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Review Article

# Exploring the Pharmacological Potential of Isoquinoline Derivatives: A Comprehensive Review

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**ABSTRACT**

The core structure is an aromatic heterocyclic organic compound i.e. Isoquinoline. Both the structures of Isoquinoline and quinoline contain a fused ring structure of benzene and pyridine. Isoquinoline, the pyridine counterpart, has a pKb of 8.6 and a pKa of 5.14, making it a weak basic. When it comes into contact with Lewis acids, such BF3, it protonates and becomes a salt. This process produces adducts. The liquid form of Isoquinoline is colorless, hygroscopic, and it has an unpleasant smell. Isoquinoline derivatives are a very significant group of natural and synthetic compounds which show various Pharmacological activities like anti-cancer, anti-oxidant, anti-microbial, anti-inflammatory, anti-microbial, analgesic, anti-fungal, anti-viral, antispasmodic and an enzyme inhibitor. Morphine and codeine are the most extensively characterized Isoquinoline alkaloids. They are made from either tyrosine or phenylalanine. Some of the Isoquinoline nucleus-containing drugs available in the market were Nelfinavir, Apomorphine, Quinapril, Praziquantel, Solifenacin, Papaverine, Metocurine, Tubocurarine. Isoquinoline alkaloids with anticancer properties may be therapeutically to target specific binding to nucleic acids, modulating polynucleic acid stability. These binds change the way that duplex B-form DNA interacts with proteins involved in DNA replication, repair, or transcription.

**Keywords:** Isoquinoline, Quinoline, Anticancer activity, Inhibitory activity, Anti-microbial activity, Antimalarial.

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## INTRODUCTION

A heterocyclic aromatic organic compound i.e., Isoquinoline (benzopyridine) which is a colourless crystalline hygroscopic liquid. It is a structural isomer of quinoline composed of pyridine (β and α position) and benzene that has been cis-fused. Isoquinoline is a significant group of natural and synthetic compounds that shows a wide array of activities in pharmacology such as anti-bacterial, anti-tumor, anti-plasmodial, and antagonism of β-adrenergic receptors.

Alkaloids of Isoquinoline have both natural and manufactured substances and also have a broad range of powerful biological actions, such as the inhibition of cell proliferation, antagonistic activity against β-adrenergic receptors, and other biological effects inhibition of enzymes involved in catecholamine metabolism as well as indoleamines like monoamino oxidase. Many naturally occurring Tetrahydroisoquinolines (THIQs) with notable anticancer and antimicrobial activity have been identified throughout the last ten years.[1]

The biological effects of naturally occurring and synthetically produced Isoquinoline derivatives have been extensively studied. Isoquinolines compounds possess analgesic, antipyretic, anti-inflammatory, antioxidant, and antihypertensive effects. Additionally proven are the antifungal, antibacterial, and antimalarial properties of isoquinoline derivatives. It was also discovered that isoquinolines may function as antipsychotic and antidepressant drugs. Many compounds with isoquinoline cores were identified to create prospective anticancer medications that show antitumor or antiproliferative activity. Notably, the tetrahydroisoquinoline derivatives are included in the structures of drugs used to treat hypertension, such as debrisoquine and quinapril and the topical anesthetic quinisocaine has this essential chemical component.[2]

The most prevalent mosquito species that transmit malaria is the female Anopheles mosquito. Therefore, the salivary glands of the mosquito are invaded by parasites, which then infect the human host. The five strains *Plasmodium falciparum, P. vivax, P. knowlesi, P. malariae* and *P. ovale* are the types responsible for malaria. Currently, Plasmodium vivax and *Plasmodium falciparum* are the ordinary protozoa species with a high death rate in continuation

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that *P. falciparum* is the most infectious in particular. Discover novel drugs having antimalarial characteristics, especially those that can combat Plasmodium strains that are resistant to chloroquine.[3]

