IJPSR (2024), Volume 15, Issue 10 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 27 March 2024; received in revised form, 22 May 2024; accepted, 24 May 2024; published 01 October 2024

SYNERGISTIC CONVERGENCE: EXPLORING COMBINATIONS OF DIVERSE PHYSIOLOGICAL ACTIVITIES - A REVIEW

Sakshi Nandkumar Patil [* 1], Vaishali Nagulwar [1] and Sanket Nandkumar Patil [2]

Department of Pharmaceutical Chemistry [1], Government College of Pharmacy, Chh. Sambhajinagar - 431005, Maharashtra, India.
H. R. Patel Institute of Pharmaceutical Education and Research [2], Shirpur, Dhule - 425405, Maharashtra, India.

Keywords:

Chalcone, Isatin, Ferrocene, Structural activity relationship, Pharmacological activities

Correspondence to Author:
Sakshi Nandkumar Patil

Student,
Department of Pharmaceutical Chemistry, Government College of Pharmacy, Chh. Sambhajinagar - 431005, Maharashtra, India.

E-mail: Sakshipatil112000@gmail.com

ABSTRACT: The development of effective therapeutic strategies for various remedial conditions often involves the exploration of synergistic interaction between two pharmacophores. The most frequent methods for multidrug therapy combining two or more active ingredients into a single, and creating hybrid molecular entities that can modulate numerous targets interaction gives a synergistic effect. As a result, the structural activity relationship is becoming more and more common in the form of hybrid molecules (multiple ligand approach) such as chalcone-isatin, ferrocene-isatin as well as ferrocene-chalcone combinations possesses multiple biological properties such as antitubercular, anticancer, antibacterial, Antimalarial, anti-inflammatory which having synergistic activity due to their combination as well as their substitutions like electron donating and withdrawing group. The evaluation of synergistic drug combinations offers promise in overcoming challenges such as drug resistance, dose-dependent toxicity, and suboptimal treatment responses. To determine the significance of the notion of molecular hybridization, the pharmacological potency of the hybrid molecules is compared to those of their separate counterparts. This review underscores the promising role of chalcone-isatin, ferrocene-isatin and ferrocene-chalcone hybrids as versatile agents with a broad spectrum of physiological activities. These compounds offer a myriad of opportunities for innovative drug design and development, making them a captivating area of research in modern pharmacology and medicinal chemistry as well as they give a synergistic effect on different target systems.

INTRODUCTION: The molecules must be specifically designed in order to optimise various properties. The most popular chemical entities to work on for developing modified scaffolds with much improved and amazing properties in the area of biology as well as medicinal science are the hybrid molecules, obtained by the combination of structural features of two differently active fragments.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.15(10).2875-94

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.15(10).2875-94

Since it is always advantageous to modify a known pharmacophore for the development of a new drug, hybrid molecules are obtained by combining structural features of two known pharmacophores. Combining two molecular entities displays peculiar characteristics and is derived from the naturally occurring variety of scaffolds with various biological profiles [1].

The synthesis of hybrid molecules and the assessment of these compounds as potent drugs and diverse pharmacological agents have been steadily increasing during the last twenty years. Significant work has been put into creating novel tactics to combat medication resistance and increase specificity [2]. Heterocyclic compounds are a

significant class of chemical compounds with notable biological and pharmacological effects [3, 4]. The hybridization of the chalcone and ferrocene nucleus moiety with other anticancer pharmacophores such as is a tin represents a promising strategy to develop novel anticancer agents with high efficacy as well as other biological activities such as antitubercular, anthelmintic, antibacterial, analgesic, and anti-inflammatory. Each sort of pharmacological entity is broken down into two main subsections, one of which includes just synthetically created pharmacophoric groups and the other of which include hybrids manufactured from natural product pharmacophores. The purpose of this review was to provide a concise summary of the most recent research on the synthesis and assessment of hybrid molecules for various drug classes and to assist the entire scientific community (both seasoned researchers and newcomers) in creating and developing better pharmacological entities. Hybrid molecules not only have more advantageous properties such as enhanced activity and improved specificity, but also could overcome drug resistance. Overall, chalcone and isatin conjugation as well as ferrocene and chalcone conjugation has resulted in the creation of substances with enhanced biological activities and fewer difficulties when compared to their distinct use [5, 6].

Chalcone: According to their chemical makeup, chalcones, also known as 1,3-diaryl-2-propen-1-ones, are open-chain flavonoids in which the two aromatic rings are connected by a three-carbon, α–β-unsaturated carbonyl system. Many chalcones that are found in nature have polyhydroxylated aryl ring [7]. The Greek word Chalcos, which means bronze, is where the word Chalcone comes from. Chalcones can exist in both cis and trans isomeric forms, with the trans form having the advantage thermodynamically. However, since removal of this structural component results in a loss of bioactivity, it is likely that the common, α- β-unsaturated ketone moiety is what is responsible for the diverse biological activities seen. New bioactive chalcone-like compounds have been created by modifying both rings while leaving this moiety alone [8]. Multiple functional group-containing chalcones displayed a broad range of biological activity, including antibacterial [9–11], antimalarial [12, 13], antitumor [14, 15], anti-inflammatory [16], antiprotozoal [17], anti-HIV [18], anti – oxidant [19, 20], and antiulcer [21] properties. Additionally, antioxidant, antibacterial, anticancer, and anti-malarial properties of chalcones and their analogues had been discovered [22, 23].

Synthetic pathway for Chalcone:

Heck Coupling: As shown in **Fig. 1** [24] creation of chalcones by combining aryl boronic acids and aryl vinyl ketones over the creation of C-C bonds. Under catalytic circumstances, aryl vinyl ketones are combined with aryl iodides or aryl boronic acids to create chalcone derivatives in exceptional yields (Pd $(ODAC)_2$, Ph_3P, K_2CO_3, DMF). Using palladium catalysts, aryl halides were carbonylative vinylated with styrene in the presence of carbon monoxide to produce chalcones [25].

Suzuki-Miyaura Coupling: Another more noteworthy metal-catalysed cross-coupling process is the Suzuki-Miyaura coupling, which produces chalcones from two chemical components that are electrically divergent [26]. According to a number of chalcones were produced by combining cinnamoyl chloride with different aryl boronic acids while using Pd $(PPh_3)_4$, Cs_2CO_3, and anhydrous toluene in an argon environment. However, the yields were only average [27].

Friedel-Crafts Acylation: This approach, which is extremely uncommon, was utilised to produce 3 highly substituted chalcones. Using Friedel-Crafts acylation with a Lewis acid catalyst, Shotter *et al.* (1978) created chalcones. Chalcones are produced via cinnamoyl chloride's acylation of aromatic ethers in the presence of a potent Lewis acid catalyst, $AlCl_3$ [28].

Witting Olefination: Chalcones were produced in THF over 30 hours at reflux or for three days in benzene at reflux using triphenyl benzoyl methylene phosphorane and benzaldehyde (Ramirez and Dershowitz 1957). Additionally, Xu *et al.* (1995) reported employing Witting olefination over a5- or 6-minute reaction period to synthesise chalcones with exceptional yields [29].

Sonogashira Isomerization Coupling: In a boiling mixture of trimethylamine and THF, under inert gas conditions, over 16–24 hours, coupling of terminal alkynes with aryl halides while using a

palladium catalyst paired with a co-catalytic quantity of CuI [30].

Julia–Kocienski Olefination: A novel Julia coupling reagent, heteroaryl sulfonyl phenylethanone, and aromatic aldehydes were condensed in a basic media to produce a variety of chalcones. Undec-7-ene (DBU) and 1,8-Diazabicyclo (benzo[d]thiazol-2yl-sulfonyl) for the creation of chalcones by Julia-Kocienski olefination, phenylethanone is the ideal base and Julia reagent pair (in **Fig. 1**) [31].

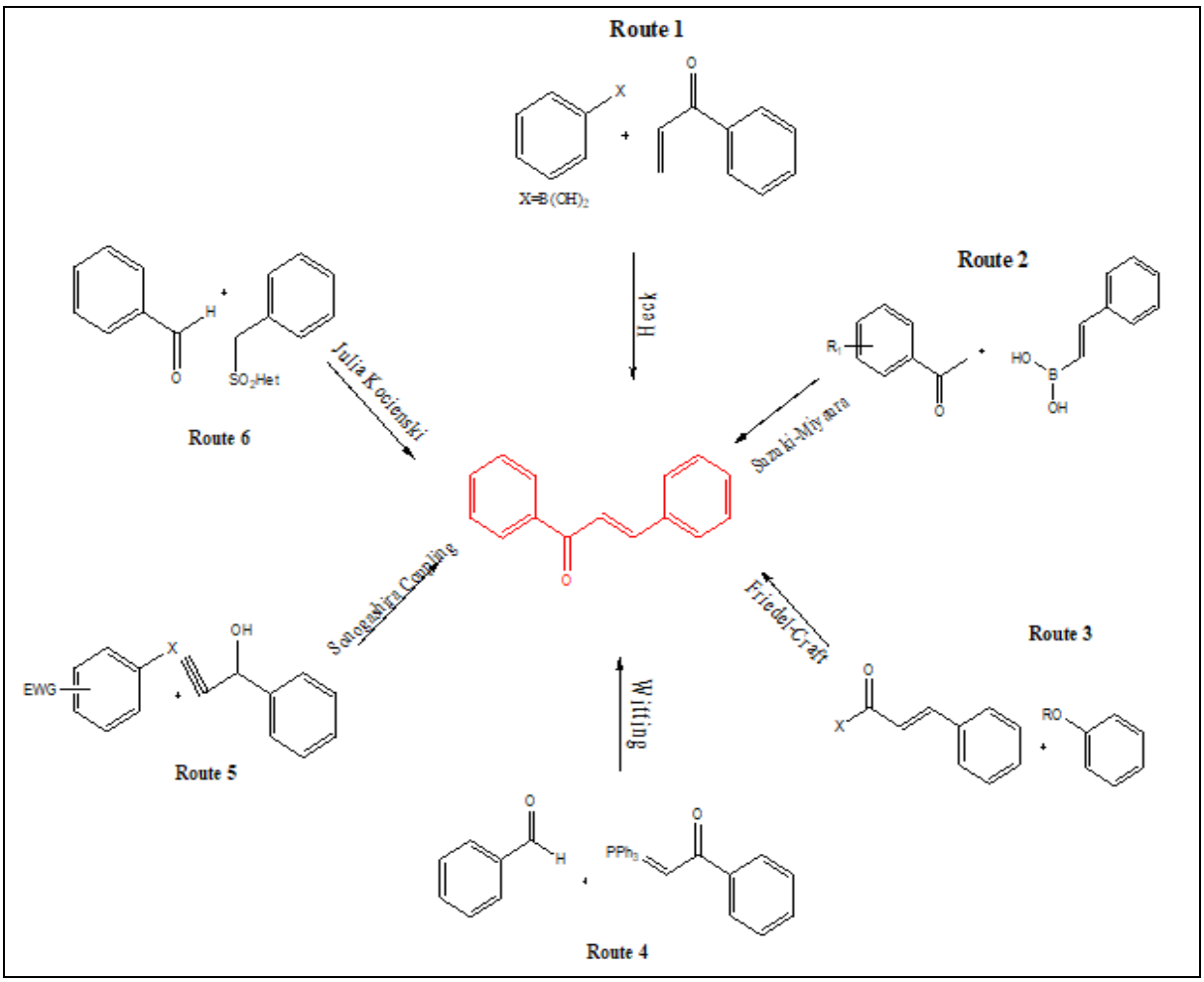

FIG. 1: SYNTHETIC PATHWAYS OF CHALCONE

Isatin: Isatin (1-indole-2,3-dione), a nitrogen-containing heterocyclic molecule also known as indole quinine and indenedione, stands out as a privileged moiety with a variety of biological activities and is regarded as a bio-active heterocyclic moiety. Isatin is a structural mixture of a nitrogen-containing five-membered ring and a six-membered benzene ring. One ring is aromatic while the other is anti-aromatic, despite the fact that they are both on the same plane. Two different rings and a single carbon atom are shared by "spiro" polycyclic molecules. The well-known natural chemical isatin, also known as indoline-2,3-dione or indole 1H-2,3-dione, is present in plants of the genus Isatis and *Couropita guianancis* aubl [32, 33]. There has been a lot of interest in the research as well as pharmacology of isatin derivatives in recent years due to their various activities and privileged electronic properties. The isatin derivatives have a variety of pharmacological activities, including anticancer activity against various cancers [34, 35], antibiotic, antidepressant properties [36], anxiolytic, sedative, anticonvulsant properties [37], antibacterial, antifungal, and antidiabetic effects [38].

