Journal of Organometallic Chemistry 937 (2021) 121716

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Bioactive isatin (oxime)-triazole-thiazolidinedione ferrocene molecular conjugates: Design, synthesis and antimicrobial activities

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ARTICLE INFO

Article history:
Received 27 July 2020
Revised 13 January 2021
Accepted 19 January 2021
Available online 22 January 2021

Keywords:
Ferrocene-molecular conjugates
Isatin (Oxime)
1,2,3-Triazole
2,4-Thiazolidinedione
Electrochemistry
Antimicrobial activity

ABSTRACT

Molecular conjugates often combine the inherent properties of the individual components and exhibit a different characteristic feature. Introduction of an organometallic moiety can indeed augment the overall effect. This article narrates the synthesis of ferrocene appended isatin−2,4-thiazolidinedione molecular hybrid linked via a triazole moiety. Isatin and 2,4-thiazolidinedione were linked via a triazole unit formed by a simple copper catalysed alkyne-azide 1,3-dipolar cycloaddition reaction. The UV–vis and electrochemical studies on all the new compounds are reported. Antimicrobial activity against some selected gram-positive and gram-negative strains was also examined for all the new derivatives and compounds **6(b), 6(c), 6(h)** and **6(i)** revealed similar antimicrobial activity for all tested microbes and similar pattern to that of standard antibiotics.

1. Introduction

Drug design using molecular hybridization approach, for developing new antimicrobial candidates that exhibit better activity, has been gaining unprecedented attention [1]. An effective and commonly used direction for the exploration of novel and highly active compounds relies on combining two or more different bioactive molecules either having complementary pharmacophoric functions or displaying variable mechanism of action against the microbial strain [2]. Quite often such type of hybrid drugs can have potential to overcome the pharmacokinetic drawbacks encountered by a number of conventional drugs [3]. Towards this, certain common heterocyclic fragments such as isatin, [4] 1,2,3-triazoles, [5] and 2,4-thiazolidinediones, [6] have demonstrated potential chemotherapeutic and antimicrobial activities as shown in (Fig. 1). Moreover, there are several published reports on the use of triazole tethered bi-functional hybrids and its role as a linker to join two different bioactive functionalities [7].

1H-indole-2,3–dione (commonly known as Isatin), has three different possibility of chemical modifications namely, N_1, C_3 and C_5 positions and also serves as a prominent scaffold for the design of several biologically active compounds [8]. These modifications result in several biological activities such as anti-cancer [9,10] anti-oxidant [11], HIV reverse transcriptase inhibition [12,13], neuroprotective [14], anti-fungal [15], antidepressant, [16] anticonvulsant, [17] anti-bacterial [18], and antidiabetic [19]. Few of the C_5 and C_6 substituted isatin derivatives exhibited inhibition against monoamine oxidase B and amongst them 5-(4-phenylbutyl) isatin was found to be 18,500-fold more potent than the parent compounds [12]. The C_3 carbonyl group of isatin is highly reactive and can be conveniently utilized for the construction of spirooxindole framework [13–15]. As indicated in recent studies, isatin can inhibit the growth of SH-SY5Y cells as well as induce apoptosis via an intrinsic apoptotic [20,21].

2,4-Thiazolidinedione, a sulphur, nitrogen and oxygen containing five-member heterocyclic moiety, also exhibits potential for a range of biological activities, often present in several drug molecules and natural products [22]. These five member heterocyclic systems have potency to reduce insulin resistance as well as effective in the treatment of cardiovascular metabolic syndrome [23]. Particularly, 4-thiazolidinones have exhibited various impor-

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https://doi.org/10.1016/j.jorganchem.2021.121716
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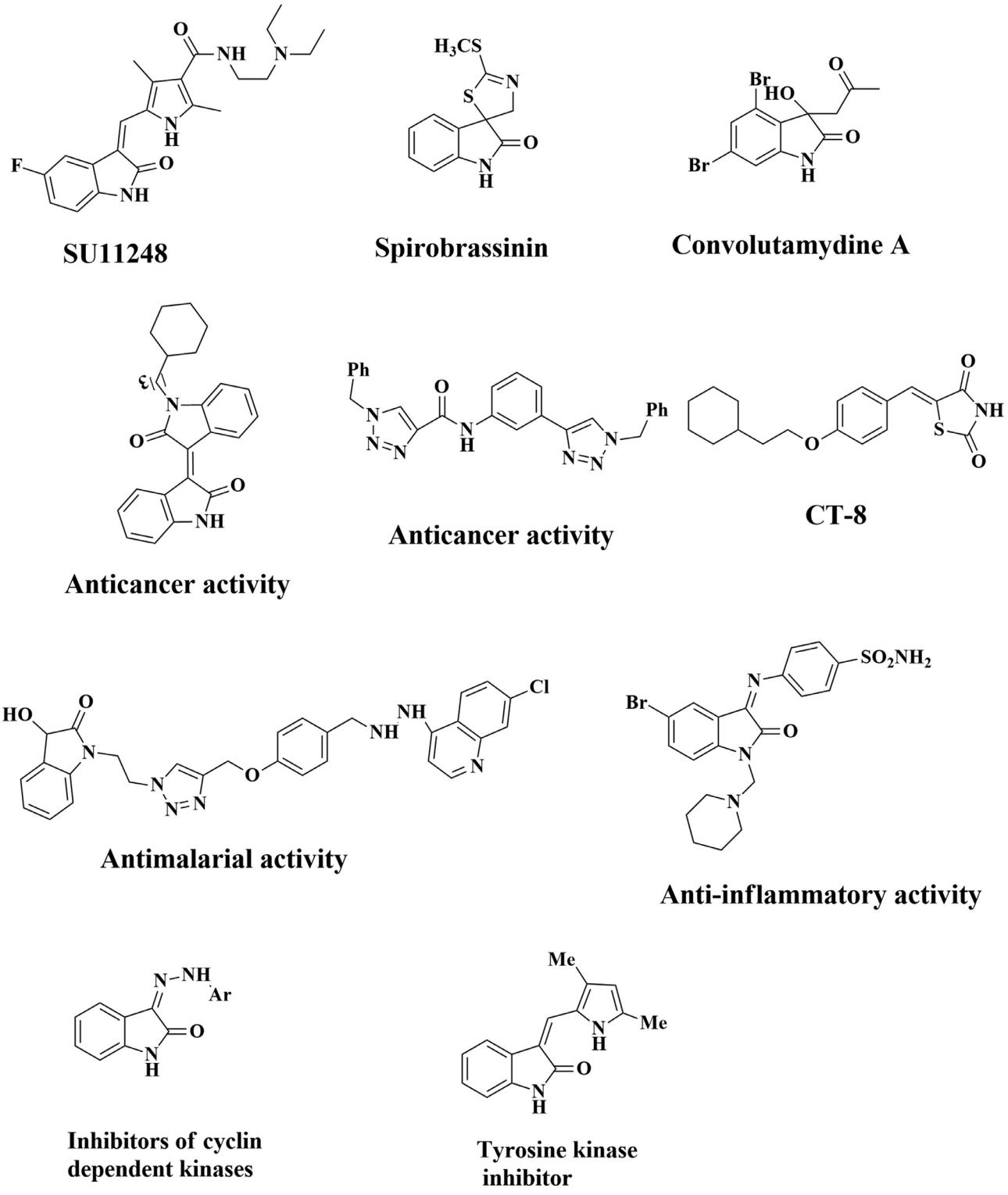
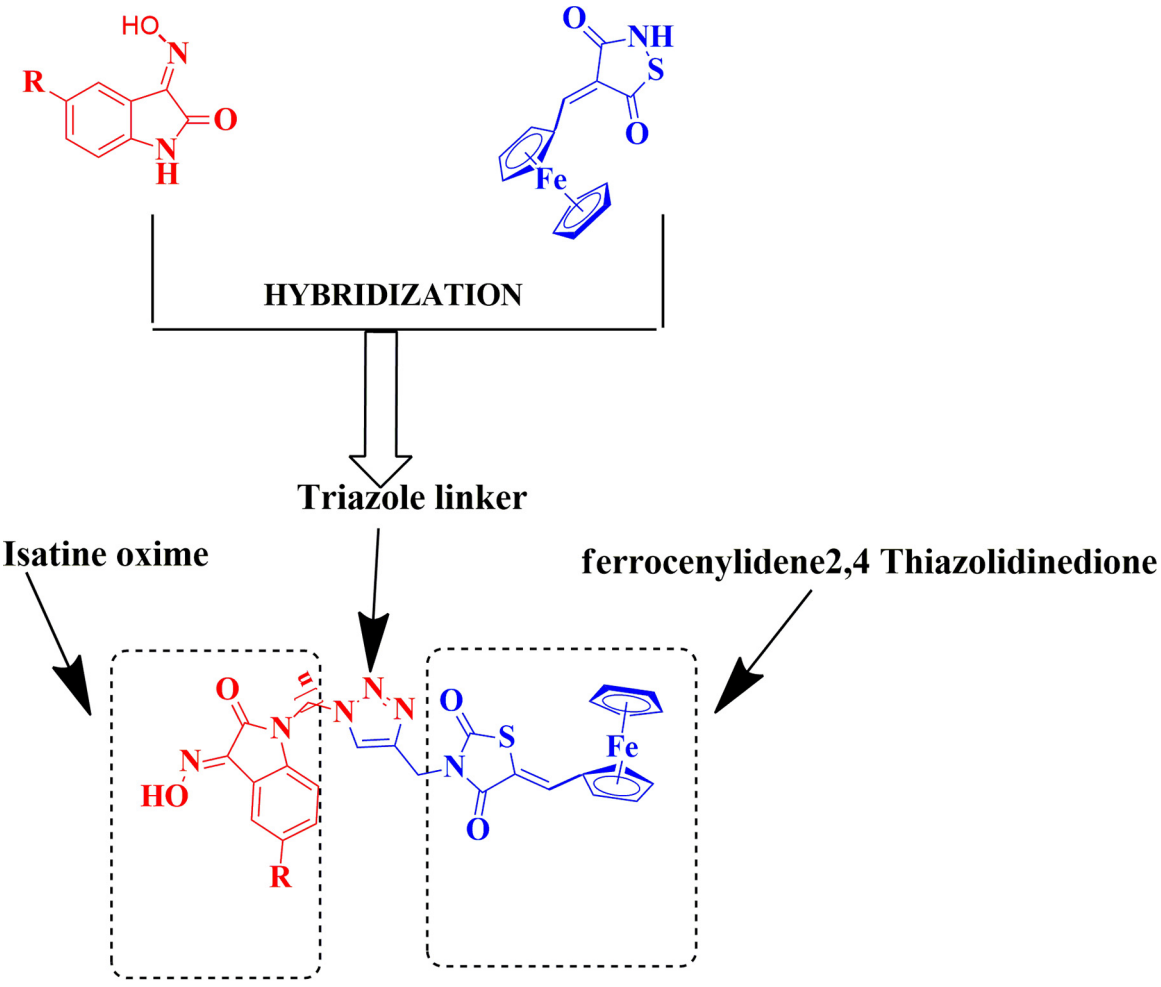