Cancer is a broad and complicated collection of diseases that can affect any region of the body and cancer refers to the uncontrolled proliferation of cells and invasion of various adjoining units of our body, further leading to death. A tumor, irregular bleeding, a chronic cough, unexplained weight loss, and gastrointestinal abnormalities are common signs of cancer. From the precancerous lesion to a malignant tumor, Cancer will be caused when normal cells undergo a multi-stage transformation into tumor cells: According to literature reports, the nitrogen atom in Isoquinoline structures makes them a dominant frame that can increase water solubility. Additionally, the Isoquinoline skeleton is abundantly found in natural products and has potent anti-cancer properties.[4]

A prominent class of heterocyclic compounds. In human cancer cell lines, Isoquinoline scaffolds have been shown to display a broad spectrum of biological activities in addition to considerable cytotoxicity and potency. They are appealing candidates for use in drug discovery because of these qualities. Furthermore, a great deal of Isoquinoline and tetrahydroquinoline compounds are effective anticancer drugs.[5]

Inflammation often occurs as a serious problem in circumstances of hypersensitivity, autoimmune conditions, and organ rejection after transplantation. Alternative therapies for inflammatory disorders have side effects and are shown to be ineffective. Non-steroidal anti-inflammatory medicines or NSAIDs are invaluable in treating severe and ongoing pain, fever, and inflammation; however, prolonged use of NSAIDs can lead to gastrointestinal bleeding, hemorrhage, and nephrotoxicity. There have been several reports of isoquinoline alkaloids having anti-inflammatory properties. Where the *in vitro* activities were performed anti-inflammatory and anticancer activities have already been assessed. Similarly, *in vivo* analgesic, antipyretic and anti-inflammatory potentials were assessed and reported.[6]

HIV-1 and HIV-2 are two subtypes of HIV (Human Immunodeficiency Virus) that have been identified, and these retroviruses are related to one another and share 30% to 60% of their total genetic makeup as well as a comparable structural and genomic organization. Globally, HIV-1 is the most common source of HIV infections because it is more virulent, contagious, and pervasive and HIV-2 has a relatively weak transmission rate. Therefore, throughout the past few decades, researchers have concentrated on developing Novel anti-HIV agents like molecules that work on various HIV therapeutic targets. The HIV reverse transcriptase and protease enzymes, which are the foundations of HAART, are no longer the only compounds that target HIV/AIDS.[7]

## Investigation of Isoquinoline derivatives on Anti-cancer activity

Silva W.A.D *et al.*, a series of 5,8-dihydroisoquinoline-4-carboxylate molecules and carbohydrates were synthesized, and their anti-tumor efficacy was assessed (Figure 1). Among all the synthesized compounds, compound 6a, which has a ring called ribofuranosidyl at the C–7 position of the quinone ring; it was the most prominent one. This compound exhibited a Half-maximal inhibitory concentration value of 37.85 μM and an SI of 2.07 against the proliferation of H1299 cells.[8]

Yang Y *et al.*, Incorporated novel derivatives of 3,4-dihydroisoquinoline and conducted scaffold hopping toward agomelatine studies and evaluated them for their potential antidepressant properties. Out of all of them, Compounds 6a-1, 6a-2, and 6a-9 showed good efficacy, with respective protection rates of 25.4%, 32.7%, and 20.3%. Additionally (Figure 2), compound 6a-1 performed effectively in a concentration-dependent manner. Furthermore, compounds like 6a-1 with $IC_{50}$ value 455.0 μM and 6a-2 showed high neuroprotective activity on corticosterone-injured PC12 cells. In addition, 6a-1 has a greater activity that can enhance cell survival, proliferation, and maturation following chronic therapy. In addition to that, less hepatotoxicity was exhibited than agomelatine, which was seen in acute toxicity data *in vitro* studies.[9]

