Potent Biological investigation of new class of sulfone derivatives endowed with quinolinyl-cyclopropane analogue

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Research Article

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"Potent Biological investigation of new class of sulfone derivatives endowed with quinolinyl-cyclopropane analogue"

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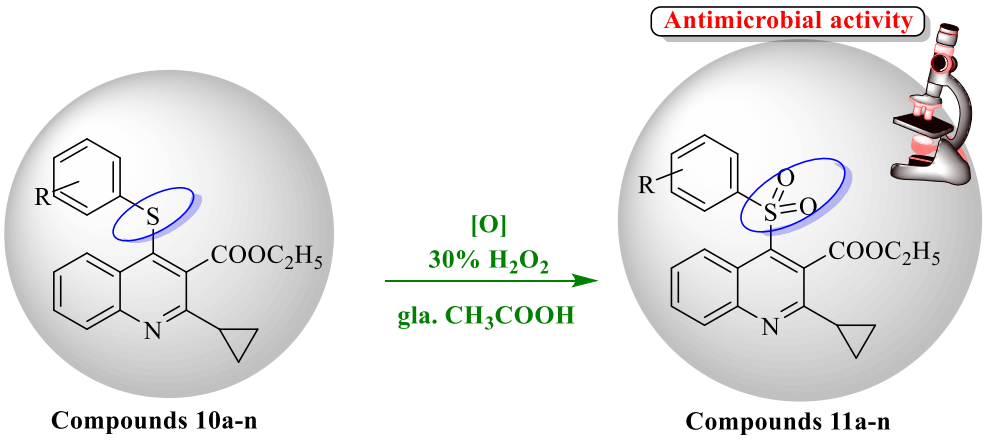
Abstract:

Novel series of quinoline derivatives incorporating cyclopropyl ring and sulfone linkage as substituents were synthesized, Oxidation of ethyl-2-cyclopropyl-4-(substituted phenylthio) quinoline-3-carboxylate **10a-n** was carried out to set ethyl-2-cyclopropyl-4(substituted phenyl sulfonyl) quinoline-3-carboxylate **11a-n**. Sulfone derivatives were afforded by reaction of glacial acetic acid and 30% hydrogen peroxide at room temperature. An eco-friendly synthesis of sulfone derivatives were afforded by using weak acid at room temperature. The synthesized quinoline incorporating sulfone linkage derivatives were evaluated for their expected antimicrobial activity; where the majority of these compounds showed potent antibacterial and antifungal activities against the tested strains of bacteria and fungi. All the final synthesized derivatives were characterized by their melting point, mass spectra, IR, ^{1}H NMR and ^{13}C NMR spectras. SAR and HOMO-LUMO studies were also carried out for proving the structural biological activity. Among them compounds **11a, 11b, 11h, 11k** and **11m** gave best results as their energy gap is very low which makes their activity higher.

Keywords: Quinoline, Sulfone, Cyclopropane, Antimicrobial activity, HOMO-LUMO study

Graphical abstract:



Introduction:

