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Progressive Insights into the Pharmacological Importance of Isoquinoline Derivatives in Modern Therapeutics

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ABSTRACT

Isoquinoline (ISOQ) is a heterocyclic aromatic organic compound composed of a benzene ring fused to a pyridine ring, referred to as benzopyridines. The chemical formula is C9H7N with a molar mass of 129.162 g/mol. This ISOQ ring derives from the natural aromatic amino acid tyrosine. It is weak alkaline in nature but is more basic than quinoline. It appears as a yellowish oily liquid, having an unpleasant odour, hygroscopic when solid, has a density of 1.099 g/cm3, a melting point of 26°C to 28°C (79°F to 82°F), the boiling point of 242°C (468°F), and dipole moment of 2.49. In the preparation of this review article, a widespread examination of the published literature in varied pharmaceutical and medical databases such as PubMed, Google Scholar, etc. was fruitfully carried out and categorized consequently. The imperative review revealed the less known biological (anti-fungal, anti-Parkinsonism, anti-tubercular, anti-tumour, anti-glaucoma, anti-Alzheimer's disease, anti-viral, anti-bacterial, anti-diabetic, anti-malarial, etc.) potentials of ISOQ (an important class of chemical compounds) and their synthetic derivatives. This knowledge will serve as a ready reference for the global researchers and will be very helpful or inspiring for the medicinal chemists or associated investigators in developing novel low-molecular-weight (LMW) inhibitors for pharmacotherapeutic applications.

Key Words: Isoquinoline, Derivatives, Pharmacology, Therapeutics, Targets, Inhibitors

INTRODUCTION

Isoquinoline (ISOQ) is a heterocyclic aromatic organic compound composed of a benzene ring fused to a pyridine ring, referred to as benzopyridines (Figure 1).[1] The chemical formula is C_9H_7N with a molar mass of 129.162 g/mol.[2] It is a structural isomer of quinoline where the nitrogen atom is present on 2nd position of the benzene ring.[3] This ISOQ ring derives from the natural aromatic amino acid tyrosine.[4] It is weak alkaline in nature but is more basic than quinoline.[5] It appears as a yellowish oily liquid, having an unpleasant odour, hygroscopic when solid, has a density of 1.099 g/cm^3, a melting point of 26°C to 28°C (79°F to 82°F), the boiling point of 242°C (468°F), and dipole moment of 2.49.[6-8] The dissolution of ISOQ is well in acetone, diethyl ether, carbon disulfide, and various organic solvents but is less soluble in water. Several studies have found that ISOQ is also soluble in dilute acids.[9]

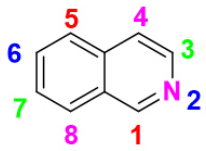

Figure 1: Structure of isoquinoline.

SYNTHETIC APPROACHES

Various synthesis protocols were reviewed regarding the development of ISOQ derivatives such as the Bischler-Napieralski reaction (Figure 2), Pictet-Spengler reaction, and Pomeranz-Fritsch reaction whereas several new methodology and modification has been reported time to time.[10,11] Overall, Pomeranz-Fritsch reaction is found to be the most efficient method for the compound preparation where amino acetoal-

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dehyde diethyl acetal and benzaldehyde are made to react in acid medium.[12] In contrast, the Schlittler-Muller synthesis involves the reaction of benzylamine with glyoxal acetal. Bischler-Napieralski reaction and Pictet-Spengler reaction are now taken into consideration by chemists for the production of substituted products.[13,14] The substituted isoquinolines were generated by these methods such as dihydroisoquinolines and tetrahydroisoquinolines, which are produced in their oxidized analogues.[15]

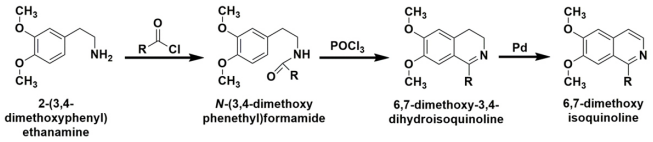


Figure 2: Bischler-Napieralski Reaction.