Fig. 1. Some of the biologically active molecules of Isatin, 1*H*-1,2,3-triazoles and 2,4-thiazolidinedione.

tant biological activities such as anti-inflammatory, anti-tubercular, antimicrobial, anticonvulsant, antiviral and anti-HIV [24].

Due to its metabolic stability and varied biological activities, 1H-1,2,3-triazole is often a preferable choice as a linker in the molecular hybridization approach [25]. The enhanced biological activities of the 1,2,3-triazole ring relies on a number of factors such as moderate dipole character, hydrogen bonding capability, rigidity as well as stability under in vivo conditions [26]. The construction of bioconjugates via triazoles is an appealing synthetic methodology. Interactions and effects of organometallic moieties conjugated to a bioactive component has developed as a full-fledged research area [27]. Over the last few years, a close association between classical organometallic chemistry and medicine, biology and molecular biotechnology has emerged [28]. In recent years, organometallic conjugates have become pivotal as medicinally important molecules which demonstrated their potential as new therapeutic as well as diagnostic agents [29]. Moreover, the high stability of the ferrocenyl group in water as well as its reversible electro-



Entry	n	R	Entry	n	R
6a	3	H	6f	4	H
6b	3	CH_3	6g	4	CH_3
6c	3	OCH_3	6h	4	Cl
6d	3	F	6i	4	F
6e	3	Br	6j	4	Br

Fig. 2. Illustration of the design strategy for triazole tethered isatin and 2,4 Thiazolidinedione.

chemistry has made ferrocene unit as a prominent organometallic entity to conjugate with drugs and biomolecules [30]. In fact, several bioorganometallic compounds exhibited anticancer properties, however, interest in antimicrobial, anti-parasitic and antibacterial activities of such compounds is gaining substantial attention.

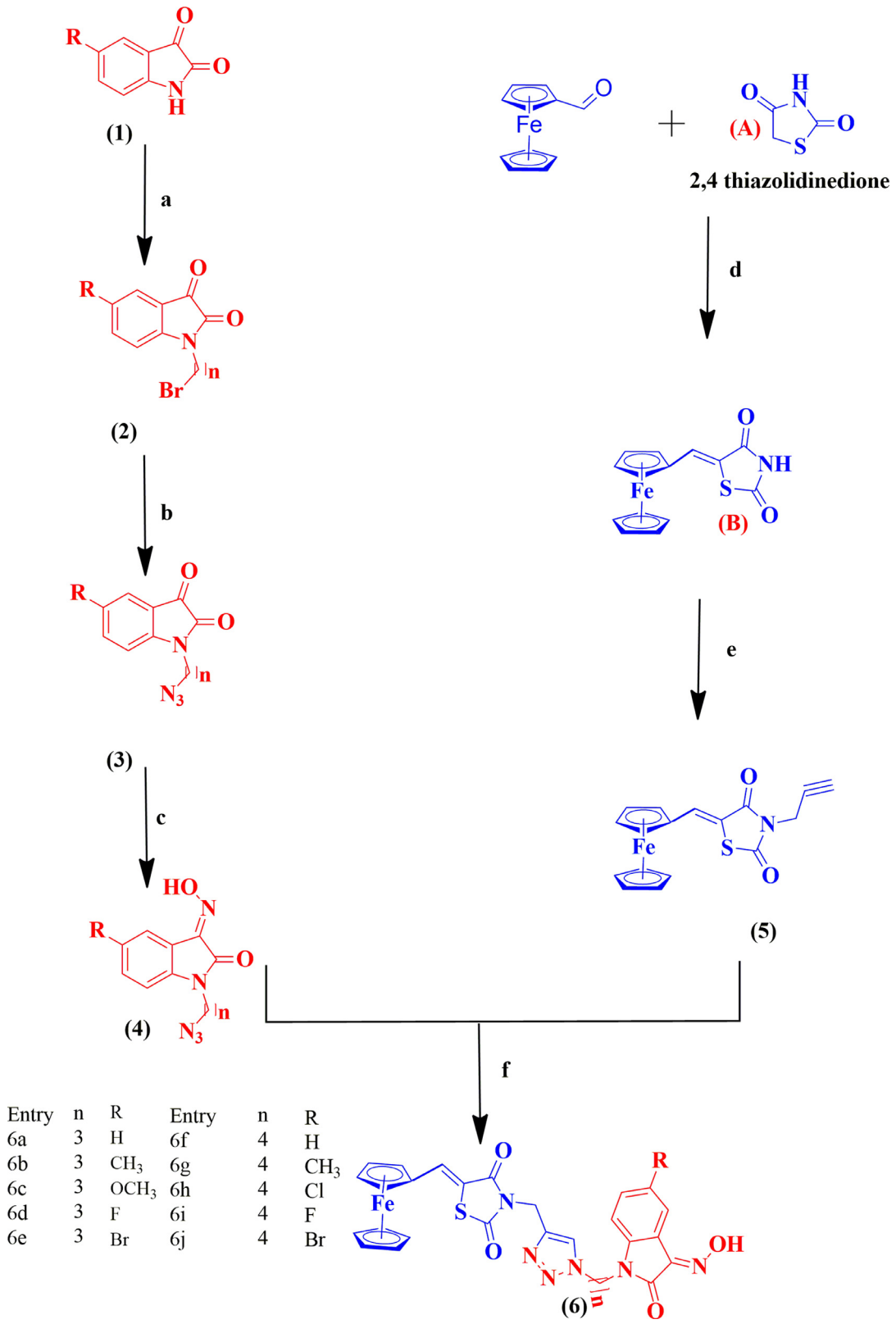
The simple synthetic procedures and favourable electronic properties of ferrocene derivatives contributed to their widespread applications as sensors, [31] catalysts, [32] and electronic probes, [33] as well as in the field of medicinal chemistry [34–37]. Ferrocifen, hydroxyferrocifen, ferrophanes and ferroquine are some of the ferrocene derivatives well known for exhibiting anti-cancer and anti-malarial activities [38–45].

Over the past decade, our group has been involved in the synthesis, characterisation and biological evaluation of a variety of ferrocene conjugates that include simple organic as well as bioactive linkers. Some of these belong to amides, triazoles, amide-triazoles, pseudo-peptides, sugar boronates, imidazolinones and 2,4-thiazolidinediones to name a few [46]. In continuation with our interest, the present work describes the synthesis, electrochemical properties and in vitro antimicrobial evaluation of 1H-1,2,3-triazole tethered isatin-ferrocene-thiazolidinedione conjugates as depicted in Fig. 2.

