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# A REVIEW ON BIOLOGICAL ACTIVITY AND SYNTHETIC METHODS OF ISOINDOLE NUCLEUS

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## ABSTRACT

Isoindole is one of the most important heterocyclic compound, strong base than pyrrole, having varied biological activities and still of great scientific interest at this time. They are extensively found in bioorganic and medicinal chemistry with application in drug discovery. Isoindole is a benzo-fused pyrrole. The compound is an isomer of indole. Nitrogen atom constitutes the core structure of pyrrole and many pharmacologically and biologically active compounds. Isoindole is among the usually occurring heterocyclic nuclei in many natural plant products. Isoindole is known to exhibit a wide range of biological properties including, anticancer, antimicrobial, antimalarial, anti-inflammatory, antibacterial, antifungal, antitubercular activities.

**KEYWORD:** Isoindole, pharmacological activities**,** antimicrobial activity, anti malarial activity, anti bacterial, antifungal activity.

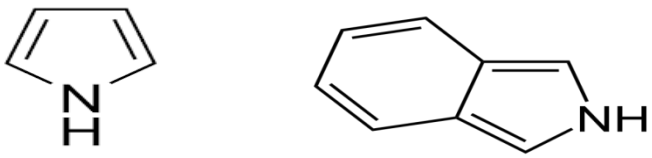
## INTRODUCTION

Isoindole is a benzo-fused pyrrole heterocyclic chemistry. The compound is an indole isomer. Isoindole has a bicyclic structure, contain a six-membered benzene ring fused to a five membered nitrogen-containing ring. The compound`s structure is alike to indoline but the nitrogen atom is in 2 position instead of the 1 position of the five membered ring. It`s reduced form is Isoindoline (2,3-dihydro-1H-isoindole). The parent isoindole is a rarely meet by chance in the skilful practiced literature, but substituted derivatives are useful and take place naturally. Isoindole components occur in phthalocynines (chemical dyes), it is composed of four isoindole components, linked by a ring of nitrogen atoms.[2] Some alkaloids containing isoindole were isolated and specified. Isoindole (2H-isoindole), known already greater than a

centurial, composed of a fused benzo pyrrole ring system and compose the regioisomer of the plentiful 1H-indole heterocycle. Conventional oxidation to the 10π- system leads to isoindole, which is generally only stable when the labile ortho- quinoid structure is inserted in a π syshment. Establishment of additional oxygen gives the isoindolinone (1, 3-dihydro-2H-isoindole-1-one) and phthalimide (1, 3-dihydro-2H-isoindole 1, 3-dione) substitution motif or design.[1] Isoindoline be made up 10 delocalized π-electrons.4 double bonds present in the isoindole and unshared lone pair of electrons of the nitrogen as 10 delocalized π electrons.[3]

**Structure of isoindole**

Isoindole is a heterocyclic organic compound ($C_8H_9N$). The basic structure of isoindole consists of benzene ring fused to a five membered nitrogen containing ring. That means Isoindole are fused benzo pyrrole ring systems. The numbering in pyrrole ($C_5H_4N$) starts from the nitrogen atom. 2H-Isoindole is the predominant tautomer relative to 1H-Isoindole.[4]




**Pyrrole** **Isoindole**

**Figure – 1.**

Preferred IUPAC Name - 2H – Isoindole

Chemical Formula - $C_8H_7N$

Molar Mass - 117.15 g/mol

**REACTION OF ISOINDOLE DERIVATIVES**

Isoindole derivatives (Fluorescent isoindole) are also formed by act of Mercapto ethanol primary amine on OPA (ortho phthal aldehyde).[5]

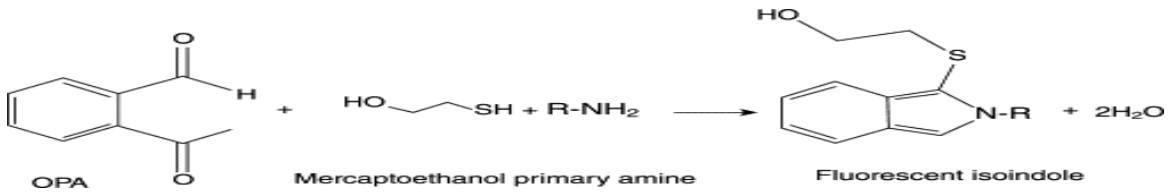



**Figure 2: Formation of fluorescent isoindole.**

Fluorolophor is formed, when o-phthal di aldehyde react with amines in present of alkyl thiol compound.[5]