PHARMACOLOGICAL POTENTIALS

ISOQ and their derivatives occur in various natural products and are considered pharmacologically active owing to their potentials in expressing a large number of biological activities like anti-malarial, anti-HIV, anti-tumour, anti-fungal, anti-fungal, anti-tubercular, anti-glaucoma, anti-bacterial, anti-Parkinson's disease, etc (Figure 3).[16-18] They are used in the manufacture of paints, dyes, and insecticides.[19] They are employed as a solvent for the extraction of resin and terpenes.[20]

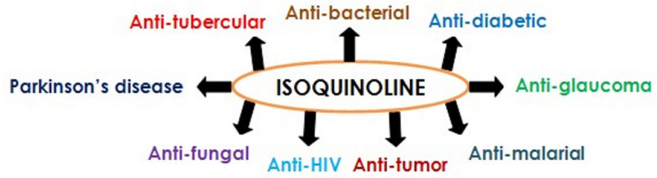
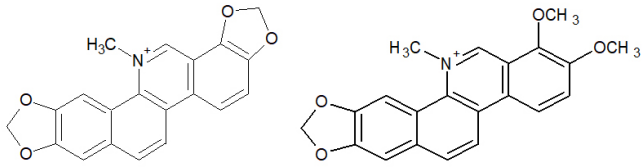


Figure 3: Therapeutic applications of Isoquinoline compounds.

Anti-fungal Activity

The fungal infections are life-threatening opportunistic infections that are an increasingly important cause of illness in patients, principally individuals having weak immune power or hospitalized with stern fundamental ailments.[21,22] The majority of these infections are caused by *Candida spp*., with over 50 % due to *Candida albicans*, a diploid fungus that grows both on yeast and filamentous.[23] These fungi are responsible for various forms of the disease, ranging from superficial infections of the mucosal surfaces or skin to systemic infections, in most cases which is life-threatening.[24] Siwek et al. synthesized and evaluated *in vitro* anti-fungal potency of 4-arylthiosemicarbazides series. Two different mechanisms of anti-fungal activity related to thiosemicarbazide derivatives have been documented. The most potent candidates were found to be *ortho*-methoxy or *ortho*-methyl group at the phenyl ring.[25] Antimycotic drugs can be also be resisted by various fungal species. Surikova et al. synthesized a series of (2,2-dimethyl-1,2,3,4-tetrahydro-benzo[f] isoquinolin-4-yl)thioacetic acid which showed remarkable anti-fungal activity.[26]

Cantrell et al. synthesized two agrochemical agents; sanguinarine (Compound 1) and chelerythrine (Compound 2) and investigated the *in vitro* antifungal potential against *Rhizoctonia solani*. These alkaloids demonstrated potent fungicidal activity with sanguinarine as the most effective candidate.[27]



Anti-Parkinson's Activity

In this disease, substantia nigra includes progressive degeneration of dopaminergic neurons.[28] The derivatives of 1,2,3,4-tetrahydroisoquinoline (TIQ) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are employed in Parkinsonism disorder in an animal model owing to the structural similarities with an endogenous neurotoxin that have been studied for symptoms.[29] Several TIQ derivatives like 1-methyl-TIQ, (*R*)-1,2-dimethyl-5,6-dihydroxy-TIQ [(*R*)-N-methyl-salsolinol)], etc. have been into applications against behavioural abnormalities.[30]

The ISOQ are homologs with MPTP and have linkage with dopaminergic cell death in Parkinson's disease.[31] The known defects in the patients such as MAO and α-ketoglutarate are inhibited by TIQs and dihydroisoquinolines which are members of ISOQ derivatives.[32] Natural substances of plants and several foods such as cheese, milk, banana, and cocoa also come under TIQ derivatives.[33,34] Therefore, these TIQ derivatives are considered to prevent Parkinson's disease.