2. Results and discussion

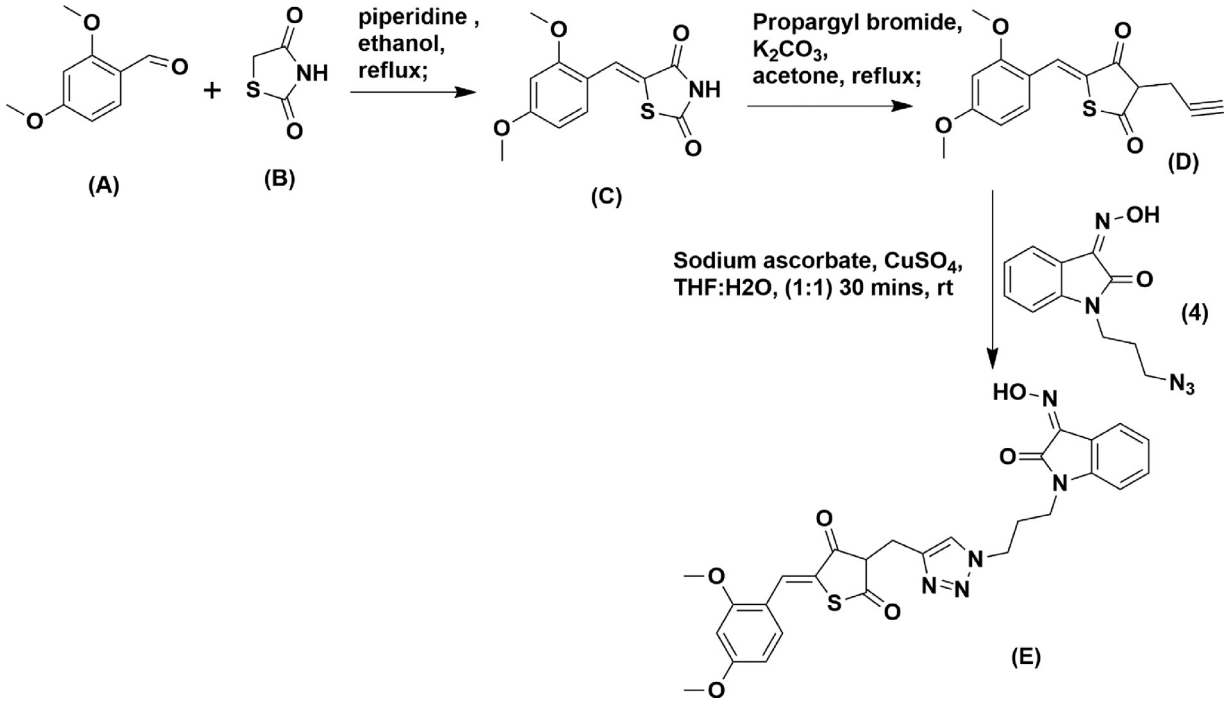
2.1. Synthesis and characterization

Scheme 1 illustrates the synthetic route followed for the preparation of the desired isatin (oxime)-triazole-2,4-thiazolidinedionehybrids, **6(a-j).** Previously reported protocol was



Entry	n	R	Entry	n	R
6a	3	H	6f	4	H
6b	3	CH_3	6g	4	CH_3
6c	3	OCH_3	6h	4	Cl
6d	3	F	6i	4	F
6e	3	Br	6j	4	Br

Scheme 1. Synthesis of triazole linked isatin- 2,4 Thiazolidinedione conjugates. Reagents and conditions: (a) Dibromoalkane, K_2CO_3, CH_3CN, 2 h, rt; (b) NaN_3, DMF, 3 h, reflux; (c) NH_2OH, NaOH, rt,1 h; (d) piperidine, ethanol, reflux; e) Propargyl bromide, K_2CO_3, DMF, rt; (f) Sodium ascorbate, $CuSO_4$, THF:H_2O, (1:1) 30 mins, rt.



Scheme 2. Synthesis of Triazole linked isatin- 2,4 Thiazolidinedione, (**E**).

followed for the preparation of C_5-substituted N-alkyl azido-isatins (**3**), [47] wherein, an initial base promoted alkylation of isatin (**1**) with dibromoalkanes forms the corresponding C5-substituted N-alkyl bromoisatins (**2**) at room temperature in acetonitrile solution. The subsequent treatment of **(2)** with sodium azide at 60°C resulted in the formation of the desired precursors **(3)** as shown in (Scheme 1). The precursor, **(3)** reacts with hydroxyl amine to give a N-alkylazido-hydxoxyiminoisatins **(4)**. The desired 1H-1,2,3-triazole tethered isatin ferrocene conjugates, **6(a-j)** were obtained from the copper promoted alkyne-azide cycloaddition reaction of compound (**4**) and ferrocenyl 2,4-thiazolidinedione alkyne (**5**).

While preparing the ferrocenyl conjugates, a parent compound (**E**) was also synthesised starting from the readily available 3,5-dimethoxy benzaldehyde (**A**). Following a similar synthetic protocol as the ferrocene conjugates, the parent compound (**E**) was obtained in moderate yield. (Scheme 2). The compound (**E**) was characterised by ^{1}H NMR, ^{13}C NMR and mass analysis along with antimicrobial properties.

^{1}H and ^{13}C NMR spectroscopic characterisation of all the compounds revealed the corresponding signal. The triazole proton signal for the triazoles **6(a-j)** was observed around δ 7.67 ppm – 7.78 ppm in the ^{1}H NMR spectra. The protons of the unsubstituted cyclopentadienyl (Cp) ring appeared as a singlet at δ 4.15 - 4.22 ppm, while those for the substituted cyclopentadienyl (Cp) ring appeared around δ 4.51 ppm and 4.59 ppm. The *N*=OH protons appeared as a broad singlet at around δ12.3 ppm –13.3 ppm. In all the triazole compounds, **6(a-j)**, the isatin (oxime) N–CH_2 was observed as a multiplet around δ3.7–3.8 ppm. The olefinic >*C*=CH proton appeared as a singlet at about δ 7.71 ppm – 8.27 ppm, in the ^{1}H NMR spectra for all the compounds, and the characteristic peaks corresponding to the Tr-N*C*H_2 protons were observed at δ 4.37 ppm –4.43 ppm. In the ^{13}C NMR spectra, for all the triazoles, the carbonyl carbon of the ferrocene substituted 2,4-thiazolidinedione fragment appeared at δ 172–163 ppm and the olefinic >*C*=CH carbon appeared at δ 112.9–108.2 ppm, while isatin (oxime) N–CH_2 carbon was observed at δ 36.4 ppm –29.7 ppm. All the compounds were characterized by the mass spectra and elemental analysis. In the FT-IR spectra, the stretching frequencies in the region 3152- 3140 cm^{-1} can be assigned to the C–H vibrations of the triazole ring, while the frequencies around 1680–1677 cm^{-1} are the characteristic C=O stretching frequencies [48].

2.2. UV–Vis spectroscopy

The isatin (oxime) derivatives exhibit characteristic UV–vis absorption spectra, wherein an increase in the intensity of the bands in the 300 nm region is observed for the electron withdrawing groups such as chloro and bromo substituted isatins [49]. Similar pattern can be expected from the isatin ferrocene conjugates, **6(a-j)**. The absorption spectra of ferrocenyl 2,4-thiazolidinedione isatin-triazole conjugates, **6(a-j)** were recorded in acetonitrile solvent (Fig. 3). Two absorption maxima were observed at 332 and 505 nm for all the compounds. The bands constitute the metal-to-ligand charge transfer [Fe(d)- Cp(π^*)] and the symmetry forbidden [Fe(a1g)-Fe(e1g)] or d-d transition for the Fe of ferrocene, respectively. It was observed that the bands corresponding to the Fe(a_{1g})→Fe(e_{1g}) or d-d transitions were weak due to the symmetry forbidden transitions, whereas the intensity of the Fe(e_{2g}))→Cp(e_{1g}) or $\pi \rightarrow \pi^*$ transitions bands was considerably higher even at the concentration range of 0.1 mM. Furthermore, these well resolved π-π^* bands indicated that the ferrocene was conjugated with the isatin moiety [50].

2.3. Electrochemical characterization

The cyclic voltammetry (CV) experiment was conducted in acetonitrile for compounds **6(a-j)** as shown in (Fig. 4). The redox potential data of the triazole compounds **6(a-j)** are summarized in (Table 1). A 0.5 mM solution of the compounds was prepared in acetonitrile solvent with 0.1 M tetrabutylammonium perchlorate (TBAP) as a supporting electrolyte. The typical conventional three-electrode cell consists of a glassy carbon as a working electrode, a platinum wire as an auxiliary electrode and a standard

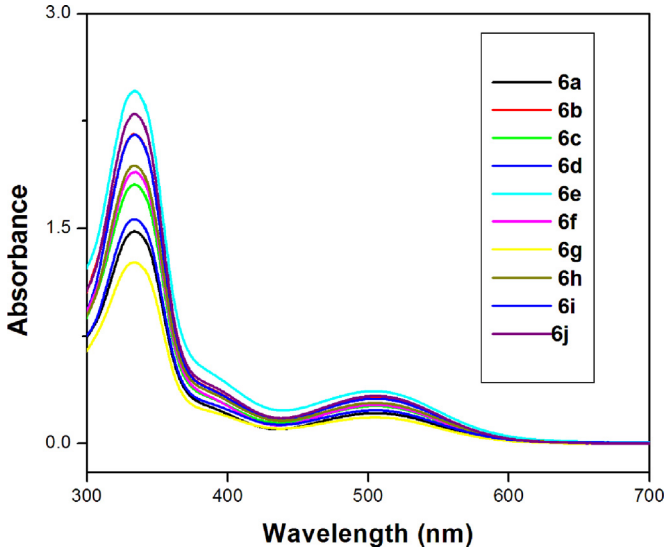


Fig. 3. UV–Vis spectra of triazole**6(a-j)** in acetonitrile at room temperature.

