A REVIEW ON BIOLOGICAL SIGNIFICANCE OF QUINOLINE-ISATIN HYBRID DERIVATIVES

A.Aruvisal Hananth*, V.Hemachandran, T.Janagi, K.Hemalatha and K.Girija

Department of Pharmaceutical Chemistry, College of Pharmacy,
Mother Theresa Post Graduate and Research Institute of Health Sciences
(A Government of Puducherry Institution),
Affiliated to Pondicherry University, Indira Nagar, Gorimedu, Puducherry- 605 006, India.

Aruvisal Hananth.A., M. Pharm, Department of Pharmaceutical Chemistry, College of Pharmacy, Mother Theresa Post Graduate and Research Institute of Health Sciences (A Government of Puducherry Institution), Affiliated to Pondicherry University, Gorimedu, Puducherry. ORCID: https://orcid.org/0009-0004-0823-6234

ABSTRACT:

Quinoline and isatin are two privileged scaffolds in Medicinal chemistry, each known for their broad spectrum of pharmacological properties. Quinoline derivatives have been extensively explored for their antimalarial, antimicrobial, anticancer, and antiviral potential, while isatin-based compounds are recognized for exhibiting diverse activities including anti-inflammatory, anticonvulsant, antitubercular, and anticancer effects. In recent years, the design and synthesis of quinoline–isatin hybrids have emerged as a promising strategy to harness the synergistic pharmacological benefits of both nuclei within a single molecular framework. Such hybrids have demonstrated significant biological potential across multiple therapeutic areas, including antimicrobial, antitubercular, antiviral, antimalarial, anticancer, and anti-inflammatory activities. This review highlights the recent advances in the development of quinoline–isatin hybrids, with a focus on their synthetic strategies, structure–activity relationships (SAR), and diverse pharmacological profiles and effort to explore several potential quinoline–isatin hybrids nucleus derivatives with a wide range of pharmacological actions.

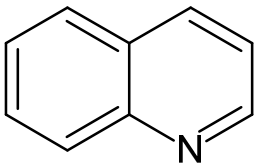
KEYWORDS:

Quinoline, Isatin, Hybrid molecules, Pharmacological activity, Drug design, Medicinal chemistry, Anticonvulsant, Antitubercular, Anticancer activity.

1. INTRODUCTION

Heterocyclic compounds occupy a central place in medicinal chemistry due to their structural diversity and broad therapeutic potential.[1] Among them, quinoline *and* isatin are two privileged scaffolds that have gained significant attention for decades. Quinoline derivatives are well known for their role in the development of antimalarial drugs such as chloroquine and Mefloquine, and more recently for their promising antimicrobial, anticancer, antiviral, and anti-inflammatory activities.[2] Similarly, Isatin (1*H*-indole-2,3-dione), a naturally occurring heterocyclic compound, exhibits diverse pharmacological activities, including anticancer, antitubercular, anticonvulsant, antibacterial, and antiviral effects.[3] The rational design of hybrid molecules by combining two or more bioactive pharmacophores into a single molecular framework has emerged as a powerful strategy in modern drug discovery. In this context, the synthesis of quinoline–isatin *hybrids* has attracted considerable interest. These hybrids aim to integrate the pharmacological strengths of both scaffolds, potentially enhancing efficacy, selectivity and overcoming the limitations of individual molecules such as resistance or reduced bioavailability. Recent studies have demonstrated that quinoline–isatin hybrids exhibit a wide spectrum of biological activities, including antimalarial, antimicrobial, antiviral, anticancer, antioxidant, and anti-inflammatory effects.[4] Given the increasing importance of such hybrid scaffolds, this review provides a comprehensive overview of quinoline–isatin hybrids with a focus on their pharmacological potential. The article discusses recent advances in their synthesis, structure–activity relationships (SAR), and therapeutic applications, highlighting their promise as lead candidates for future drug development.[5]

QUINOLINE



Four out of the top five selling medications in the US are believed to include at least one heterocyclic molecule, which has diverse pharmacological properties including antitumor, anticancer, antibacterial, and anti-inflammatory properties. Quinoline and its derivatives are essential in many drug core structures as well as for its biological and pharmacological activities. Quinoline, which is a prime example of a bicyclic heterocyclic molecule. A pyridine ring and a benzene ring fused with two nearby carbons make up the aromatic N-heterocyclic basic chemical known as quinoline.

PHYSICAL AND CHEMICAL CHARACTERISTICS OF QUINOLINE

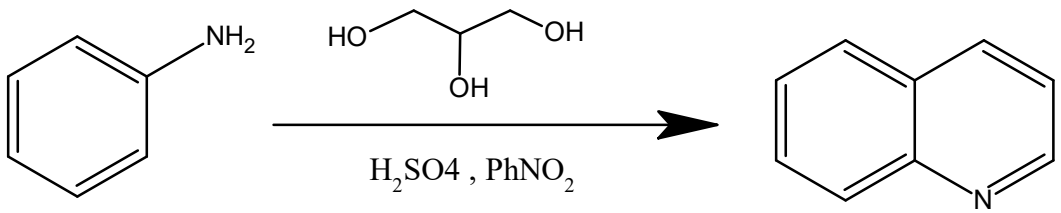
The pKa of pure quinoline, also known as benzo [b] pyridine, in water at 20°C is 4.85. It is an oily, colourless, hygroscopic liquid. Its molecular weight is 129.16 and its chemical formula is C_9H_7N. It is exceedingly stable and frequently employed as a high-boiling solvent (b.p. 237 °C), even though it darkens when exposed to light. The acidic pKa is 4.85 and the logP value is 2.04. A weak tertiary base is quinoline. With acids, it can form a salt and exhibits reactions similar to those of pyridine and benzene. Both nucleophilic and electrophilic substitution reactions are shown in Quinoline nucleus. It is nontoxic to humans on oral absorption and inhalation.

NATURAL OCCURRENCE OF QUINOLINE

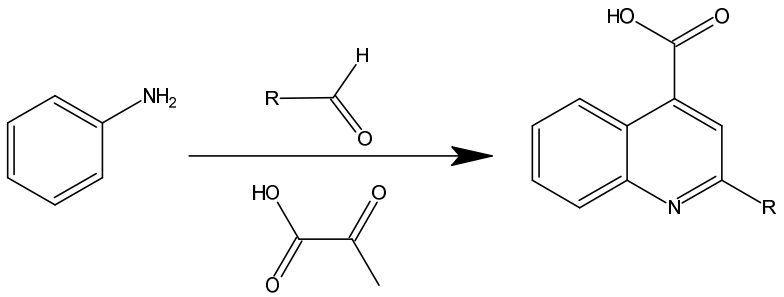
Quinoline, a valuable compound, is naturally found in various sources like animals, plants, and microorganisms, with coal tar being its primary source. The Cinchona plant's bark contains quinine, quinidine, and cinchonine, which are combined into the antimalarial drug "Quinimax." *Zanthoxylum nitidum*, a citrus plant, yields Nitidine, a dimethoxylated quinoline with anticancer properties. Isoquinoline reticuline, found in medicinal plants like *Asimina triloba* and *Papaver somniferum*, has significant therapeutic uses. Skimmianine, from *Skimmia japonica*, is utilized in sedatives and anticonvulsants, while Nocardioides sp. produces sanamycin, known for its antibacterial and anticancer activities.

ESTABLISHED METHODS OF QUINOLINE SYNTHESIS

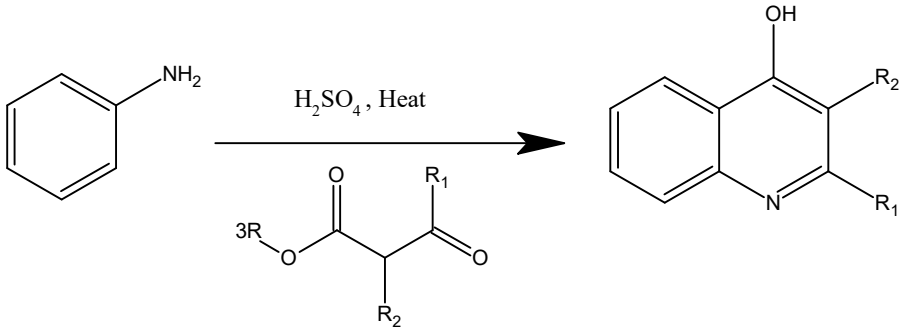
Skarup synthesis: One of the oldest and most enduring of such procedures is the Skraup reaction. In 1880, Czech chemist Zdenko Hans Skraup heated aniline and glycerol with an oxidant in concentrated sulfuric acid, a method that is still commonly used for the production of heteroring-unsubstituted quinolones.



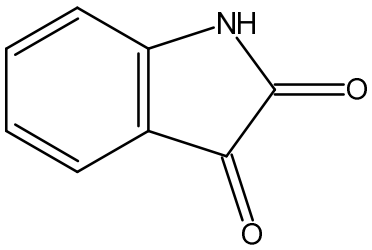
Doebner method: The Doebner method, introduced by Oscar Doebner in 1887, combines aniline with an aldehyde and pyruvic acid to give 2-substituted quinoline-4- carboxylic acids.



The Conrad– Limpach reaction: The Conrad– Limpach reaction, reported in 1887, is also conducted by refluxing in acid, but uses β-ketoesters as the annulation partner to give 2- and 3-substituted quinolin-4-ols.



ISATIN



Isatin (1*H*-indole-2,3-dione) moiety is present everywhere in naturally in plants and animals, and its derivatives easily pass through the blood-brain barrier. Isatin derivatives have a wide range of pharmacological properties due to their potential to inhibit numerous enzymes and receptors, including acetylcholinesterase, butyrylcholinesterase, carbonic anhydrase, DNA gyrase, histone deacetylase reverse transcriptase, serine proteases, tyrosine kinase and tubulin. Isatin and its derivatives have a wide range of biological properties, including anticancer, antibacterial, anti-

inflammatory, anti-TB, analgesic, anticonvulsant, antiviral, anti-HIV, antioxidant, and CNS depressive properties. Isatin was discovered in 1841 by Linne Erdman and Auguste Laurent from indigo dye. Indigo was oxidised in the presence of nitric acid and chromic acid, yielding bright orange- coloured monoclinic crystals of Isatin as a product.

CHEMISTRY OF ISATIN

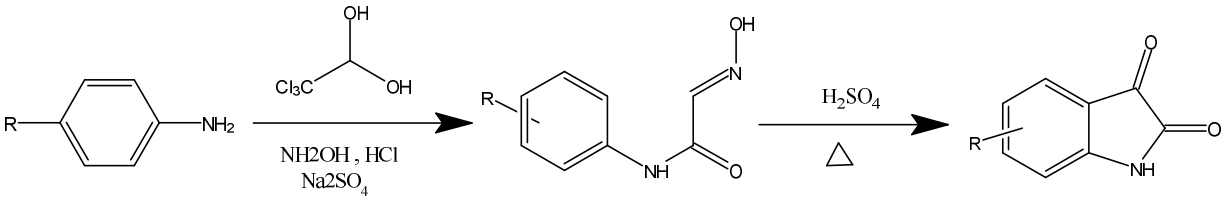
Isatin, a physiologically active compound with diverse properties, is also known as indole quinine or indenedione. It features two carbonyl groups at the C2 and C3 positions, a nitrogen heteroatom at position 1, and both a ketone and a-lactam moiety on the benzene ring. Also called oxindole, isatin is a heterocyclic compound with one nitrogen atoms within its six-membered ring structure. It's a crystalline solid soluble in ethers, benzene, and alcohols, serving as an intermediate in synthesizing various chemicals. Isatin also undergoes aromatic substitution reactions, where an aromatic group is substituted for a hydrogen atom in the ring. The resulting products are useful intermediates in the synthesis of a variety of organic compounds.