Anti-tubercular Activity

Mycobacterium tuberculosis is a bacterium that is responsible for a contagious disease, an infection called tuberculosis (TB).[35] This disease has a high rate of mortality in the world where about 3 million people die every year and 8 million new cases are estimated each year in 95% of developing nations.[36] The current therapy includes the combination (Isoniazid, Rifampin, or Pyrazinamide) for 2 months, followed by 4 months of follow-up therapy with isoniazid and rifampin.[37] However, due to the arising of multidrug-resistant (MDR)-TB, the development of new therapeutic agents with

a unique mechanism of action are required for treating these MDR forms.[38,39]

Benzo[*g*]isoquinoline-5,10-diones were synthesized from 2-methyl-1,4-naphthoquinone and screened against virulent strain where higher anti-tubercular potency was observed for derivatives having position-3 substitution. The minimal inhibition concentrations (MICs) of these compounds lie in the range of 1.05 µM to 28.92 µM, respectively along with acute cytotoxic concentrations of >128 µM.[40]

Anti-tumour Activity

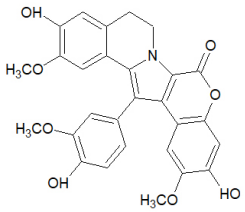
ISOQ has been identified as bioactive ingredients in natural products-based therapeutics. ISOQs exhibit potential anti-cancer activity which makes them an important basis for treating cellular proliferation.[41] Liu et al. evaluated the anti-neoplastic activity of various substituted isoquinoline-1-carboxyaldhyde thiosemicarbazones (Compound 3) where 4-amino and 4-(methylamino) have been identified as potential candidates.[42,43]

Current chemotherapies for cancer are mostly cytotoxics with serious side-effects and high incidence of drug resistance which escalated the need for new anti-tumour agents with reduced toxicity, excellent stability, significant anticancer activity, and increased efficacy.[44,45] Because of the ability of human transferrin to undergo receptor-mediated endocytosis, it has been used previously for targeting the LP's.[46]

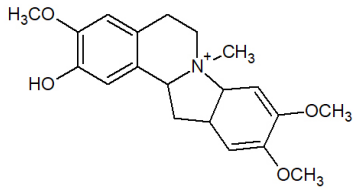
Derivatives of isoquinoline and α-methylene-γ-butyrolactones were screened using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Compound 4) which was identified as the most potent anti-cancer agent.[47] There are several kinds of biological activities such as an anti-*Trypanosoma cruzi*, an antibiotic tryptanthrin, and a cytotoxic luotonin which comprised of benzimidazoisoquinoline structure.[48,49]

The anti-cancer potential of [1,2,4]-triazolo[3,4-a]isoquinolines and pyrrolo[2,1a]isoquinolines have been identified in the past few years. For the synthesis of some anti-tumour (anti-leukemic, tubulin polymerization properties) alkaloids like lamellarins and crysrinepyrrolo, [2,1-a]isoquinoline serves as an intermediate.[50] For the inhibition of estrogen (ER) receptors, acetoxysubstituted 5,6-dihydropyrrolo[2,1-a]isoquinoline (Compound 5) serves a major role.[51] Also, isoquinoline derivatives like Lamellarin D act as a potent topoisomerase-I inhibitor and induce apoptosis through the mitochondria-mediated pathway towards cancer cell lines.[52]

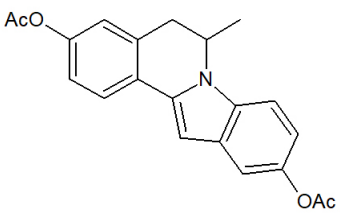
Tamoxifen, the selective estrogen receptor modulators (SERMs) is employed for treating breast cancer that works by preventing the binding of estrogen to the estrogen receptors and thereby slowing down the estrogen-induced cellular proliferation.[53,54] Newly introduced pyrrolo[2,1-a]-isoquinoline derivatives and 1,2-diaryl-5,6-dihydropyrolo[2,1a]-isoquinoline derivatives (Compound 6) have shown better suppression of breast cancer as compared to the standard tamoxifen.[55]



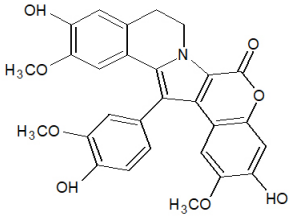
(Compound 3)