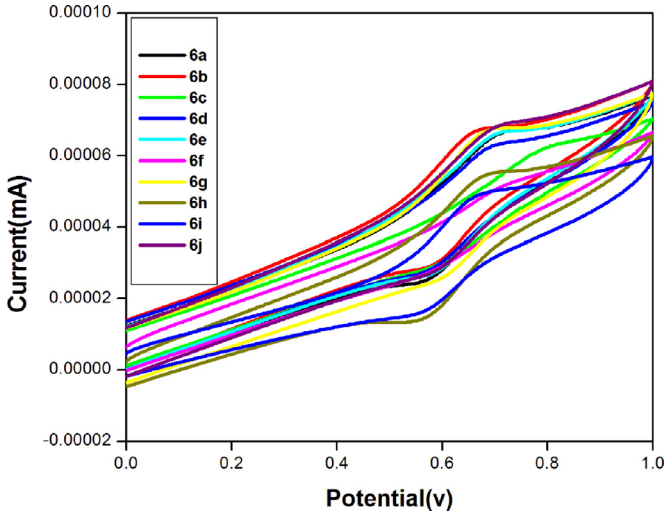


Fig. 4. Electrochemical oxidative potential curves of **6(a-j)** in acetonitrile at room temperature. All the compounds **6(a-j)** in CH_3CN with TBAP (supporting electrolyte) at 25 °C at a scan rate of 100 mV s^{-1}.

Calomel electrode (SCE) as the reference electrode. The potential was scanned with a scan rate of 100 mVs^{-1} over the range 200–1100 mVs^{-1}. A quasi-reversible redox couples of Fe(II)/Fe(III) were obtained in the cyclic voltammograms of **6(a-j)**, as shown in Fig. 4. The values of the half-wave potential ($E_{1/2}$) are shown in (Table 1). The peak current ratio, $i_{pa}/i_{pc} \cong 1$, with high peak separation, similar to those reported in earlier literature was obtained for all the ferrocene derivatives [48]. The oxidation potentials (E_{pa}) for all the isatin ferrocene hybrids, **6(a-j)** were higher than the unsubstituted ferrocene.

2.4. Biological activity

2.4.1. Anti microbial activity

The antibacterial profile of all the synthesized novel triazole conjugates (**6(a-j)**) and aryl compound (**E**) is given in (Table 2). The compounds **6(b), 6(c), 6(h)** and **6(i)** displayed excellent antimicrobial activity towards all the test organisms and the values were comparable to the standard compounds Streptomycin and Flucanazole. While the compound **6(g)** had good antimicrobial activity, the compounds **6(a), 6(d), 6(e), 6(f)** exhibited moderate antimicrobial activity and the lowest activity was shown by the compound **6(j)**. Similar trend has been noticed with selected fungal strains (*Candida albicans* and *Aspergillus oryzae*). Hybrid aryl compound (**E**) exhibited very less activity when compared to the synthesized novel triazole conjugates (**6(a-j)).** The observed higher biological activity for the compound may be attributed to substituted group of isatin ring and due to the combination of triazole and ferrocene unit. Ferrocene and triazole compounds show interesting antibacterial antifungal activities, as per previous reports [51a,b,c].

Table 1
CV and UV data for the isatin conjugated 2,4 Thiazolidinedione Triazole **6(a-j)** obtained from voltammograms (vs. SCE)[a].

Compound code	E_{pa} (mV)	E_{pc} (mV)	ΔE_p (mV)	$E_{1/2}$ (mV)	i_{pa}/i_{pc}
6a	694	550	144	622	1.33
6b	658	577	81	617	0.85
6c	773	616	157	694	0.75
6d	688	573	115	585	1.13
6e	696	580	116	638	0.92
6f	707	612	95	659	1.08
6 g	671	605	66	638	0.92
6h	673	560	113	616	1.05
6i	668	532	136	600	1.29
6j	690	592	98	641	0.93

[a] All the compounds in CH_3CN with TBAP (supporting electrolyte) at 25 °C at a scan rate of 100 mV s^{-1}. $E^0ox = (E_{pc} + E_{pa}/2)$, $\Delta Ep = (E_{pa} - E_{pc})$, i_{pa}/i_{pc} (ratio between anodic and cathodic peak current).

Based on the above results, the MIC of all the compounds were further evaluated against the cultures used for the antimicrobial activity as shown in (Table 3). A MIC value of 4 μg ml^{-1}against the bacterial strains and 32 μg ml^{-1} against the fungal strain was obtained for the compounds **6(b), 6(c), 6(h)** and **6(i)**. This observation is interesting to note that the tested compounds **(6b), (6c), (6 h), (6i)** performed same activity with double the concentration to that of streptomycin (2 $\mu g\ mL^{-1}$) and Fluconazole (16 $\mu g\ mL^{-1}$)

3. Conclusion

In conclusion, a series of isatin-ferrocene conjugates have been synthesized via Cu-promoted alkyne-azide cycloaddition reactions and evaluated for their antimicrobial activities. Absorption spectroscopy and electrochemical studies have shown that the compounds are stable in acetonitrile solvent. The compounds **6(b), 6(f), 6(g), 6(j)** exhibited a reversible oxidation wave and the compounds **6(a), 6(c), 6(d), 6(e), 6(h), 6(i)** exhibited quasi-reversible behaviour. All the compounds demonstrated their characteristic transitions Fe(a1g)→Cp(e2g) and Fe(a1g)→Fe(e1g) transitions) in the UV-Visible spectra. All the synthesized triazole compounds exhibited moderate to good antimicrobial activity. The antibacterial activity of all the synthesized triazole conjugates **6(a-j)** against both Gram-positive (*Bacillus subtilis, Bacillus megaterium, Mycobacterium smegmatis, Klebsiella pneumonia*) and Gram-negative (*Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa,Pseudomonas putida*) bacterial strains were compared against Streptomycin. The *in vitro* antifungal activity of all the synthesized triazole conjugates **6(a-j)** was studied against the two fungal strains (*Candida albicans* and *Aspergillus oryzae)* and Fluconazole was used as a standard drug.

4. Experimental section

All reagent grade chemicals were purchased from Sigma–Aldrich and used as supplied. The Thin Layer Chromatography (TLC) was performed on Merck silica gel F254 plates using hexane and ethylacetate as eluting agents. The products were characterized by ^1H and ^{13}C NMR and Mass (ESI) spectroscopy. All ^1H and ^{13}C NMR spectra were recorded in a mixture of ($CDCl_3$+DMSO–d_6) solvents on Avance 300 or Avance 400 or Avance New 500

Table 2
Antimicrobial activity of compounds **6(a-j)**[a].

Compounds	Gram-positive bacteria				Gram-negative bacteria				Fungal strains	
	B.subtillis	*B.megaterium*	*M.smegmatis*	*K. pneumoniae*	*E.coli*	*S. typhi*	*P.putida*	*P. arguinosa*	*C.albicans*	*A. oryzae*
6a	14±0.4	12±0.3	15±0.4	12±0.4	15±0.3	10±0.4	16±0.3	12±0.4	15±0.4	13±0.3
6b	**19**±0.2	**21**±0.2	**20**±0.2	**20**±0.3	**19**±0.3	**18**±0.2	**21**±0.2	**19**±0.2	**20**±0.3	**20**±0.2
6c	**20**±0.2	**20**±0.3	**22**±0.2	**21**±0.2	**18**±0.2	**19**±0.3	**19**±0.2	**19**±0.3	**19**±0.2	**20**±0.3
6d	13±0.4	13±0.4	16±0.4	14±0.3	15±0.4	12±0.4	16±0.4	13±0.4	14±0.4	16±0.4
6e	13±0.4	13±0.4	15±0.4	17±0.4	15±0.3	12±0.4	16±0.3	12±0.4	12±0.2	15±0.2
6f	12±0.4	14±0.2	15±0.3	13±0.4	14±0.3	11±0.4	13±0.4	15±0.4	16±0.3	15±0.3
6 g	**17**±0.2	**16**±0.4	**15**±0.3	**17**±0.2	**16**±0.2	**15**±0.3	**15**±0.4	**11**±0.4	**16**±0.4	**17**±0.2
6h	**18**±0.2	**19**±0.2	**21**±0.2	**19**±0.2	**20**±0.2	**19**±0.3	**21**±0.2	**18**±0.2	**20**±0.3	**20**±0.2
6i	**19**±0.4	**21**±0.4	**20**±0.4	**20**±0.4	**19**±0.4	**21**±0.4	**19**±0.4	**19**±0.4	**20**±0.4	**19**±0.4
6j	14±0.4	12±0.4	12±0.4	12±0.4	13±0.4	10±0.4	14±0.4	12±0.4	14±0.4	13±0.4
E	10±0.2	11±0.4	11±0.3	11±0.4	10±0.3	10±0.2	10±0.2	11±0.2	10±0.3	11±0.4
Standard drug[b]	21±0.2	22±0.2	25±0.2	22±0.2	21±0.2	21±0.2	23±0.2	20±0.2	21±0.2	22±0.2
DMSO	0	0	0	0	0	0	0	0	0	0

[a] Zone of inhibition by compounds against selected test organisms.
[b] Streptomycin and Fluconazole were used as standard drug, respectively, for antibacterial and antifungal activity evaluation.

Table 3
MIC values of compounds **6(a-j)** in μg mL^{-1}.