Zheng C H *et al.*, performed study on a series of compounds, 1-phenyl-1,2,3,4-dihydroisoquinoline for their cytotoxicity and ability to inhibit tubulin polymerization (Figure 3). Among the evaluated Compounds, 5n with the $IC_{50}$ value 11.4 mM provides an optical bioactivity and further they proceeded for X-ray diffraction analysis. Molecular docking was performed to establish compound 5n binding mode to tubulin protein and this kind of structure is useful for creating new anti-cancer drugs.[10]

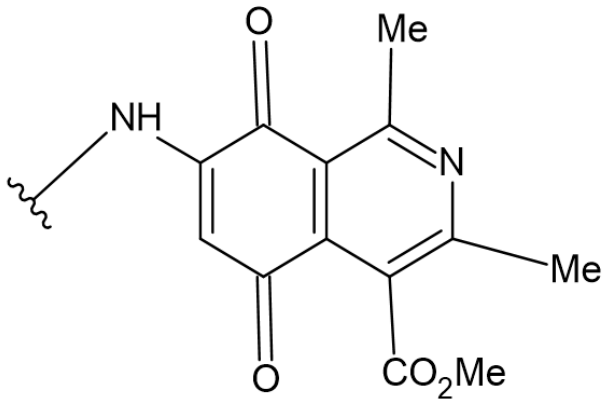



**Figure 1:** Methyl-7-((methyl-5-deoxy-2,3-O-isopropyli dene-β-D-ribofuranosid-5-yl) methylamino)- 1,3-dimethyl-5,8-dioxo5,8-dihy droisoquinoline-4-carboxylate.

Alvarez F N *et al.*, Evaluated a series 6,7-dihydroxy-3,4-dihydroisoquinolines for their inhibitory action of nuclear factor-kB (NF-kB) and for their ability to incursion in Murine Mammary cancer cells *in vitro* (Figure 4). Compounds 1, 2 and 7 having promising effect on inhibition of the canonical and non-canonical NF-kB pathway, whereas compound 7 shows inhibitory action on tumor cells incursion through extracellular matrix along with its anti-NF-kB activity. Based on the SAR result analysis Compound 7 comparatively shown higher potent activity than Compound 1 and 2.[11]

Xu Y P *et al.,* Assessed, radio-synthesised and determined the*in vitro* of their Potential tumor imaging activity of a novel sequence of [131I]-5-iodo-N-[2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-yl)-ethyl] -2-methoxy-benzamide derivatives (Figure 5). In this study, they observed that a possible breast SPECT {Single Photon Emission Computed Tomography} agent for breast tumour. In this experiment, the tributylstanny precursor 8 was 38% overall yield. The tracer has a decent yield of labelling 94% and the tracer's RCP yield was more than 95%. The breast cancer cell line MCF-7 showed substantial absorption of the tracer, further they said confidently that they will be extending the study to assess some more essential activities.[12]

ZIiemska J *et al.*, Created a series of dihydroisoquinoline derivatives and carried out biological, toxicological, and molecular docking investigations to assess their significant anticancer potential (Figure 6). Among the synthesized compounds, Compound 3b demonstrated essential antiproliferative action against the following: camptothecin-resistant CEM/C2 leukemia cells with mutant topoisomerase I catalytic site, LoVo colon cancer, Burkitt's lymphoma Raji and prospective antiproliferative activity against LAP. Compound 3b also showed a good selectivity index for