NATURAL OCCURRENCE OF ISATIN

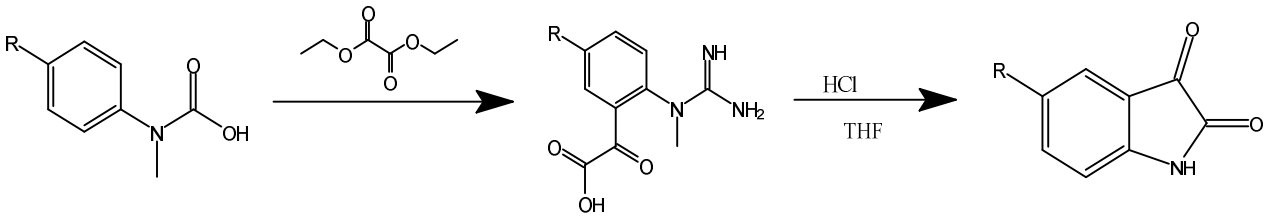
Isatin is found in the natural world, notably in Calanthe discolor LINDL and other plants of the Isatis genus. It has also been identified in *Couroupita guianensis* Aubl and in the parotid gland secretions of Bufo frogs. In humans, isatin appears as a metabolic byproduct of adrenaline. Additionally, plants may contain substituted isatins, such as melosatin alkaloids or methoxy phenylpentyl isatins, which have been isolated from fungi and the Caribbean plant *Melochia tomentosa*, known to cause tumors. Compounds like five (3'-methylbuten-2'-yl) isatin and six (3'-methylbuten-2'- yl) Isatin have been isolated from Chaetomium globosum and *Streptomyces albus*, respectively. Isatin is also a component found in coal tar.

GENERAL METHODS OF SYNTHESIS OF ISATIN

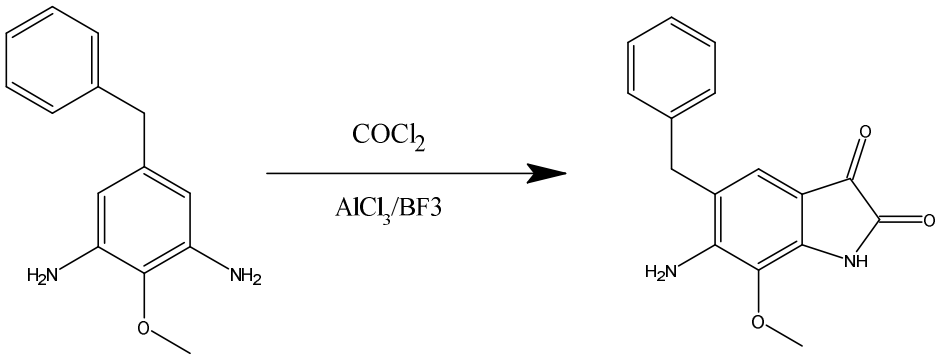
Sandmeyer's Isatin Synthesis: The Sandmeyer synthesis is a chemical reaction used to synthesize isatin, which are organic compounds that are derived from indole. It is named after the Swiss chemist Leon L. Sandmeyer, who first reported it in 1883. Aniline, chloral hydrate, and hydroxylamine hydrochloride were combined in aqueous sodium sulphate to produce an isonitroso acetanilide, which was separated and then treated with concentrated sulfuric acid to produce isatin, which accounts for >75 percent of the final product.



Metalation of Anilide Isatin Synthesis: The most recent method for synthesizing Isatin depends on the ortho-metalation (dom) of N-pivaloyl- and N- (t- butoxycarbonyl)-anilines. Diethyl oxalate is used to treat the dianions, and when the intermediate a-ketoesters are deprotected and cycled, isatins are produced. This method has the benefit of being regioselective for the synthesis of 4-substituted isatins from meta-substituted anilines.



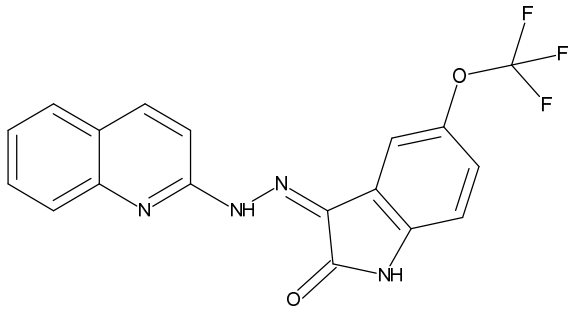
Stolle's Isatin Synthesis: The Stolle method is a chemical process used to synthesize isatin, an important organic compound used in pharmaceuticals, agrochemicals, and dyes. The method is named after the German chemist Wilhelm Stolle, who developed it in 1896. This process is particularly efficient for preparing isatin and its derivatives. Substituted aniline is converted in the presence of oxalyl chloride and Lewis's acids such as BF3 or AICI3 to form substituted isatin. This approach is also effective for producing 1 -Maryland polycyclic isatin from phenothiazine, phenoxazine, dibenzoazepine, and indole.



2. PHARMACOLOGICAL ACTIONS OF QUINOLINE-ISATIN HYBRIDS

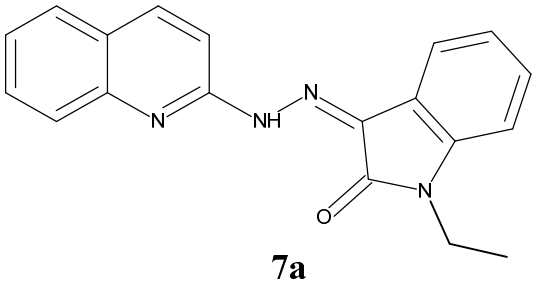
2.1 Antitubercular activity

Eman F. Khaleel *et al.*, (2024) reported the synthesis of quinolone-isatin hybrids targeting *Mycobacterium tuberculosis* enoyl-ACP reductase (InhA) to combat drug-resistant TB. Compounds 7a and 5g showed strong activity with MICs of 55 and 62.5 µg/mL, and IC50 values of 0.35 ± 0.01 and 1.56 ± 0.06 µM, respectively, outperforming Isoniazid. Docking and simulation studies revealed stable binding and key hydrophobic interactions, supporting their potential as novel antitubercular agents.[6]



5g

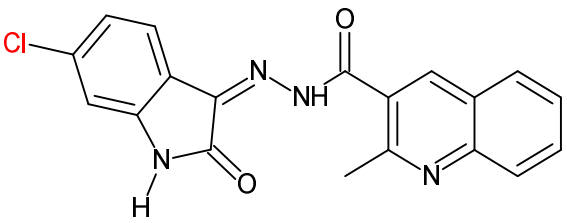
IC_{50} (InhA) = 1.56µM



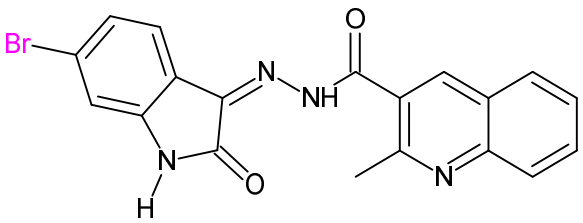
7a

IC_{50} (InhA) = 0.35 µM

Priyanka V. Gandhi *et al.*, (2021) were designed and synthesized isatin incorporated quinoline hybrids to improve biological activity and were characterized using TLC, IR, NMR and MASS spectral data. They were evaluated for anti-tubercular activity. Among those derivatives, compound 7a and 7b showed good activity.[7]



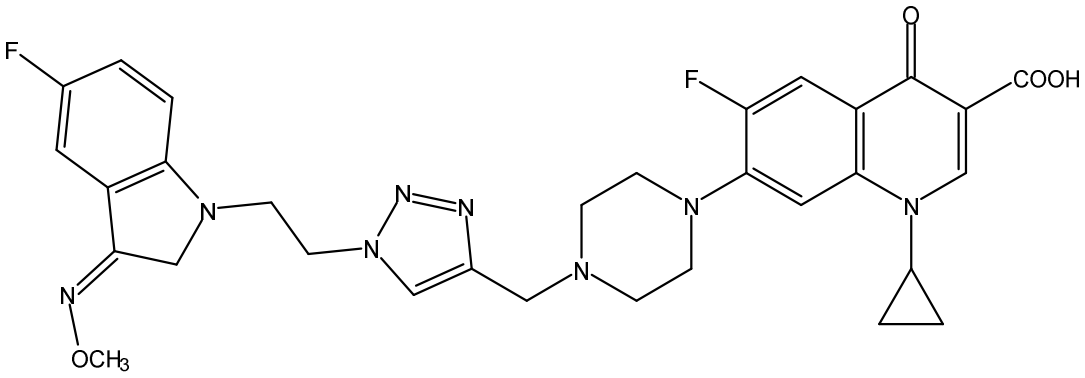
7a



7b

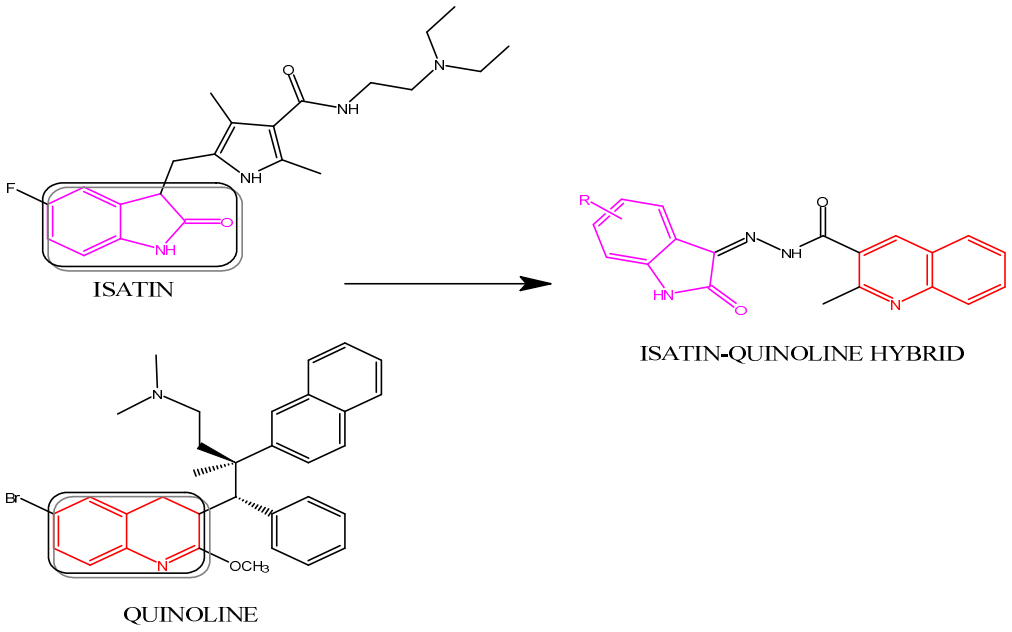
Hu Y *et al* (2017) developed and synthesized eight new 1*H*-1,2,3-triazole-tethered ciprofloxacin-isatin conjugates, evaluating their *in vitro* anti-mycobacterial efficacy against

Mycobacterium smegmatis and *Mycobacterium tuberculosis* (MTB) H37Rv strains. Against MTB H37Rv, all conjugates showed excellent inhibitory activity with MIC ranging from 1.56 to 25 µg/ml. Remarkably, 5h (MIC: 1.56 µg/ml) was twice as potent as ciprofloxacin (MIC: 3.12 µg/ml).[8]