Chemical Properties of Isatin: Isatin itself can generate hybrid molecules because of its flexible locations, which are capable of a wide range of reactions. While the -NH group in isatin can be N-alkylated, N-arylated or N-acylated, the reactivity

of the carbonyl group at position C-2 can be investigated for the production of spirocyclic compounds, such as indigo and indirubins. Indole reacts with an alkyl halide in the presence of sodium hydride to produce N-alkylated indole, whereas it reacts with an alkyl lithium in the presence of lithium aluminium hydride to produce 3-alkyl indole [Route 1]. In DMF solvent [Routes 2 and 8], the first -NH position may be alkylated or acetylated with the aid of a base. In the presence of silver salts, the second position can be transformed into O-alkylated Regio isomers by using an alkyl halide [Route 3]. In [39, 40], some of the most typical reactions to isatin are depicted. At the fifth position of [Route 4], the common electrophilic substitution process, such as halogenation, nitration, or sulphonation, takes place. Isatin can be made from anthranilic acid, but it can also be transformed back into the acid by oxidation in the presence of hydrogen peroxide or chromium trioxide/acetic acid [Route 5]. Another is alkene production *via* the Witting reaction employing phosphonium ylide at the third position of isatin [Route 6]. Indole reacts with an alkyl halide in the presence of sodium hydride to produce N-alkylated indole, whereas it reacts with an alkyl lithium in the presence of lithium aluminium hydride to produce 3-alkyl indole [Route 7] as shown in **Fig. 2** [41].

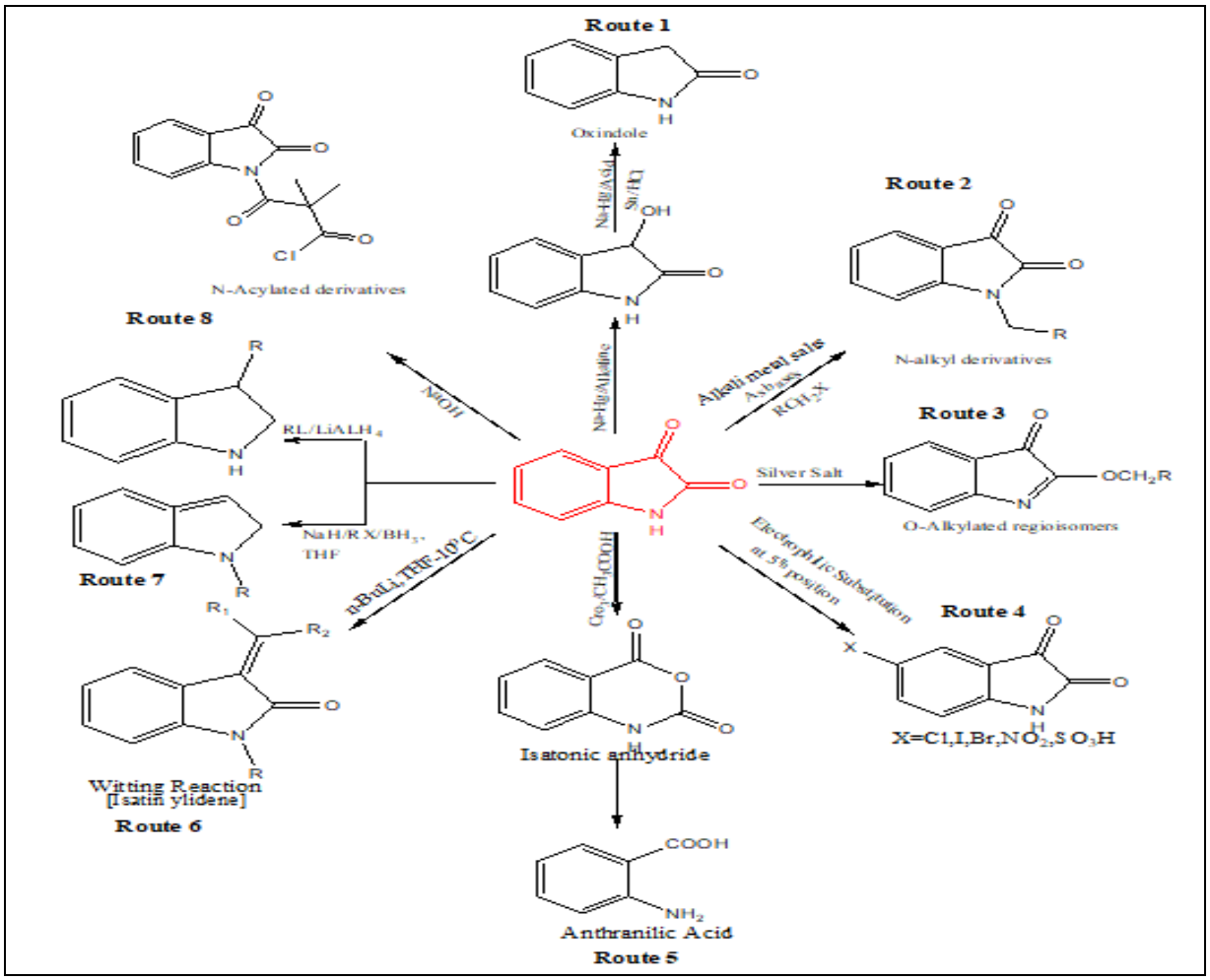

FIG. 2: CHEMICAL PROPERTIES OF ISATIN

Synthetic Pathway for Isatin: The method involved cyclization of N,N-diphenyloxalimidoyl dichloride in the presence of concentrated sulphuric acid [Route 1]. The isatin compound was also obtained from O-nitro benzoyl chloride which converted into cyanide with the help of potassium thiocyanate and then into acid via hydrolysis. Further, the nitro group is reduced into amino and then cyclization takes place to form isatin [Route 2]. The Sandmeyer process involves a condensation reaction between primary arylamine and chloral hydrate in the presence of hydroxylamine and sodium sulphate [Route 3]. The next method is the conversion of ethyl-2-aminobenzoate to phenyl 2-

(2-aminophenyl)-2-oxoacetate, which undergoes cyclization to form isatin [Route 4]. The other method includes the conversion of p-amino toluene into oxindole derivatives on heating with dichloroacetic acid which on further oxidation and hydrolysis, give isatinderivatives [Route 5]. Isatin derivatives were also synthesized by treating azalactones of ortho-nitro benzaldehydes with 10% sodium hydroxide under reflux [Route 6] [42]. The other method i.e., Stolle process uses N-functionalization of aniline with oxalyl chloride to get chlorooxalylanilide, which upon cyclization in the presence of Lewis acid gives isatin. The uses aniline as starting material, converted into 2-oxo-2-(phenylamino) acetyl chloride by reacting with phosgene chloride, which further undergoes hydrolysis to yield isatin [Route 7] [43]. The synthesis includes cyclization from 2-aminobenzoyl cyanide synthesized from the different starting materials [Route 8] in **Fig. 3** [41].

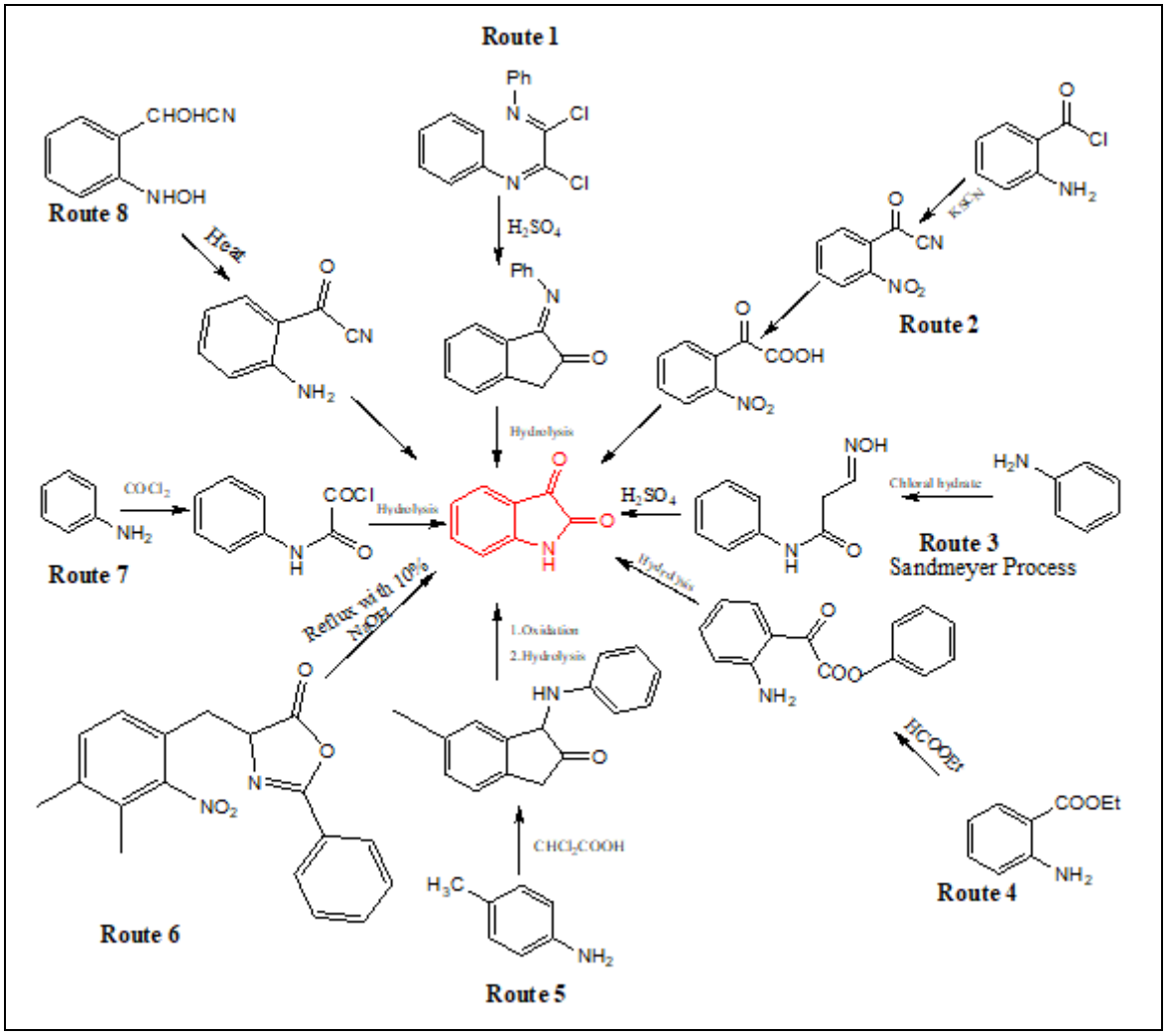

FIG. 3: SYNTHETIC PATHWAYS OF ISATIN

Ferrocene: Ferrocene has cyclopentadienide ligands that form a C_2H_5 bond with the ion such that the iron is located in the complex's centre, forming a sandwich structure [44]. A lipophilic, electron-donating substance without any hydrogen bond acceptor or donor properties is ferrocene. The kind of the substituents on the ferrocene ring has a significant impact on this process, which the ferrous ion can go through reversible oxidation-reduction [45]. The activity profiles of the physiologically active organic pharmacophores have been significantly improved by the addition of metal complexes. The ferrocenyl (Fc) moiety is thought to be the most desirable of all the metallocene's because of its distinctive qualities, including non-toxicity, neutrality, and chemical stability. Due to its high and unexpected stability, Wilkinson and Fischer [46] did not separately propose the right structure until shortly after. Woodward gave the new compound the name "ferrocene"

because of its similarity in reactivity to benzene. Ferrocene and its derivatives are highly well-liked compounds for biological applications and for conjugation with biomolecules due to the stability of the ferrocenyl group in aqueous, aerobic environments, the accessibility of a wide variety of derivatives, and its attractive electrochemical properties.

Synthetic Pathways of Ferrocene: The Grignard reagent is treated with iron chloride (II), ferrocene was formed [Route 1]. Cyclopentadiene is treated with sodium metal to form cyclopentadienides, which on reacting with $FeCl_2$ formed ferrocene [Route 2]. Cyclopentadiene treated with iron chloride in the presenceof a strong base, ferrocene was obtained [Route 3]. Using laboratory method of preparation ferrocene, cyclopentadiene treated in presence of strong base and the further intermediate reacted with iron chloride (II) [Route 4].

Cyclopentadienides in presence of sodium and xylene formed intermediate, then it treated with $FeCl_2$ and THF to formed ferrocene [Route 5] in **Fig. 4** [47].