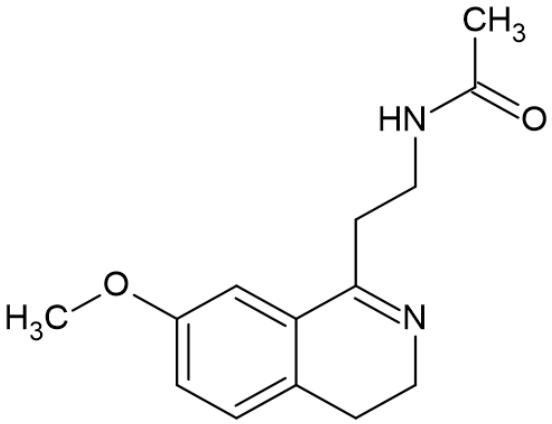



**Figure 2:** N-[2-(7-methoxy-3,4-dihydroisoquinolin-1-yl) ethyl]acetamide.

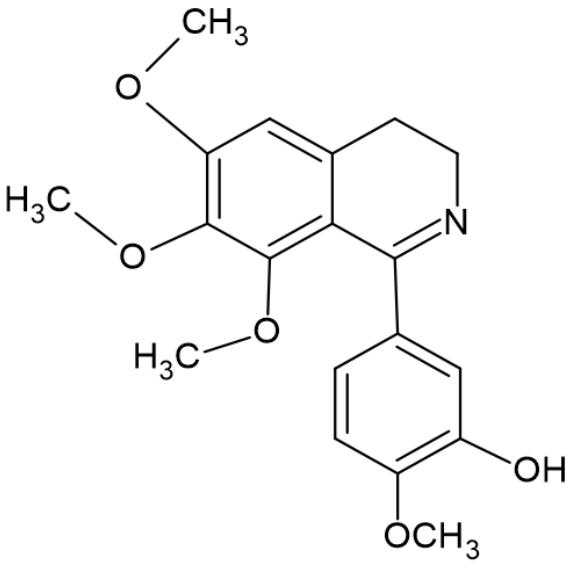



**Figure 3:** 2-methoxy-5-(6,7,8-trimethoxy-3,4-dihydroisoquinolin-1-yl) phenol.

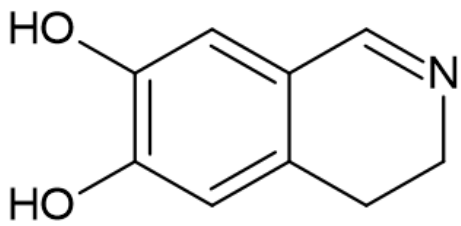



**Figure 4:** 3,4-dihydroisoquinoline-6,7-diol.

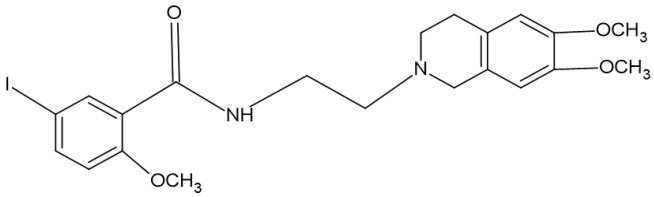



**Figure 5:** [131I-5-iodo-N-[2-(6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-yl)-ethyl]-2-methoxy- benzamide.

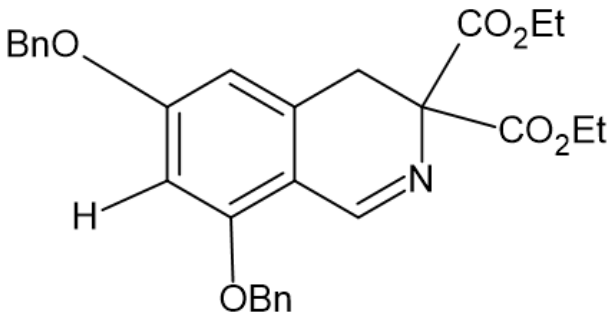



**Figure 6:** Diethyl 6,8-dibenzyloxy-3,4-dihydroisoquinoline-3,3-dicarboxylate.

cancer compared to normal mammalian cells and a toxicological analysis determined that it is safe to employ in subsequent research.[13]

## Investigation of Isoquinoline derivatives on inhibitory activity

Ali F *et al.*, dihydroisoquinoline Carbothioamide analogues were synthesized and assessed for their potential urease-inhibiting action *in vitro* among the evaluated compounds (Figure 7). compounds 1, 2, 4 and 7 displayed potential ($IC_{50}$=11.2 to 20.4 µM) inhibitory activity than that of standard thiourea ($IC_{50}$=21.7 µM) and the potential compounds also projected a potential protein ligand interaction profile against synthesized compounds.[14]