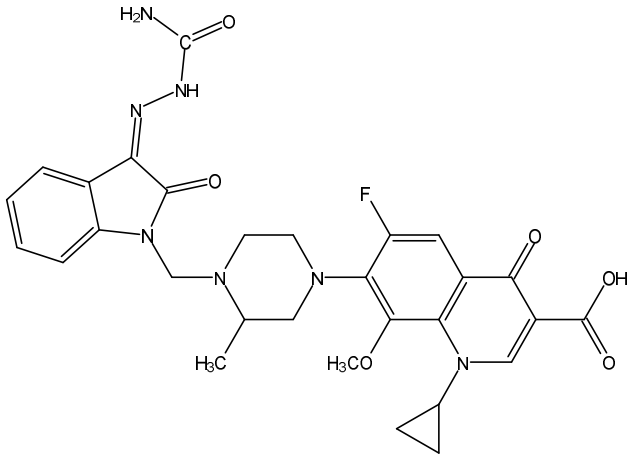


5h

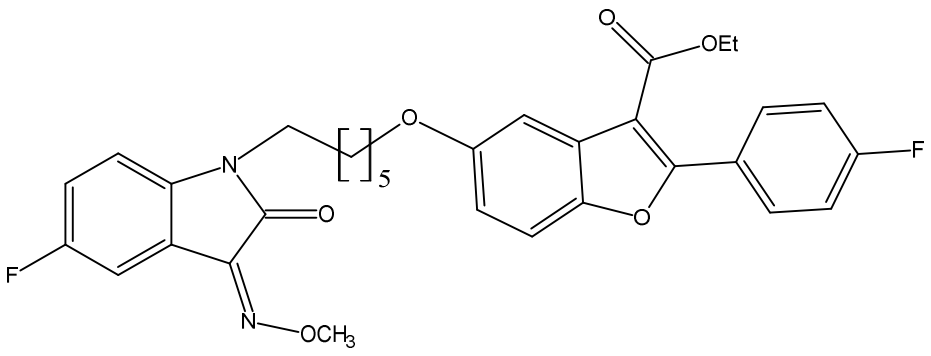
Srinubabu Maddela et al., (2016) reported the design and synthesis of isatin-quinoline hybrids using a hybrid pharmacophore approach to combat MDR-TB. The resurgence of tuberculosis, driven by the AIDS epidemic and drug resistance, highlights the urgent need for new therapies. All synthesized hybrids were evaluated by molecular docking studies against the enoyl-ACP reductase enzyme, a key target in anti-tubercular drug discovery.[9]



Sriram D *et al* (2006) were synthesised the 7-substituted gatifloxacin derivatives and evaluated for antimycobacterial activity *in vitro* and *in vivo* against *Mycobacterium tuberculosis* H37Rv (MTB) and multi-drug-resistant *M. Tuberculosis* (MDR-TB), and also tested for the ability to inhibit the supercoiling activity of DNA gyrase from *M. Tuberculosis*. Among the synthesized compounds 1-cyclopropyl-6-fluoro-8-methoxy-7- [[N4- [10- (5-isatinyl-b-semicarbazo)] methyl]3-methyl] N1-piperazinyl]-4-oxo-1,4-dihydro-3-quinoline carboxylic acid was found to be the most active compound *in vitro* with an MIC of 0.0125 lg/ml against MTB and MTR- TB.[10]

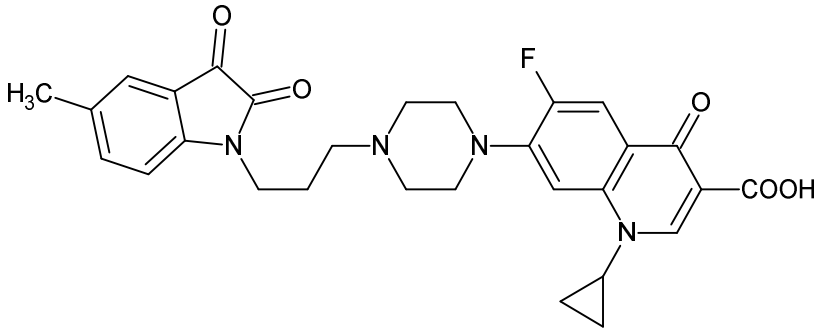


Feng Gao et al., (2019) reported the synthesis of benzofuran-isatin hybrids linked by alkyl chains. Hybrids showed excellent anti- mycobacterial activity (MIC: 0.125–16 µg/mL) against two *MDR-M.tuberculosis* strains with low cytotoxicity towards CHO cells (CC_{50}: 64–>512 µg/mL). Hybrid **7e** exhibited the highest activity, outperforming Ciprofloxacin, Rifampicin, and Isoniazid, but showed inferior metabolic stability and pharmacokinetics.[11]



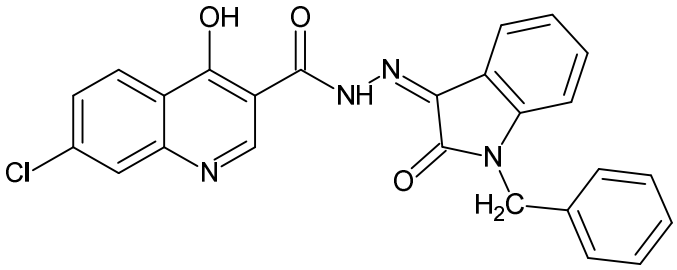
7e

Wang R *et al* (2018) were studied a series of novel propylene-linked isatin- ciprofloxacin hybrids and evaluated for their cytotoxic, antibacterial, and anti-mycobacterial activities. These hybrids exhibited considerable inhibitory effects on the tested strains. Notably, the most potent hybrid, referred to as the compound 3b, showed low cytotoxicity and was more effective against MTB H37Rv and MDR-TB compared to the marketrd drugs, ciprofloxacin and Rifampicin.[12]



3b

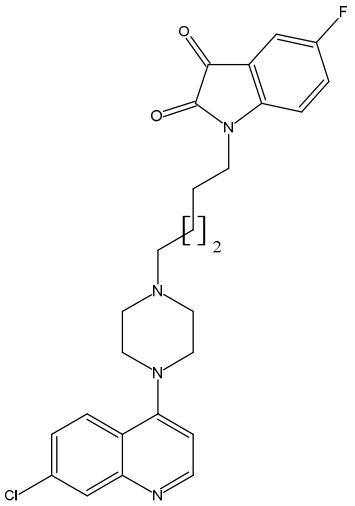
Abdelrahman et al., (2022) explored the design of isatin-tethered quinoline derivatives (Q6a–h and Q8a–h) as novel anti-tubercular agents. Bioisosteric replacement of the 3,4,5-trimethoxy-benzylidene moiety in lead compound IV (MIC = 6.24 µg/mL) with an isatin scaffold led to Q6a–h, followed by N-substitution yielding Q8a–h. Compound Q8b exhibited potent activity against drug-susceptible, MDR, and XDR *M.tuberculosis* strains with MICs of 0.06, 0.24, and 1.95 µg/mL, respectively.[13]



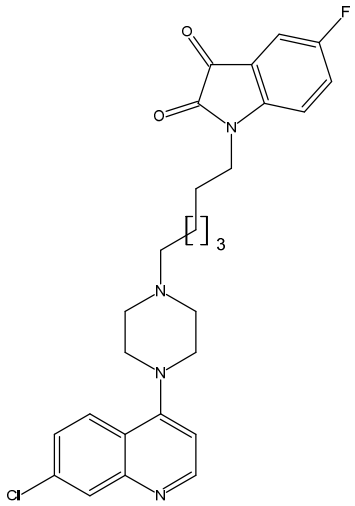
Q8b

Raghu Raj *et al.*, (2014) synthesized 7-Chloroquinoline – isatin Conjugates and evaluated their antimalarial and anti-tubercular efficacy against *Plasmodium falciparum* chloroquine resistant strain and *Mycobacterium tuberculosis* respectively, while cytotoxic profiles were evaluated against 3T6 cell line, a permanent embryonic fibroblast cell line of the mouse. A clear preference

for fluoro substituent is evident for good anti-TB efficacy as observed in case of 5f and 5j, being six times more potent than Cephalexin.[14]

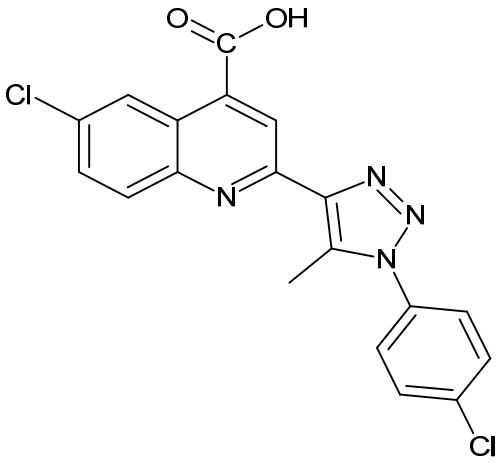


5f



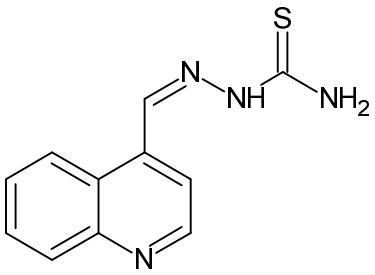
5j

Ahmed Sabt *et al.*, (2024) synthesized 24 novel compounds, created by combining 4-carboxyquinoline with triazole structures, and evaluated their effectiveness against *M. bovis BCG*, *M. tuberculosis*, and *M. abscessus*, alongside their InhA inhibitory activity. Several synthesized molecules showed promise against *M. tuberculosis*, with compound 5n demonstrating the highest efficacy, achieving a MIC value of 12.5 µg/mL, and notably exhibiting significant InhA inhibitory activity comparable to the reference drug, Isoniazid.[15]



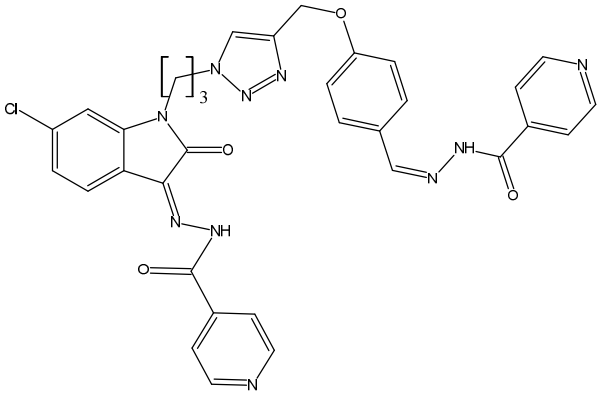
5n

Chun-Xiu *et al.*, (2022) synthesized a series of seven compounds (1–7) utilizing the combination principle, merging quinoline or isoquinoline derivatives with thiosemicarbazide pharmacophores. These synthesized compounds exhibited activity against the *M. tuberculosis* H37Rv strain, displaying Minimum Inhibitory Concentration (MIC) values ranging from 2 to 8 μg/ml. Compound 5 was identified as having remarkable antimycobacterial activity (MIC = 2 μg/ml) and was therefore chosen for subsequent mechanism of action analysis. Initial molecular docking suggested that compound 5 could occupy the active site of the *M. tuberculosis* KatG protein.[16]



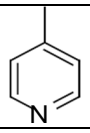
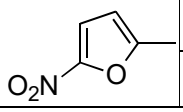
(Compound 5)

Matt D. Johansen *et al*., (2021) a new series of isatin-isoniazid hybrid compounds was developed and tested for their ability to fight *Mycobacterium tuberculosis*. Many of these hybrids showed strong antibacterial activity, with some being even more potent than the commonly used drug Isoniazid (INH). Among them, compound 11e was especially effective, not only against free-living bacteria but also inside infected macrophages, where it showed better performance than INH. These compounds work by inhibiting mycolic acid synthesis, a crucial component of the bacterial cell wall, and require activation by the enzyme KatG, similar to INH.[17]

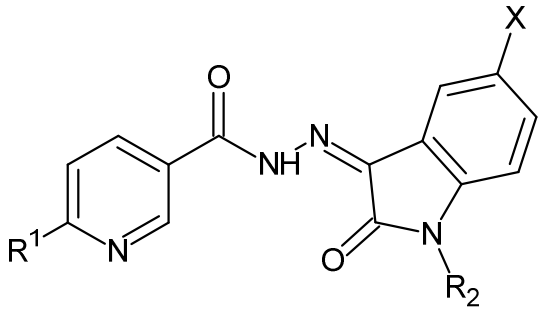


11e

Tarek Aboul-Fadl *et al*., (2015) A collection of 143 isatin-based Schiff compounds was screened for antitubercular activity, leading to the identification of ten derivatives with strong effects against the wild-type *Mycobacterium tuberculosis*, showing MIC values ranging from 10 to 0.156 µg/mL. Among them, compounds A2, A6, D5, and D8 demonstrated notable potential and were further evaluated against six drug-resistant TB strains. Derivative D8 showed improved efficacy against the streptomycin-resistant strain and showed comparable potency to isoniazid (INH) against rifampin-resistant TB. Remarkably, it was also found to be four times more effective than rifampin against strains resistant to ofloxacin.[18]