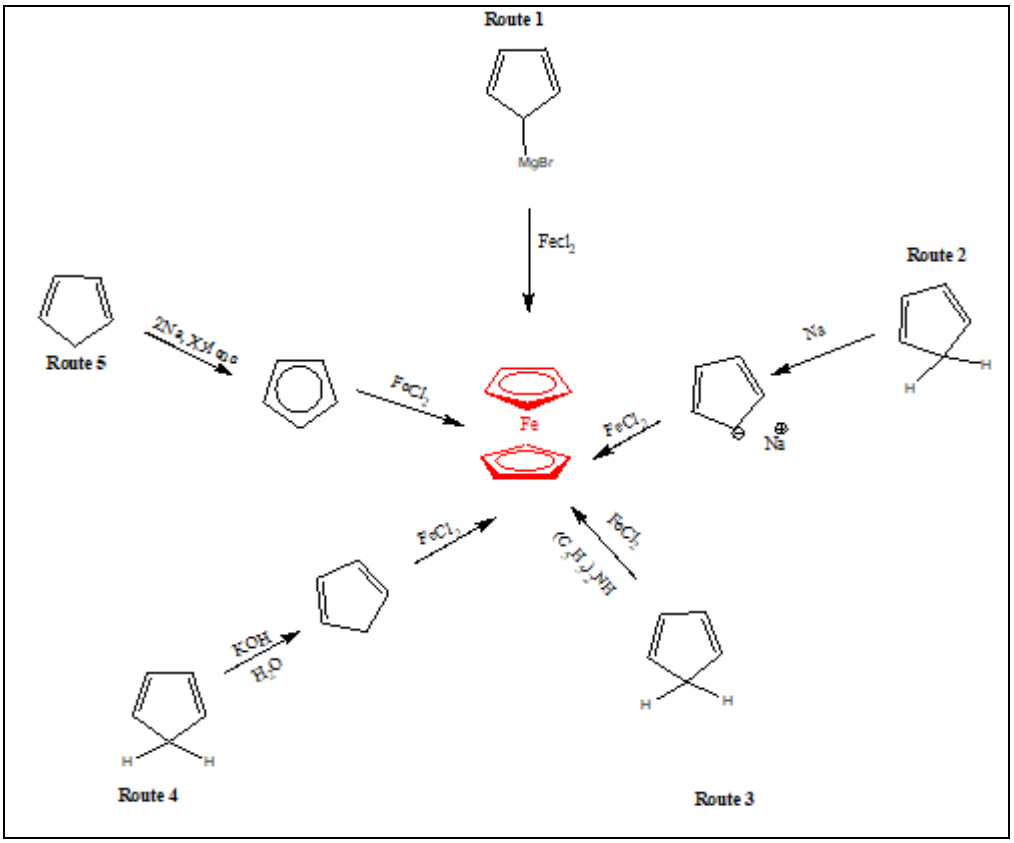

FIG. 4: SYNTHETIC PATHWAYS OF FERROCENE

Chalcone-isatin/Chalcone-ferrocene / Ferrocene-isatinsynergistic Conjugates with Different Biological Activities: In this account, "hybrid molecules" are defined as chemical entities with two (or more) structural domains that serve different biological functions. "Chimeric structure" is another possible name, but "hybrid" is preferred. "Dual activity" or “synergistic activity” refers to a hybrid molecule's capacity to act as two different pharmacophores [48]. The hybrid molecule's two halves may or may not be targeting different biological targets. Contrast these hybrid compounds with prodrugs. Chalconeand ferrocene moiety hybridization with other pharmacophores like isatin represents a promising strategy to develop novel anticancer agents with high efficacy because hybrid molecules not only have more advantageous properties such as enhanced activity and improved specificity, but also could overcome drug resistance.

Chalcone hybrids have been created in large quantities and tested for their anticancer activity recently. Some of them showed good *in-vitro* and *in-vivo* potency, indicating their promise as possible anticancer medicines [49, 50].

Antitubercular Activity: Singh *et al.,* in 2018examined a number of novel piperazyl-alkyl-ether link 7-chloroquinoline-chalcone/ferrocenyl chalcone moiety were produced and tested for their anti-mycobacterial activity against the mc^2 6230 strain of Mycobacterium Tuberculosis.

The results of the Quantitative Structure - activity Relationship (SAR) revealed that (in **Fig. 5A**), the activities were influenced by the type of aryl ring in the chalcone and the size of the alkyl chain utilised as a spacer. Most of these combinations were inactive among the conjugates that had a methyl substitution on chalcone ring. Fluoro's substitution of a methyl group with just an electron-withdrawing substituent did not significantly increase activity. But even at shorter chain lengths, the anti-mycobacterial activity was significantly enhanced by the addition of an electron-donating methoxy group at the C-4 position of chalcone ring, with compounds 1a (n=2) and 1b (n=4) exhibiting MIC_{50} values of 15 and 41 µg/mL, respectively. Also at longer chain lengths, the activities were lost when a further methoxy group was added to the aromatic ring using 2,3,4-trimethoxybenzaldehyde as an aldehyde equivalent. Remarkably, the anti-tubercular actions were generally improved by the substitution of the ferrocene nucleus for the aromatic ring, with conjugates 2a (n=4), 2b (n=5), and 2c (n=6) showing MIC_{50} values of 29, 14, and 22 µg/mL, respectively. The most effective compound (in **Fig. 6** [1, 2]) in the series was the ferrocenyl-chalcone hybrid 2b with pentyl chain as spacer, which had a Minimum Inhibitory Concentration (MIC) of 14 µg/ Ml [51].

Singh *et al.,* in 2017 examined ferrocenylchalcone, created by incorporating a ferrocene scaffold into the chalcone core, either dramatically increases the biological activity. It is possible to attribute the dependency of activity on the formal oxidation potential for the improvement in biological effects brought about by the addition of a ferrocene core [52]. Cu-promoted azide-alkyne cycloaddition processes were used to synthesise 4-aminoquinoline-ferrocenylchalcone conjugates, were then tested for their anti-tuberculosis properties [53]. The SAR of the result revealed that (**Fig. 5** [B]) having the types of substituentson the quinoline ring and the length of the alkyl chain utilised as a spacer were both found to affect the activity profile of the produced conjugates. The MIC_{99} value for conjugates having a piperazine ring at the C–4 position of quinoline was 55µM and the activity decreased with increasing chain length. Except for the compounds which had MIC_{99} values in the range of 55–60µM, the antitubercular activity were reduced when the piperazine ring was replaced with an aminophenol. When compared to conjugates with cyclic linkers, the activity profiles were significantly improved by the addition of an acyclic, flexible amino-alcohol chain on the quinoline ring (piperazine and aminophenol). Containing MIC_{99} values ranging from 38 to 55µM, the conjugates with an amino–ethanol as a linker demonstrated strong anti–tuberculosis action. The activity profiles were further enhanced by the substitution of aminopropanol for aminoethanol, with MIC_{99} values falling between 30-40µM. The most effective of the produced conjugates, with a MIC_{99} value of 30µM, was conjugates compounds, which had the quinoline ring substituted with aminopropanol in the best possible way and a pentyl chain length added as a spacer. The most potent antitubercular activity of compounds such as 3a (37±3µM), 3b(37±3µM), 3c(37±3µM) and 3d(30±3µM) had the most potent onces (in **Fig. 6** [3]). Comparing the activity profiles of the conjugates with acyclic flexible chains (aminoethanol/ aminopropanol) and those with cyclic substituents (piperazine/aminophenol), it was found that the former had better activity profiles [54].

Kumar *et al.,* in 2013 examined 1H1,2,3-Triazole-Tethered Spiroisatin, Ferrocene, and Isatin Conjugates were synthesised and assessed for their anti-mycobacterial activity against Mycobacterium Tuberculosis.

According to the Quantitative Structure - activity Relationship (SAR) results revealed that (in **Fig. 5** [C]), adding a ferrocene nucleus significantly improves the activities profiles both for N-alkylazidospiroisatins and N-alkylazidoisatins. The lengths of the alkyl chain, the kind of substitution at the C-5 positioning of the isatin, and whether a ketocarbonyl or ketal unit is present at the C-3 of anisatin rings are also found to be unrelated to the activity profiles. The compound 4a and 4b exhibits strong activity with MIC ranges of 144-287µM and 137-274µM, respectively. Further introduction of

the ferrocene ring increases the activity such compound 5a and 5b gives off strong activity within the MIC ranges such as 194µM and 189 µM. The compound such as 4a, 4b, 5a and 5b had the most potent activity (in **Fig. 6** [4,5]) [55]. Kumar *et al.*, in 2013 examined the antitubercular structure–activity interactions within the isatin–ferrocene triazole conjugate family, 16 distinct triazoles had been synthesised using a Cu–mediated azide–alkyne cycloaddition technique. The SAR of the result revealed that(fig 5 [D]), the ferrocene nucleus was introduced among precursor N-alkyl azidoisatin, with a preference for halogen (F, Cl) substituent at C-5 position of isatin and propyl chain length as a spacer, and antitubercular evaluation experiments showed a considerable improvement in activity. The inclusion of a fluoro-substituent at the C-5 position of the isatin ring increased the activity profiles when compared between N-alkyl azido-isatins linked via an ethyl linker. When N-alkyl azido-isatins with propyl linkers were compared in a similar way, it was discovered that with the chloro substituent had the best activity profile out of all the test compounds. With the addition of the ferrocene nucleus to the series, the antitubercular efficacy had improved, with hybrids and that include fluoro and chloro substituents at the C-5 positions, respectively, as well as a propyl linker, demonstrating superior activity among the isatin–ferrocene hybrids (158-167µM). Using Cu-mediated azide-alkyne cycloaddition processes, the present article presents the synthesis of isatin-ferrocene and introduction of chalcone group to forms isatin-ferrocenylchalcone hybrids and their assessments as anti-TB compounds which was irrespective of the substituent at C-5 position. When their antimycobacterial activity was tested, it was discovered that the activity profile was dependent on the isatin ring's C-5 substituent and the length of the alkyl chain, with an affinity for halogen substituents (F, Cl) and a longer chain length (n = 3) in the case of isatin-ferrocene hybrids. Without regard to the presence of C-5 substituents or the length of the alkyl chain, the antimycobacterial activity of the synthesised isatin-ferrocenylchalcone hybrids was enhanced by the addition of a chalcone nucleus. The compounds such as 6a (107-214µM), 7a (109-218µM), 7b (105-211µM) had potent antimycobacterial activity (in **Fig.** 6 [6, 7]) [56].