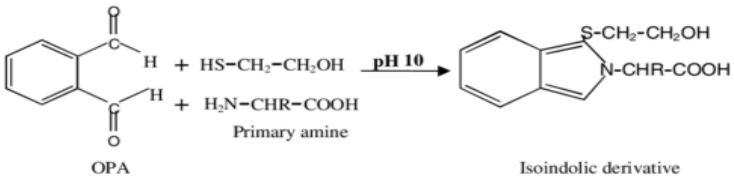



**Figure 3: Formation of isoindolic derivative.**

O-Phthal aldehyde (OPA) and homoarginine (hArg) were used into hArg-OPA-NAC adduct in the presence of N-Acetyl cysteine (NAC), which act as a catalyst.[4]

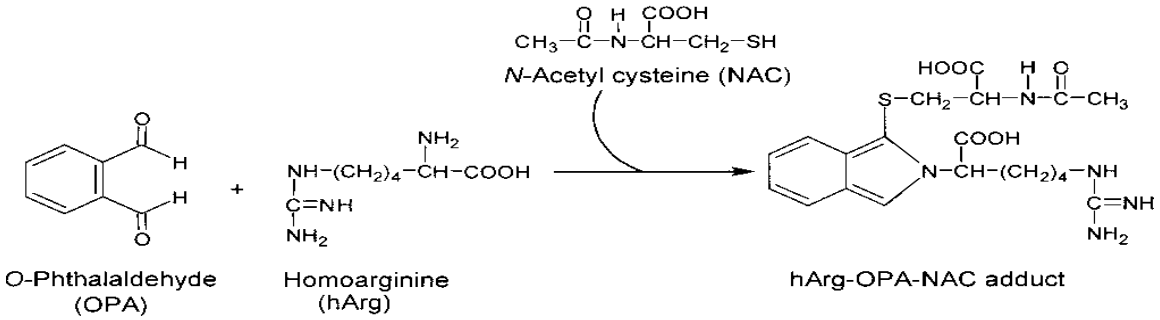



**Figure 4: Formation of isoindolic derivative.**

Reaction of amino acids with o-phthal di aldehyde and β-Mercapto ethanol to form a isoindole derivative.[3]

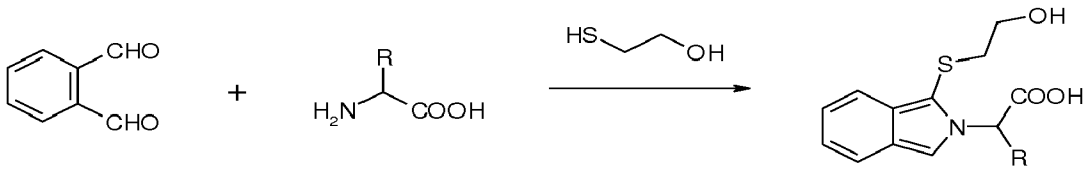


**Figure 5: Formation of isoindolic derivative.**

## SYNTHESIS OF ISOINDOLES

The parent isoindole was prepared by flash vacuum pyrolysis of an N-substituted Isoindoline. N-methoxycarbonyloxy Isoindoline was pyrolyzed in the vapor phase at $500^0$C and the product trapped at low temperature.[6]

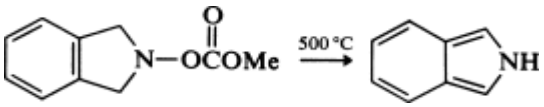



**Figure 6: synthesis of isoindole.**

**Frister and Michels** introduced a method for measuring residual proteins based on an assay for amino acids that used o-phthal di aldehyde (OPA) in the presence of a Mercapto ethanol to form an isoindole.

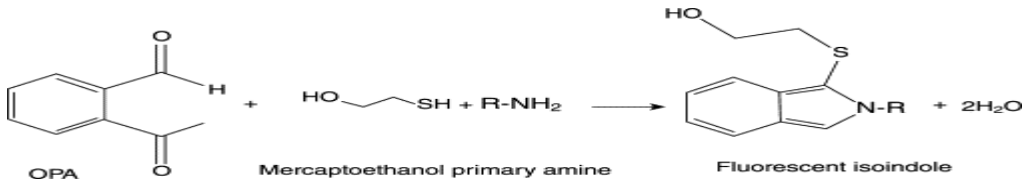



**Figure 7: synthesis of isoindole.**

**By condensation reaction**

Synthesis of isoindole from intermolecular condensation of benzyl azides with α-aryl diazoesters.[7]

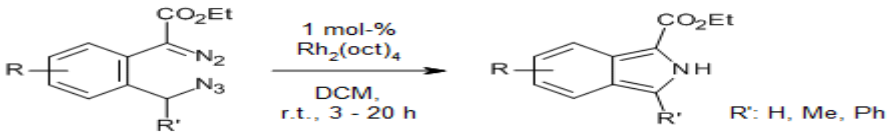



**Figure 8: synthesis of isoindole.**

A Rh-catalyzed intermolecular condensation of the benzyl azides with α-aryldiazoesters provides isoindole in very good yields. The reaction proceeded through nucleophilic attack of the organic azide onto a rhodium carbenoid, release of nitrogen gas and tautomerization of intermediate imino esters.