Ziemska J *et al.*, Conduct a study on a series of novel 3,4-Dihydroisoquinoline scaffold and they were evaluated leucine aminopeptidase inhibitory action with *in silico* screening. Among all the synthesized compounds, several compounds were displayed drug likeness properties (Figure 8), pharmacokinetics characteristics and toxicity profiles and specifically, the first compound in the series found out to be an excellent place to start for developing new synthetic derivatives with greater yields. This study demonstrated the potency of a drug with a 3,4-dihydroisoquinoline component to obstruct LAP.[15]

Liao Y *et al.*, A number of novel 1-phenyl-3,4-dihydro-isoquinoline scaffolds were designed and synthesized, and their specific phosphodiesterase-4 inhibitory activity was assessed. Out of all the compounds studied (Figure 9), compound 15 showed the strongest inhibitory action in both *in vitro* and *in vivo*, along with outstanding selectivity. This is a key lead for the creation of a new line of selective PDE-4 inhibitors in the future days.[16]

Gitto R *et al.*, synthesized and evaluated 3,4-Dihydroisoquinoline-2-(1-H)-sulphonamide derivatives as prominent carbonic anhydrase inhibitory agents and also conducted enzyme-ligand X-ray studies (Figure 10). Where compound 2 was the most active one, which form a complex with hCAII and they evaluated the interaction promoting the hCAIX and hCAXIV activity, and selectivity of compound 6 was analyzed by docking studies.[17]

Markmee S *et al.*, evaluated a novel compound of Isoquinoline derivatives as potential acetylcholinesterase inhibitory action (Figure 11). Many alkaloids of bis-benzylisoquinoline exhibited the inhibition on the enzyme of acetylcholinesterase. Where 1-Benzylisoquinoline compounds were original sequence to construct the potent acetylcholinesterase inhibitors and it showed prominent activity displayed by compound 10 and 13.[18]

Zaman K *et al.*, designed, synthesized and evaluated thymidine phosphorylase, angiogenic inhibitory activity and *in silico* studies for Isoquinoline derivatives (Figure 12). Among all the synthesized compounds, KA-12 to 16 showed the most effective inhibitory angiogenic activity. Analogs of Isoquinoline

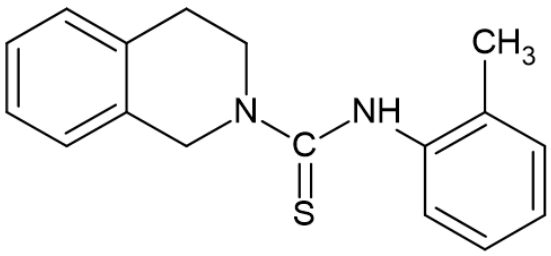



**Figure 7:**
N-(2-methylphenyl)-3,4-dihydroisoquinoline-2(1H)-carbothioamid.

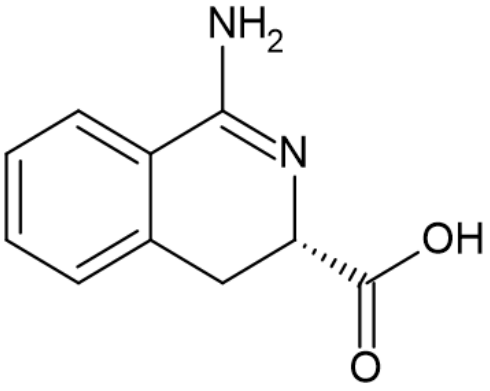
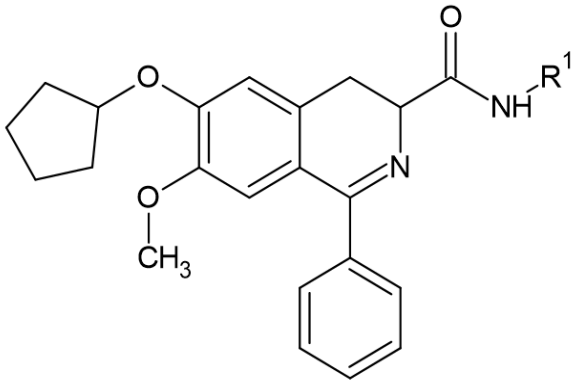