The rapid growth of the world population results in a continuous increase in disease and its demand for proper cure. At the same time about 10 millions of the global health's around the world are being destroyed due to a diverse range of diseases of microorganisms like bacteria and fungi. Both of these factors are nowadays the reason for the growing interest in the development of new selective and an efficient antimicrobial agents. Moreover, infections caused by multi-drug resistant bacteria and fungi are difficult to diagnose and treat. So, development and discovery of new antimicrobial drugs are urgently needed to overcome the growing of drug-resistant microbes [1,2]. Many researchers focused to develop anti-microbial drug related compound [3,4]. Quinoline ring systems are attractive candidates in medicinal chemistry. They constitute the building blocks for many natural and synthetic pharmacologically active compounds [5]. Quinoline ring is a part of the naturally occurring antimicrobial agents, such as an antimalarial (Chlorosquine, Mefloquine, Amodiaquinine, Primaquine etc.), as an antibacterial (Ciprofloxacin, Sparfoxacin, Gatifloxacin etc.) or as an anticancer drugs (Camptothecin, Irinotecan, Topotecan etc.) Shown in **Fig. 1**. Simple quinoline derivatives are applied in the manufacture of dyes, paints, insecticides and antifungals [6,7]. They also are employed as solvents for the extraction of resins and terpenes and as corrosion inhibitors [8]. However, the quinoline ring is also a key structural unit for numerous natural products and privileged scaffoSlds in medicinal chemistry (**Fig. 2**). A quinoline nucleus is generally present in a large number of synthetic and natural molecules with relevant parasite growth inhibition properties. Herein, we synthesized quinoline nucleus by using Conrad-limpach synthesis. Synthesized in 1908 by fromn and witmann [9], Dapsone bis(4-aminophenyl)sulfone is still the only representative member of its pharmacological class. In this context, sulfone derivatives provide an example of an important class of bioactive compounds with a wide spectrum of activities. Literature described sulfone as antifungal [10], anti-inflammatory [11], anti-HIV [12], antitubercular [13], anticancer [14], insecticidal [15], herbicidal [16], anti hepatitis [17] and antitumor [18] agents. Some polymers containing sulfone groups like (Bisphenol S & 4,4'-dichlorodiphenyl sulfone) are useful engineering plastics. They exhibit high strength and resistance to oxidation, corrosion, high temperatures and creep under stress [19].