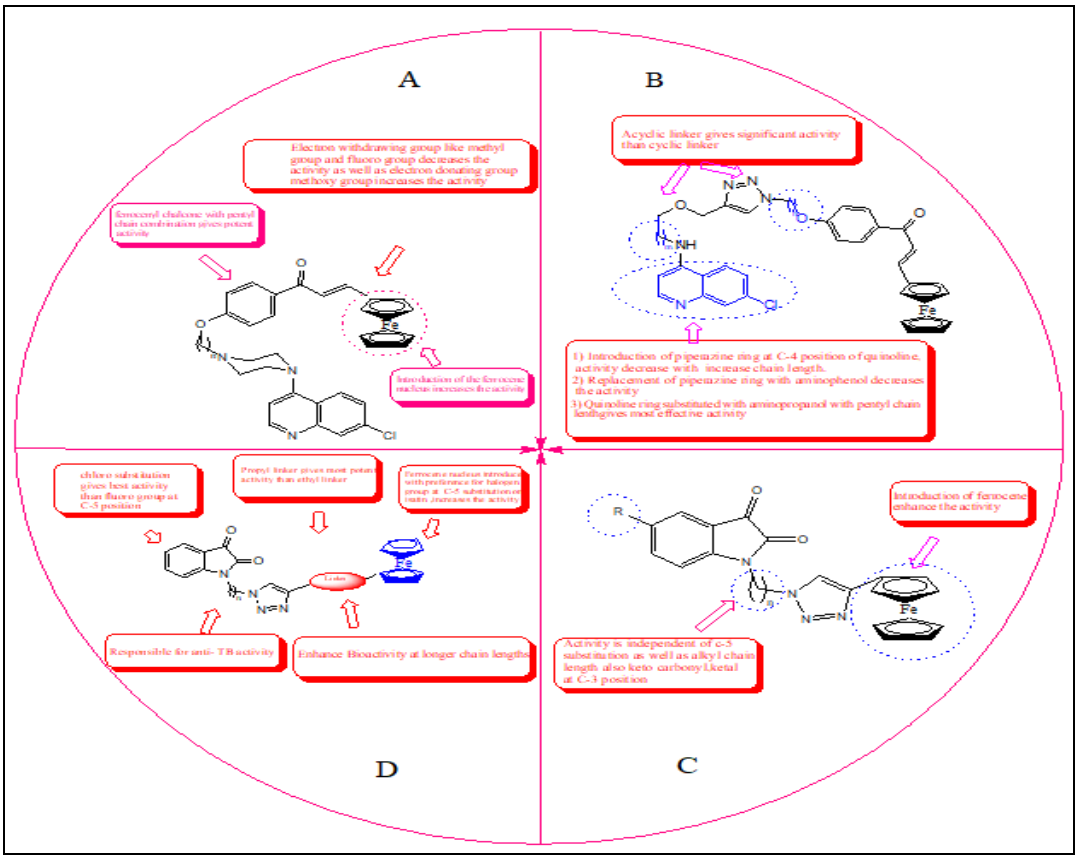

FIG. 5: DESIGNED SAR OF ISATIN-FERROCENE-CHALCONE HYBRIDSFOR ANTITUBERCULAR ACTIVITIES

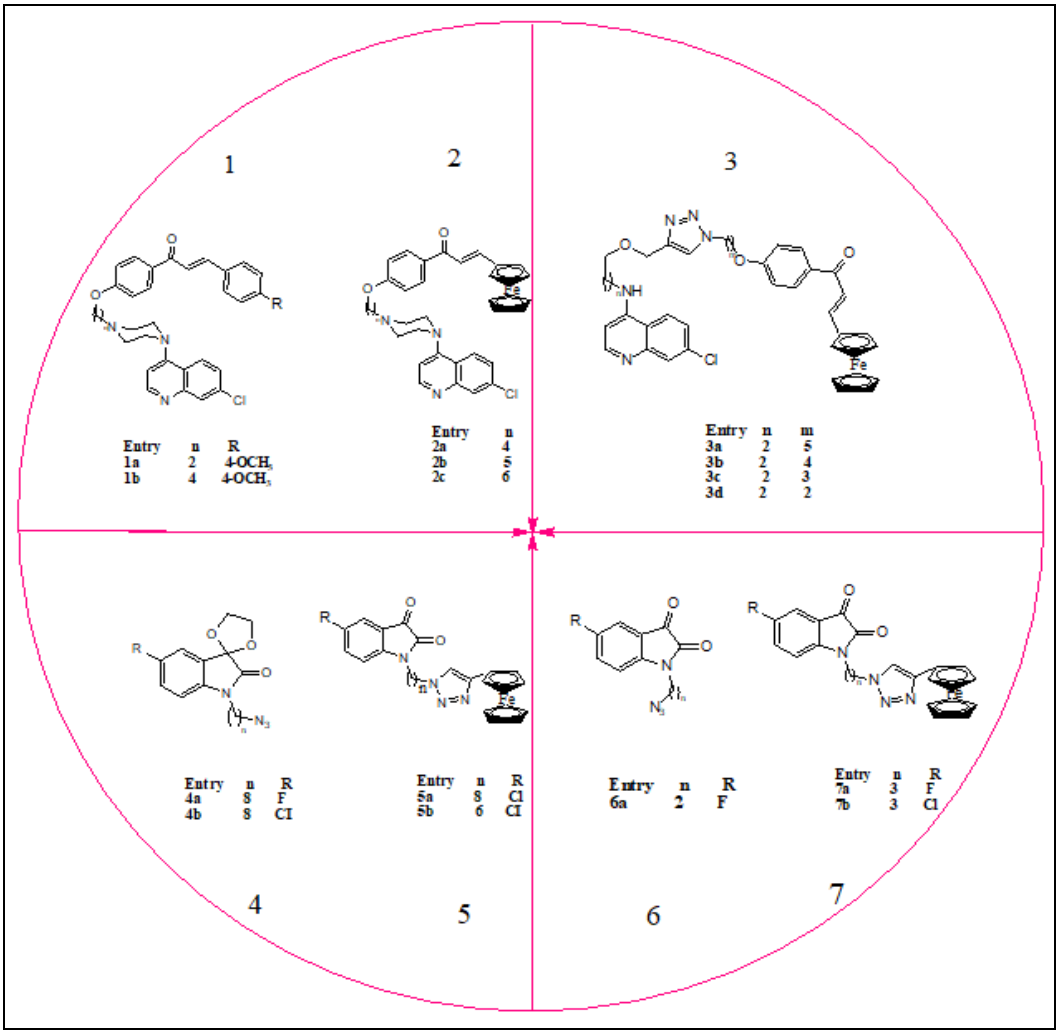

FIG. 6: POTENT DERIVATIVES OF ISATIN-FERROCENE-CHALCONE HYBRIDS FOR ANTITUBERCULAR ACTIVITIES

Anticancer Activity: Sharma *et al.*, in 2020 investigated Tetrahydro-*β*-carboline, or (TH*β*C), had been shown to be anti-cancer, anti-plasmodial, and anti-fungal. With the intention of examining their anti-proliferative properties, tetrahydro-*β*-carboline and chalcones/ferrocenylchalcones were combined in a single framework against the triple-negative MDA-MB-231 and estrogen-responsive MCF-7 cell lines.

According to the SAR of the study (in **Fig. 7** [E]), the type of chalcone core (aryl/ferrocenyl), the type of substituent (on aryl ring) and the length of the alkyl chain were all shown to affect the activity. When conjugates were compared using SAR, it became clear that aryl chalcone-based conjugates had superior anti-proliferative effects on both cell lines examined. The longer even alkyl chain compounds of the ferrocenylchalcone-TH*β*C conjugates with the exception of were shown to be inactive against both cell lines. MCF-7 cells responded favourably to the conjugates with odd alkyl chain lengths. Adding ferrocenyl core to the developed hybrids might be justified by the fact that it would increase their anti-proliferative effectiveness, as shown by ferrocifens and ferrocephenols. With special qualities including simplicity in production, stiffness, metabolic stability, and H-bonding interactions in biological environments, 1H-1,2,3 triazoles hold particular importance as linkers.

In TH*β*C-chalcone conjugates, the length of the alkyl chain barely had an impact on the activities, however the type of the substituent on the phenyl ring of the chalcone primarily had a key role in improving the cytotoxicity on breast cancer cell lines. When compared to compounds with mono-methoxy substituents, which were inactive on both breast cancer cell lines, compounds with tri-

methoxy substituents on the phenyl ring demonstrated notable cytotoxicity's on breast cancer cells. The drug that used a pentyl chain as a spacer had MDA-MB-231 cells, making it roughly 3 times as effective as tamoxifen. The anti-proliferative properties of mono-methoxylated conjugates were totally absent in MCF-7 cells. Among all the produced conjugates, the compounds with electron-withdrawing fluoro substitution at the phenyl ring were determined to be the most active compound such as 8a(n=2) and 9a(n=5) displaying IC_{50} of 19.00 and 31.62μM. Confirming the impact of alkyl chain lengths on the activities of fluoro-substituted conjugates, the conjugates with butyl and hexyl chain lengths were ineffective against both cells. The most potent compounds such as 8a and 9a (in **Fig. 8** [8,9]) [57].

Singh *et al.,* in 2018 investigated a variety of 1H-1,2,3-triazole-tethered uracil-ferrocenyl chalcone conjugates were created using Huisgen'sazide-alkyne cycloaddition procedure in order to test their in vitro anti-proliferative effectiveness on human leukaemia (CCRF-CEM) and human breast cancer (MDAMB-468) cell lines. The structural activity relationship of the result exposed that(in **Fig. 7[**F]), a closer look showed that cytotoxicity depended on the length of the alkyl chain used as a spacer, with a preference for longer chain lengths, whilst the type of substituents used to modify uracil at the C-5 position did not appear to affect the activity profiles.

After 72 hours against the CCRF-CEM cells, the conjugates with longer alkyl chain lengths of compounds 10b (n = 5); 10c (n = 6); 10d (n = 8); 10e (n = 5); 10f (n = 6)and 10g (n = 6) added as a spacer inhibited cell proliferation by about 70%. The majority of the conjugates were inert even after 72 hours, according to a comparable examination of their cytotoxic effects against MDA-MB-468 the exceptions were conjugates compounds 10b and 10f, which both had pentyl chains and reduced cell growth by 59 and 62 %, respectively. The cytotoxic characteristics of seven of the most powerful conjugates (in **Fig. 8** [10]), namely 10a, 10b, 10c, 10d, 10e and 10g against a normal kidney cell line (LLC-PK1, ATCC CL-101) were also assessed approximately 57% to 98%, and the results were compared with doxorubicin [58]. Singh *et al.,* in 2018 examined that, the antiproliferative effects of 1H-1,2,3-triazole-tethered isatin-ferrocene, ferrocenyl-methoxy-isatin, and isatin-ferrocenylchalcone conjugates against MCF-7 (ER) and MDA-MB-231 human breast cancer cell lines. The SAR of the results revealed that (in **Fig. 7** [G]), the synthesised hybrids reported stimulation of cytoprotective enzymes, however activity was lost when the chalcone moiety was added. When compared to MDA-MB-231 cell lines, the 1H-1,2,3-triazole-tethered isatin ferrocene conjugates 11a, 11e, 11f, and11h (in fig 8 [11]) shown greater potency against MCF-7 cell lines, with IC_{50} values of 31.62, 53.48, 57.10, and 34.99 μM, respectively [59]. Ammar *et al.,* in 2017examinedone of the leading to adverse effects of chemotherapy was drug resistance, which can develop after using the chemotherapeutic agent for a long time [60].

Structural activity relationship suggested that the phenyl rings in chalcones were typically replaced with heterocyclic rings and polyaromatic groups [61, 62], various substituents were added to the phenyl moieties [63], and the chalcone was cycled to produce stiff analogues [64]. It was discovered that the chalcones' double bond of the enonemoiety is necessary for their anticancer activity [65, 66]. According to SAR of the result revealed that (in **Fig. 7** [H]), the introduction of the acetyl group with the replacement of the amino group increases the activity of potent carcinoma cell line MCF-7, HepG-2, and HCT-116, and MCF-12A normal breast cell line as compared with the acetamide group.

Furthermore, no substitution or replacement of amino group diminished the activity. He performed the tested compounds showed favourable activity against MCF-7 breast cells with IC_{50} ranging from 2.88 to 51.08μM. Compounds 12a, 13a and 14a revealed higher antitumor activity (IC_{50} values ranging from 2.88, 9.95 and 7.93μM) against the MCF-7 cell line when compared with the standard drug Imatinib (IC_{50} 12.29μM).For the HepG-2 lung cell line, compounds also showed higher activity (IC_{50} 9.23, 10.20, 5.22 and 7.70μM), in comparison to Imatinib (IC_{50} 11.16μM).The same compounds, 13a-15a, showed potent activity against the HCT-116 cell line for colon in which the IC_{50} were 9.38, 11.4, 2.95 and 8.65μM, respectively. Compounds were the most active, with IC_{50} ranging from 2.88 to 18.12μM for the three cell lines, while

compound 14a also showed moderate activity against HepG-2, MCF-7 and HCT-116 with IC_{50} 13.95, 31.66 and 11.78µM, respectively. Furthermore, compound 10 showed high activity against HepG-2 cells with IC_{50} 12.84µM. Compound 15b was shown to be the most potent against both HepG-2 andHCT-116 cell lines, while compound 15a is the most potent against MCF-7 (in **Fig. 8** [12-15]) [67].

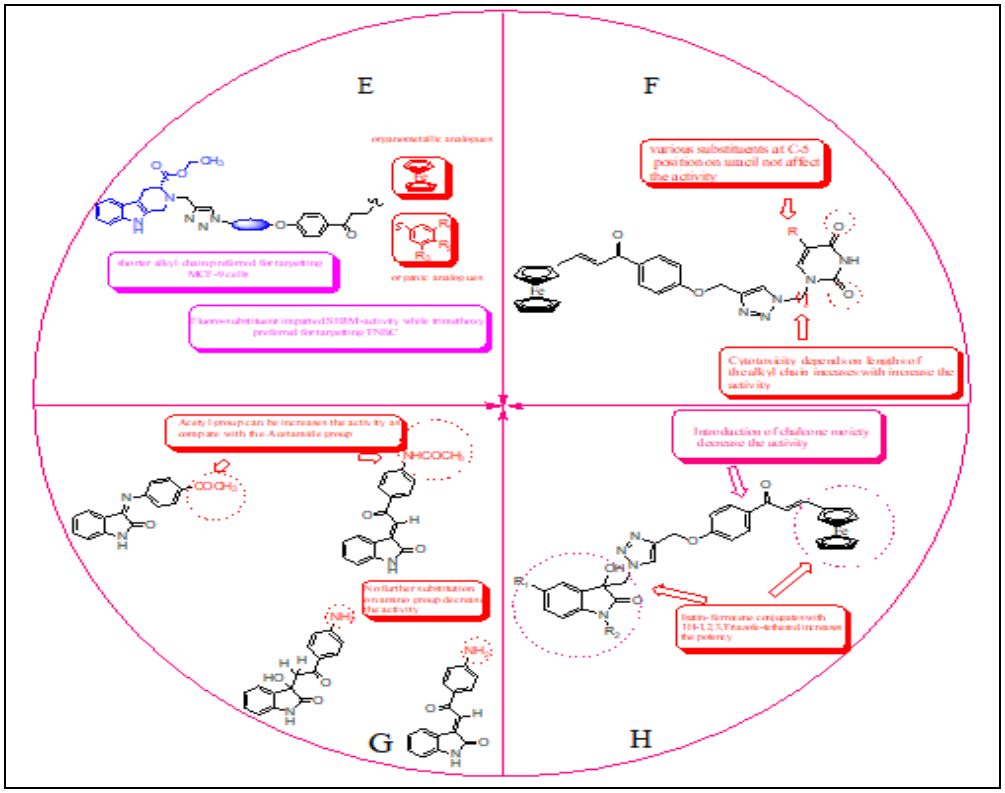

FIG. 7: DESIGNED SAR OF ISATIN-FERROCENE-CHALCONE HYBRIDS FOR ANTICANCER ACTIVITY

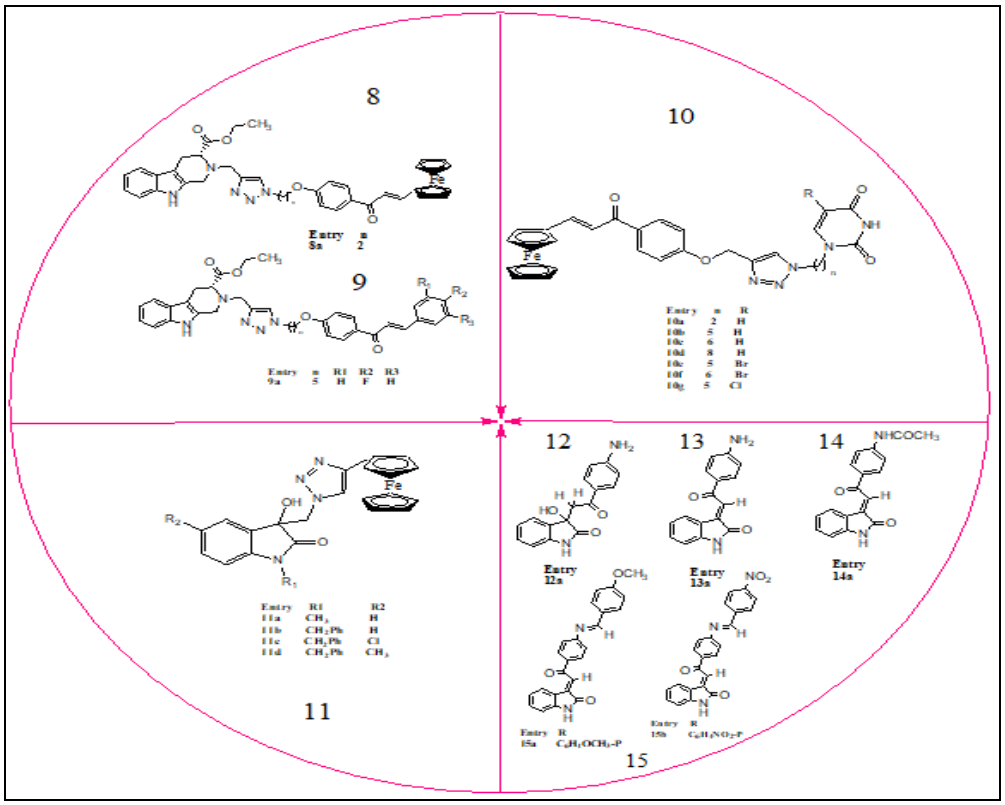

FIG. 8: POTENT DERIVATIVES OF ISATIN-FERROCENE-CHALCONE HYBRIDS FOR ANTICANCER ACTIVITY

Antimalarial Activity: Singh *et al.,* in 2017 described the synthesized 4-amino quinolinechalcones/ ferrocenyl-chalcone conjugates were evaluated for their anti-plasmodial activities against the chloroquine-resistant and mefloquine sensitive W2 strain of *P. falciparum.*