**Figure 8:** (3S)-1-amino-3,4-dihydroisoquinoline-3-carboxylic acid.




**R1=2-methoxyphenyl**

**Figure 9:** 1-phenyl-3,4-dihydroisoquinoline analogue (compound 15).

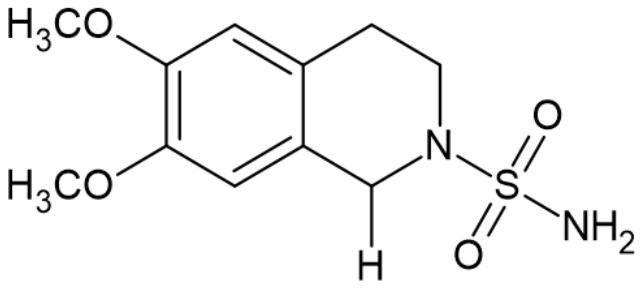



**Figure 10:** 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-sulfonamide.

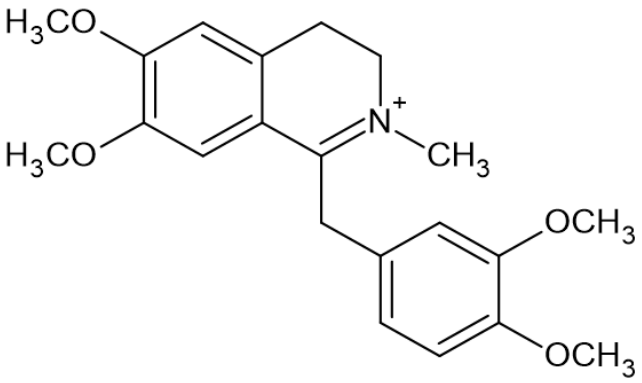


**Figure 11:** Dihydroisoquinoline derivatives.

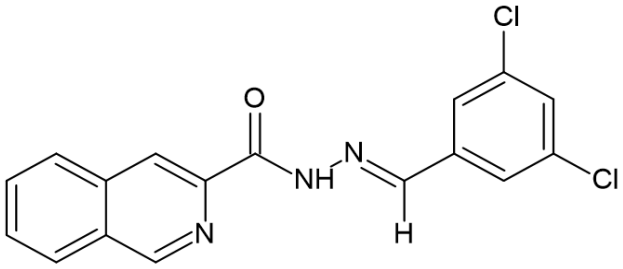


**Figure 12:** *N*'-[(*E*)-(3,5-dichlorophenyl) methylidene]isoquinoline-3-carbohydrazide.

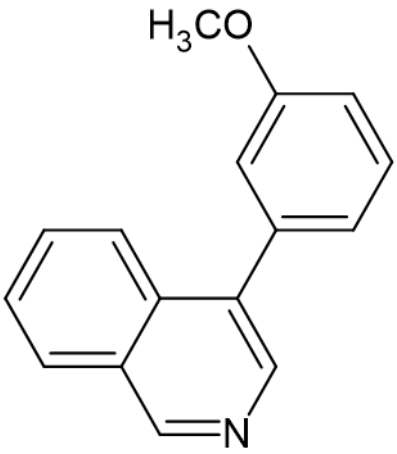


**Figure 13:** 4-(3-methoxyphenyl)isoquinoline.

(compounds KA-1 to 16) were created and examined to see if they could prevent the thymidine phosphorylase enzyme in E. coli. SAR studies are carried out for all the compounds, largely predicated on the substitution pattern of the phenyl ring and also molecular docking studies are conducted.[19]