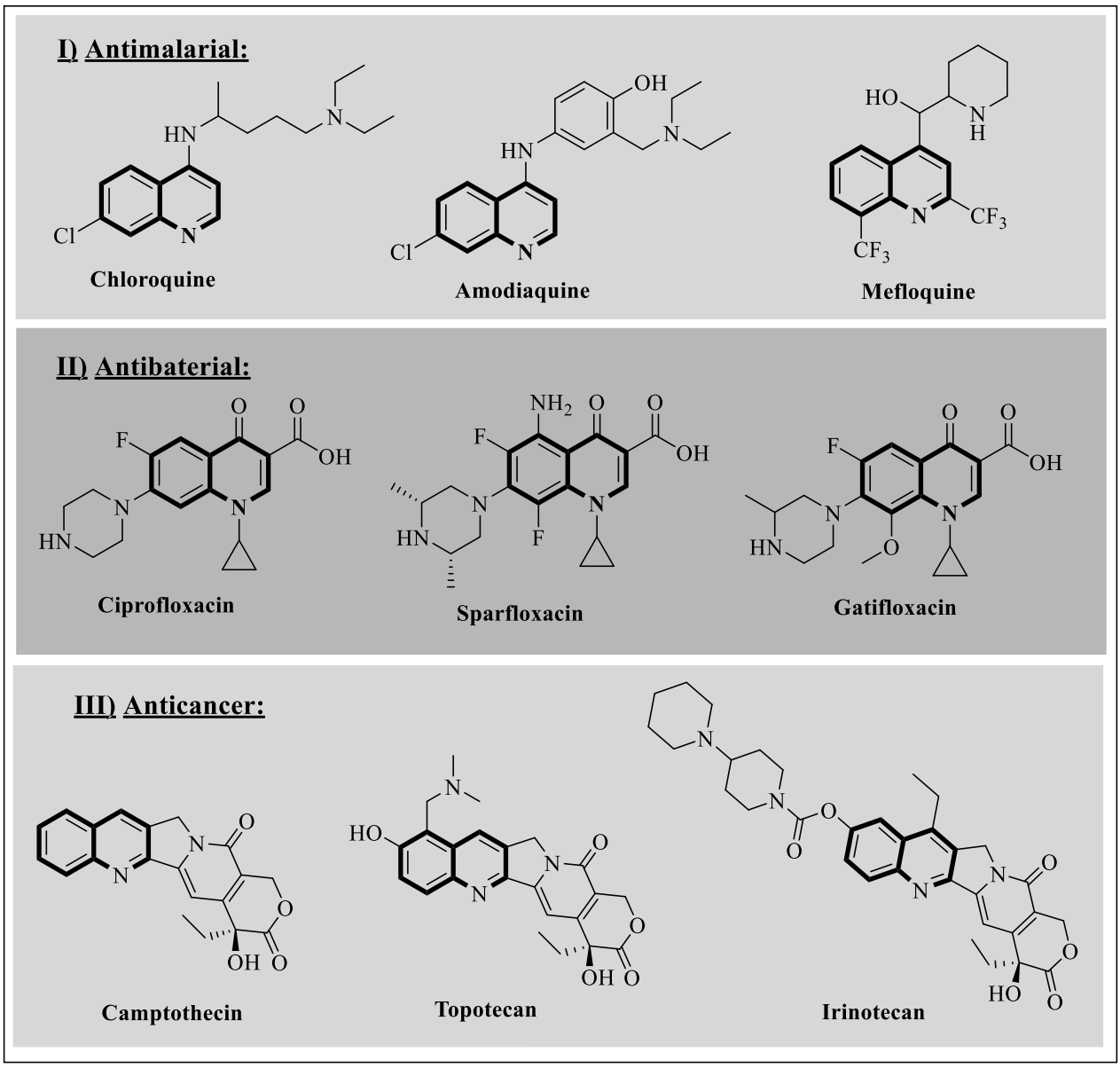


Fig. 1: Quinoline containing drugs available in market.

Heterocyclic species like quinoline represent a novel emerging major chemical entity as antimalarial [20], antibacterial [21], antifungal [22], anthelmintic [23], cardiotoinc [24], anticonvulsant [25], anti-inflammatory [26], analgesis [27], antiviral [28] and anti hypertension [29] etc. Maintaining our investigations into the preparation of novel antimicrobial agents we turned our attention to compounds possessing a sulfone group.