A-azido carbonyl compounds bearing a 2-alkenylaryl moiety at the α- position are promising precursors for synthesis of isoindole and Isoquinoline derivatives via 1, 3- dipolar cyclo addition of azides onto alkenes and 6π electro Cyclization of N-H imines intermediates, respectively.[8]

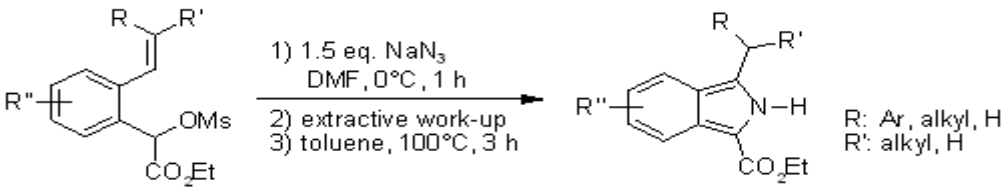



**Figure 9: synthesis of isoindole derivative.**

## BIOLOGICAL ACTIVITY OF ISOINDOLE

**Anti inflammatory activity:** In 2021, 22 Dominika szkatula et al., synthesized a new N-substituted 1H isoindole – 1,3(2H)-Dione derivative and evaluated their affinity for cycloxygenase based on in- vitro studies and molecular doc their king. The biological properties were determined in terms of their cycloxygenase (COX) inhibitory activity.

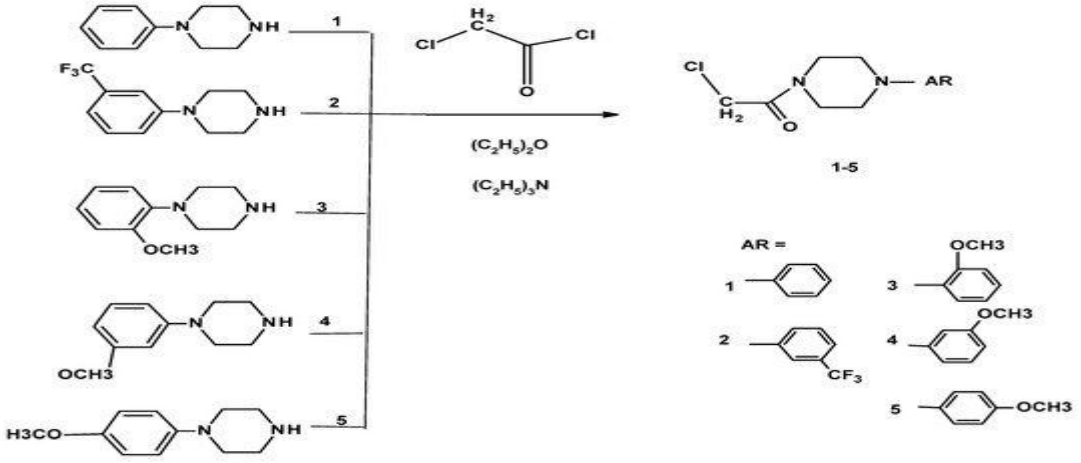



**Figure 10: isoindole derivatives.**

In 2012, Khalid Z matalka et al., synthesized some Anti inflammatory aminoactylenic isoindoline-1,3-diaone derivatives that modulate cytokines production from different spleen cell populations.

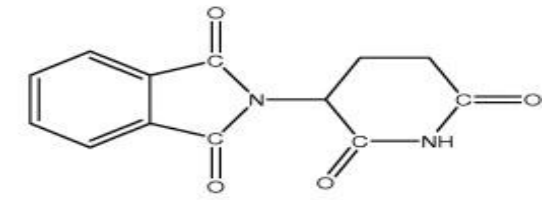



**Figure 11: isoindole derivative.**

**Anti-microbial activity:** Neumann H et al., reported that some N-analogue of the corollosporine have notable antibiotic activity. The compounds of which were prepared by the conversion of n-methyl - 4 –a minophthalimides with different equivalent to Grignard reagents. Thus 7 amino- 3-hexyl 3 – Hydroxy- 2-methyl -2,3- dihydroisoindole-1-one and its 2,4,6- tri methyl derivative were found to be active against staphylococcus areus (inhibition zone).