## Investigation of Isoquinoline derivatives on anti-malarial activity

Theeramunkong S *et al.*, created, produced and assessed a novel sequence of Isoquinoline compounds for their antimalarial

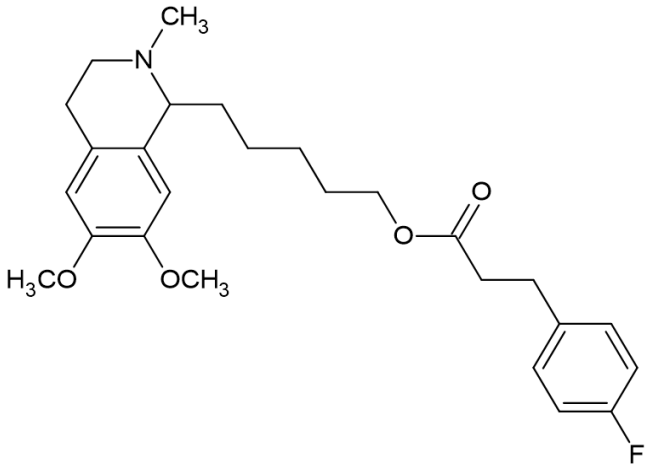


**Figure 14:** N-Methyl-1-[(400-fluorophenylpropanoate) pentyl]-6,7-dimethoxy-1,2,3,4-THIQ.

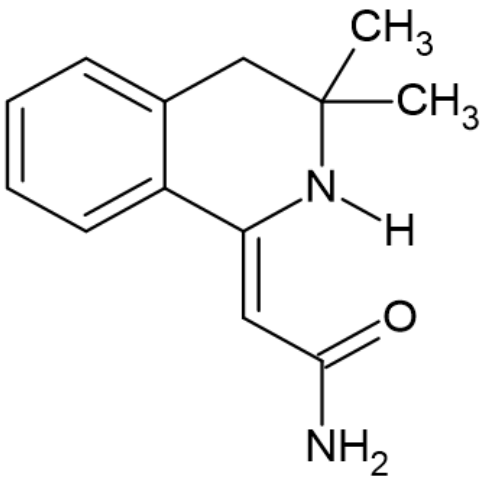


**Figure 15:** (2Z)-2-(3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-ylidene)acetamid.

activity. Many compounds are evaluated (Figure 13), Compound 6 demonstrated most potent anti-plasmodial action against 3D7 i.e. chloroquine-sensitive and K1 i.e. chloroquine-resistant strains when compared to reference standard antimalarial medicines. Numerous compounds are examined compound, (1-13) investigated in the Isoquinoline phenyl derivative series. Compound 15 from the Isoquinoline-triazole derivative series showed encouraging results in combating the resistant strain.[20]

## Investigation of Isoquinoline derivatives on anti-microbial activity

Galan A *et al.*, designed, created, and assessed a novel series of Isoquinoline compounds for antimicrobial efficacy. Where all the compounds are synthesized and structural activity relationship for the bactericide and fungicide activities were executed (Figure 14). Numerous compounds are evaluated; compound 13, 17, 18, 21, 22 showed most promising bactericidal activity and also compound 10, 14 and 22 exhibited the prominent antifungal activity.[21]