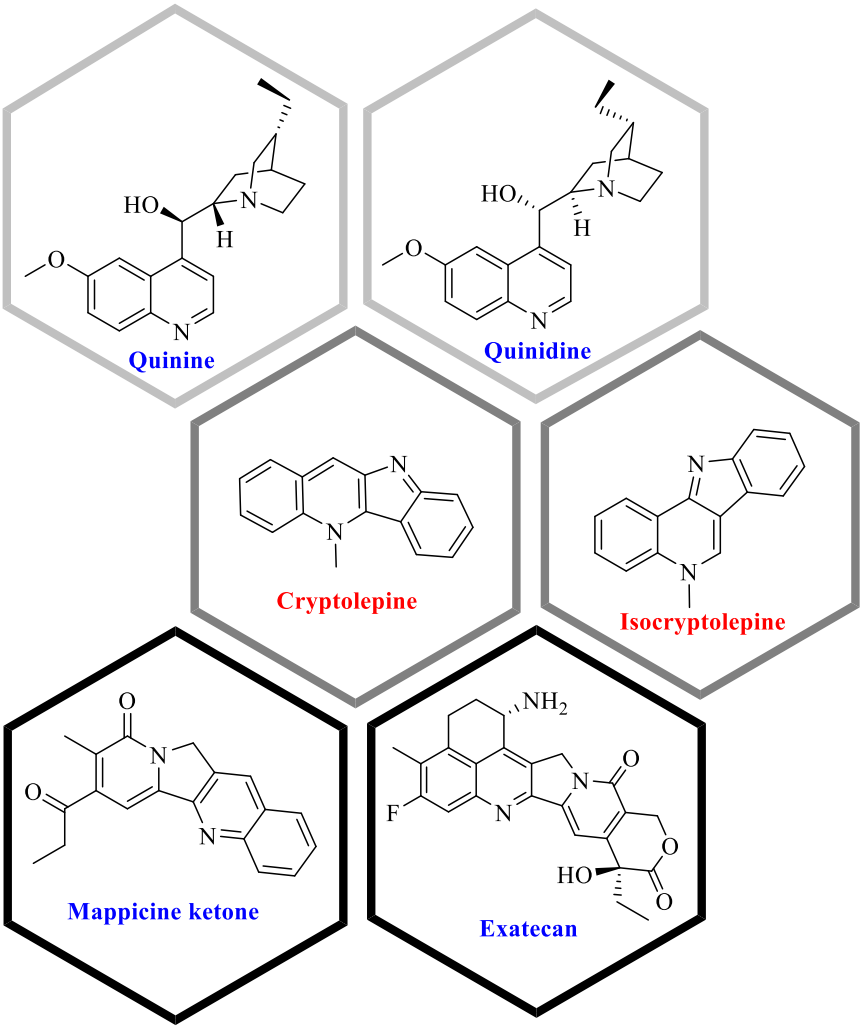


Fig. 2: Quinoline containing molecules available in nature

During these studies we have found that compounds in which the sulfone is not part of a ring that gives very good biological activities. Some available drugs that contain sulfone group as an aryl substituent (**Fig. 3**). Besides these, a molecule that contain cyclopropane ring as substituent enhances its biological activity. Many drugs that are available in market having cyclopropane as its core unit is potent biological active agents such as Ciprofloxacin, Pitavastatin and Nevirapine etc. Substitution of sulfone group and cyclopropane ring both moieties have shown enhanced biological activities in molecule. For example, pyrimidine substitution on cyclopropane ring displayed high antimicrobial property [30], quinazoline substitution on cyclopropane ring displayed anti-HIV activity [31]. Efforts in this direction by use of hybridization of known molecules like Pitavastatin, RVT-101 and Nevirapine led us to design

and test some new heterocyclic systems containing a quinoline ring condensed with aromatic moiety in the S-dioxide state and cyclopropane ring as substituents. (**Fig. 4**)