Compound	R	R1	R2
A2		Cl	H
A6		NO_2	H
D5		OCF_3	H
D8		H	$PhCH_2$

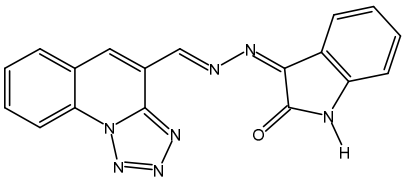
Zainab M. Elsayed *et al.*, (2021) designed and synthesized novel sets of isatin-nicotinohydrazide hybrids (5a–m and 9a–c) in a focused effort against Tuberculosis, aiming to develop potent anti-tubercular and antibacterial agents. Evaluation against the drug-susceptible *M. tuberculosis* strain (ATCC 27294) revealed that hybrids 5d, 5g, and 5h were as potent as the reference drug Isoniazid (INH), all yielding a minimum inhibitory concentration 0.24 mg/mL, also the activity was evaluated against Isoniazid/ Streptomycin resistant M. tuberculosis (ATCC 35823). Critically, compounds 5g and 5h maintained excellent activity MIC = 3.9 m mg/mL when tested against the Isoniazid/Streptomycin resistant *M. tuberculosis* strain (ATCC 35823).[19]



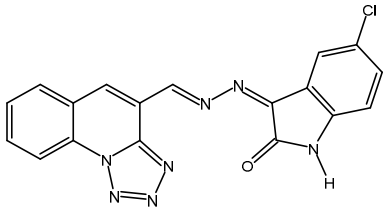
5	R_1	X	R_2
g	H	Br	Propyl
h	H	Br	Isobutyl

2.2 Anticancer activity

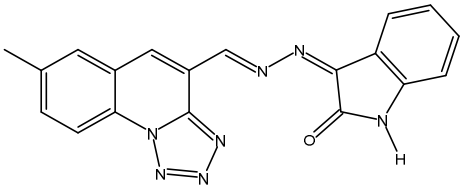
Nippu B.N *et al.*, (2022) were designed and synthesized new tetrazole fused quinoline bridged isatin (TQI) molecules. In vitro cytotoxicity studies against the MIA PaCa-2 human pancreatic cancer cell line identified TQI1, TQI2, TQI6, and TQI7 as having acceptable inhibitory capabilities, with IC50 values of 60.17 ±3.12 μM, 74.49 ±3.45 μM, 93.63 ±4.10 μM, and 93.63 ±4.10 μM, respectively.[20]



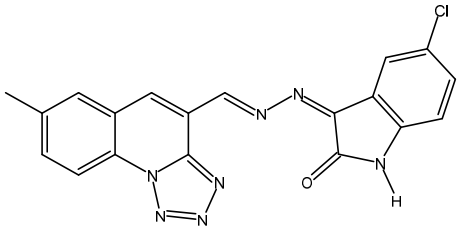
TQI 1



TQI 2

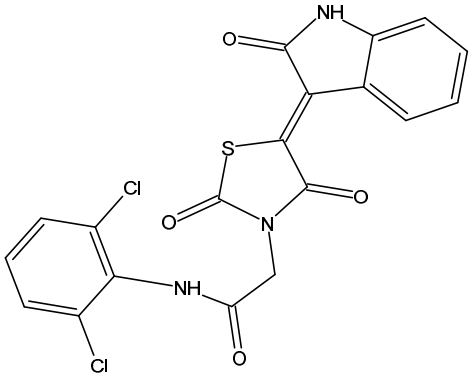


TQI 6



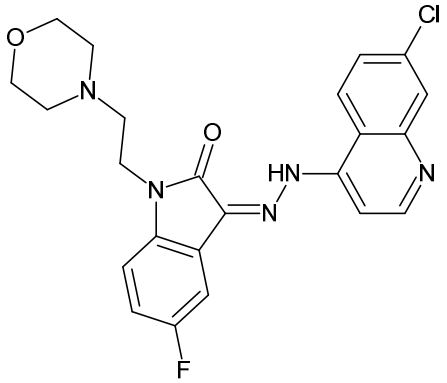
TQI 7

Taghour *et al.,* (2023) were designed, synthesized, and evaluated new quinoline and isatine derivatives as potential anti-angiogenic VEGFR-2 inhibitors. Compound 12 exhibited significant cytotoxicity against A549, Caco2, and MDA cell lines (IC50 values of 5.40, 0.58, and 0.94 mM, respectively). These results were either superior or comparable to doxorubicin and molecular docking, confirmed the correct binding of these compounds to VEGFR-2, similar to sorafenib.[21]



(Compound 12)

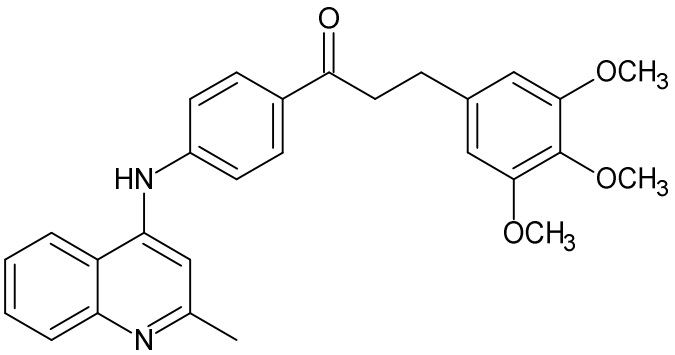
Atamjit *et al.,* (2021) synthesized a series of novel hydrazine-linked morpholinated isatin–quinoline hybrid compounds and biologically evaluated for their anti-breast cancer potential. The most potent compound, AS-4 (with a GI50 of 4.36 μM against MCF-7 cells), was found to induce mitotic arrest at the G2/M phase. These studies suggest that AS-4 has the capacity to completely block ERα. AS-4 as a promising lead compound for the future development of potent and safer anti-breast cancer agents.[22]



(AS-4)

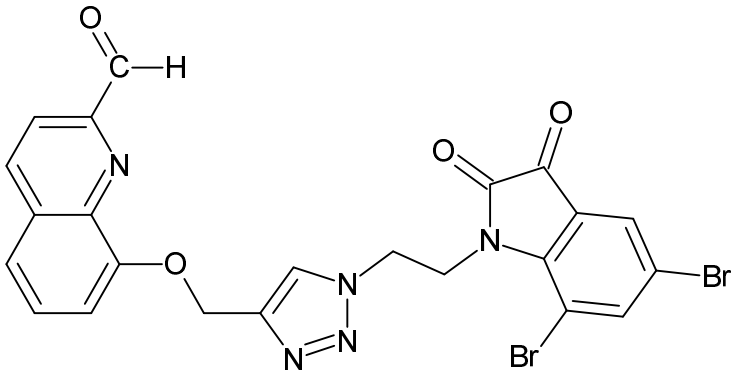
Yong-Feng *et al.,* (2021) synthesis of novel quinoline-chalcone derivatives, which were then evaluated for their antiproliferative effects against MGC-803, HCT-116, and MCF-7 cancer cell

lines among the synthesized compounds, compound 12e demonstrated superior inhibitory potency, achieving IC50 values of 1.38, 5.34, and 5.21 μM against MGC-803, HCT-116, and MCF-7 cells, respectively.[23]



(Compound 12e)

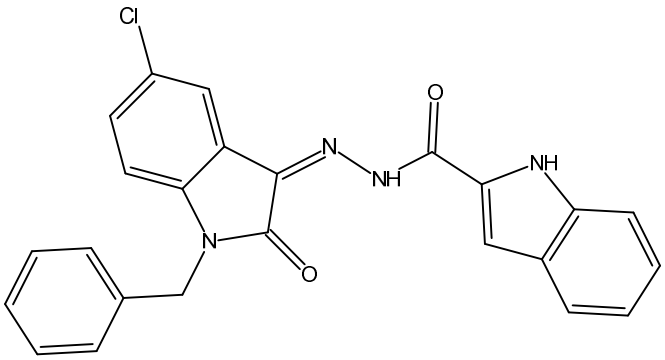
Paul Awolade *et al.*, (2020) synthesized 1*H*-1,2,3-triazole-linked quinoline-isatin molecular hybrids and evaluated their potential as drug candidates against breast cancer and MRSA. The research identified compounds 7g-i as the most potent cytotoxic agents against MCF-7 cells, and notably, compound 7h emerged as the best candidate against both MDA-MB-231 and MRSA cells. 1H-1,2,3-triazole-linked quinoline-isatin hybrids are viable chemotypes that can serve as templates for developing new anti-breast cancer and anti-MRSA agents.[24]



(Compound 7h)

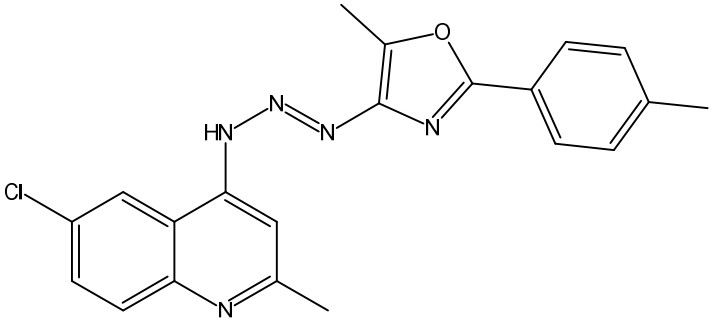
Al-wabli et al. (2020) reported the synthesis of some isatin-indole molecular hybrids 5a-g and the evaluation of their properties as antiproliferative agents against human breast (ZR-75), colon (HT-29), and lung (A-549) tumor cell line. The hybrid **5c** showed potent antiproliferative activity

with an IC50 value of 1.17 μM, which was approximately sevenfold greater than sunitinib, a well-known anticancer medication.[25]



5c

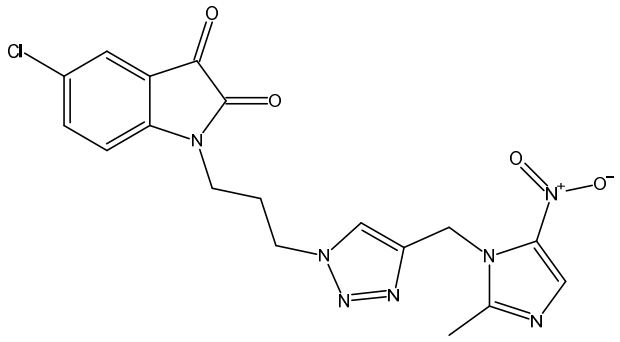
Shailesh R. Shah *et al.*, (2020) reported the combined effect of oxazole and quinoline components linked by an imine has been documented. In the quest for effective quinoline-derived anticancer agents, twelve hybrid compounds, designated as 4a-l, were synthesized. Among these, compound 4d demonstrated the greatest potency. Biological testing revealed that electron-donating groups, such as methyl and methoxy, on the phenyl group connected to the oxazole significantly influenced the anticancer activity.[26]



4d

Sumit Kumar *et al.*, (2018) A series of 1H-1,2,3-triazole-linked Imidazole–Isatin and Imidazole–Isatin–thiosemicarbazone conjugates were synthesized and tested for their antiproliferative effects on MCF-7 and MDA-MB-231 breast cancer cell lines. The study found that compounds with combination of longer alkyl chains as spacer and halogen substitutions on the isatin ring showed enhanced activity. Among them, compound 6g, which features a chloro-