An interesting SAR was revealed by the results analysis (in **Fig. 9** [I]), with activity mostly based on the length of the alkyl chain between the 4-aminoquinoline and chalcone and reliant on the type of substituent at the aryl ring of the chalcone. The amount of methylene between the two pharmacophoric fragments elevated anti-plasmodial activities. In contrast, a drop in IC_{50} was seen with an increase in alkyl chain length from ethyl to pentyl when an electron-withdrawing substituent (R=F) was added to the C-4 position of chalcone ring B. With the most active conjugate of compound 16a (n=5), with an IC_{50} of 0.78μM, the replacement of fluoro with an electron-donating methoxy group at the C-4 position did not change antiplasmodial activity. Finally, compound was created by substituting ferrocene for the aryl ring of the chalcone. The antimalarial effectiveness assessed, and it was discovered that activity was dependent on the length of the alkyl chain linker. Exploration of SAR demonstrated that activities are dependent on the length of the alkyl chain used as a spacer, however the type of the substituent at chalcone did not appear to have an impact on activity. The most effective and non-cytotoxic compound 16b (in **Fig. 10** [16]), with an IC_{50} value of 0.41μM. It had the ideal combination of hexyl chain length as a linker and an unsubstituted phenyl ring [68].

Singh *et al.,* in 2017 investigated the anti-plasmodial activity of the synthesised 4-aminoquinoline-ferrocenylchalcone conjugates against the chloroquine-resistant W2 strain of *P. falciparum* were tested. The SAR demonstrates that (in **Fig. 9** [J]), the type of the substituents added to the quinoline ring and the length of the alkyl chain added as a linker between two pharmacophores have a significant impact on the activities. The IC_{50} values for the piperazine-linked conjugates in the range of 2.55–5.08μM. Compound 17a (n=2) was the strongest in this sequence, while activity appears to be unaffected by the length of the inserted alkyl chain. With the exception respectively, replacing the piperazine ring with 4-aminophenol did not increase antiplasmodial efficacy. This indicates that antiplasmodial activity improves with lengthening the alkyl chain. As seen for conjugates, the activity profiles were improved by the addition of amino-alcohols as substituents on the quinoline core. The activity of the conjugates among the amino-ethanol substituted scaffolds decreased as the chain length increased, whereas the activity increased as the chain length increased. The conjugates were shown to be the most potent among the investigated compounds, with activity that were essentially independent of the length of the alkyl chain linker, according to a similar comparison among aminopropanol substituted compounds, conjugate of compound 18a which had the best ratio of amino-propanol as a substituent and an n-pentyl chain linker was the most effective of the evaluated compounds. The compounds such as 17a and 18a had most potent antimalarial activity (in **Fig. 10** [17, 18]) [69].

Kumar *et al.,* in 2014 examined the antimalarial characteristics of the synthesised β-lactam-ferrocenylchalcone conjugates against the CQ-S 3D7 and CQ-R W2 strains of *P. falciparum*.

The SAR of the study reveals (shown in fig 9 [K]), the antimalarial effectiveness of β-lactam nucleus was greatly increased by the addition of the ferrocene nucleus. While the length of the linker and the presence of mono- and bis-ferrocenylchalcones appeared to play a supporting function, SAR exposed a high dependency of activity profiles at the N1 substituent of the β-lactam ring.

Going to rely on the type of substituent present at the β-N-1 lactam's position, while the amount of mono- and bis-ferrocenylchalcone and the length of the alkyl chain used as a linker had only a minor impact. When comparing the mono-ferrocenyl-chalcone-β-lactam conjugates against the 3D7 strain, it was found that the presence of N-alkyl substituents, such as cyclohexyl and cycloheptyl, improved the activity profiles compared to N-aryl substituents. Of the compound 19a proved to be the most potent, with an IC_{50} value of 5.81μM. Another ferrocenyl chalcone unit was added, but no improvement was noticed. Similar comparisons of the bis-ferrocenylchalcone-β-lactam conjugates

against the 3D7 strain showed that the activities were only dependent on the substituent at the N-1 position of the b-lactam ring, and no improvement was shown with the addition of more ferrocenylchalcone units. The conjugates which have a N-aryl substituent at the N-1 position of the β-lactam ring, have similar activity profiles and are less powerful than their N-alkyl counterparts.

The N-cyclohexyl substituent in compound 20a made it the most effective of the sequence, with an IC_{50} value of 4.80μM, respectively, the compounds 20a and 20b with the best configuration of N-alkyl (Cyclohexyl) moiety, and the involvement of bis-ferrocenylchalcone unit demonstrated to be the most potent among the series (in **Fig. 10** [19-20]) [70].

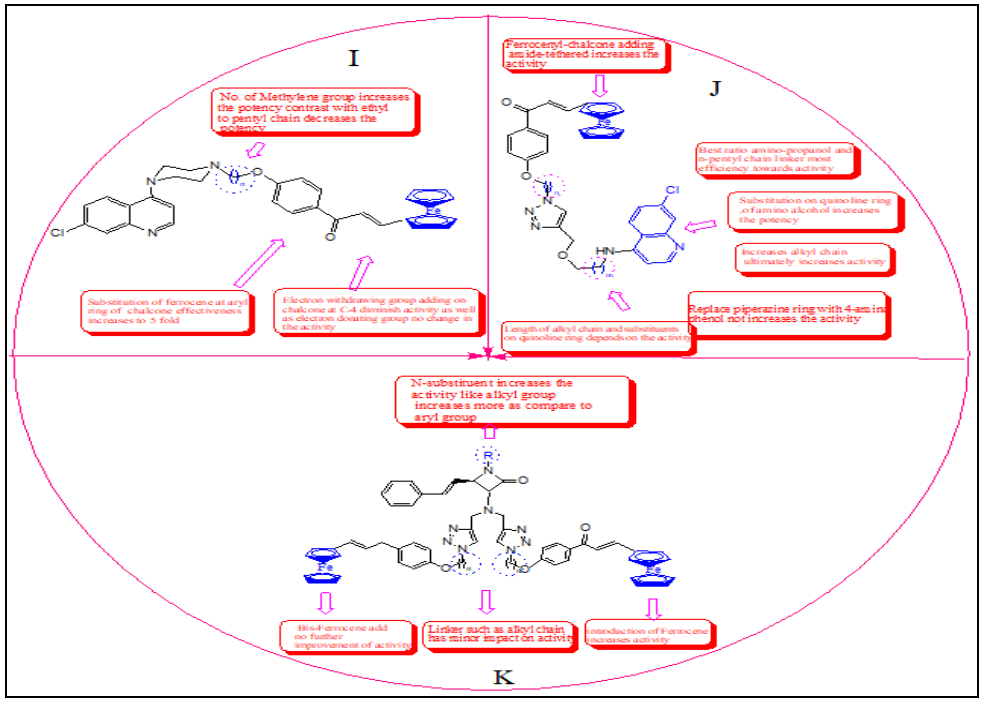

FIG. 9: DESIGNED SAR OF ISATIN-FERROCENE-CHALCONE HYBRIDS FOR ANTIMALARIAL ACTIVITY

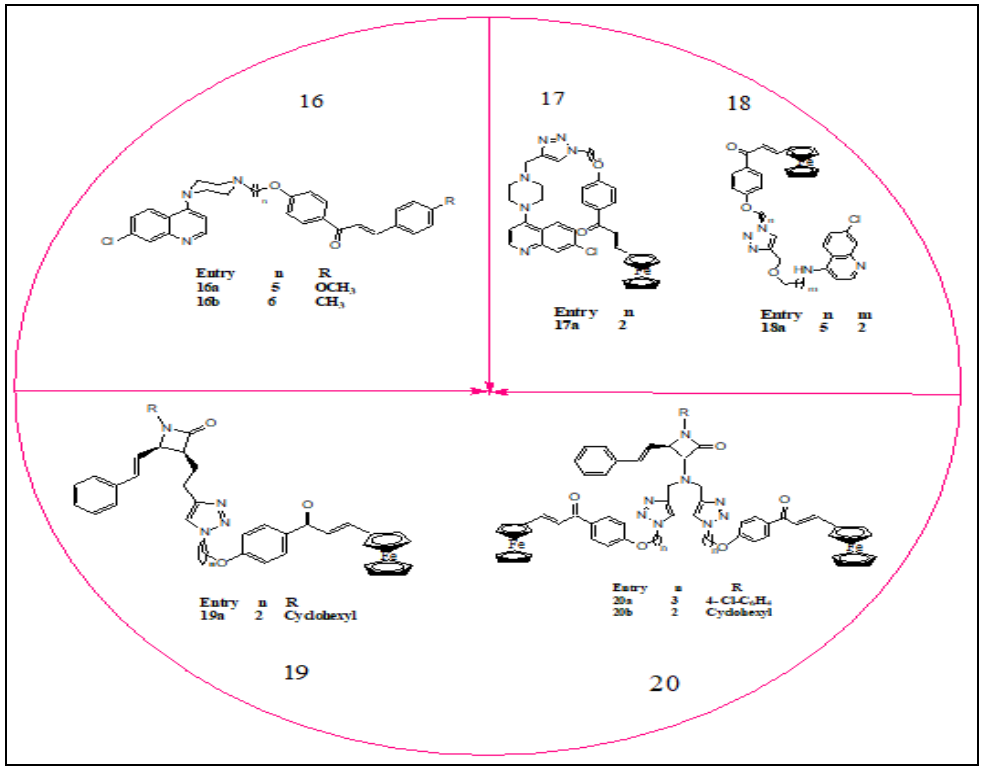

FIG. 10: POTENT DERIVATIVES OF ISATIN-FERROCENE-CHALCONE HYBRIDS FOR ANTIMALARIAL ACTIVITY

Antibacterial Activity: Yagnam *et al.,* in 2021 examined that, 1H-1,2,3-triazole tethered isatin-ferrocene-thiazolidinedione conjugates were tested *in-vitro* for antibacterial activity. The Structure Activity Relationship (SAR) analysis (in **Fig. 11** [L]) showed that all synthetically produced new triazole conjugates and aryl compounds had outstanding antimicrobial activity toward all of the test organisms, and their values were comparable to those of the widely used drugs streptomycin and fluconazol. When compared to the newly produced novel triazole conjugates, the hybrid aryl molecule had significantly reduced activity. The compound's substituted isatin ring group and the combination of the triazole and ferrocene moiety may be responsible for the compound's observed enhanced biological activity. The compounds 21a, 21b, 21c and 21d (in **Fig. 12** [21]) demonstrated MIC values of 4 µg /ml against bacterial strains. The difference in MIC values between Gram-negative and Gram-positive bacteria may be caused by the lengthening of the alkyl chain. There was a tendency for the chalcones to inhibit Gram-positive bacteria more than Gram-negative bacteria[71].

Singh *et al.,* in 2019 examined 1H-1,2,3-triazole-linked isatin-ferrocene, ferrocenylmethoxy-isatin, and isatin-ferrocenyl chalcone conjugates were made *via* copper-promoted azide-alkyne cycloadditions. The growth inhibitory activity of the produced conjugates *viz* against *T. vaginalis* was assessed.

