitutions on benzaldehyde ring.

α -Amylase Inhibitor

Rafaila Rafique et al were reported synthesis of a variety of sulfonohydrazide substituted indazoles by multi-step reaction. In first step; 4-oxyindazole was formed by reacting dimedone, dimethylformamidedimethylacetal (DMF-DMA), phenylhydrazine in the presence of catalytic amount of $CuCl_2.2H_2O$ in ethanol for 3 h. In the next step, 4-oxyindazole was treated with different sulfonylhydrazide derivatives in ethanol in the presence of pyridine as catalyst and refluxed for 2 h to obtain the desired sulfonohydrazide substituted indazoles as shown in scheme.[17]



R= Alkyl or Aryl

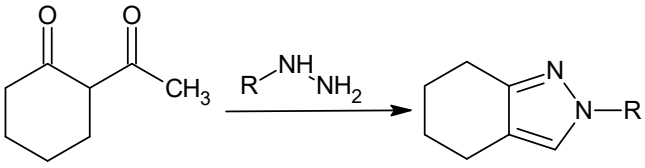
Synthesis of sulfonohydrazide substituted indazole derivatives

Antioxidant activity:

Efrain Polo et al were reported the synthesis of tetrahydroindazole derivatives with different patterns of substitution using a modified Paal-Knorr reaction between 1, 3-dicarbonyl compounds and hydrazines as shown in scheme. These coupling reactions were performed under reflux and MW irradiation, that helped obtain the best results. A small series of tetrahydro indazoles was prepared, starting from 2-acetylcyclohexanoneand different hydrazines using reflux and a focused microwave reactor. Microwave irradiation favored the formation of the desired products with improved yields and shortened reaction times.

The in vitro antioxidant activity was evaluated using the DPPH and ABTS methods. In these assays, 2-(4-fluorophenyl)-3-methyl-4,5,6,7-tetrahydro-2H-indazole showed moderate DPPH decolouring activity, while 3-methyl-4,5,6,7-tetrahydro-1H-indazole, 3-methyl-2-phenyl-4,5,6,7- tetrahydro-2H-indazole and 2-(4-fluorophenyl)-3-methyl-4,5,6,7-tetrahydro-2H-indazole were the most active in the ABTS assay. The results reveal that most of the synthesized

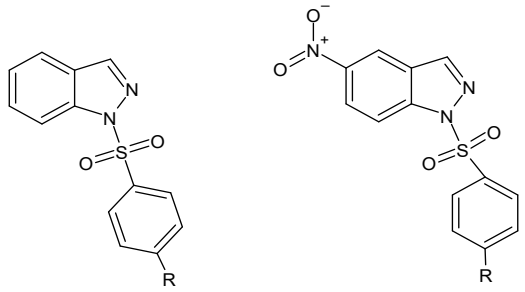
tetrahydroindazoles can be considered as a scaffold for the development of novel and effective antioxidant agents. The antioxidant activity shown by the compounds obtained is totally dependent on the concentration and the type of substituent having the tetrahydroindazole ring. The use of other substituents can lead to improvements in antioxidant activity reported.[18]



R = H-H_2O, C_6H_5, 4-BrC_6H_4, 4-CNC_6H_4, 4-$CO_2HC_6H_4$, 4-FC_6H_4.

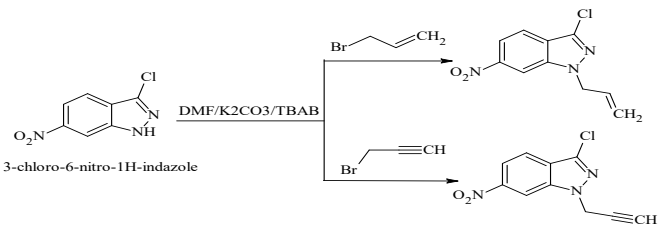
Anti-bacterial activity:

Farha Naazet al were reported the synthesis of 1-*H*Indazole, 5-NO2-Indazole (shown in fig-2) derivatives which shows significant antibacterial activity. [19]



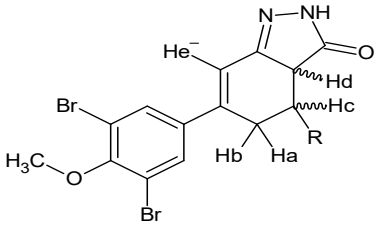
Antileishmanial candidates:

Mohamed Mokhtar Mohamed Abdelahi et al were reported synthesis of Dipolarophiles in good yields(88–92%) via alkylation reactions of 3-chloro-6-nitro-1*H*-indazolewith allyl bromide or propargylbromide under phase transfer catalysis conditions using tetra-n-butyl ammonium bromide (TBAB) as catalyst and potassium carbonate as a base in dimethylformamide at room temperature as shown in scheme. [20]



Antitubercular activity:

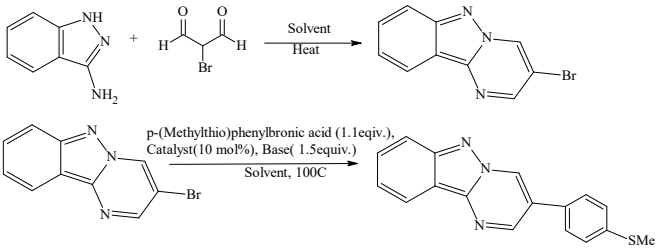
D H Vyas et al were reported some indazole derivatives showing ant tubercular activity. The antitubercular activity data were compared with that of standard drug Rifampin at 0.25 µg/mL concentration.[21]



Where R is Aryl

Neuroprotective activity:

Jismy, B were et al were reported synthetic strategy starting from commercially available 1H-indazol-3-amines, which were converted to various 3-bromoheterotricyclic derivatives and further functionalized via Suzuki-Miyaura coupling reaction. Derivatives selectively inhibited human MAO-B isoform in a reversible and competitive manner as confirmed by kinetic experiments and docking studies. Some derivatives protect human neuroblastoma SH-SY5Y cells against 6 hydroxydopamine-induced cell death, which confirms the applicability of the pyrimido[1,2- b]indazoles as potential antiparkinsonian agents. [22]



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HOW TO CITE: Kousalya Patil*, Dr. Somashekhar M Metri, Divya Shirke, Synthetic Strategy And Pharmacological Approaches Of Benzopyrazole: A Review, Int. J. in Pharm. Sci., 2023, Vol 1, Issue 7, 261-268. https://doi.org/10.5281/zenodo.8161568