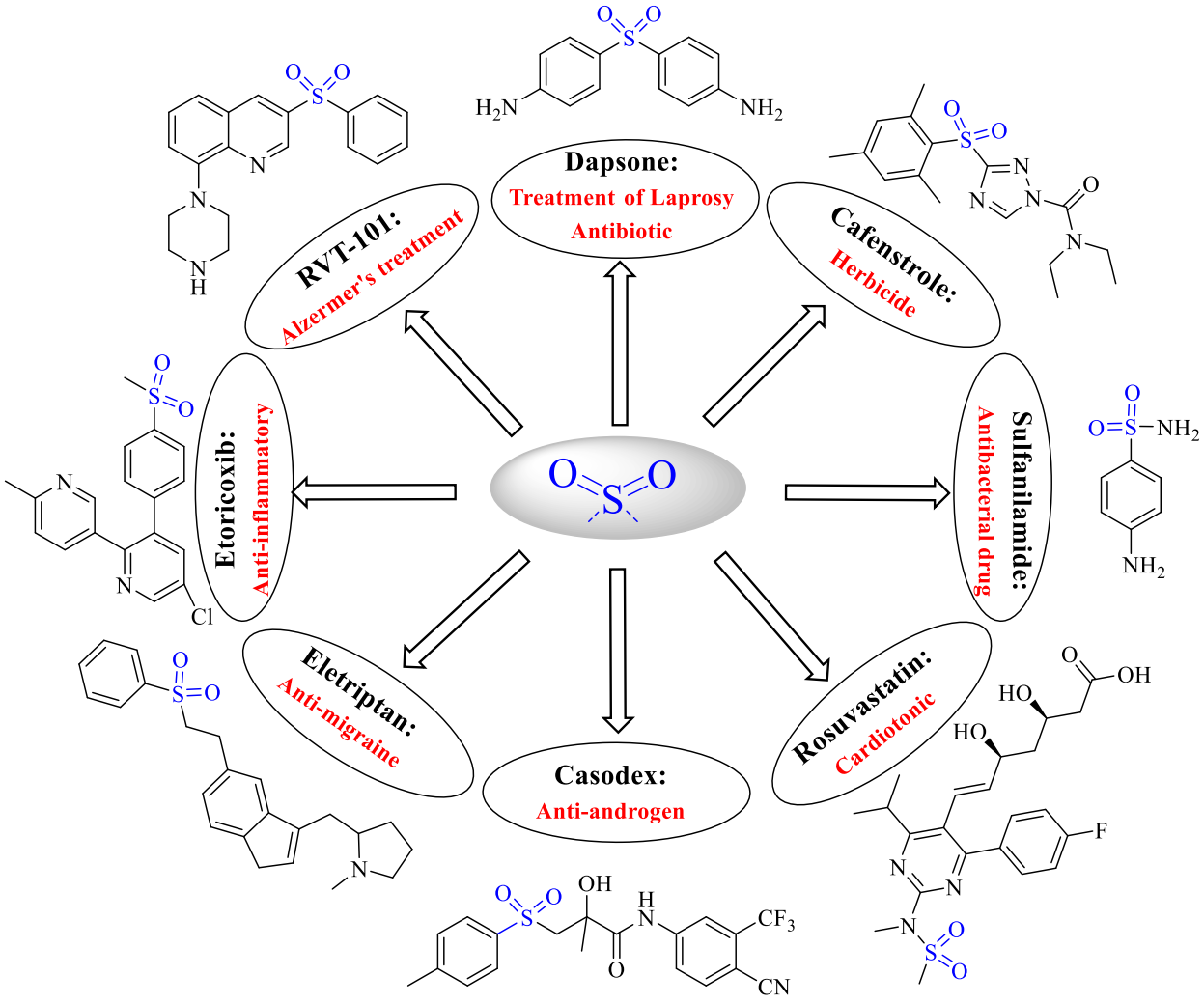


Fig. 3: Some available drugs in market contain aryl-sulfone moiety

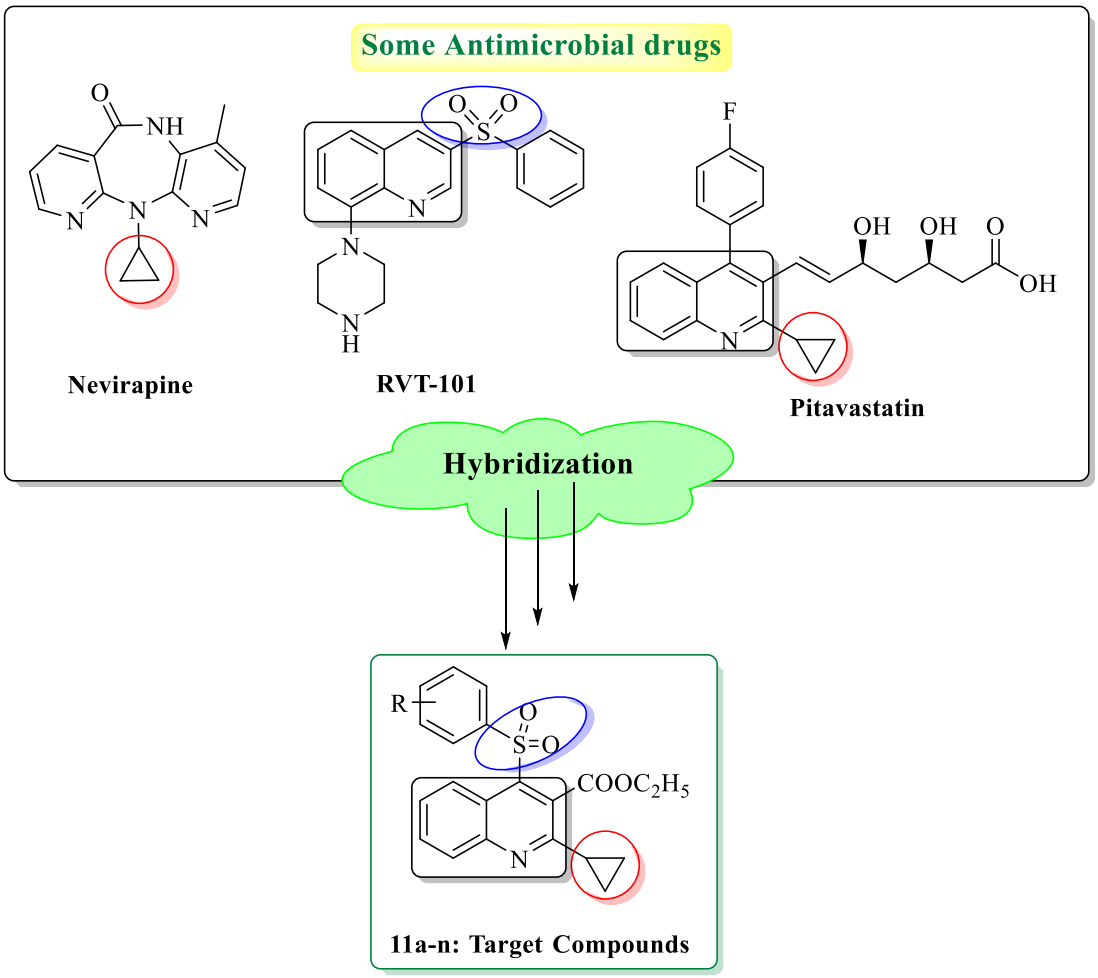
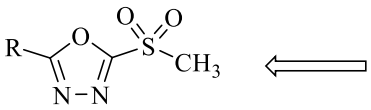