Minimum inhibitory concentration (μg mL^{-1}) of compounds (6a-j)against the tested bacterial and fungal strains										
Compounds	Gram-positive bacteria				Gram-negative bacteria				Fungal strains	
	B.subtillis	*B.megaterium*	*M.smegmatis*	*K. pneumoniae*	*E.coli*	*S. typhi*	*P.putida*	*P. arguinosa*	*C.albicans*	*A. oryzae*
6a	32	64	32	64	32	64	32	64	32	64
6b	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**32**
6c	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**32**
6d	64	64	32	32	32	64	32	64	32	64
6e	64	64	32	16	32	64	32	64	64	64
6f	64	32	32	64	32	64	64	32	32	64
6 g	16	32	32	16	32	32	32	64	64	16
6h	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**32**
6i	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**32**
6j	32	64	64	64	64	64	32	64	64	64
E	64	64	64	64	64	64	64	64	64	64
Standard drug[a]	2	2	2	2	2	2	2	2	16	16

[a] Streptomycin sulphate for bacterial strains, and fluconazole for fungal strains were used as standard drugs.

spectrometers. The chemical shifts (δ) for protons were reported in ppm downfield from TMS as the internal standard and the carbon shifts were referenced to the ^{13}C signal of $CDCl_3$ at $\delta = 77.0$ ppm. Coupling constants (*J*) were expressed in Hz.Infrared spectra were obtained with a Thermo Nicolet Nexus 670 spectrometer using KBr discs. Melting points were measured on a BUCHI melting point machine in open capillary tubes. The UV-visible spectra were recorded with a Varian Cary 500 spectrophotometer over the range 250–700 nm using 1 cm path length cuvettes. Cyclic voltammetry (CV) was performed with a conventional three electrode configuration consisting of glassy carbon as a working electrode, platinum as an auxiliary electrode and a saturated calomel electrode (SCE) as a reference electrode. Cyclic voltammograms were recorded in presence of 0.1 M tetrabutylammonium perchlorate (TBAP) as the supporting electrolyte at a scan rate of 100 mV s^{-1}, using a CHI620 model electrochemical analyser at room temperature.

4.1. General procedure for the synthesis of compound (*2*)

To a stirred suspension of potassium carbonate (2.76 g, 20 mmol) in acetonitrile (10 ml), add isatin **1** (1.47 g, 10 mmol), and stir at room temperature for 10 min followed by the addition of 1,3 and 1,4-dibromoalkane (10 mmol) in acetonitrile at room temperature for 2 h. After the completion of reaction, as evidenced by TLC, K_2CO_3 was filtered off, and the solution was extracted with ethyl acetate (50 mL). Acetonitrile was removed by rotary evaporator and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and the product was obtained by the removal of the solvent under vacuum. It was purified by column chromatography on silica, using a hexane-ethyl acetate (80:20) solvent mixture to afford compound furnished the desired *N*-alkyl *l* bromo isatin in good yields.

4.2. General procedure for the synthesis of compound (*3*)

To a stirred solution of *N*-alkyl bromo isatin **(2)** (1 mmol) in DMF (10 mL), NaN_3 (1.5 mmol) was added. The mixture was stirred at reflux for about 3 h (monitored by TLC). Upon completion of reaction, the mixture was washed with water andextracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and filtered, concentrated in vacuum. The obtained azides **(3)** were used without further purification.

4.3. General procedure for the synthesis of compound (*4*)

Compound (**3**) (1 mmol) along with NaOH (1.5 mmol) was dissolved in ethanol and later hydroxyl amine (1.5 mmol) was added slowly. The reaction mixture was stirred at room temperature for 1 h (monitored by TLC). Upon completion of reaction, the mixture was washed with water and extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and the product was obtained by the removal of the solvent under vacuum. It was purified by column chromatography on silica, using a hexane-ethyl acetate (70:30) solvent mixture to afford compound furnished the desired compound **(4)** in good yields.

4.4. General procedure for the synthesis of compound (*5*)

2,4-Thiazolidinedione **(A)** was prepared by literature method [52] and was condensed with ferrocenecarboxaldehyde under Kno-

evenagel conditions to form ferrocenylidene 2,4-thiazolidinedione **(B)** in the presence of piperidine as catalyst in dry ethanol. In the next step, compound **(B)** was coupled with propargyl bromide in the presence of K_2CO_3 in dry DMF under inert atmosphere at room temperature for 16 h to obtain the intermediate alkyne (**5**) [53].

4.5. General procedure for the preparation of **6(a-j)**

Copper sulphate (0.05 mmol) and sodium ascorbate (0.13 mmol)was added to a stirred solution of compound **(5)** (1 mmol) and 1-(2-azidoalkyl)−3-(hydroxyimino) indolin-2-one **(4)** (1 mmol) in THF:water (1:1) mixture. The reaction mixture was allowed to stir at room temperature for 30 min. After completion of reaction as evidenced by TLC, water (20 mL) was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, concentrated under reduced pressure and purified via column chromatography using 40:60 (hexane:EtOAc) mixture.

4.6. Procedure for the preparation of compounds (**C**) and (**D**)

2,4-Thiazolidinedione **(B)** was prepared by literature method [53] and was condensed with aldehydes under Knoevenagel conditions to form arylidene 2,4-Thiazolidinedione **(C)** in the presence of piperidine as catalyst in dry ethanol. In the next step, compound **(C)** was coupled with propargyl bromide in the presence of K_2CO_3 in dry acetone under inert atmosphere at reflux temperature for 4 h to obtain the intermediate alkyne **(D)** [54a,b].

4.7. General procedure for the preparation of compound (**E**)

Copper sulphate (0.05 mmol) and sodium ascorbate (0.13 mmol) was added to a stirred solution of compound **(D)** (1 mmol) and 1-(2-azidoalkyl)−3-(hydroxyimino) indolin-2-one **(4)** (1 mmol) in THF:water (1:1) mixture. The reaction mixture was allowed to stir at room temperature for 30 min. After completion of reaction as evidenced by TLC, water (20 mL) was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, concentrated under reduced pressure and purified via column chromatography using 40:60 (hexane: EtOAc) mixture to obtain compound (**E**) in good yield.

According to the general procedure, the reaction of compound (**5**) (351 mg, 1 mmol) and 1-(3-azidopropyl)−3-(hydroxyimino) indolin-2-one (245 mg, 1 mmol) resulted in **6(a)** as a red solid. Yield, (464 mg, 78%); mp: 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 12.3 (s, 1H, OH), 8.13 (d, J = 7.3 Hz, 1H, Ar-*H*), 7.84 (s, 1H, =CH), 7.78 (s, 1H, triazole), 7.37 (t, J = 7.6 Hz, 1H, Ar-*H*), 7.09 (t, J = 7.6 Hz, 1H, Ar-*H*), 6.81 (d, J = 7.8 Hz, 1H, Ar-*H*), 5.02 (s, 2H, N–CH_2), 4.56 (s, 4H, C_5H_4), 4.40 (t, J = 6.7 Hz, 2H, triazole-NCH_2), 4.19 (d, J = 9.5 Hz, 5H, C_5H_5), 3.82 (t, J = 6.5 Hz, 2H, isatin-NCH_2), 2.40 – 2.31 (m, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 167.4(C=O), 165.0(C=O), 164.5(C=O), 143.7(isatin, 4°), 142.4(triazole, 4°), 141.6(=*C*), 136.7(triazole, 3°), 131.7(C_6H_5), 127.8(C_6H_5), 124.1(C_6H_5), 123.1(C_6H_5), 116.8(C_6H_5), 116.0(C_6H_5), 108.2(C=CH), 76.3(C_5H_4), 72.2(C_5H_4), 70.5(C_5H_4), 69.9(C_5H_5), 47.6(triazole, N–CH_2), 36.8(N–CH_2), 36.3(isatin, N–CH_2), 28.2(CH_2). HRMS (ESI) Calcd. For ($C_{28}H_{24}FeN_6O_4S$) [M + H] $^+$=597.10019; found: 597.10062; IR (KBr, ν_{max}/ cm^{-1})=3141, 3078, 2922, 1728, 1677, 1606, 1461, 1360, 1050, 877, 480; UV–Vis (CH_3CN): λ_{max}[ε in M^{-1} cm^{-1}] =333(4454), 502(639) nm. Anal. calcd for ($C_{28}H_{24}FeN_6O_4S$): C, 56.39; H, 4.06; N, 14.09; S, 5.36; found: C, 56.64; H, 4.26; N, 14.90; S, 5.06.

4.8. Compound **6(b)**

According to the general procedure, the reaction of compound (**5**) (351 mg, 1 mmol) and 1-(3-azidopropyl)−3-(hydroxyimino) 5-methylindolin-2-one (259 mg, 1 mmol) resulted in **6(b)** as a red solid. Yield, (488 mg, 80%) mp: 182–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO, ppm): δ 12.93 (s, 1H, OH), 7.97(d, J = 22.7 Hz, 1H, Ar-*H*), 7.85(s, 1H, =CH), 7.77 (s, 1H, triazole), 7.16 (d, J = 7.9 Hz, 1H, Ar-*H*), 6.70 (d, J = 8.0 Hz, 1H, Ar-*H*), 5.01 (s, 2H, N–CH_2), 4.57 (s, 4H, C_5H_4), 4.44 – 4.35 (m, 2H, triazole-NCH_2), 4.21(s, 5H, C_5H_5), 3.79 (t, J = 6.5 Hz, 2H, isatin-NCH_2), 2.33 – 2.28 (m, 2H, CH_2), 1.35 – 1.17 (m, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO, ppm): δ 167.4(C=O), 165.0(C=O), 164.4(C=O), 156.0(isatin, 4°), 144.0(triazole, 4°), 141.6(=C), 136.7(triazole, 3°), 136.1(C_6H_5), 124.1(C_6H_5), 117.1(C_6H_5), 116.8(C_6H_5), 116.6(C_6H_5), 114.0(C_6H_5), 108.7(C=CH), 76.3(C_5H_4), 72.2(C_5H_4), 70.6(C_5H_4), 70.0(C_5H_5), 55.9(CH_3), 47.7(triazole,N–CH_2), 36.9(N–CH_2), 36.4(isatin, N–CH_2), 28.2(CH_2). HRMS (ESI) Calcd. For ($C_{29}H_{26}FeN_6O_4S$) [M + H] $^+$= 611.11584; found: 611.11604; IR (KBr, ν_{max}/ cm^{-1}) = 3150, 3027, 2859, 1712, 1680, 1607, 1474, 1355, 1040, 895, 482. UV–Vis (CH_3CN): λ_{max}[ε in M^{-1} cm^{-1}] =332(6750), 501(1000) nm. Anal. calcd for ($C_{29}H_{26}FeN_6O_4S$): C, 56.94; H, 4.25; N, 13.75;S, 5.24; found: C, 57.06; H, 4.31; N, 13.97; S, 4.99.