The SAR revealed that (shown in **Fig. 11** [M]) the type of a substituent at the C-5 and N-1 positions of the isatin ring, as well as the kind of linker employed, were shown to affect the synthesised substance's activity. The kind of a substituent at the C-5 and N-1 positions of the isatin ring, as well as the type of linker employed, were discovered to affect the synthesised substance's activity. The activities were improved overall when N-CH_3 was switched out for N-benzyl, with conjugate 22b showing a growth inhibition of about 94%. The generated hybrids lost activity when the ferrocenyl-chalcone moiety was induced, particularly in the case of N-benzyl substituted scaffolds. The N-methylated equivalents showed strong inhibition, proved to be the most effective. An intriguing structure-activity relationship with dependency on the substituent at N-1 of the isatin ring was discovered by comparing the obtained activity profile information using ferrocene-methoxy isatin conjugates. It is clear that the compounds containing N-CH3 failed to stop the growth. Regardless of the kind of substituent at the C-5 position of the isatin ring, the replacement of N-CH_3 with N-benzyl resulted in an improvement in activity with inhibition efficiency in the range of 84.43-87.63µM. The IC_{50} values of the most potent conjugates discovered through percentage inhibition experiments were assessed (concentration in which inhibited 50% parasite growth) Conjugates 22a, 22b, 22c, 23a and 23b displayed IC_{50} values that were greater than the typical FDA-approved medication at 28.9, 30.1, 28.3 and 27.0µM (shown in **Fig. 12** [22,23]) [72].

Singh *et al.,* in 2018 evaluated the antibacterial efficacy of isatin-ferrocenyl chalcone and 1H-1,2,3-triazole-tethered isatin-ferrocene conjugates against the human mucosal pathogen *Trichomonas vaginalis.*

The structure-activity relationship (SAR) revealed that (in **Fig. 11** [N]) displayed an intriguing interaction, with the type of substituent at the isatin ring's C-5 location and the extent of the alkyl chain used as a linker influencing activity. According to the activities of moiety having unsubstituted (R = H) indicates that the impact appeared to improve as the chain length increased from n = 2 to n = 4, however the activity decreased as the chain length increased further. The activity was reduced when a methyl substituent was added to the isatin ring's C-5 position, with the exception of (n = 2) or even (n = 4). Depending on length of the alkyl chain linker, the introduction of the electron-withdrawing substituents fluoro and chloro generally increased the growth inhibition effect against *T. vaginalis*. The most effective test compound with 100% growth inhibition were the conjugates of compounds 24a (R = F, n = 4) as well as 24b (R = Cl, n = 2), which had the best configuration of electron-withdrawing groups at the C-5 location of the isatin ring. With the exception of situations at which octyl (n = 8) chain was used, the activity of the 1H-1,2,3-triazole-tethered conjugates was found to be independent of the type of substituent occurring at the C-5 positioning of the isatin ring and the magnitude of the alkyl chain used as the spacer. The conjugates of series 25a-d (shown in

Fig. 12 [24,25]) showed growth inhibition rates of 64.70, 49.16, 52.70, and 35.3 %, respectively, demonstrating that the addition of the octyl chain length lowered the antitrichomonal actions [73].

Mondal *et al.*, in 2017 investigated the synthesis of some novel isooxazoline derivatives from chalconisedisatin derivatives and screened them for their biological activities against gm (+ve) and gm (-ve) bacteria, in continuation of our research on the synthesis of biologically active heterocyclic compounds. From various substituted chalconised indole-2,3-dione that was created from various chalconisedisatins, 1- 3-dihydro-2H-indole-2-one were synthesised.

According to SAR of the result revealed (in **Fig. 11** [O]), methoxy (-OCH3) substitution on phenyl ring at para position and hydroxy (-OH) group gives potent activity. Chloro (-Cl) gives potent antimicrobial, analgesic and anthelmintics as well as Nitro(-NO2) gives potent anthelmintics. The Isooxazoline analogs possess indole nucleus this indole nucleus having most potent activity regarding antibacterial activity. Antibacterial activity by using the cup plate method, *in-vitro* was performed against *Pseudomonas mirabilis* (ATCC-224), *Pseudomonas aeruginosa* (ATCC-32), E. coli (ATCC-3), and *Staphylococcus aureus* were evaluated for resistance to the chemicals (ATCC-44). Ampicillin was a commonly used antibacterial medication for comparing the results. With the above-mentioned sequence of bacteria, the computed zone of inhibition produces more results such as compounds 26a (11, 09, 10.5, 10.5µM), 26b (10.5, 07, 10.8, 12µM), 26c (11.5, 09, 11, 11.7µM) compare with the reference Ampicillin (22, 21, 23, 26µM). Mondal *et al.* studied compounds 26d, 26e and 26f (shown in **Fig. 12** [26]) among them have excellent activity exclusively against gm (-ve) bacteria but not against gm (+ve), which are weak. The compounds such as 26a, 26b, as well as 26c have good activity against gm (+ve) and gm (-ve) bacteria [74].

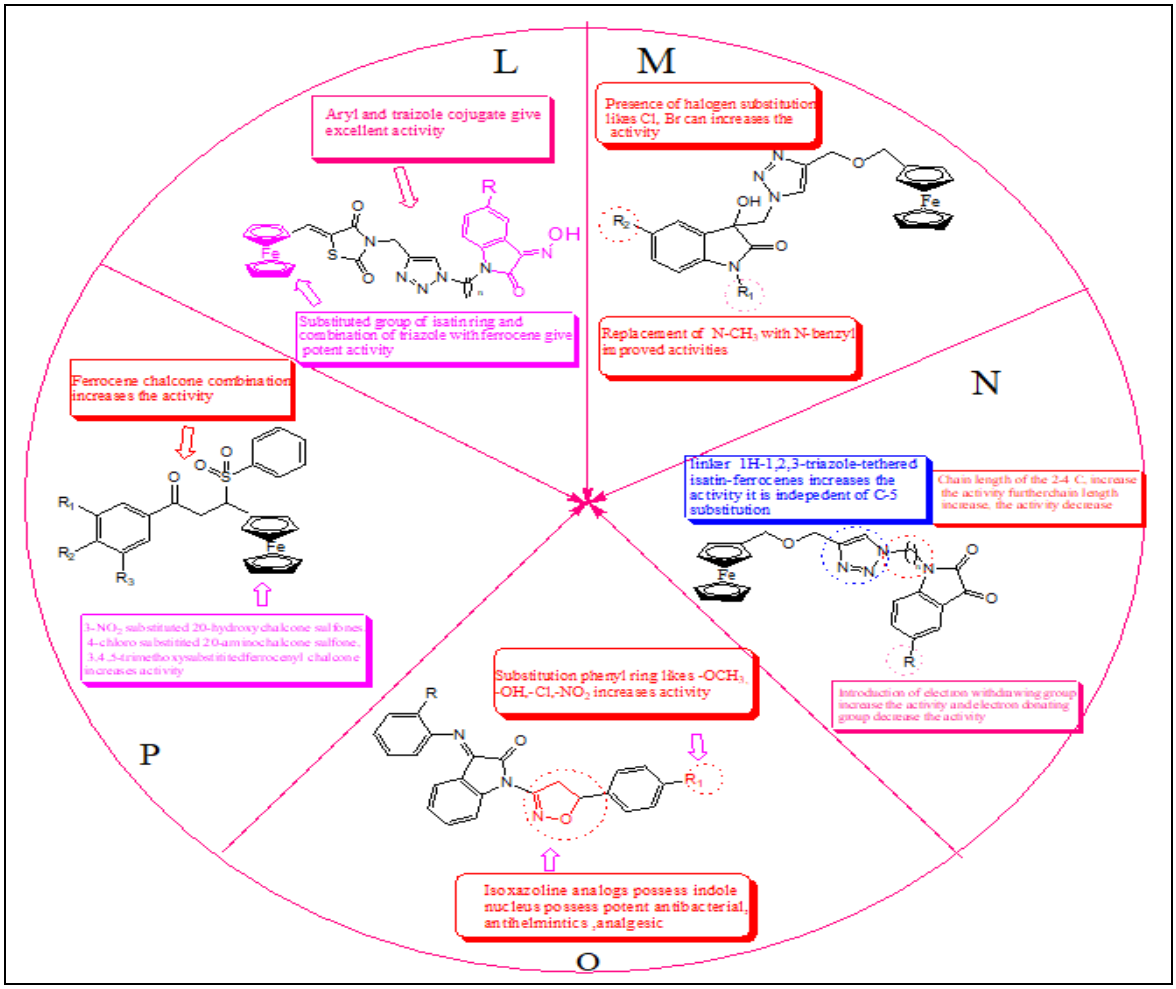

FIG. 11: DESIGNED SAR OF ISATIN-FERROCENE-CHALCONE HYBRIDS FOR ANTIBACTERIAL ACTIVITY

Ahmed *et al.*, in 2014 synthesized new class of organic chalcone-based sulfones and bis-sulfones based on ferrocenyl and tested for their antibacterial activity. Structure Activity Relationship (SAR) analysis showed that (in **Fig. 11** [P]) compounds with 3-NO2 substituted on the B ring of sulfones based on 20-hydroxychalcone have greater antibacterial effect than those with 4-methyl, 4-Chloro, and 3, 4, 5-trimethoxy substituents.

Compared to other substituents like 4-methyl and 3-nitro, compounds with 4-chloro on the B ring had better antibacterial action against *S. aureus* in the case of 20-aminochalcone-based sulfones. In comparison to other substituents, such as 4-Chloro, 3-NO2 containing compounds, the 4-methyl substitution on the B ring of bis sulfone has improved antibacterial action against *P. aeruginosa*. 3,4,5-trimethoxy substituted on the A ring and 3,4-dimethyl substituted on the B ring in ferrocenyl chalcone based sulfone had increased antibacterial activity against nearly all tested stains. Chalcone-based sulfones and bis-sulfones' antibacterial properties also demonstrated the impact of substituents on chalcone nuclei. Excellent antibacterial action was demonstrated by 3-NO2 substituted 20-hydroxychalcone sulfones, 4-chloro substituted 20-aminochalcone sulfones, 3,4,5-trimethoxy, and 3,4-dimethyl substituted ferrocenyl chalcone sulfones.

The investigated compounds' antibacterial activity was in the following order: bis-sulfones > 20-hydroxychalcone sulfones > 20-aminochalcone sulfones. The most effective antibacterial compounds against most of Gram-positive and negative bacteria were compounds 27a, 28b, and 28c (in **Fig. 12** [27, 28]) [75].

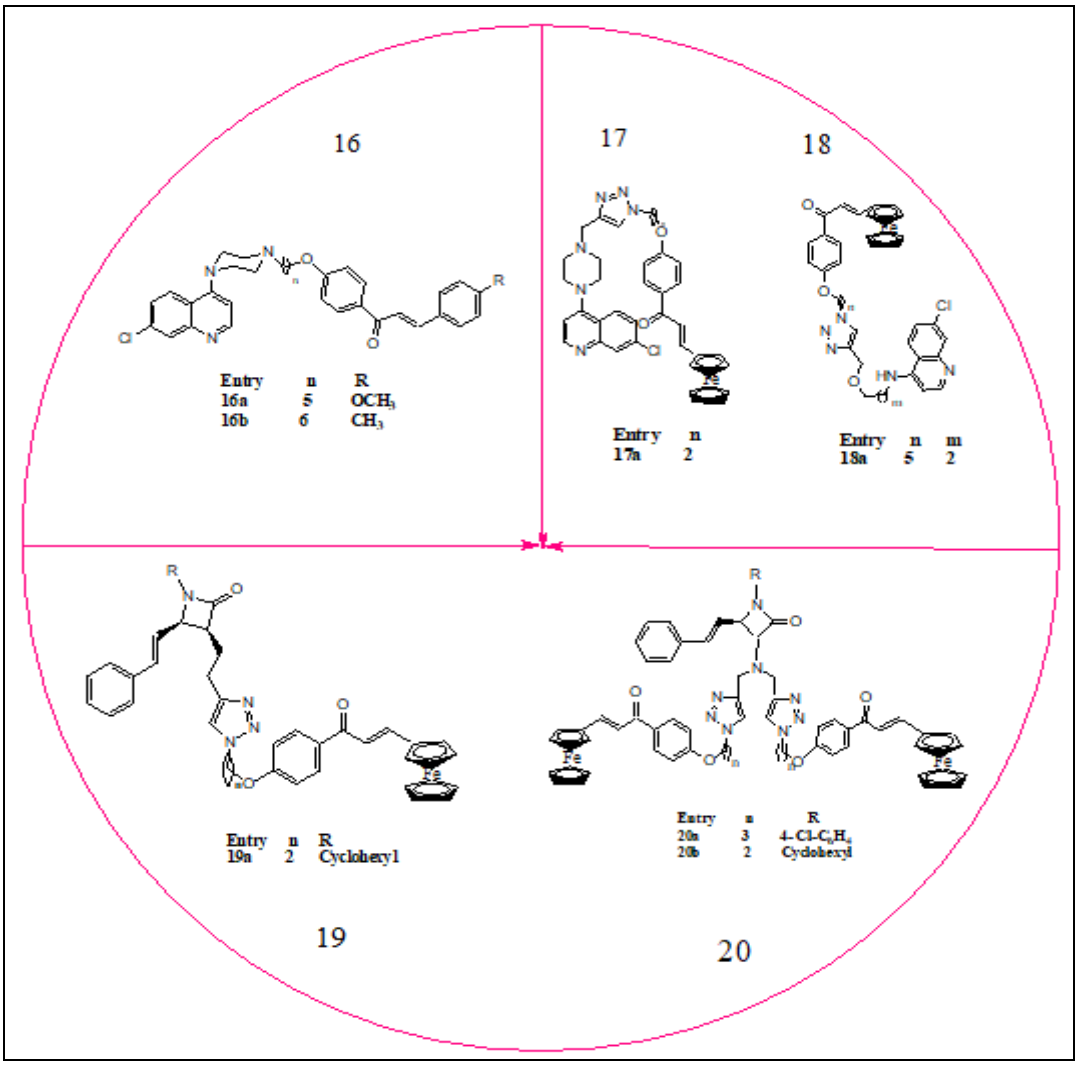

FIG. 12: POTENT DERIVATIVES OF ISATIN-FERROCENE-CHALCONE HYBRIDS FOR ANTIBACTERIAL ACTIVITY

Anti-inflammatory Activity: Rohini *et al.*, in 2019 investigated a novel, environmentally sustainable, and effective synthesis method. Under microwave irradiation, chalcone linked isatin derivatives on Schiff bases are also produced. The anti-inflammatory effects of a number of new Chalcone linked isatin derivatives, including cyclooxygenase inhibition, were studied. According to the SAR of the study (in **Fig. 13** [Q]), the substantial anti-inflammatory properties of compounds 29a and 29b might be attributable to the substituted chalcone nucleus that is connected to the Indole ring system's third position. The chance that these recently created chalcone linked isatin derivatives may be useful as a starting point for the design and synthesis of enhanced anti-inflammatory drugs is increased by study results. Compound 29a and 29b shown maximum inhibition of 70.44%; 74.01% respectively, whereas the rest of the compounds tested exhibited a minimum inhibition compared to the standard Diclofenac sodium, which showed a reduction in oedema volume by 93.76 % in a carrageen-induced rat hind paw oedema model, compound 29a and compound 29b (in **Fig. 14** [29]) showed the highest levels of inhibition at 70.44 % and 74.01 %, respectively [76].