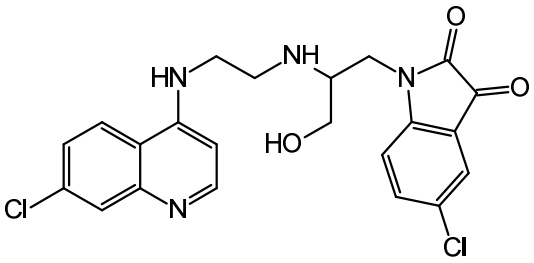
substituent at the C-5 position of the Isatin ring and a butyl spacer, exhibited the highest activity with IC_{50} values of 54.25 μM and 26.12 μM against MCF-7 and MDA-MB-231 cells, respectively, while also demonstrating low cytotoxicity.[27]



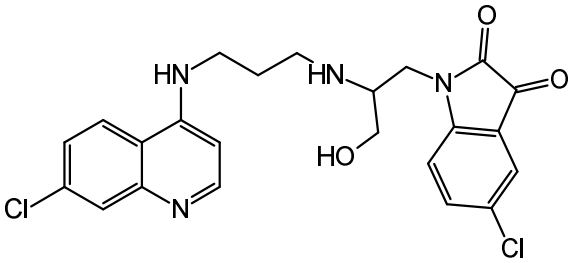
6g

2.3 Anti-malarial activity

Nisha *et al.*, (2014) synthesized a series of β-amino alcohol tethered 4-aminoquinoline-isatin conjugates. The research aimed to evaluate the antimalarial potential of these conjugates, particularly against drug-resistant strains and key findings revealed that two specific conjugates, 11b and 11f, demonstrated potent antimalarial efficacy comparable to Chloroquine.[28]

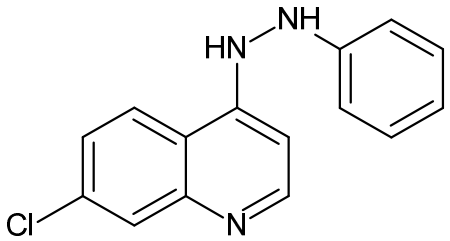


11b



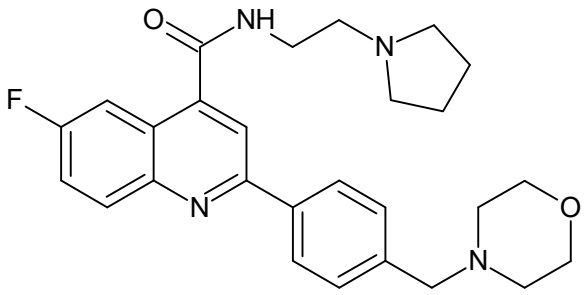
11f

Roberta Reis Soares *et al.*, (2015) investigated the antiplasmodial activity of ten novel synthetic quinoline derivatives, comprising five compounds linked to sulfonamide and five to hydrazine or hydrazide groups. When tested *in vivo*, the hydrazine derivative compound 1f showed antimalarial activity against blood parasites comparable to that of chloroquine.[29]



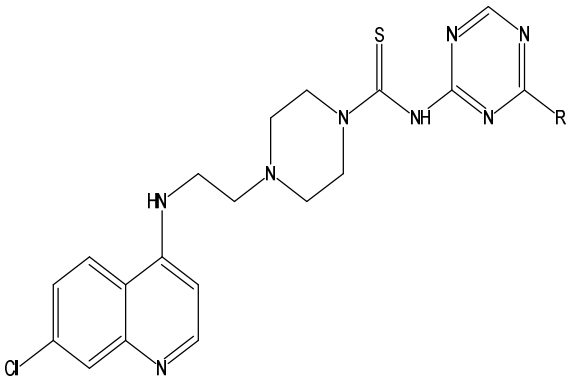
(Compound 1f)

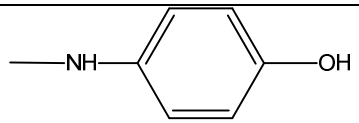
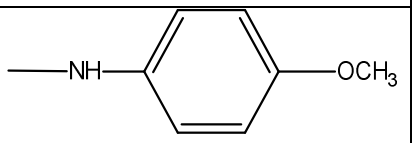
Beatriz Baragañ *et al.,* (2016) developed a series of quinoline-4-carboxamide derivatives, initially identified through a phenotypic screen against the blood stage of *Plasmodium falciparum* (3D7), has been developed for their antimalarial potential. Compound 2 (DDD107498) was advanced to preclinical development due to its favorable potency, selectivity, drug-metabolism and pharmacokinetic (DMPK) properties, efficacy, and a novel mechanism of action involving the inhibition of translation elongation factor 2 (PfEF2).[30]



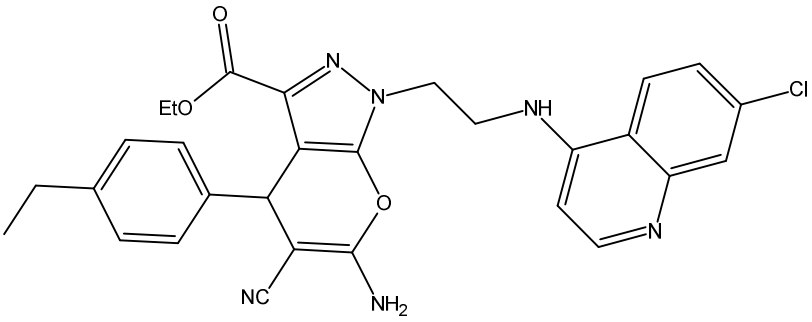
(Compound 2)

Hans Raj Bhat *et al.,* (2015) synthesized a series of novel hybrid 4-aminoquinoline 1,3,5-triazine derivatives through a five-step reaction and subsequently evaluated for their *in vitro* antimalarial activity against both chloroquine-sensitive (3D7) and chloroquine-resistant (RKL-2) strains of *Plasmodium falciparum* and two specific derivatives, 9a and 9c, exhibited good activity against both *P. falciparum* strains.[31]



COMPOUND	SUBSTITUENT
9a	
9c	

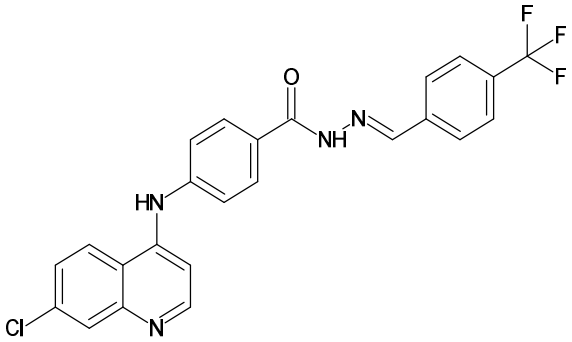
Shamsuddin *et al.*, (2021) synthesized a series of molecules by covalently linking pyrano [2,3-c] pyrazole and 4-aminoquinoline scaffolds via an ethyl linker. Among these, compound 4b emerged as a highly potent anti-plasmodial agent, demonstrating nanomolar efficacy against both chloroquine-sensitive (3D7) and chloroquine-resistant (K1) *P. falciparum* strains (EC50 values of 0.0130 ± 0.0002 µM and 0.02 ± 0.01 µM, respectively).[32]



(Compound 4b)

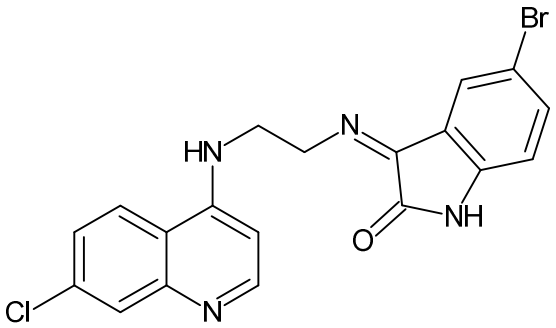
2.4 Anti-bacterial Activity

Ayesha *et al.*, (2024) synthesized and evaluated of novel 4-aminoquinoline-benzohydrazide-based molecular hybrids (HD1-23) and isatin warheads (HS1-12) as potential antibacterial agents**.** Compound HD6 emerged as particularly promising, demonstrating impressively low minimum inhibitory concentrations (MICs) ranging from 8–128 µg/mL against *B. subtilis*, *S. aureus*, and *P. aeruginosa* and a significant finding was the synergistic effect observed when HD6 was combined with ciprofloxacin.[33]



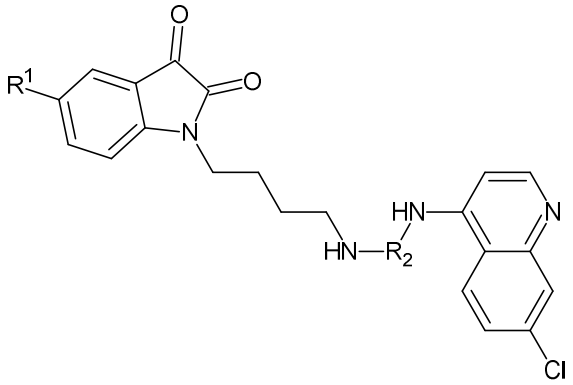
HD-6

Sakir *et al.*, (2025) investigated Schiff's bases (LT-SB1-23 and SB1-SB12) and novel quinoline-isatin hybrids were synthesized and microbiologically evaluated for their potential as antibacterial agents. In vitro screening revealed that many of these compounds exhibited significant antibacterial activity, achieving 90–100% inhibition at 200 µg/mL against various bacterial strains including *Escherichia coli*, *Enterococcus faecalis*, *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella typhi* among that one specific Schiff's base, LT-SB7, demonstrated potent synergistic activity against *E. coli* and *S. typhi*, leading to a 16–64-fold reduction in MIC values.[34]



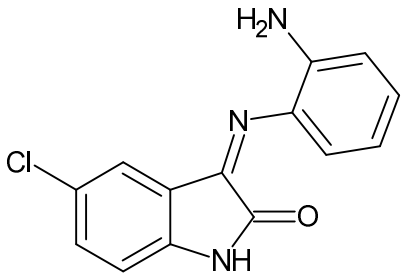
(LT-SB7)

Elshaymaa *et al.*, (2022) created new compounds called isatin–quinoline conjugates (10a–f and 11a–f) and tested them for antibacterial and anti-biofilm effects. All the compounds showed strong activity against harmful bacteria, with some being even more effective (lower MIC values) than standard antibiotics like chloramphenicol and ampicillin. Among them, 10a, 10b, and 10f worked best against all tested bacterial strains.[35]



	R1	R2
10a	H	0
10b	H	-$(CH_2)_2$-
10f	Br	-$(CH_2)_3$-

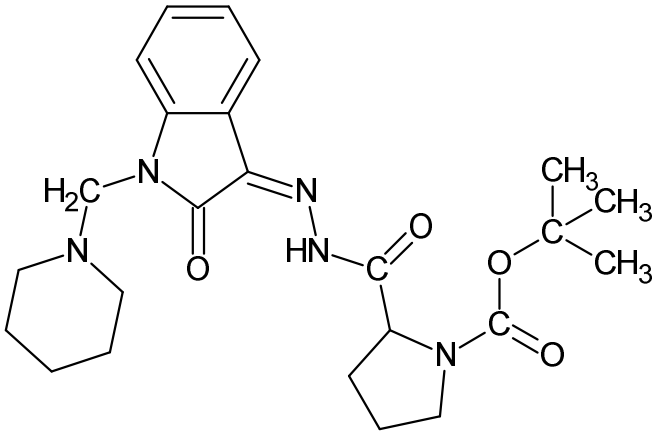
Sumitra *et al.*, (2023) synthesis and characterization of new Schiff base derivatives derived from isatin and *o*-phenylenediamine, utilizing both synthetic and microwave methods. Several novel isatin derivatives exhibited potent antimicrobial activity with compounds 3c, 3d, 6a, 6b, and 6d proving particularly effective. Notably, compound 3c demonstrated superior antimicrobial activity compared to the standard drug Amoxicillin against *Staphylococcus aureus* at a higher concentration (16 µg/mL) and against *Escherichia coli* at a lower concentration (1 µg/mL).[36]