(Compound 4)



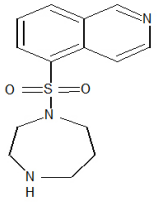
(Compound 5)



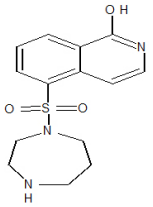
(Compound 6)

Anti-glaucoma

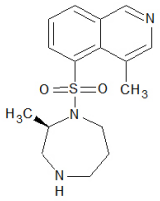
Most of the surveys on glaucoma have reported that after cataract, it is the second leading cause of blindness worldwide.[56] ISOQ sulphonamides-based moderate Rho-kinase Inhibitors; Fasudil (Compound 7) has been successfully evaluated for clinical studies.[57,58] It is oxidized *in vivo* to hydroxyfasudil (Compound 8) which is slightly more active than the corresponding drug. Further, optimizations (methyl substituents at 4-position and 2-position in the ISOQ scaffold) of the compound led to the development of a compound with improved potency; dimethylfasudil (Compound 9).[59,60] By varying the position of the methyl group the effect of methylation on the homopiperazine ring was studied. Compound 10 with an unsubstituted homopiperazine ring and compounds (Compounds 11-13) with homopiperazine ring substituted with a methyl group at 3-position, 5-position, and 6-position exhibited a very low potency towards Rho-kinase II. Methylation at 7-position of the ring (Compound 14) showed potent inhibition against Rho-kinase II. However, methyl substitution at 2-position of the homopiperazine ring was found to be most ideal in terms of selectivity as well as potency.[61,62]



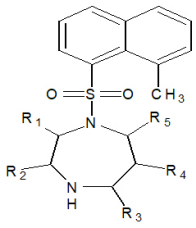
(Compound 7)



(Compound 8)



(Compound 9)

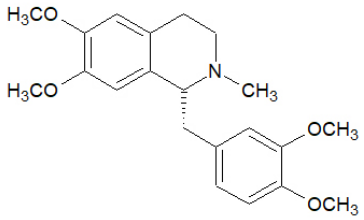


Compounds	R_1	R_2	R_3	R_4	R_5
10	H	H	H	H	H
11	H	CH_3	H	H	H
12	H	H	CH_3	H	H
13	H	H	H	CH_3	H
14	H	H	H	H	CH_3

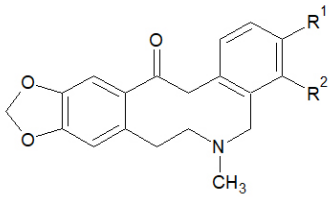
Anti-Alzheimer's Disease

Alzheimer's disease (AD) is an age-related, progressive, neurodegenerative disorder, with onset usually in later ages (65 years to 85 years).[63] AD has two characteristic pathological hallmarks; extracellular accumulation of β-amyloid peptide (amyloid plaques), and intraneuronal formation of hyperphosphorylated τ-protein filaments leading to progressive loss of neurons and disintegration of the neural circuits, particularly in the cerebral cortex.[64] Use of the currently available drugs in AD correlate with dementia severity and mostly relies on the cholinergic hypothesis that decreases in cholinergic transmission in the neocortex and hippocampus.[65,66]

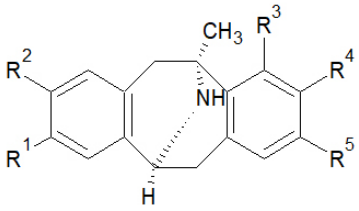
Various NMDA blockers and cholinesterase inhibitors (ChEIs) are under clinical trials.[67] The United States Food and Drug Administration (USFDA) has approved donepezil, galanthamine, and rivastigmine to treat the symptoms of Alzheimer's disease.[68] Galanthamine and donepezil are taken as selective AChE inhibitors, while rivastigmine is a dual inhibitor of cholinesterases.[69] As discussed above, both AChE and BChE are responsible for the breakdown of ACh in the synapses. Therefore, the inhibition of both enzymes represents a beneficial approach in AD treatment.[70,71] Laudanosine (Compound 15), Protopine (Compound 16), Allocryptopine (Compound 17), Argemonine (Compound 18), Platycerine (Compound 19), Munitagine (Compound 20), and Norargemonine (Compound 21) have been identified as potential ISOQ and ISOQ-based derivatives with potential anti-Alzheimer's disease.