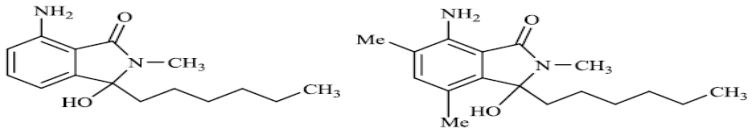


**Figure 11: 7-amino-3-hexyl-2-methyl-2,3-dihydroisoindol-1-one and its 2,4,6- trimethyl derivative.**

**Anticancer activity:** In 2017 Aytekin Kose et al., synthesized some isoindole-1-3-dione derivatives on HeLa, $C_6$ and A549 cancer cell lines. An exo-cycloadduct prepared from the Diels- Alder reaction of furan and maleic anhydride furnished imide derivatives.

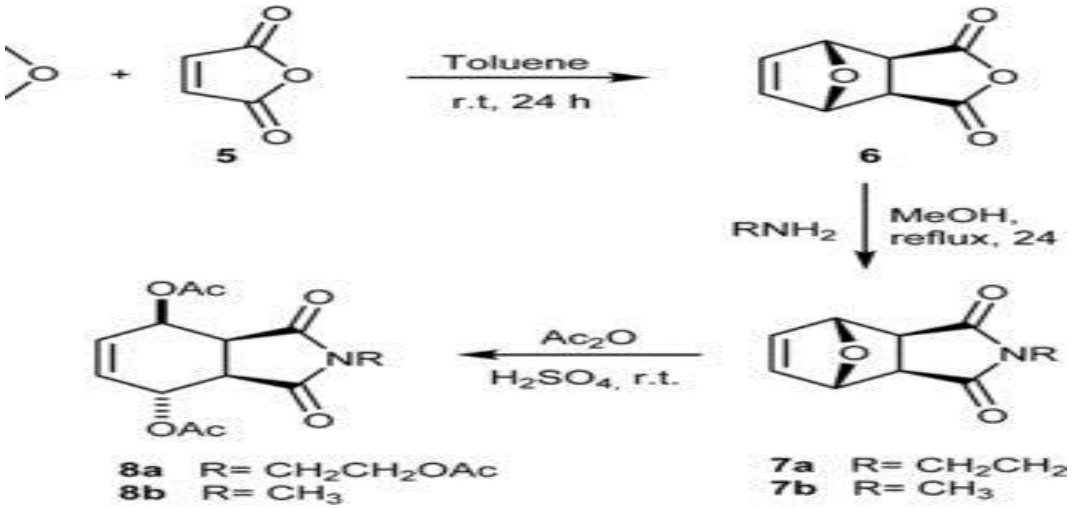



**Figure 12: isoindole derivative.**

**Antiviral activity:** Jamil et al., reported that the biphenyl propyl 4-piperidinyl-2,3-dihydro-1H-isoindole-1-one derivative (BMS-200150) inhibits selectively the microsomal transfer protein(MTP)-mediated transfer of triglyceride(TG) and cholestenyl ester(CE) between membranes.

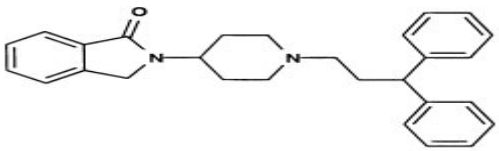
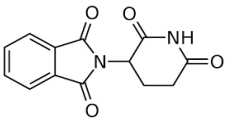
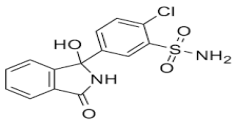
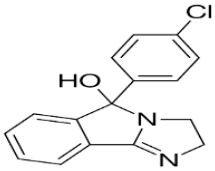
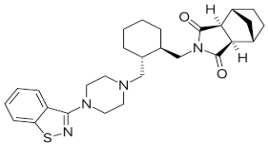
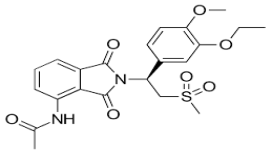


**Figure 13: Structure of compound 2-[1-(3, 3-di phenyl)-4-piperidinyl]-2,3-dihydro-1H-isoindole-1-one.**

**MARKET PREPARATION HAVING ISOINDOLE NUCLEUS[10]**

**Table 01.**

| S.No | Marketed drug | Company | Use | Structure |
|---|---|---|---|---|
| 1 | Thalidomide | Chemie grunenthal | Cancer, Leprosy |  |
| 2 | Chlorthalidone | Janus biotech | Diuretic, Hepatic cirrhosis |  |
| 3 | Mazindol | ifa celtics | Obesity |  |
| 4 | Lurasidone | Torrent Pharma | Antipsychotic |  |
| 5 | Apremilast | Glanmark | Psoriasis, Arthritis |  |

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