4.9. Compound **6(c)**

According to the general procedure, the reaction of compound (**5**) (351 mg, 1 mmol) and1-(3-azidopropyl)−3-(hydroxyimino) 5-methoxyindolin-2-one (275 mg, 1 mmol) resulted in (**6c**) as a red solid. Yield, (469 mg, 75%); mp: 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO, ppm): δ 12.93 (s, 1H, OH), 7.84 (d, J = 21.6 Hz, 1H, Ar-*H*), 7.78 (s, 1H, =CH), 7.77 (s, 1H, triazole), 6.91 (dd, J = 8.5, 2.6 Hz, 1H, Ar-*H*), 6.72 (d, J = 8.5 Hz, 1H, Ar-*H*), 5.02 (s, 2H, N–CH_2), 4.56 (s, 4H, C_5H_4), 4.40 (t, J = 6.7 Hz, 2H, triazole-NCH_2), 4.20 (s, 5H, C_5H_5), 3.80 (s, 3H, OCH_3), 3.78 (d, J = 6.8 Hz, 2H, isatin-NCH_2), 2.35 – 2.28 (m, 2H, CH_2).^{13}C NMR (101 MHz, $CDCl_3$+DMSO, ppm): δ 167.4(C=O), 165.0(C=O), 164.4(C=O), 156.0(isatin, 4°), 144.0(triazole, 4°), 141.6(=C), 136.7(triazole, 3°), 136.1(C_6H_5), 124.1(C_6H_5), 117.1(C_6H_5), 116.8(C_6H_5), 116.6(C_6H_5), 114.0(C_6H_5), 108.78(C=CH), 76.3(C_5H_4), 72.2(C_5H_4), 70.6(C_5H_4), 70.0(C_5H_5), 55.9(OCH_3), 47.7(triazole, N–CH_2), 36.9(N–CH_2), 36.4(isatin, N–CH_2), 28.2(CH_2). HRMS (ESI) Calcd. For ($C_{29}H_{26}FeN_6O_5S$) [M+H] $^+$= 627.11076; found: 627.11150; IR (KBr, ν_{max}/ cm^{-1}) = 3148, 3028, 2858, 1719, 1680, 1606, 1471, 1357, 1072, 898, 487. UV–Vis (CH_3CN): λ_{max}[ε in M^{-1} cm^{-1}] = 332(5774), 505 (838) nm. Anal. calcd for ($C_{29}H_{26}FeN_6O_5S$): C, 55.49; H, 4.15; N, 13.39; S, 5.1; found: C, 55.36; H, 4.28; N, 13.77; S, 5.25.

4.10. Compound **6(d)**

According to the general procedure, the reaction of compound (**5**) (351 mg, 1 mmol) and 1-(3-azidopropyl)−3-(hydroxyimino) 5-fluoroindolin-2-one (263 mg, 1 mmol) resulted in (**6d**) as a red solid. Yield, (429 mg, 70%); mp: 172–174 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO, ppm): δ 13.39 (s, 1H, OH), 7.96 (s, 1H, =CH), 7.82 (dt, J = 12.2, 6.1 Hz, 1H, Ar-*H*), 7.76 (s, 1H, triazole), 7.11 (td, J = 8.9, 2.5 Hz, 1H, Ar-*H*), 6.83 (dd, J = 8.5, 3.9 Hz, 1H, Ar-*H*), 4.94 (d, J = 25.4 Hz, 2H, N–CH_2), 4.59 (s, 4H, C_5H_4), 4.43 (t, J = 6.7 Hz, 2H, triazole-NCH_2), 4.15 (s, 5H, C_5H_5), 3.81 (t, J = 6.5 Hz, 2H, isatin-NCH_2), 2.41 – 2.20 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO, ppm): δ 166.2(C=O), 163.9(C=O), 163.0(C=O), 156.1(isatin, 4°), 140.5(triazole, 4°), 137.7(=C), 135.5(triazole, 3°), 123.1(C_6H_5), 117.1(C_6H_5), 116.7(C_6H_5), 115.8(C_6H_5), 114.2(C_6H_5), 113.9(C_6H_5), 108.2(C=CH), 75.3(C_5H_4), 71.3(C_5H_4), 69.6(C_5H_4), 69.0(C_5H_5), 46.6(triazoleN–CH_2), 36.0(N–CH_2), 35.4(isatin, N–CH_2),

27.1(CH_2). HRMS (ESI) Calcd. For ($C_{28}H_{23}FFeN_6O_4S$) [M+H] $^+$= 615.09077; found: 615.09095; IR (KBr, ν_{max}/ cm^{-1}) =3152, 3022, 2923, 1719, 1677, 1605, 1470, 1330, 1073, 876, 486. UV–Vis (CH_3CN): λ_{max}[ε in M^{-1} cm^{-1}] =334(6718), 509 (968) nm.. Anal. calcd for ($C_{28}H_{23}FFeN_6O_4S$): C, 54.63; H, 3.74; N, 13.66; S, 5.2; found: C, 54.83; H, 3.87; N, 13.96; S, 4.98.

4.11. Compound **6(e)**

According to the general procedure, the reaction of compound (**5**) (351 mg, 1 mmol) and 1-(3-azidopropyl)−3-(hydroxyimino) 5-bromoindolin-2-one (323 mg, 1 mmol) resulted in **6(e**) as a red solid. Yield, (532 mg, 79%); mp: 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO, ppm): δ 13.35 (s, 1H, OH), 8.27 (s, 1H, =CH), 7.86 (d, J = 10.7 Hz, 1H, Ar-*H*), 7.78 (s, 1H, triazole), 7.57 – 7.43 (m, 1H, Ar-*H*), 6.83 – 6.65 (m, 1H, Ar-*H*), 5.01 (s, 2H, N–CH_2), 4.51 (d, J = 51.9 Hz, 4H, C_5H_4), 4.49 – 4.32 (m, 2H, triazole-NCH_2), 4.17 (s, 5H, C_5H_5), 3.80 (s, 2H, isatin-NCH_2), 2.39 – 2.25 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO, ppm): δ 167.6(C=O), 165.2(C=O), 164.1(C=O), 142.9(isatin, 4°), 141.8(triazole, 4°), 139.3(=C), 136.9(triazole, 3°), 134.3(C_6H_5), 130.6(C_6H_5), 124.2(C_6H_5), 117.5(C_6H_5), 115.7(C_6H_5), 114.1(C_6H_5), 109.9(C=CH), 76.4(C_5H_4), 72.3(C_5H_4), 70.7(C_5H_4), 70.1(C_5H_5), 47.7(triazole, N–CH_2), 37.1(N–CH_2), 29.7(isatin, N–CH_2), 22.7(CH_2). HRMS (ESI) Calcd. For ($C_{28}H_{23}BrFeN_6O_4S$) [M+H] $^+$= 677.0109077; found: 677.01595; IR (KBr, ν_{max}/ cm^{-1}) =3413, 3148, 2925, 1725, 1679, 1602, 1463, 1357, 1045, 886, 488. UV–Vis (CH_3CN): λ_{max}[ε in M^{-1} cm^{-1}] =334(8448), 505(1068) in nm.. Anal. calcd for ($C_{28}H_{23}BrFeN_6O_4S$): C, 49.63; H, 3.40; N, 12.41; S, 4.73; found: C, 49.80; H, 3.48; N, 12.54; S, 5.01.

4.12. Compound **6(f)**

According to the general procedure, the reaction of compound (**5**) (351 mg, 1 mmol) and 1-(3-azidobutyl)−3-(hydroxyimino) indolin-2-one (259 mg, 1 mmol) resulted in **6(f**) as a red solid. Yield, (475 mg, 78%); mp: 171–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 12.93 (s, 1H, OH), 8.11 (d, J = 7.5 Hz, 1H, Ar-*H*), 7.77 (s, 1H, =CH), 7.67 (s, 1H, triazole), 7.36 (t, J = 7.8 Hz, 1H, Ar-*H*), 7.06 (t, J = 7.6 Hz, 1H, Ar-*H*), 6.83 (d, J = 7.9 Hz, 1H, Ar-*H*), 4.98 (s, 2H, N–CH_2), 4.57 (s, 4H, C_5H_4), 4.41 (t, J = 7.0 Hz, 2H, triazole-NCH_2), 4.19 (s, 5H, C_5H_5), 3.79 (t, J = 6.8 Hz, 2H, isatin-NCH_2), 1.96 (dd, J = 14.8, 7.3 Hz, 2H, CH_2), 1.73 (dt, J = 13.7, 6.8 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 167.6(C=O), 165.2(C=O) 164.2(C=O), 144.4(isatin, 4°), 143.2(triazole, 4°), 141.8(=C), 137.0(triazole, 3°), 132.4(C_6H_5), 128.3(C_6H_5), 123.6(C_6H_5), 123.3(C_6H_5), 116.8(C_6H_5), 115.7(C_6H_5), 108.6(C=CH), 76.4(C_5H_4), 72.2(C_5H_4), 70.7(C_5H_4), 70.0(C_5H_5), 49.5(triazole, N–CH_2), 38.8(N–CH_2), 36.4(isatin, N–CH_2), 27.3(CH_2), 24.1 (CH_2). HRMS (ESI) Calcd. For ($C_{29}H_{26}FeN_6O_4S$) [M+H] $^+$= 611.11584; found: 611.11849; IR (KBr, ν_{max}/ cm^{-1}) =3418, 3143, 2924, 1726, 1679, 1605, 1462, 1363, 1015, 823, 495. UV–Vis (CH_3CN): λ_{max}[ε in M^{-1} cm^{-1}] =334(5906), 510 (1062) nm. Anal. calcd for ($C_{29}H_{26}FeN_6O_4S$): C, 56.94; H, 4.25; N, 13.75; S, 5.24; found: C, 57.06; H, 4.39; N, 13.67; S, 5.35.