(Compound 15)



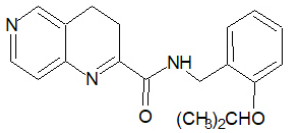
(Compound 16) $R^1 = R^2 = OCH_2O$ (Compound 17) $R^1 = R^2 = OCH_3$



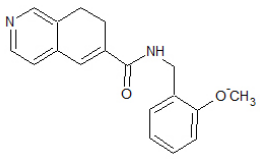
Compounds	R^1	R^2	R^3	R^4	R^5
18	$-OCH_3$	$-OCH_3$	-H	$-OCH_3$	$-OCH_3$
19	$-OCH_3$	$-OCH_3$	-OH	$-OCH_3$	-H
20	-OH	$-OCH_3$	-OH	$-OCH_3$	-H
21	-OH	$-OCH_3$	-H	$-OCH_3$	$-OCH_3$

Anti-viral Activity

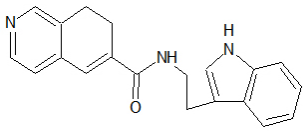
Bedard et al. demonstrated anti-viral activity of 1,6-naphthyridine ISOQ derivatives against human cytomegalovirus (HCMV) where excellent results have been observed.[72] The selected compounds were characterized by the presence of a 1,6-naphthyridine (Compound 22) or a dihydroisoquinoline (Compounds 23-24).[73] Compound 2 with a dihydroisoquinoline scaffold was found to be less potent than ganciclovir (GCV) whereas Compound 3 was 3-times to 9-times more active than GCV. The naphthyridine derivative (Compound 22) was found to have the highest HCMV activity with an IC_{50} of 39-fold to 223-fold lower than GCV.[74]



(Compound 22)



(Compound 23)



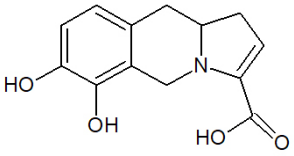
(Compound 24)

Anti-bacterial Activity

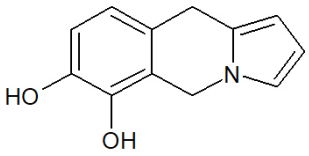
There are ISOQ alkaloids with potent anti-microbial activities which encouraged the synthesis new antimicrobial

compounds such as 1-pentyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (THIQs) with dihyroisoquinolinium salts, chlorobenzoates, methyl pentanoate-THIQ, fluorophenylpropanoate/chlorophenylpropanoate ester, phenethyl/chlorophenethyl carbamates, halogenated phenyls, 1-pentanol-THIQ, and carbamates derivatives have been developed for bactericidal and fungicidal activities.[75-77]

Nord et al. isolated new anti-bacterial secondary metabolites; 6,7-dihydroxy-5,10-dihydropyrrolo[1,2-b]isoquinoline-3-carboxylic acid, Spathullin A (Compound 25) and 5,10-dihydropyrrolo[1,2-b]isoquinoline-6,7-diol, Spathullin B (2) from culture broths of *Penicillium spathulatum* and screened against both Gram-negative and Gram-positive species like *E. coli.*, *A. baumannii*, *E. cloacae*, *K. pneumonia*, *P. aeruginosa*, and *S. aureus.* Compound 25 was identified as less potent but more cytotoxic than Compound 26. The biosynthesis of Compound **25** was suggested to proceed from cysteine, tyrosine, and methionine via an enzyme that is a non-ribosomal peptide synthetase.[79]



(Compound 25)

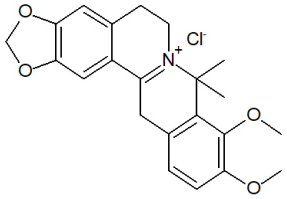


(Compound 26)