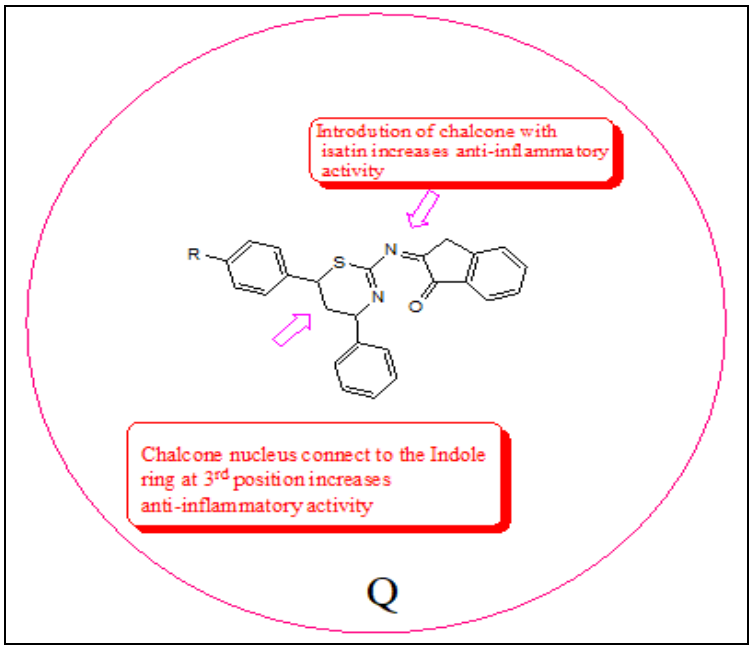

FIG. 13: DESIGNED SAR OF CHALCONE LINKED ISATINHYBRIDS FOR ANTI-INFLAMMATORY ACTIVITY

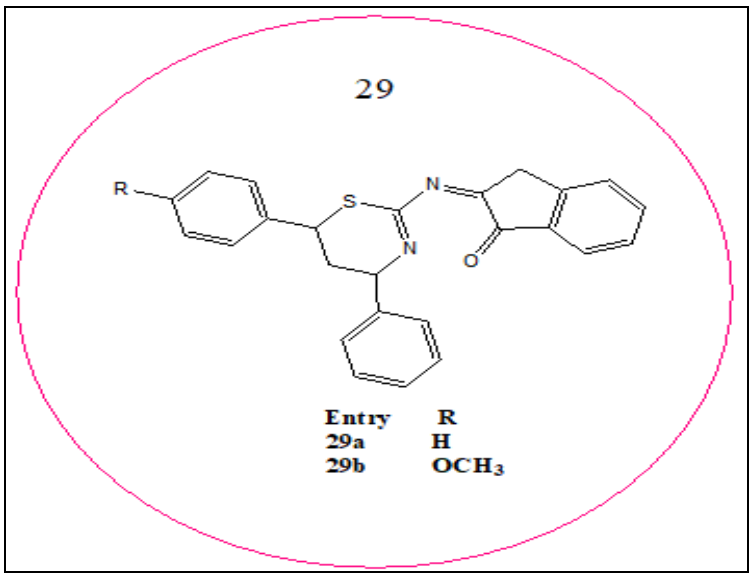

FIG. 14: POTENT DERIVATIVES OF CHALCONE LINKED ISATIN DERIVATIVES HYBRIDS FOR ANTI-INFLAMMATORY ACTIVITY

CONCLUSIONS: Chalconederived / Isatin derived / Ferrocene derived combinations exhibited promising *in-vitro* and *in-vivo* activity against both drugsusceptible and drugresistant cancers as well as other biological activities such as antibacterial, antimalarial, anti-inflammatory. Thus, on a critical overview of chalcone-isatin, chalcone-ferrocene, isatin-ferrocene moiety is a useful template for the development of novel agents it has found that some structural activity relationship for improving the biological activities. Promising treatment may result from the hybridization of different pharmacophores. A hybrid moiety's potency entirely depends on adding and removing the various substituents like electron donating and electron withdrawing groups relating to the increasing and decreasing the activity is created by analysing structural activity relationships towards the desired activity. Furthermore, heterocyclic nucleus moiety especially provides desirable activity as well as a favourable location for the substitution, so structural activity relationships disclose information regarding the intended activity.

ACKNOWLEDGMENTS: The authors are thankful to principal of Government College of pharmacy, Chh. Sambhajinagar, Maharashtra, India 431005 for providing the continuous support and encouragement.

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Tilekar K, Shelke O, Upadhyay N, Lavecchia A and Ramaa CS: Current status and future prospects of molecular hybrids with thiazolidinedione (TZD) scaffold in anticancer drug discovery. J Mol Struct 2022; 1250: 131767. doi:10.1016/j.molstruc.2021.131767
2. Giordano A, Pinto C and Pentimalli F: Cancer research and care in the future post Covid 19 ERA. Annals of Research in Oncology 2021; 01(01): 4. doi: 10.48286/aro.2021.01
3. Akhtar J, Khan AA, Ali Z, Haider R and Shahar Yar M: Structure-activity relationship (SAR) study and design strategies of nitrogen-containing heterocyclic moieties for their anticancer activities. Eur J Med Chem 2017; 125: 143-189. doi:10.1016/j.ejmech.2016.09.023
4. Hassan F, Azad I and Asif M: Isatin Conjugates as Antibacterial Agents: A Brief Review. Med Chem (Los Angeles) 2023; 19(5): 413-430. doi:10.2174/1573406418666220930145336
5. Feng LS, Xu Z and Chang L: Hybrid molecules with potential *in-vitro* antiplasmodial and *in-vivo* antimalarial activity against drug-resistant Plasmodium falciparum. Med Res Rev 2020; 40(3): 931-971. doi: 10.1002/med.21643
6. Shaveta, Mishra S and Singh P: Hybrid molecules: The privileged scaffolds for various pharmaceuticals. Eur J Med Chem 2016; 124: 500-536. doi: 10.1016/j.ejmech.2016.08.039
7. Dhaliwal JS, Moshawih S and Goh KW: Pharmacotherapeutics Applications and Chemistry of Chalcone Derivatives. Molecules 2022; 27(20): 7062. doi: 10.3390/molecules27207062
8. Bosch T: Recent advances in therapeutic apheresis. Journal of Artificial Organs 2003; 6(1): 1-8. doi:10.1007/s100470300000
9. Syahri J, Hilma R, Nurlaili, Saputri H, Nasution SZ and Nurohmah BA: Synthesis, characterization, biological evaluation, and docking simulation of chalcone derivatives as potent antibacterial agents. In 2023; 020044. doi: 10.1063/5.0130012
10. Eldaly SM and Metwally NH: Green synthesis of some new azolopyrimidines as antibacterial agents based on thiophene-chalcone. Synth Commun 2024; 54(5): 348-370. doi:10.1080/00397911.2023.2297971
11. Henry EJ, Bird SJ, Gowland P, Collins M and Cassella JP: Ferrocenyl chalcone derivatives as possible antimicrobial agents. J Antibiot (Tokyo) 2020; 73(5): 299-308. doi: 10.1038/s41429-020-0280-y
12. Syahri J, Hilma R and Ali AH: Chalcone Mannich base derivatives: synthesis, antimalarial activities against Plasmodium knowlesi and molecular docking analysis. RSC Adv 2023; 13(51): 36035-36047. doi: 10.1039/D3RA05361J
13. Mulula A, Bouzina A, Nsomue J, Mambu H, Tshingamb M and Zaki A: Synthesis, *in-vitro* antimalarial activity and *in-silico* molecular docking study of amino chalcone derivatives from 1-(2-aminophenyl)-3-(4- substituted-phenyl) prop-2-en-1-one and Dihydroquinolone Derivatives. Journal of Advanced Pharmacy Research. 2023; 7(3): 133-143. doi:10.21608/aprh.2023.207345.1217
14. Baek S, Nah S and Park JY: A novel chalcone derivative exerts anticancer effects by promoting apoptotic cell death of human pancreatic cancer cells. Bioorg Med Chem 2023; 93: 117458. doi:10.1016/j.bmc.2023.117458
15. Muhammad Z, Yau J, Zezi AU, Magaji MG and Hamza AN: Synthesis and anti-tumor activity of piperonal substituted chalcone. American Journal of Pharmacotherapy and Pharmaceutical Sciences 2023; 2: 11. doi:10.25259/AJPPS_2023_011
16. Mittal R, Sharma S, Kushwah AS, Yaqoob O and Kumari D: A comprehensive review on the anti-inflammatory activity of chalconesderived moieties. Current Traditional Medicine 2024; 10(1). doi: 10.2174/2215083809666230301085620
17. Brasil AMV, Lopes JR de F, Chagas AF da S and Franco AMR: Therapeutic potential of hesperidin methyl chalcone in the experimental treatment of *Cutaneous leishmaniasis*. Acta Amazon 2024; 54(1). doi: 10.1590/1809-4392202203181
18. Liu C, Zhang Y and Li P: Development of chalcone-like derivatives and their biological and mechanistic investigations as novel influenza nuclear export inhibitors. Eur J Med Chem 2023; 261: 115845. doi: 10.1016/j.ejmech.2023.115845
19. Sivakumar PM, Prabhakar PK and Doble M: Synthesis, antioxidant evaluation, and quantitative structure-activity relationship studies of chalcones. Medicinal Chemistry Research 2011; 20(4): 482-492. doi:10.1007/s00044-010-9342-1
20. Ramírez-Bedoya C, Cardona-Galeano W, Herrera-Ramírez A and Yepes AF: A Promising Therapeutic Scaffold

Fusing Chalcone/Coumarin Targeting Colorectal Cancer: Design, Synthesis, Biological and ADME-tox Modelling. Chemistry Select 2024; 9(16). doi:10.1002/slct.202400777