3c

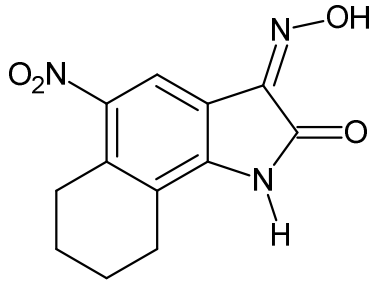
Jabbar *et al.*, (2018) studied condensation of isatin (2, 3-indolinendione) with piperidine (hexahydropyridine), hydrazine hydrate, and Boc-amino acids has produced a number of new isatin derivatives (3a–d) in quest of a novel antibacterial agent. Additionally, the well diffusion approach has been used to investigate the in vitro antibacterial capabilities against E. coli, P.

aeruginosa, Bacillus cereus, and S. aureus. According to compound comparisons, 3d was shown to be the most active compound.[37]



2.5 Anti-inflammatory activity

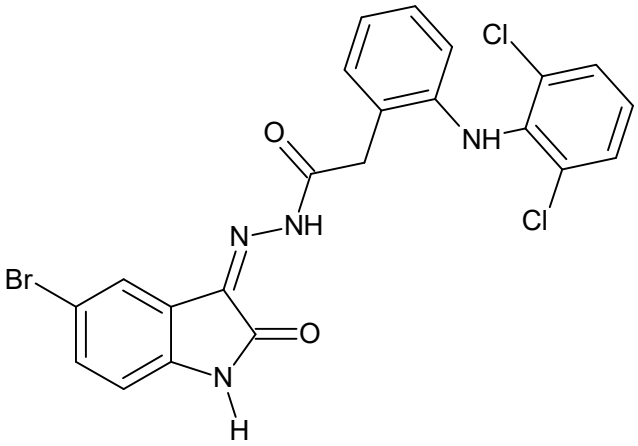
Alexander *et al.,* (2025) focused on the synthesis and evaluation of tricyclic isatin oxime derivatives, identifying compounds 5a and 5d as potent inhibitors of cellular inflammatory responses. Compound 5d (also known as NS-102) showed particular potency towards 12 kinases, such as DYRK1A, DYRK1B, PIM1, Haspin, HIPK1-3, IRAK1, NEK10, and DAPK1-3. Molecular modeling confirmed their binding interactions within the catalytic sites of DYRK1A and PIM1, suggesting that tricyclic isatin oximes represent promising candidates for developing anti-inflammatory and potentially neuroprotective drugs for neurodegenerative diseases.[38]



(Compound 5d)

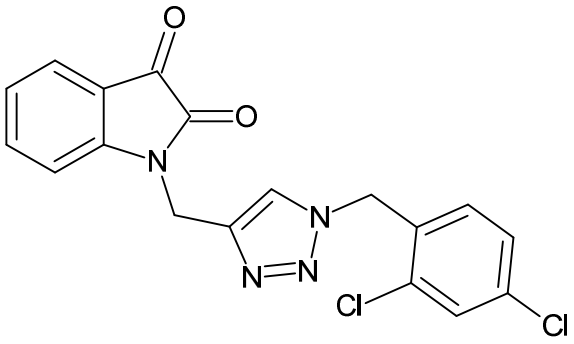
Ibrahim *et al.,* (2018) focused on developing novel non-steroidal anti-inflammatory drugs (NSAIDs) by designing and synthesizing various Diclofenac Schiff's bases (M1, M2, M4, M7,

and M8) through Schiff's condensation reactions. All synthesized compounds demonstrated anti-inflammatory activity comparable to Diclofenac, with compound M2 notably exhibiting the highest in vivo activity at 61.32% inhibition, surpassing Diclofenac's 51.36% inhibition.[39]



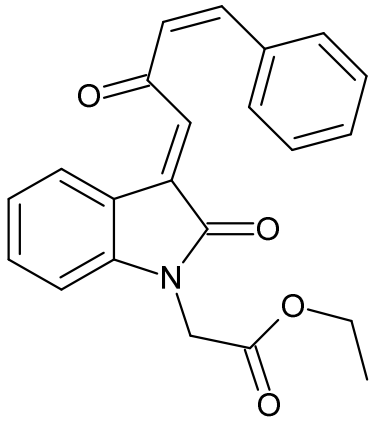
(Compound M2)

Niranjana kumar *et al.,* (2025) focused on designing and synthesizing a series of nine isatin-1,2,3-triazole conjugates, evaluating their anti-inflammatory potential in-vitro experiments. Specifically, these compounds were tested for their ability to reduce proinflammatory cytokine production in lipopolysaccharide (LPS)-induced human leukemia monocytic THP-1 cells. These findings suggest that isatin-1,2,3-triazole hybrid analogues, particularly compound 3e, are promising non-toxic and effective anti-inflammatory agents.[40]



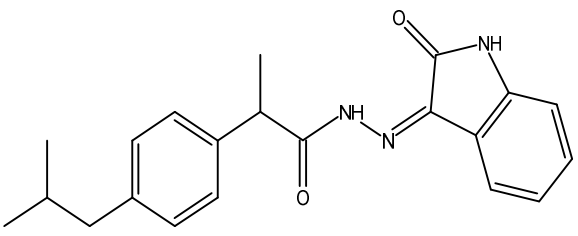
(Compound 3e)

Rongrong *et al.,* (2025) successfully designed and synthesized three series of novel isatin–chalcone hybrid derivatives, subsequently evaluating their anti-neuritis activities in BV2 microglial cells. Compound 4b emerged as the most potent, demonstrating an IC50 of 1.6 μM and a therapeutic index of 21.6. In silico molecular modeling indicated that compound 4b potentially binds to inflammation-related proteins such as TLR4/MD2 and p38. These findings position tricyclic isatin–chalcone hybrids, particularly compound 4b, as promising candidates for the development of anti-neuroinflammatory and neuroprotective agents.[41]

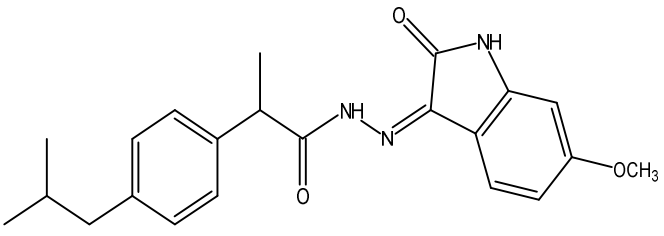


Compound 4b

Wassan F. Ismail *et al.,* (2022) this study focused on the synthesis of novel Ibuprofen-Isatin derivatives by linking Ibuprofen hydrazide with various isatin compounds through a condensation reaction. The resulting compounds were characterized using FTIR and 'H-NMR spectroscopy. Their anti-inflammatory activity was assessed by egg-white induced edema method, where compounds 5 and 6 showed greater activity than Ibuprofen (Standard compound).[42]



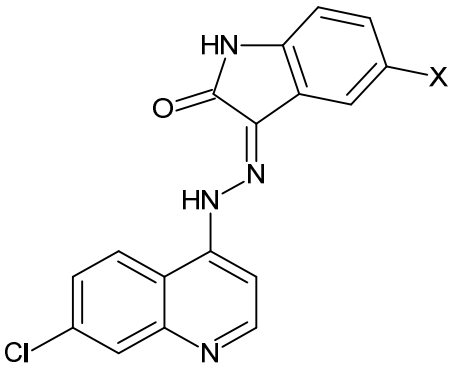
5



6

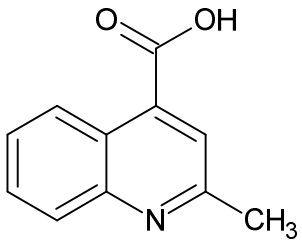
2.6 Anti-leishmanial activity

Ahmed *et al.*, (2022) synthesized twenty quinoline-isatin hybrids were synthesized and evaluated for their *in vitro* antileishmanial activity against *Leishmania major*. All synthesized compounds demonstrated promising activity against the promastigote form in a low micromolar range (IC50 = 0.5084–5.9486 μM), surpassing the effectiveness of the reference drug miltefosine (IC50 = 7.8976 μM). Compounds 4e, 4b, and 4f were identified as the most active against both promastigote and amastigote forms, and their mechanism of action was confirmed to be antifolate, targeting both dihydrofolate reductase-thymidylate synthase (DHFR-TS) and pteridine reductase 1 (PTR1).[43]



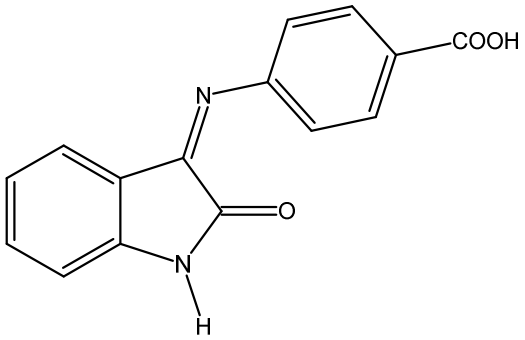
Compound	X
4e	5-Br
4b	5-F
4f	5-OCH_3

Mazin *et al.*, (2019) synthesized fifteen quinoline-4-carboxylic acids (Q1-Q15) using the Pfitzinger reaction from isatin derivatives and α-methyl ketones. All synthesized compounds were subsequently evaluated *in vitro* for their antileishmanial activity against *Leishmania donovani* promastigotes, with their half-maximal inhibitory concentrations (IC50) determined and compared to standard drugs. Compound Q1 (2-methylquinoline-4-carboxylic acid) emerged as the most active among the synthesized derivatives, demonstrating superior potency compared to positive controls like sodium stibogluconate and amphotericin B.[44]



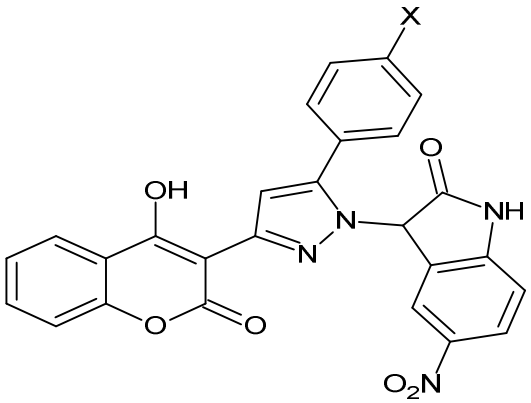
Q1

Farshid Hassanzadeh *et al.*, (2024) A series of N-alkyl-isatin-3-imino aromatic amine derivatives were synthesized and evaluated for their anticancer and anti-leishmanial potential. Among them, compounds 5c and 4d showed moderate cytotoxicity (IC = 50 μM), while compound 5b exhibited anti-leishmanial activity, particularly after 72 hours (IC30 41 μM). Molecular docking against the EGFR tyrosine kinase revealed strong binding for compound 4d (docking score: -7.33 kcal/mol), highlighting it as promising candidate for further development.[45]



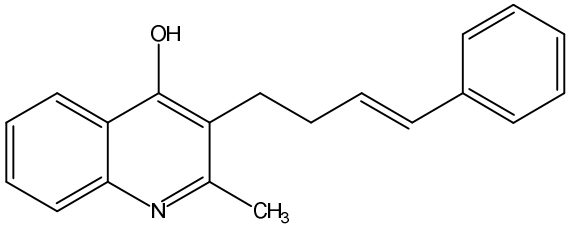
5b

Rasha Z. Batran *et al.*, (2025) focused on synthesizing and evaluating fifteen hybrid compounds (7a-c, 10a-j, and 13a-b) derived from 4-hydroxycoumarin and pyrazolyl indolin-2-one motifs. These compounds were assessed for their *in vitro* efficacy against *Leishmania major*, demonstrating remarkable activity against both promastigote and intracellular amastigote forms, notably surpassing the reference drug miltefosine (IC50 = 7.83 μM and 8.07 μM, respectively). Specifically, compounds 7a and 7b emerged as exceptionally potent against both parasitic forms and maintained favorable safety profiles.[46]