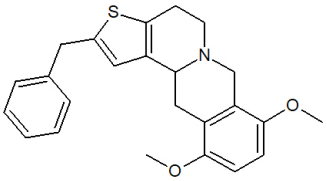
Anti-diabetic Activity

Type-2 diabetes mellitus (T2DM) morbidity and mortality is increasing worldwide and is the rising form of DM.[80] The biggest challenge in the modern era is the management or treatment and healing the complication associated with T2DM. Berberine (BBR) is an ISOQ-based natural product extracted from *Coptis chinensis* known to have glucose reducing properties by mitochondrial respiratory chain complex-I suppression mechanism (via activation of the AMPK signalling pathway), which simultaneously stimulates glycolysis (decreases the rate of protons pumped from matrix to inner membrane space) and consumption of glucose (consequently lowers the mitochondrial membrane potential).[81]

BBR derivatives were created by Zhang et al. and were evaluated for glucose-lowering potentials (promoting glucose consumption) where derivatives possessing amide bond and amidogen at 9-position better potency than parent BBR.[82] Recently, accumulating evidence has indicated that BBR synthetic analogues have displayed high anti-diabetic activities and anti-hyperlipidemic activities which lead to an enhanced interest in their applications.[83,84] Ren et al. discovered that dihydroberberine (dhBBR) (Compound 27) had better *in vivo* hypoglycemic efficacy in high-fat-fed rodents, enhanced oral bioavailability, and analogous potency compared with BBR by similar pathway.[85] Cheng et al. designed and synthesized 8,8-dimethyldihydroberberine (Compound 28) which showed improved bioavailability and oral efficacy as compared to dhBBR via analogous mechanism.[86]



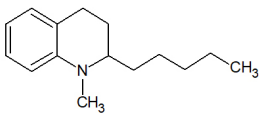
(Compound 27)



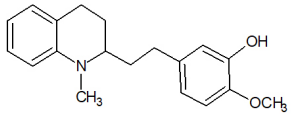
(Compound 28)

Anti-malarial Activity

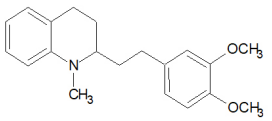
Angustureine (Compound 29), galipeine (Compound 30), cuspareine (Compound 31), and galipinine (Compound 32), obtained from the bark extract of *Galipea Officinalis*, commonly known as "angostura", belongs to the group of 2-alkyl-1-methyl-1,2,3,4-tetrahydroquinoline naturally occurring alkaloid.[87,88] Due to the stereogenic centre at position-2, they are chiral active molecules. Among the 20 species of *Galipea* genus, the shrub *G. Officinalis* is known ethnobotanically for treating dyspepsia, dysentery, chronic diarrhoea, and mainly shows anti-malarial activity.[89]



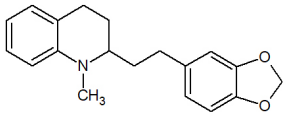
(Compound 29)



(Compound 30)



(Compound 31)



(Compound 32)

CONCLUSION

The imperative review revealed the less known biological (anti-fungal, anti-Parkinsonism, anti-tubercular, anti-tumour, anti-glaucoma, anti-Alzheimer's disease, anti-viral, anti-bacterial, anti-diabetic, anti-malarial, etc.) potentials of ISOQ (an important class of chemical compounds) and their synthetic derivatives. This knowledge will serve as a ready reference for the global researchers and will be very helpful or inspiring for the medicinal chemists or associated investigators in developing novel low-molecular-weight (LMW) inhibitors for pharmacotherapeutic applications.

Conflict of Interest

Authors declare no conflict of interest regarding the publication of this article.

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AUTHORS CONTRIBUTION

KRD: Physically authored the whole manuscript

PMM: Complete literature survey performed

DKM: Made all Figures, Wrote Structured Abstract, Drawn Graphical Abstract, Set References

MNM: Final reviewing of this manuscript

UNM: Provided suggestions and corrected few errors

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