4.13. Compound **6(g)**

According to the general procedure, the reaction of compound (**5**) (351 mg, 1 mmol) and 1-(3-azidobutyl)−3-(hydroxyimino) 5-methylindolin-2-one (273 mg, 1 mmol) resulted in **6(g**) as a red solid. Yield, (499 mg, 80%); mp: 146–148 °C;^{1}H NMR (300 MHz, $CDCl_3$+DMSO, ppm): δ 12.98 (s, 1H, OH), 7.93 (s, 1H, =CH), 7.76 (s, 1H, triazole), 7.75 (s, 1H, Ar-*H*), 7.19 (dd, J = 14.0, 5.2 Hz, 1H, Ar-*H*), 6.73 (t, J = 9.3 Hz, 1H, Ar-*H*), 5.04 – 4.90 (m, 2H, N–CH_2), 4.58 (s, 4H, C_5H_4), 4.40 (t, J = 6.9 Hz, 2H, triazole-NCH_2), 4.18 (s, 5H, C_5H_5), 3.77 (t, J = 6.7 Hz, 2H, isatin-NCH_2), 2.33 (s, 3H, CH_3), 1.94 (dd, J = 14.8, 7.2 Hz, 2H, CH_2), 1.70 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO, ppm): δ 172.0(C=O), 169.7(C=O), 168.9(C=O), 148.7(isatin, 4°), 146.3(triazole, 4°), 145.3(=C), 141.3(triazole, 3°), 137.0(C_6H_5), 136.8(C_6H_5), 133.1(C_6H_5), 128.2(C_6H_5), 121.5(C_6H_5), 120.7(C_6H_5), 112.9(C=CH), 81.1(C_5H_4), 77.0(C_5H_4), 75.3(C_5H_4), 74.7(C_5H_5), 54.2(CH_3), 43.4(triazoleN–CH_2), 41.1(N–CH_2), 34.3(isatin, N–CH_2), 32.1(CH_2), 25.7(CH_2). HRMS (ESI) Calcd. For ($C_{30}H_{28}FeN_6O_4S$) [M+H] $^+$= 625.13149; found: 625.13432; IR (KBr, ν_{max}/ cm^{-1}) =3417, 3143, 2923, 1724, 1677, 1606, 1475, 1363, 1060, 817, 488. UV–Vis (CH_3CN): λ_{max}[ε in M^{-1} cm^{-1}] = 333(3906), 504 (625) nm. Anal. calcd for ($C_{30}H_{28}FeN_6O_4S$): C, 57.64; H, 4.48; N, 13.44; S, 5.12; found: C, 57.06; H, 4.39; N, 13.67, S, 5.35.

4.14. Compound **6(h)**

According to the general procedure, the reaction of compound (**5**) (351 mg, 1 mmol) and 1-(3-azidobutyl)−3-(hydroxyimino) 5-chloroindolin-2-one (293 mg, 1 mmol) resulted in **6(h**) as a red solid. Yield, (528 mg, 82%);mp: 150–152 °C;^{1}H NMR (400 MHz, $CDCl_3$+DMSO, ppm): δ 13.25 (s, 1H, OH), 8.11 (d, J = 2.1 Hz, 1H, Ar-*H*), 7.71 (s, 1H, =CH), 7.73 (s, 1H, triazole), 7.34 (dd, J = 8.4, 2.2 Hz, 1H, Ar-*H*), 6.78 (d, J = 8.4 Hz, 1H, Ar-*H*), 4.98 (s, 2H, N–CH_2), 4.57 (s, 4H, C_5H_4), 4.47 – 4.35 (m, 2H, triazole-NCH_2), 4.21 (s, 5H, C_5H_5), 3.77 (t, J = 6.8 Hz, 2H, isatin-NCH_2), 1.95 (dd, J = 14.6, 7.2 Hz, 2H, CH_2), 1.69 (m, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO, ppm): δ 167.3(C=O), 164.9(C=O), 163.8(C=O), 142.9(isatin, 4°), 141.6(triazole, 4°), 141.1(=C), 136.6(triazole, 3°), 131.1(C_6H_5), 130.9(C_6H_5), 128.7(C_6H_5), 127.9(C_6H_5), 127.6(C_6H_5), 123.3(C_6H_5), 116.8(C_6H_5), 116.7(C_6H_5), 109.3(C=CH), 76.2(C_5H_4), 72.1(C_5H_4), 70.5(C_5H_4), 69.9(C_5H_5), 49.3(triazole, N–CH_2), 38.7(N–CH_2), 36.3(isatin, N–CH_2), 27.2(CH_2), 24.2(CH_2). HRMS (ESI) Calcd. For ($C_{29}H_{25}ClFeN_6O_4S$) [M+H] $^+$= 645.07687; found: 645.07939; IR (KBr, ν_{max}/ cm^{-1}) =3417, 3144, 2925, 1728, 1678, 1605, 1462, 1371, 1059, 817, 488. UV–Vis (CH_3CN): λ_{max}[ε in M^{-1} cm^{-1}] = 334(6258), 505 (870) nm. Anal. calcd for ($C_{29}H_{25}ClFeN_6O_4S$): C, 53.95; H, 3.87; N, 13.02; S, 4.96; found: C, 54.01; H, 3.91; N, 13.13; S, 4.23.

4.15. Compound **6(i)**

According to the general procedure, the reaction of compound (**5**) (351 mg, 1 mmol) and 1-(3-azidobutyl)−3-(hydroxyimino) 5-flouroindolin-2-one (277 mg, 1 mmol) resulted in **6(i**) as a red solid. Yield, (477 mg, 76%);mp: 165–167 °C;^{1}H NMR (300 MHz, $CDCl_3$+DMSO, ppm): δ 13.31 (s, 1H, OH), 7.82 (dt, J = 8.4, 4.2 Hz, 1H, Ar-*H*), 7.76 (s, 1H, =CH), 7.75(s, 1H, triazole), 7.09 (tt, J = 16.3, 8.2 Hz, 1H, Ar-*H*), 6.80 (dt, J = 25.3, 12.7 Hz, 1H, Ar-*H*), 5.06 – 4.90 (m, 2H, N–CH_2), 4.59 (s, 4H, C_5H_4), 4.42 (t, J = 6.9 Hz, 2H, triazole-NCH_2), 4.22 (s, 5H, C_5H_5), 3.78 (t, J = 6.7 Hz, 2H, isatin-NCH_2), 1.95 (dd, J = 14.8, 7.3 Hz, 2H, CH_2), 1.77 – 1.62 (m, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO, ppm): δ 166.5(C=O), 164.1(C=O), 163.1(C=O), 142.6(isatin, 4°), 140.8(triazole, 4°), 138.0(=C), 135.8(triazole, 3°), 122.7(C_6H_5), 117.2(C_6H_5), 116.9(C_6H_5), 115.9(C_6H_5), 114.4(C_6H_5), 114.2(C_6H_5), 108.3(C=CH), 75.5(C_5H_4), 71.5(C_5H_4), 69.8(C_5H_4), 69.2(C_5H_5), 48.6(triazole, N–CH_2), 38.0(N–CH_2), 35.6(isatin, N–CH_2), 28.7(CH_2), 23.4(CH_2). HRMS (ESI) Calcd. For ($C_{29}H_{25}FFeN_6O_4S$) [M+H] $^+$= 629.10642; found: 629.10911; IR (KBr, ν_{max}/ cm^{-1}) =3417, 3140, 2923, 1726, 1677, 1605, 1471, 1370, 1064, 817, 484. UV–Vis (CH_3CN): λ_{max}[ε in M^{-1} cm^{-1}] = 332(5000), 506 (741) nm. Anal. calcd for ($C_{29}H_{25}FFeN_6O_4S$): C, 55.36; H, 3.97; N, 13.35; S, 5.08; found: C, 55.42; H, 4.01; N, 13.47; S, 5.26.