COMPOUND	X
7a	F
7b	Cl

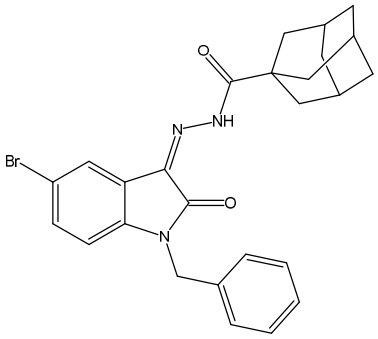
Andre´ Gustavo Tempone *et al.*, (2005) a study synthesized and evaluated four novel 3-substituted quinoline derivatives, with allyl and cinnamyl motifs, for their *in vitro* activity against *Leishmania chagasi.* Among these compounds, compound 3b (2-methyl-3-[(2E)-3-phenylprop-2-enyl]quinolin-4-ol) was identified as the most potent antileishmanial agent, exhibiting superior efficacy against both promastigote (IC50 0.091 μg/ml), proving 22-fold more effective than pentamidine, and intracellular amastigote forms (IC50 3.55 μg/ml), demonstrating 8.3-fold greater activity than pentavalent antimony.[47]



3b

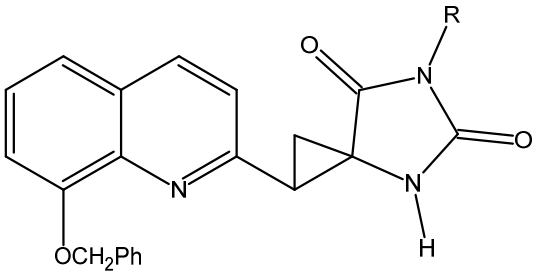
2.7 Anti-convulsant activity

Hind M. Osman *et al.*, (2021) In this study, six Schiff bases combining isatin and adamantane-1-carbohydrazide (compounds 18–23) were synthesized using molecular hybridization and evaluated for anticonvulsant activity in a PTZ-induced seizure model. All compounds showed significant protection, with compound 23 displaying the strongest effect by increasing seizure latency, reducing duration, and lessening neurological symptoms. Molecular docking pointed to the GABA-A receptor as a likely target, and ADME analysis confirmed compound 23's drug-like properties, identifying it as a promising lead for further anticonvulsant drug development.[48]



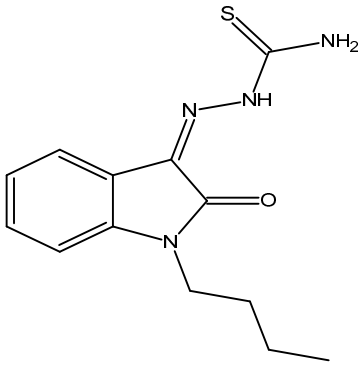
(Compound 23)

Xianran He *et al.*, (2011) focused on developing novel anticonvulsants, a series of sixteen new 1-(8-(benzyloxy) quinolin-2-yl)-6-substituted-4,6-diazaspiroheptane-5,7-diones was synthesized. hese compounds were evaluated for anticonvulsant activity and neurotoxicity using standard screening models, including the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) tests, with neurotoxicity assessed via the rotorod test. Among the synthesized compounds, two (compounds 8e and 8j) demonstrated particularly promising anticonvulsant properties in both seizure models.[49]

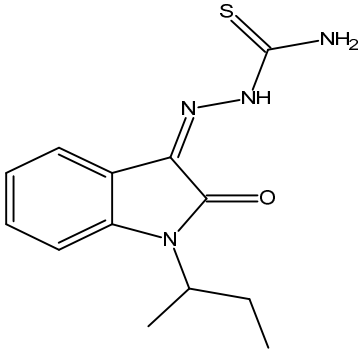


Compound	R
8e	CH3CH2(CH2OH)CH
8j	4-NO2C6H4

Masoumeh Divar *et al*., (2017) researchers synthesized 14 Isatin-based semicarbazone and thiosemicarbazone derivatives and evaluated their anticonvulsant activity in rodent models. In PTZ-induced seizures in mice, compounds b, d, f, i, j, k, l, m, and n delayed seizure onset and extended survival. In a chronic kindling model in rats, derivatives k and n notably prevented seizures and improved motor coordination. These results highlight the potential of Isatin derivatives as promising anticonvulsant agents.[50]

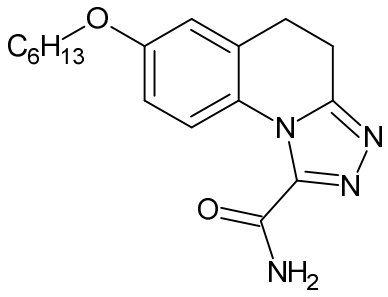


k



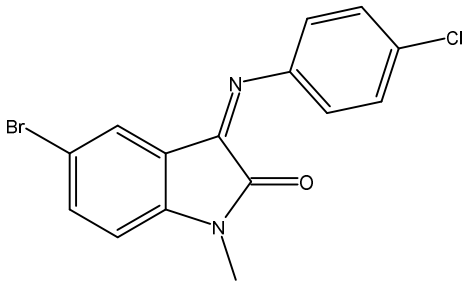
n

Cheng-Xi Wei *et al.*, (2010) study focused on synthesizing and evaluating the anticonvulsant activity of 1-formamide-triazolo[4,3-a]quinoline derivatives (6a-6n), a class of compounds inspired by the presence of the carboxamide group, which is considered a key functional unit in traditional anticonvulsant drugs like Carbamazepine and Rufinamide. Initial pharmacological testing using the Maximal Electroshock Seizure (MES) test indicated that all tested compounds were active and capable of preventing seizure spread. The results demonstrated that compound 7-(hexyloxy)-4,5-dihydro-[1,2,4] triazolo[4,3-a]quinoline-1-carboxamide (6d) was the most active one and also had the lowest toxicity.[51]



6d

Manjusha Verma *et al*., (2004) A series of Schiff bases derived from N-methyl and N- acetyl isatin with various aryl amines were synthesized and evaluated for anticonvulsant activity using MES and ScMet models. Among them, N-methyl-5-bromo-3-(p- chlorophenylimino) isatin (compound 2) showed significant activity in both models with an LD_{50} exceeding 600 mg/kg, outperforming standard drugs like phenytoin, carbamazepine, and valproic acid. These results suggest that compound 2 holds promise as a lead candidate for developing new anticonvulsant agents.[52]



(Compound 2)

REFERENCES:

1. Joule JA, Mills K. *Heterocyclic Chemistry*. 5th ed. Wiley; 2010.
2. O'Neill PM, Bray PG, Hawley SR, Ward SA, Park BK. 4-Aminoquinolines—past, present, and future: a chemical perspective. *Pharmacol Ther.* 1998;77(1):29–58.
3. Vine KL, Matesic L, Locke JM, Ranson M, Skropeta D. Recent highlights in the development of isatin-based anticancer agents. *Bioorg Med Chem.* 2009;17(8):2950–2961.
4. Nepali K, Sharma S, Sharma M, Bedi PMS, Dhar KL. Rational approaches, design strategies, structure–activity relationship and mechanistic insights for anticancer hybrids. *Eur J Med Chem.* 2014;77:422–487.
5. Verma M, Pandeya SN, Singh KN, Stables JP. Anticonvulsant activity of Schiff bases of isatin derivatives. *Acta Pharm.* 2004;54(1):49–56.
6. Khaleel, Eman F., Ahmed Sabt, Malgorzata Korycka-Machala, Rehab Mustafa Badi, Ninh The Son, Nguyen Xuan Ha, Mohamed Farouk Hamissa et al. "Identification of new anti-mycobacterial agents based on quinoline-isatin hybrids targeting enoyl acyl carrier protein reductase (InhA)." *Bioorganic Chemistry* 144 (2024): 107138.
7. Gandhi, Priyanka V., Shubham R. Burande, Manoj S. Charde, and Rita D. Chakole. "A review on isatin and its derivatives: synthesis, reactions and applications." *Journal of Advanced Scientific Research* 12, no. 04 (2021): 1-11.
8. Hu, Yuan-Qiang, Ling-Dan Meng, Min Qiang, and Xu-Feng Song. "Design, synthesis, and in vitro anti-mycobacterial evaluation 1H-1, 2, 3-triazole-tethered ciprofloxacin and isatin conjugates." *Journal of Heterocyclic Chemistry* 54, no. 6 (2017): 3725-3729.
9. Maddela, Srinubabu, and Ajitha Makula. "Design, synthesis and docking study of some novel isatin-quinoline hybrids as potential antitubercular agents." *Anti-Infective Agents* 14, no. 1 (2016): 53-62.
10. Sriram, Dharmarajan, Alexandra Aubry, Perumal Yogeeswari, and L. M. Fisher. "Gatifloxacin derivatives: synthesis, antimycobacterial activities, and inhibition of *Mycobacterium tuberculosis* DNA gyrase." *Bioorganic & medicinal chemistry letters* 16, no. 11 (2006): 2982-2985.
11. Gao, Feng, Lei Ye, Yabin Wang, Fangong Kong, Shijia Zhao, Jiaqi Xiao, and Gang Huang. "Benzofuran-isatin hybrids and their in vitro anti-mycobacterial activities against multi-

drug-resistant *Mycobacterium tuberculosis*." *European journal of medicinal chemistry* 183 (2019): 111678.

12. Wang, Ruo, Xueyang Yin, Yaohuan Zhang, and Weitao Yan. "Design, synthesis and antimicrobial evaluation of propylene-tethered ciprofloxacin-isatin hybrids." *European Journal of Medicinal Chemistry* 156 (2018): 580-586.
13. Abdelrahman, Mohamed A., Hadia Almahli, Tarfah Al-Warhi, Taghreed A. Majrashi, Marwa M. Abdel-Aziz, Wagdy M. Eldehna, and Mohamed A. Said. "Development of novel isatin-tethered quinolines as anti-tubercular agents against multi and extensively drug-resistant *mycobacterium tuberculosis*." *Molecules* 27, no. 24 (2022): 8807.
14. Raj, Raghu, Christophe Biot, Séverine Carrère-Kremer, Laurent Kremer, Yann Guérardel, Jiri Gut, Philip J. Rosenthal, Delphine Forge, and Vipan Kumar. "7-Chloroquinoline–isatin Conjugates: Antimalarial, antitubercular, and cytotoxic evaluation." *Chemical Biology & Drug Design* 83, no. 5 (2014): 622-629.
15. Sabt, Ahmed, Maha-Hamadien Abdulla, Manal S. Ebaid, Jakub Pawełczyk, Hayam A. Abd El Salam, Ninh The Son, Nguyen Xuan Ha et al. "Identification of 2-(N-aryl-1, 2, 3-triazol-4-yl) quinoline derivatives as antitubercular agents endowed with InhA inhibitory activity." *Frontiers in Chemistry* 12 (2024): 1424017.
16. Liu, Chun-Xiu, Xin Zhao, Lei Wang, and Zai-Chang Yang. "Quinoline derivatives as potential anti-tubercular agents: Synthesis, molecular docking and mechanism of action." *Microbial Pathogenesis* 165 (2022): 105507.
17. Johansen, Matt D., Shalini, Sumit Kumar, Clement Raynaud, Diana H. Quan, Warwick J. Britton, Philip M. Hansbro, Vipan Kumar, and Laurent Kremer. "Biological and biochemical evaluation of isatin-isoniazid hybrids as bactericidal candidates against *Mycobacterium tuberculosis*." *Antimicrobial agents and chemotherapy* 65, no. 8 (2021): 10-1128.
18. Aboul-Fadl, Tarek, Mohammed K. Abdel-Hamid, and Adel F. Youssef. "Schiff bases of indoline-2, 3-dione (isatin) derivatives as efficient agents against resistant strains of *Mycobacterium tuberculosis*." *Der Pharma Chem* 7 (2015): 217-225.
19. Development of novel isatin–nicotinohydrazide hybrids with potent activity against susceptible/resistant *Mycobacterium tuberculosis* and bronchitis causing–bacteria