Fig. 4: Design of cyclopropyl-quinolinyl-sulfone hybrid derivatives

As a consequence and from all the literature surveys we revealed that a compound that contains cyclopropane ring, quinoline core and sulfone linkage gives very good biological activity. In an attempt to increase the fitting to the pharmacophoric model and possibly to obtain new microbials, herein we report the synthesis, characterization and antimicrobial activity and the structure activity relationship (SAR) study of new ethyl-2-cyclopropyl-4-substituted phenylsulfonyl)quinoline-3-carboxylate (**11a-n**). As part of an ongoing research, Weiming et al. [32] designed and synthesis a novel series of 2-sulfonyl-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole derivatives and examined their antifungal activity against *F.oxysporum* and *C.mandshurica.* Also, Silvestri and co-workers [33] have synthesized a novel series of indolyl-aryl-sulfones and examined their 3-D QSAR, docking studies and checked their anti-HIV activity. Inspired from these work herein we have synthesized quinoline based sulfone linkage

between aryl ring and quinoline ring at 4th position having cyclopropane ring at 2nd position and examined their biological potential. Shown in **Fig. 5**.

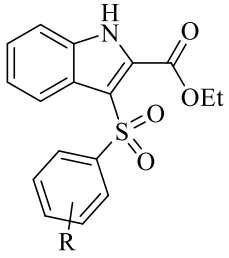
Previous work on 1,3,4-oxadiazole moiety:



Weiming et al. (2011)

Where, R= 2-$CF_3C_6H_4$, 2,3,4-TriFC_6H_2, 2-FC_6H_4, 2,2'-DiFC_6H_3, 2,2'-DiClC_6H_3, 2-$OCH_3C_6H_4$, 2-$CH_3C_6H_4$, 2-BrC_6H_4 etc.

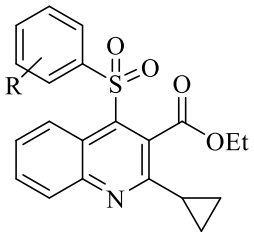
Previous work on Indole moiety:



Ragno et al. (2005)

Where, R= H, 2-NH_2, 5-Cl, 2-CH_3, 4-CH_3, 4-F, 4-Cl, 4-isoPr, 2,6-diCl

This work on Quinoline moeity:



Compounds 11a-n

Where, R= H, 2-Cl, 3-Cl, 4-Cl, 2-CH_3, 3-CH_3, 4-CH_3, 2-F, 3-F, 4-F, 3-OCH_3, 4-OCH_3, 3-NO_2, 4-$CH(CH_3)_2$

Fig. 5: Sulfone linkage between three different pharmacophores expected to appear with better antimicrobial activity

In view of these facts, there is a continuous demand and perusal to identify new antimicrobial agents with high efficiency, broad spectrum and safety. Hence, the present investigation pertains to the hybridization of two active pharmacophore (Quinoline & cyclopropane ring) with aromatic ring *via* a sulfone linkage. In this paper we have presented conventional method of synthesis of Ethyl-(2-cyclopropyl-4-(substituted phenylsulfonyl) quinoline-3-carboxylate **11a-n** (**Scheme-1**) and evaluated their *in-vitro* antibacterial and *in-vitro*

antifungal activities and also carried out their HOMO-LUMO study for proving the structural biological activity. Theoretical calculations DFT at B3LYP level has been carried out to determine the structure activity relationship.