*4.16. Compound **6(j)***

According to the general procedure, the reaction of compound (**5**) (351 mg, 1 mmol) and 1-(3-azidobutyl)−3-(hydroxyimino) 5-bromoindolin-2-one (337 mg, 1 mmol) resulted in **6(j)** as a red solid. Yield, (429 mg, 77%); mp: 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO, ppm): δ 13.10 (s, 1H, OH), 8.17 (t, J = 19.4 Hz, 1H, Ar-*H*), 7.73 (s, 1H, =CH), 7.67 (s, 1H, triazole), 7.45 (dd, J = 8.4, 2.0 Hz, 1H, Ar-*H*), 6.76 (dd, J = 26.0, 8.1 Hz, 1H, Ar-*H*), 4.95 (s, 2H, N–CH_2), 4.54 (s, 4H, C_5H_4), 4.37 (t, J = 6.9 Hz, 2H, triazole-NCH_2), 4.18 (s, 5H, C_5H_5), 3.74 (t, J = 6.8 Hz, 2H, isatin-NCH_2), 1.98 – 1.86 (m, 2H, CH_2), 1.67 (dd, J = 14.7, 7.1 Hz, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$+DMSO, ppm): δ 167.4(C=O), 165.0(C=O), 163.7(C=O), 142.8(isatin, 4°), 141.7(triazole, 4°), 141.5(=C), 136.7(triazole, 3°), 134.0(C_6H_5), 130.3(C_6H_5), 123.3(C_6H_5), 117.3(C_6H_5), 116.7(C_6H_5), 115.3(C_6H_5), 109.7(C=CH), 76.3(C_5H_4), 72.2(C_5H_4), 70.5(C_5H_4), 69.9(C_5H_5), 49.3(triazole, N–CH_2), 38.7(N–CH_2), 36.3(isatin, N–CH_2), 27.2(CH_2), 24.2(CH_2). HRMS (ESI) Calcd. For ($C_{29}H_{25}BrFeN_6O_4S$) [M] $^+$= 689.02636; found: 689.02694; IR (KBr, ν_{max}/ cm^{-1}) =3421, 3146, 2925, 1728, 1677, 1604, 1463, 1371, 1051, 817, 488. UV–Vis (CH_3CN): λ_{max}[ε in M^{-1} cm^{-1}] =333(7931), 513 (1103) nm. Anal. calcd for ($C_{29}H_{25}BrFeN_6O_4S$): C, 50.50; H, 3.63; N, 12.19; S, 5.09; found: C, 51.03; H, 3.56; N, 12.49, S, 4.86.

*4.17. Compound (**C**)*

According to the general procedure, the reaction of compound (**A**) (167 mg, 1 mmol) and 2,4-Thiazolidinedione **(B)** (117 mg, 1 mmol) resulted in compound **(C)** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.80 (s, 1H, NH), 7.74 (s, 1H, =CH), 7.07 (dd, J = 8.5, 1.9 Hz, 1H, Ar-*H*), 6.91 (dd, J = 18.2, 5.2 Hz, 2H, Ar-*H*), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3).^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 167.26(C=O), 166.74(C=O), 151.46(C_6H_4), 149.39(=C), 134.66(C_6H_4), 125.87(C_6H_5), 124.93(C_6H_4), 119.47(C_6H_5), 112.42(C_6H_5), 111.43(C_6H_5), 56.12(OCH_3), 55.99(OCH_3).Mass Calcd. For ($C_{12}H_{11}NO_4S$)[M] $^+$=265.04;found: 265.90. Anal Calcd for ($C_{12}H_{11}O_4NS$): C, 54.33; H, 4.18; N. 5.26; S, 12.07; found: C, 55.15; H, 4.52; N, 5.62; S, 11.92.

*4.18. Compound (**D**)*

According to the general procedure, the reaction of compound **(C)** (265 mg, 1 mmol) and in compound **(D)** as a yellow solid.^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.89 (s, 1H, =CH), 7.15 (dd, J = 8.4, 2.1 Hz, 1H, Ar-*H*), 7.02 – 6.94 (m, 2H, Ar-*H*), 4.49 (dd, J = 12.3, 2.5 Hz, 2H, -CH_2), 3.95 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 2.27 (q, J = 2.7 Hz, 1H, Acetylic). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 166.98(C=O), 165.23(C=O), 151.45 (C_6H_4), 149.40 (C_6H_5), 134.85(=C), 125.98(C_6H_4), 124.90(C_6H_4), 118.13 (=C), 112.43(C=), 111.44(C_6H_5), 76.20 (≡C), 72.18 (≡C), 56.13 (OCH_3), 56.00 (OCH_3), 30.65(CH_2).Mass Calcd. For ($C_{15}H_{13}NO_4S$) [M] $^+$=303.33; found: 303.90. Anal Calcd for ($C_{15}H_{13}O_4NS$): C, 59.40; H, 4.32; N. 4.62%; S, 10.56; found: C, 60.06; H, 4.00%; N, 5.08%, S, 10.91.

*4.19. Compound (**E**)*

According to the general procedure, the reaction of compound **(D)** (303 mg, 1 mmol) and 1-(3-azidopropyl)−3-(hydroxyimino) indolin-2-one (245 mg, 1 mmol) resulted in **(E)** as a yellow solid.

^{1}H NMR (400 MHz, DMSO, ppm) δ 10.16 (s, 1H, OH)), 8.37 (s, 1H, =CH), 8.16 (s, 1H, Tr-*H*), 8.02 (d, J = 8.8 Hz, 1H, Ar-*H*), 7.92 (dd, J = 8.8, 2.0 Hz, 1H, Ar-*H*), 7.42 (d, J = 9.1 Hz, 2H, Ar-*H*), 7.35 (dd, J = 8.8, 3.0 Hz, 1H, Ar-*H*), 6.86 (d, J = 9.1 Hz, 2H, Ar-*H*), 4.18 (d, J = 14.9 Hz, 2H, CH_2), 3.35 (s, 6H, 2–OCH_3), 3.03 (d, J = 4.8 Hz, 2H, CH_2), 2.51 (dd, J = 3.6, 1.8 Hz, 2H, CH_2), 1.62 – 1.59 (m, 2H, CH_2).^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 167.58 (C=O), 165.88 (C=O), 162.30(C_6H_4), 152.94(C_6H_4), 149.37(C_6H_4), 142.09 (=CH), 134.56, 132.64 (Tr-4°C), 128.43(C_6H_5), 124.81(C_6H_5), 124.27 (C_6H_4), 123.56 (=CH), 121.96(C_6H_5), 118.44(C_6H_5), 112.45(C_6H_4), 111.43(C_6H_5), 108.63(C_6H_5), 56.10(OCH_3), 56.00 (OCH_3), 47.68(CH_2), 37.11(CH_2), 31.96(CH_2), 29.73 (N–CH_2). Mass Calcd. For ($C_{26}H_{24}N_6O_6S$) [M] $^+$=548.57; found: 548.90. Anal Calcd for ($C_{26}H_{24}O_6N_6S$): C, 56.87; H, 4.37; N. 15.31; S, 5.83; found: C, 57.15; H, 5.02; N, 14.97; S, 5.42.

5. Culture and maintenance of test microorganisms for antimicrobial activity

Pure cultures of selected bacteria and fungi strains were obtained from the Microbial Type Culture Collection and Gene Bank (MTCC), Institute of Microbial Technology (IMTECH), Chandigarh. The bacterial cultures were maintained on nutrient broth while fungal strains were on yeast peptone dextrose broth (YPD). These microbial strains were subcultured regularly on their respective media and stored at 4 °C till further use.

5.1. In vitro *antibacterial and antifungal activity*

All the synthesized novel triazole conjugates (**6(a-j))** compounds were evaluated for their in vitro antimicrobial activity against four Gram-positive bacterial strains(*B.subtillis, B.megaterium, M.smegmatis, K. pneumoniae) four Gram-negative bacterial strains (E.coli, S. typhi, P.putida, P. arguinos and two fungal strains (C.albicans, A. oryzae).* The assay was performed using the agar well diffusion method. In brief, Mueller-Hinton agar (MHA) medium is prepared, autoclaved and poured in a sterile Petriplates under sterile conditions. After solidification, 50 μL (106 CFU mL^{-1}) of test bacterial culture were inoculated and spread uniformly by sterile cotton swabs and 8 mm wells were made on agar plate using sterile cork borer. A 100 μg mL^{-1} stock solution of test compounds and standard drugs streptomycin sulphate for bacterial strains and fluconazole as a standard for fungal strains were prepared using DMSO (Dimethyl sulfoxide) as a solvent. DMSO was used as negative control. 100 μL of the test samples, streptomycin and DMSO were loaded individually in separate wells. The plates were incubated at 37 °C for 18 h and the zone of inhibition measured by using calibrated scale and expressed in mm. All the experiments were carried out in triplicates and mean values were considered for data representation [55].

Minimum inhibitory concentration (MIC) is defined as the lowest concentration able to inhibit any visible bacterial growth. The assays were performed by broth dilution techniques. The different dilutions (0.5,1, 2, 4, 8, 16, 32,64 μg mL^{-1} in DMSO) of compounds, streptomycin sulphate and fluconazole as standards as well as positive controls were prepared and transferred to the test bacterial and fungal cultures which were grown in Mueller Hinton broth. The tubes were incubated in shaking incubator for 12 h at 37 °C and subsequently checked for the growth of bacteria and fungi by taking absorbence at 560 nm. The test organisms are then added to the dilutions of the synthesized and incubated for growth.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Acknowledgments

This work was financially supported by the CSIR-IICT (in-house project MLP-0007) and DST (EMR/2016/006410). Swetha Yagnam is grateful to the University Grants Commission (UGC), New Delhi for the award of a research fellowship. We thank Director, CSIR-IICT (Ms. No. **IICT/Pubs./2020/204**) for providing all the required facilities to carry out the work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2021.121716.

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