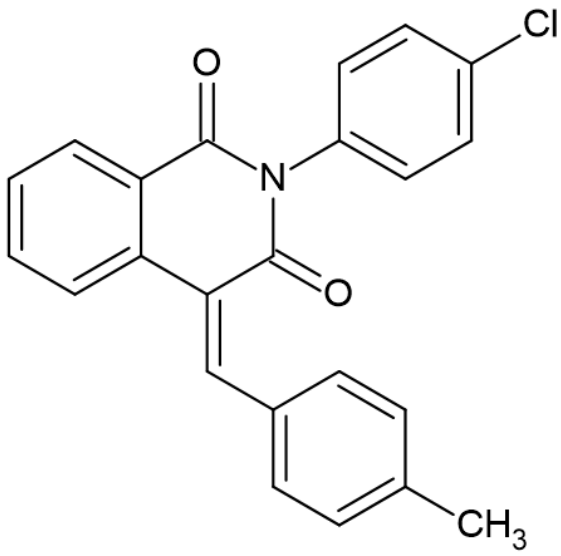



**Figure 16:** (4*Z*)-2-(4-chlorophenyl)-4-[(4-methylphenyl) methylidene]isoquinoline-1,3(2*H*,4*H*)-dione.

Pershina N.N *et al.*, (2020): synthesized and evaluated 2-(3,3-dimethyl-3,4-dihydroisoquinolin-1-yl) acetamides derivatives for their anti-hypoxic, analgesic and antimicrobial activity (Figure 15). Compound 1c showed greater analgesic activity than other compounds. Among evaluated compounds, compound 1d showed most active anti-hypoxic activity. Compound 1c and 1e showed significant activity against *Staphylococcus aureus.*[22]

### Investigation of Isoquinoline derivatives on analgesic, anti-inflammatory and antipyretic activity

Manikandan A *et al.*, designed, synthesized and evaluated a new sequence of Isoquinoline derivatives for their analgesic, anti-inflammatory and antipyretic activity (Figure 16). Where many compounds are evaluated, compound 5g>5d>5h showed most prominent activity which can be compared with the control group. This study suggests that, these derivatives have significant inhibitory activity on cyclooxygenase enzymes. Further drug development evaluation can be conducted in upcoming days.[6]

## CONCLUSION

The distinctive class of substituted Isoquinoline derivatives has a wide range of pharmacological actions, such as anti-inflammatory, anti-tumor, anti-malarial, anti-inhibitory, analgesic and antipyretic. Substitution at 3-position of Isoquinoline analogue shows better anti-cancer activity which can increase cell survival and promotes cell maturation also decreases cell proliferation. Further substitution at 4-position of Isoquinoline shows most prominent anti-malarial activity over inhibiting their survival and replication.

Isoquinoline, which are altered in the 2-position shows potent inhibitory activity that is closer to that of the Isoquinoline ring. Substitution at both 1 and 2-position of Isoquinoline's shows prominent antimicrobial activity which can also enhance the selectivity of the compound for specific microbial targets, such as enzymes or receptors vital for their survival and replication. Additionally, positions 2, 3 and 4 shows potent analgesic, anti-inflammatory and antipyretic activity respectively. This current review attempts to provide an overview of the biological activity and synthesis of a number of Isoquinoline derivatives. It is anticipated that future investigators in the field of designing drugs based on Isoquinoline would find this review useful.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**HCl:** Hydrochloric acid; **Pkb:** Base dissociation constant; **Pka:** Acid dissociation constants; **BF3:** Boron trifluoride; **DNA:** Deoxyribonucleic acid; **β:** Beta; **α:** Alpha; **THIQ:** Tetrahydroisoquinoline; **RES:** Reticuloendothelial System; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **AIDS:** Acquired Immune Deficiency Syndrome; **HIV:** Human immunodeficiency virus; **$IC_{50}$:** Half-maximal inhibitory concentration; **PC12 cells:** Adrenal phaeochromocytoma; **NF-κB:** Nuclear factor kappa-light-chain-enhancer of activated B cells; **SAR:** Structure-Activity Relationship; **RCP:** Rapid Control Prototyping; **MCF-7:** Michigan Cancer Foundation-7; **LAP:** Loan against Property; **ADME:** absorption, distribution, metabolism and excretion; **PDE4:** Phosphodiesterase-4; ***E. coli*:** *Escherichia coli;* **COX:** Cyclooxygenase; **LOX:** Lipoxygenase; **MAPK:** Mitogen-activated protein kinase.

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