21. Pereira de Oliveira Borlot JR, Schlittler dos Santos L and Schwarzt Sampaio GJ: Synthesis, Docking Studies and Evaluation of Chalcones as Anti- Helicobacter pylori and antitumoral Agents. Chem Biodivers 2023; 20(10). doi:10.1002/cbdv.202301066
22. Greeff J, Joubert J, Malan SF and Van Dyk S: Antioxidant properties of 4-quinolones and structurally related flavones. Bioorg Med Chem 2012; 20(2): 809-818. doi:10.1016/j.bmc.2011.11.068
23. Abdel Ghani SB, Weaver L, Zidan ZH, Ali HM, Keevil CW and Brown RCD: Microwave-assisted synthesis and antimicrobial activities of flavonoid derivatives. Bioorg Med Chem Lett 2008; 18(2): 518-522. doi: 10.1016/j.bmcl.2007.11.081
24. Rammohan A, Reddy JS, Sravya G, Rao CN and Zyryanov G V: Chalcone synthesis, properties and medicinal applications: a review. Environ Chem Lett 2020; 18(2): 433-458. doi:10.1007/s10311-019-00959-w
25. Kolambe J, Yogita Shinde DR, Kalpana Patankar Jain DR and Gunwanti Sinwal DR: Review on Substituted Chalcones 2023.
26. Said Eddarir NCYB: An efficient synthesis of chalcones based on the Suzuki reaction. Tetrahedron Letters, 44(28), 5359–5363. 10.1016/s0040-4039(03)01140-7. Tetrahedron Letters. Published 2003. Accessed September 8, 2023. https://sci-hub.se/https://doi.org/10.1016/S0040-4039(03)01140-7
27. Lin D, Yang H and Zhang X: Palladium-catalysed Suzuki–Miyaura coupling of α,β-unsaturated superactive triazine esters. Chemical Communications 2023; 59(32): 4810-4813. doi:10.1039/D3CC00336A
28. Kmjjfj RGS: Reactions of unsaturated acid halides IV. Tetrahedron 34(6): 741–746. 10.1016/0040-4020 (78)88113-7. Tetrahedrone 1997; 34: 741-746. Accessed September 8, 2023. https://sci-hub.se/https://doi.org/10.1016/0040-4020(78)88113-7
29. Mulugeta D: A review of synthesis methods of chalcones, flavonoids, and coumarins. Science Journal of Chemistry 2022; 10(2): 41. doi:10.11648/j.sjc.20221002.12
30. Ubba E, Nawaz Khan FR, Teja C and Dalavai R: One pot sequential aldol condensation - michael addition – sonogashira, and heck arylation toward highly functionalized quinolines. Polycycl Aromat Compd 2023; 43(3): 1987-2000. doi:10.1080/10406638.2022.2039225
31. Kumar A, Sharma S, Tripathi VD and Srivastava S: Synthesis of chalcones and flavanones using Julia-Kocienski olefination. Tetrahedron 2010; 66(48): 9445-9449. doi:10.1016/j.tet.2010.09.089
32. Bergman J, Lindström JO and Tilstam U: The structure and properties of some indolic constituents in *Couroupita guianensis* aubl. Tetrahedron, 41(14), 2879–2881 | 10.1016/s0040-4020(01)96609-8. Tetrahedron 1985; 41(14): 2879-2881.
33. Da Silva JFM, Garden SJ and Pinto AC: The Chemistry of Isatins: A Review from 1975 to 1999. J Braz Chem Soc 2001; 12(3): 273-324. doi: 10.1590/s0103-50532001000300002
34. Adhikari HS, Garai A and Yadav PN: Synthesis, characterization, and anticancer activity of chitosan functionalized isatin based thiosemicarbazones, and their copper (II) complexes. Carbohydr Res 2023; 526: 108796. doi:10.1016/j.carres.2023.108796
35. Altamimi M, Syed SA, Tuzun B, Alhazani MR, Alnemer O and Bari A: Synthesis biological evaluation and molecular docking of isatin hybrids as anti-cancer and anti-microbial agents. J Enzyme Inhib Med Chem 2024; 39(1). doi: 10.1080/14756366.2023.2288548
36. Muthukumaran T, K AK and M Saleshier F: Docking, synthesis, and *in-vitro* anti-depressant activity of certain isatin derivatives. Curr Comput Aided Drug Des 2024; 20(5): 431-440. doi:10.2174/1573409919666230523114134
37. Nath Pandeya S, Smitha S, Jyoti M and Sridhar SK: Biological activities of isatin and its derivatives. Acta Pharma 2005; 55: 27-46.
38. Varun, Sonam and Kakkar R: Isatin and its derivatives: a survey of recent syntheses, reactions, and applications. Medchemcomm 2019; 10(3): 351-368. doi: 10.1039/c8md00585k
39. Nazeer E, URA and Dharan SS: 2, 3-Dioxoindoline Derivatives: Synthesis, Reactions and Exploring Pharmacological Activities. International Journal of Research and Review 2022; 9(12): 109-123. doi:10.52403/ijrr.20221212
40. Nath R, Pathania S, Grover G and Akhtar MJ: Isatin containing heterocycles for different biological activities: Analysis of structure activity relationship. J Mol Struct 2020; 1222: 128900. doi:10.1016/j.molstruc.2020.128900
41. Nath R, Pathania S, Grover G and Akhtar MJ: Isatin containing heterocycles for different biological activities: Analysis of structure activity relationship. J Mol Struct 2020; 1222. doi:10.1016/j.molstruc.2020.128900
42. Popp PD: The Chemistry of Isatin. Adv Heterocycl Chem. 1975; 18(C): 1-58. doi:10.1016/S0065-2725(08)60127-0
43. Verma DK, Sahu R and Berdimurodov E: Isatin as a new core in the development of corrosion inhibitors: A comprehensive review. J Mol Struct 2023; 1294: 136313. doi: 10.1016/j.molstruc.2023.136313
44. Rauf U, Shabir G, Bukhari S, Albericio F and Saeed A: Contemporary developments in ferrocene chemistry: physical, chemical, biological and industrial aspects. Molecules 2023; 28(15): 5765. doi: 10.3390/molecules28155765
45. Sideri IK, Stangel C and Stergiou A: Covalently modified mos2 bearing a hamilton-type receptor for recognizing a redox-active ferrocene-barbiturate guest *via* multiple h-bonds. Chemistry - A European Journal 2023; 29(45). doi:10.1002/chem.202301474
46. Asqarov I, Otakhonov Q, Madrahimov Lecturer G and Avazbekov Master I: Student D. Synthesis of Some Ferrocene Derivatives. www.americanjournal.org
47. Rammohan A, Reddy JS, Sravya G, Rao CN and Zyryanov G V: Chalcone synthesis, properties and medicinal applications: a review. Environ Chem Lett 2020; 18(2): 433-458. doi:10.1007/s10311-019-00959-w
48. Xu S, Shieh M, Paul BD and Xian M: Hydrogen sulfide: Recent development of its dual donors and hybrid drugs. Br J Pharmacol. Published Online 2023 doi: 10.1111/bph.16211
49. Shaveta, Mishra S, Singh P. Hybrid molecules: The privileged scaffolds for various pharmaceuticals. Eur J Med Chem 2016; 124: 500-536. doi:10.1016/j.ejmech.2016.08.039
50. Feng LS, Xu Z and Chang L: Hybrid molecules with potential *in-vitro* antiplasmodial and *in-vivo* antimalarial activity against drug-resistant Plasmodium falciparum. Med Res Rev 2020; 40(3): 931-971. doi: 10.1002/med.21643
51. Singh A, Viljoen A, Kremer L and Kumar V: Synthesis and antimycobacterial evaluation of piperazyl-alkyl-ether linked 7-chloroquinoline-chalcone/ferrocenyl chalcone

conjugates. Chemistry Select 2018; 3(29): 8511-8513. doi:10.1002/slct.201801453
52. Koszytkowska-Stawińska M and Buchowicz W: Ferrocene-triazole conjugates: do we know why they are biologically active? Dalton Transactions 2023; 52(6): 1501-1517. doi:10.1039/D2DT03161B
53. Mishra S and Jana P: Chalcones as anti-infective agents for effective management of tuberculosis. polycycl aromat compd. Published online 2023; 1-23. doi:10.1080/10406638.2023.2261593
54. Singh A, Viljoen A, Kremer L and Kumar V: Azide-alkyne cycloaddition en route to 4-aminoquinoline-ferrocenylchalcone conjugates: Synthesis and anti-TB evaluation. Future Med Chem 2017; 9(15): 1701-1708. doi:10.4155/fmc-2017-0098
55. Kumar K, Biot C and Carrère-Kremer S: Base-promoted expedient access to spiroisatins: Synthesis and antitubercular evaluation of 1 h -1,2,3-triazole-tethered spiroisatin-ferrocene and isatin-ferrocene conjugates. Organometallics. 2013; 32(24): 7386-7398. doi:10.1021/om4009229
56. Kumar K, Carrère-Kremer S, Kremer L, Guérardel Y, Biot C and Kumar V:1 H -1,2,3-Triazole-tethered isatin-ferrocene and isatin-ferrocenylchalcone conjugates: Synthesis and *in-vitro* antitubercular evaluation. Organometallics 2013; 32(20): 5713-5719. doi: 10.1021/om301157z
57. Sharma B, Gu L and Pillay RP: Design, synthesis, and anti-proliferative evaluation of 1: H -1,2,3-triazole grafted tetrahydro-β-carboline-chalcone/ferrocenylchalcone conjugates in estrogen responsive and triple negative breast cancer cells. New Journal of Chemistry 2020; 44(26): 11137-11147. doi:10.1039/d0nj00879f
58. Singh A, Mehra V, Sadeghiani N, Mozaffari S, Parang K and Kumar V: Ferrocenylchalcone–uracil conjugates: synthesis and cytotoxic evaluation. Medicinal Chemistry Research 2018; 27(4): 1260-1268.
59. Singh A, Saha ST, Perumal S, Kaur M and Kumar V: Azide−alkyne cycloaddition En route to 1H 1,2,3-triazole-tethered isatin−ferrocene, ferrocenylmethoxy−isatin, and isatin− ferrocenylchalcone conjugates: Synthesis and antiproliferative evaluation. ACS Omega 2018; 3(1): 1263-1268. doi:10.1021/acsomega.7b01755
60. Muller TJ, Conradie J and Erasmus E: A spectroscopic, electrochemical and DFT study of para-substituted ferrocene-containing chalcone derivatives: Structure of FcCOCHCH(p- tBuC6H4). Polyhedron 2012; 33(1): 257-266. doi:10.1016/j.poly.2011.11.034
61. Luqmani YA: Mechanisms of drug resistance in cancer chemotherapy. In: Medical Principles and Practice. Vol 14. S. Karger AG 2005; 35-48. doi:10.1159/000086183
62. Shi HB, Zhang SJ, Ge QF, Guo DW, Cai CM and Hu WX: Synthesis and anticancer evaluation of thiazolyl-chalcones. Bioorg Med Chem Lett 2010; 20(22): 6555-6559. doi:10.1016/j.bmcl.2010.09.041
63. Firoozpour L, Edraki N and Nakhjiri M: Cytotoxic activity evaluation and QSAR study of chromene-based chalcones. Arch Pharm Res 2012; 35(12): 2117-2125. doi:10.1007/s12272-012-1208-2
64. Aryapour H, Riazi GH and Foroumadi A: Biological evaluation of synthetic analogues of curcumin: Chloro-substituted-20-hydroxychalcones as potential inhibitors of tubulin polymerization and cell proliferation. Medicinal Chemistry Research 2011; 20(4): 503-510. doi: 10.1007/s00044-010-9344-z
65. Shan Y, Zhang J, Liu Z, Wang M and Dong Y: Developments of Combretastatin A-4 Derivatives as Anticancer Agents 2011; 18.
66. Letafat B, Shakeri R and Emami S: Synthesis and *in-vitro* cytotoxic activity of novel chalcone-like agents 2013; 16.
67. Ammar YA, Fayed EA and Bayoumi AH: New chalcones bearing isatin scaffold: synthesis, molecular modeling and biological evaluation as anticancer agents. Research on Chemical Intermediates 2017; 43(12): 6765-6786. doi:10.1007/s11164-017-3019-z
68. Singh A, Rani A, Gut J, Rosenthal PJ and Kumar V: Piperazine-linked 4-aminoquinoline-chalcone/ferrocenyl-chalcone conjugates: Synthesis and antiplasmodial evaluation. Chem Biol Drug Des 2017; 90(4): 590-595. doi:10.1111/cbdd.12982
69. Singh A, Gut J, Rosenthal PJ and Kumar V: 4-Aminoquinoline-ferrocenyl-chalcone conjugates: Synthesis and anti-plasmodial evaluation. Eur J Med Chem. 2017; 125: 269-277. doi: 10.1016/j.ejmech.2016.09.044
70. Kumar K, Pradines B, Madamet M, Amalvict R and Kumar V: 1H-1,2,3-triazole tethered mono- and bis-ferrocenylchalcone-β-lactam conjugates: Synthesis and antimalarial evaluation. Eur J Med Chem 2014; 86: 113-121. doi:10.1016/j.ejmech.2014.08.053
71. Yagnam S, Trivedi R, Krishna S, Giribabu L, Praveena G and Prakasham RS: Bioactive isatin (oxime)-triazole-thiazolidinedione ferrocene molecular conjugates: Design, synthesis and antimicrobial activities. J Organomet Chem 2021; 937. doi:10.1016/j.jorganchem.2021.121716
72. Singh A, Zhang D, Tam CC, Cheng LW, Land KM and Kumar V: Click-chemistry approach to synthesis of functionalized isatin-ferrocenes and their biological evaluation against the human pathogen Trichomonas vaginalis. J Organomet Chem 2019; 896: 1-4. doi:10.1016/j.jorganchem.2019.05.025
73. Singh A, Fong G and Liu J: Synthesis and Preliminary Antimicrobial Analysis of Isatin-Ferrocene and Isatin-Ferrocenyl Chalcone Conjugates. ACS Omega 2018; 3(5): 5808-5813. doi:10.1021/acsomega.8b00553
74. Purohit SS: Microbiology Fundamentals and Applications Seventh Revised and Enlarged Edition Agrobios India 2006.
75. Ahmed N, Konduru NK and Owais M: Design, synthesis and antimicrobial activities of novel ferrocenyl and organic chalcone based sulfones and bis-sulfones. Arabian Journal of Chemistry 2019; 12(8): 1879-1894. doi:10.1016/j.arabjc.2014.12.008
76. Rohini C and Arasan KT: Synthesis and IR spectroscopic characterization of some synthesized chalcone linked isatin derivatives. Int J Curr Res 2021; 13(10): 19355-19357. doi:10.24941/ijcr.42508.10.2021

How to cite this article:
Patil SN, Nagulwar V and Patil SN: "Synergistic convergence: exploring combinations of diverse physiological activities - a review". Int J Pharm Sci & Res 2024; 15(10): 2875-94. doi: 10.13040/IJPSR.0975-8232.15(10).2875-94.