20. Nippu, B. N., Abdul Rahman, H. M. Kumaraswamy, and N. D. Satyanarayan. "Design and synthesis of novel tetrazolo quinoline bridged isatin derivatives as potential anticancer leads against MIA PaCa-2 human pancreatic cancer cell line." *Journal of Molecular Structure* 1263 (2022): 133103.
21. Taghour, Mohammed S., Hazem Elkady, Wagdy M. Eldehna, Nehal El-Deeb, Ahmed M. Kenawy, Abeer E. Abd El-Wahab, Eslam B. Elkaeed, Bshra A. Alsfouk, Ahmed M. Metwaly, and Ibrahim H. Eissa. "Discovery of new quinoline and isatine derivatives as potential VEGFR-2 inhibitors: design, synthesis, antiproliferative, docking and MD simulation studies." *Journal of Biomolecular Structure and Dynamics* 41, no. 21 (2023): 11535-11550.
22. Singh, Atamjit, Harneetpal Kaur, Saroj Arora, and Preet Mohinder Singh Bedi. "Design, synthesis, and biological evaluation of novel morpholinated isatin–quinoline hybrids as potent anti-breast cancer agents." *Archiv der Pharmazie* 355, no. 2 (2022): 2100368.
23. Guan, Yong-Feng, Xiu-Juan Liu, Xin-Ying Yuan, Wen-Bo Liu, Yin-Ru Li, Guang-Xi Yu, Xin-Yi Tian et al. "Design, synthesis, and anticancer activity studies of novel quinoline-chalcone derivatives." *Molecules* 26, no. 16 (2021): 4899.
24. Awolade, Paul, Nosipho Cele, Oluwakemi Ebenezer, Nagaraju Kerru, Lalitha Gummidi, Liang Gu, Gabriella Palma, Mandeep Kaur, and Parvesh Singh. "Synthesis of 1H-1, 2, 3-triazole-linked quinoline-isatin molecular hybrids as anti-breast cancer and anti-methicillin-resistant Staphylococcus aureus (MRSA) agents." *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)* 21, no. 10 (2021): 1228-1239.
25. Al-Wabli, Reem I., Aliyah A. Almomen, Maha S. Almutairi, Adam B. Keeton, Gary A. Piazza, and Mohamed I. Attia. "New isatin–indole conjugates: Synthesis, characterization, and a plausible mechanism of their in vitro antiproliferative activity." *Drug Design, Development and Therapy* (2020): 483-495.
26. Shah, S. R., K. D. Katariya, and D. Reddy. *Quinoline-1, 3-oxazole hybrids: Syntheses, anticancer activity, and molecular docking studies. ChemistrySelect, 2020, 5 (3), 1097-1102*.
27. Kumar, Sumit, Sourav Taru Saha, Liang Gu, Gabriella Palma, Shanen Perumal, Ashona Singh-Pillay, Parvesh Singh, Amit Anand, Mandeep Kaur, and Vipan Kumar. "1 H-1, 2,

3-Triazole Tethered Nitroimidazole–Isatin Conjugates: Synthesis, Docking, and Anti-Proliferative Evaluation against Breast Cancer." *ACS omega* 3, no. 9 (2018): 12106-12113.

28. Gut, Jiri, Philip J. Rosenthal, and Vipan Kumar. "β-amino-alcohol tethered 4-aminoquinoline-isatin conjugates: Synthesis and antimalarial evaluation." *European journal of medicinal chemistry* 84 (2014): 566-573.
29. Soares, Roberta Reis, José Marcio Fernandes da Silva, Bianca Cecheto Carlos, Camila Campos da Fonseca, Laila Salomé Araújo de Souza, Fernanda Valério Lopes, Rafael Mafra de Paula Dias et al. "New quinoline derivatives demonstrate a promising antimalarial activity against Plasmodium falciparum in vitro and Plasmodium berghei in vivo." *Bioorganic & medicinal chemistry letters* 25, no. 11 (2015): 2308-2313.
30. Baragana, Beatriz, Neil R. Norcross, Caroline Wilson, Achim Porzelle, Irene Hallyburton, Raffaella Grimaldi, Maria Osuna-Cabello et al. "Discovery of a quinoline-4-carboxamide derivative with a novel mechanism of action, multistage antimalarial activity, and potent in vivo efficacy." *Journal of medicinal chemistry* 59, no. 21 (2016): 9672-9685.
31. Bhat, Hans Raj, Udaya Pratap Singh, Anjali Thakur, Surajit Kumar Ghosh, Kabita Gogoi, Anil Prakash, and Ramendra K. Singh. "Synthesis, antimalarial activity and molecular docking of hybrid 4-aminoquinoline-1, 3, 5-triazine derivatives." *Experimental Parasitology* 157 (2015): 59-67.
32. Shamsuddin, Mohd Asyraf, Amatul Hamizah Ali, Nur Hanis Zakaria, Mohd Fazli Mohammat, Ahmad Sazali Hamzah, Zurina Shaameri, Kok Wai Lam et al. "Synthesis, molecular docking, and antimalarial activity of hybrid 4-aminoquinoline-pyrano [2, 3-c] pyrazole derivatives." *Pharmaceuticals* 14, no. 11 (2021): 1174.
33. Ubaid, Ayesha, Mohd Shakir, Asghar Ali, Sobia Khan, Jihad Alrehaili, Razique Anwer, and Mohammad Abid. "Synthesis and structure–activity relationship (SAR) studies on new 4-aminoquinoline-hydrazones and isatin hybrids as promising antibacterial agents." *Molecules* 29, no. 23 (2024): 5777.
34. Shakir, Mohd, Asghar Ali, Swati Lakshmi, Manika Garg, Haider Thaer Abdulhameed Almuqdadi, Iram Irfan, Mohan Kamthan et al. "Synthesis and mechanistic studies of 4-aminoquinoline-Isatin molecular hybrids and Schiff's bases as promising antimicrobial agents." *European Journal of Medicinal Chemistry* 283 (2025): 117127.

35. Elmongy, Elshaymaa I., Abdullah AS Ahmed, Ibrahim El Tantawy El Sayed, Ghady Fathy, Hanem M. Awad, Ayah Usama Salman, and Mohamed A. Hamed. "Synthesis, Biocidal and Antibiofilm Activities of New Isatin–Quinoline Conjugates against Multidrug-Resistant Bacterial Pathogens along with Their In Silico Screening." *Antibiotics* 11, no. 11 (2022): 1507.
36. Nain, Sumitra, Garima Mathur, Tulika Anthwal, Swapnil Sharma, and Sarvesh Paliwal. "Synthesis, characterization, and antibacterial activity of new isatin derivatives." *Pharmaceutical Chemistry Journal* 57, no. 2 (2023): 196-203.
37. Jabbar, Sarrah Sattar. "Synthesis, characterization and antibacterial activity of carbamate derivatives of isatin." *Oriental Journal of Chemistry* 34, no. 4 (2018): 2026.
38. Uvarov, Alexander V., Igor A. Schepetkin, Mark T. Quinn, and Andrei I. Khlebnikov. "Tricyclic Isatin Derivatives as Anti-Inflammatory Compounds with High Kinase Binding Affinity." *Molecules* 30, no. 14 (2025): 2914.
39. Ibrahim, Musab Mohamed, Tilal Elsaman, and Mosab Yahya Al-Nour. "Synthesis, Anti-Inflammatory Activity, and In Silico Study of Novel Diclofenac and Isatin Conjugates." *International journal of medicinal chemistry* 2018, no. 1 (2018): 9139786.
40. Niranjana Kumar, A., S. R. Das, J. K. Kumar, K. V. N. S. Srinivas, and S. D. Tetalib. *Design and development of an isatin-1, 2, 3-triazole hybrid analogue as a potent anti-inflammatory agent with enhanced efficacy and gene expression modulation. RSC Adv. 15, 2023–2033*. 2025.
41. Wang, Rongrong, Zhili Zhang, Wei Jiang, Junyi Liu, Chao Tian, and Meng Wang. "Novel Isatin–Chalcone Hybrid Molecules: Design, Synthesis and Anti-Neuroinflammatory Activity Evaluation." *Molecules* 30, no. 7 (2025): 1421.
42. Ismail, Wassan F., May Mohammed Jawad Al-Mudhafar, and Ammar A. Fadhil. "Synthesis, characterization of new isatin-ibuprofen derivatives with expected biological activity." (2022).
43. Sabt, Ahmed, Wagdy M. Eldehna, Tamer M. Ibrahim, Adnan A. Bekhit, and Rasha Z. Batran. "New antileishmanial quinoline linked isatin derivatives targeting DHFR-TS and PTR1: Design, synthesis, and molecular modeling studies." *European Journal of Medicinal Chemistry* 246 (2023): 114959.

44. Abdelwahid, Mazin AS, Tilal Elsaman, Malik S. Mohamed, Sara A. Latif, Moawia M. Mukhtar, and Magdi A. Mohamed. "Synthesis, characterization, and antileishmanial activity of certain quinoline-4-carboxylic acids." *Journal of Chemistry* 2019, no. 1 (2019): 2859637.
45. Hassanzadeh, Farshid, Seyed Hossein Hejazi, Elham Jafari, and Hojjat Sadeghi-aliabadi. "Molecular docking and synthesis of N-alkyl-isatin-3-imino aromatic amine derivatives and their antileishmanial and cytotoxic activities." *Research in Pharmaceutical Sciences* 19, no. 2 (2024): 238-250.
46. Batran, Rasha Z., Manal S. Ebaid, Sherry N. Nasralla, Ninh The Son, Nguyen Xuan Ha, Hoda Atef Abdelsattar Ibrahim, Mahmoud Abdelrahman Alkabbani et al. "Synthesis and mechanistic insights of Coumarinyl-Indolinone hybrids as potent inhibitors of Leishmania major." *European Journal of Medicinal Chemistry* 288 (2025): 117392.
47. Tempone, André Gustavo, Ana Cláudia Melo Pompeu da Silva, Carlos Alberto Brandt, Fernanda Scalzaretto Martinez, Samanta Etel Treiger Borborema, Maria Amélia Barata da Silveira, and Heitor Franco de Andrade Jr. "Synthesis and antileishmanial activities of novel 3-substituted quinolines." *Antimicrobial agents and chemotherapy* 49, no. 3 (2005): 1076-1080.
48. Osman, H.M., Elsaman, T., Yousef, B.A., Elhadi, E., Ahmed, A.A., Eltayib, E.M., Mohamed, M.S. and Mohamed, M.A., 2021. Schiff Bases of Isatin and Adamantane-1-Carbohydrazide: Synthesis, Characterization and Anticonvulsant Activity. *Journal of Chemistry*, *2021*(1), p.6659156.
49. He, Xianran, Min Zhong, Tao Zhang, Jin Yang, Zhongyuan Wu, Yuling Xiao, Hao Guo, Guofu Qiu, and Xianming Hu. "Synthesis and anticonvulsant activity of 1-(8-(benzyloxy) quinolin-2-yl)-6-substituted-4, 6-diazaspiro [2, 4] heptane-5, 7-diones." *European journal of medicinal chemistry* 48 (2012): 338-346.
50. Divar, Masoumeh Masoumeh, Yasaman Yeganeh, Akram Jamshidzadeh, Soghra Khabnadideh, and Reza Heidari. "Anticonvulsant activity of some semicarbazone and thiosemicarbazone derivatives of isatin on PTZ induced seizure." *Journal of Innovations in Applied Pharmaceutical Science (JIAPS)* (2017): 04-14.

51. Wei, Cheng-Xi, Xian-Qing Deng, Kyu-Yun Chai, Zhi-Gang Sun, and Zhe-Shan Quan. "Synthesis and anticonvulsant activity of 1-formamide-triazolo [4, 3-a] quinoline derivatives." *Archives of pharmacal research* 33, no. 5 (2010): 655-662.
52. Verma, Manjusha, Surendra Nath Pandeya, Krishna Nand Singh, and James P. Stables. "Anticonvulsant activity of Schiff bases of isatin derivatives." *Acta Pharmaceutica* 54, no. 1 (2004): 49-56.