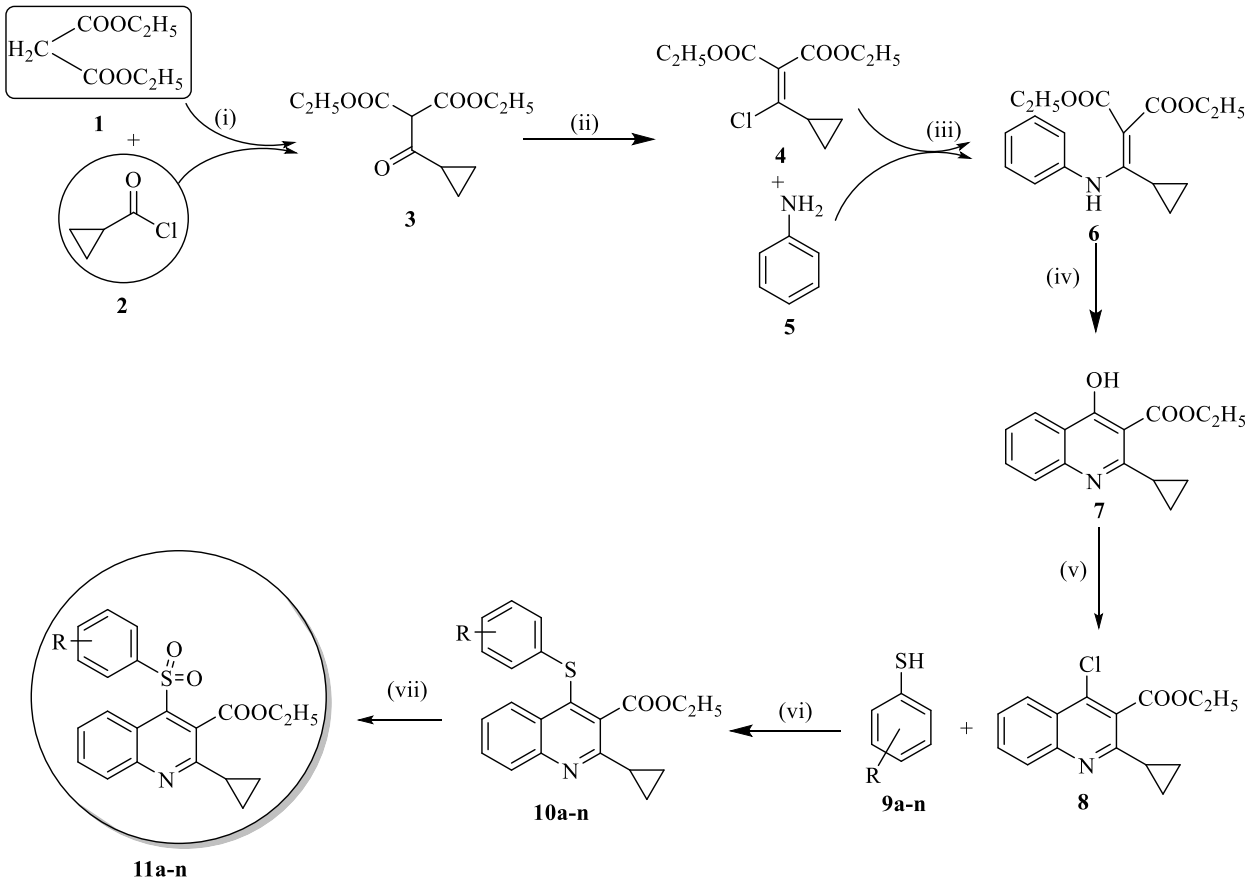
Chemistry:

In view of high pharmacological activity profile of quinoline compounds we have designed and synthesized this class of compounds **11a-n**. This part deals with the synthesis of novel quinolinyl-cyclopropane based analogues involving sulfone moiety. Different sulfone derivatives were condensed to the quinoline motif and the effect presence/absence of different group to sulfone on various biological activities of the final analogues has been studied. Hence, in the present study the first step comprises the formation of intermediate **3** in very good yield 80%. The first step is the acylation of diethyl malonate **1** with cyclopropane carbonyl chloride **2** in presence of magnesium chloride, triethyl amine and acetonitrile as solvent at 0°C to room temperature yielded diethyl-2-(cyclopropane-carbonyl)malonate **3** through reported method of Rathke et al. [34]. In the second step chlorination of diethyl-2-(cyclo propane-carbonyl)malonate **3** was occurred *via* phosphorus oxychloride in presence of triethyl amine at 110°C for 5-6 hours to get compound **4** diethyl-2-(chloro(cycloproryl)methylene)malonate by the reported method of More et al.[35]. Then, in third step substitution of –Cl atom has taken place by use for aniline **5** to get compound **6** diethyl-2-(cyclopropyl(phenylamino)methylene) malonate in presence of K_2CO_3 & DMF. In addition, cyclization of compound **6** has take place with the help of diphenyl ether at high temperature to get compound **7** ethyl-2-cyclopropyl-4-hydroxyquinoline-3-carboxylate. Then, chlorination of compound **7** by using $POCl_3$ and toluene as solvent at 80°C temperature yielded compound **8** ethyl-4-chloro-2-cyclopropyl-quinoline-3-carboxylate.

Besides these, different substituted thiophenols **9a-n** were used at compound **8** by nucleophilic substitution reaction of –Cl atom to get compound **10a-n** ethyl-2-cyclopropyl-(4-substituted phenylthio)quinoline-3-carboxylate by using NaH and THF as solvent for 6-18 hours by the reported method of Zhao et al. [36]. Oxidation of thio group was occurred by using 30% hydrogen peroxide and glacial acetic acid for 3-4 hours at room temperature to get the final sulfone derivatives **11a-n** ethyl-2-cyclopropyl-4-substituted phenylsulfonyl)quinoline-3-carboxylate (**Scheme-1**). All the final synthesized derivatives were characterized by melting point, mass spectra, IR, ^{1}H NMR, ^{13}C NMR which is elucidated in the experimental part. The

final analogues were then analyzed for their *in-vitro* antimicrobial activity against bacteria (Gram +ve and Gram –ve) and fungi using the agar streak dilution method. The bioassay results and relative comparison are discussed in the results and discussion part.

Scheme-1: Synthetic pathway of compounds 11a-n



Synthesis of final sulfone derivatives, Reagents and condition: (i) $MgCl_2$, TEA, CH_3CN, 0°C to R.T., 12 hours, (ii) $POCl_3$, TEA, 110°C, 5-6 hours, (iii) K_2CO_3, DMF, 100°C, 16-18 hours, (iv) Diphenyl ether, 170-230°C, ½ to 1 hour, (v) $POCl_3$, Toluene, 80°C, (vi) NaH, THF, R.T., 6-18 hours, (vii) Glacial CH_3COOH, 30% H_2O_2, 3-4 hours.

Herein, we also report log *P* value of the synthesized title compounds which is used in QSAR studies and rational drug design as a measure of molecular hydrophobicity which affects drug bioavailibity, absorption, hydrophobic drug receptor interactions, metabolism of molecules as well as toxicity of the compounds. Log *P* value must not be more than 5.0.

Medicinal chemistry part:

***In-vitro* evaluation of antimicrobial activity:**

In order to study the antimicrobial properties of the novel hybrid cyclopropyl-quinolinyl-sulfone derivatives, several bacterial (*Staphylococcus aureus* MTCC 96, *Staphylococcus pyogenus* MTCC 442, *Pseudomonas aeruginosa* MTCC 741, *Escherichia coli* MTCC 443) and fungal (*Candida albican* MTCC 227, *Aspergillus niger* MTCC 282, *Aspergillus clavatus* MTCC 1323) species were selected and minimum inhibitory concentration (MIC) of the compound was determined by the agar streak dilution method [37]. A stock solution of the tested compound (100 µg/mL) in dimethyl sulfoxide was prepared and graded quantities of the test compounds were incorporated in a specified quantity of molten sterile agar, i.e. nutrient agar for the evaluation of antibacterial and sabouraud dextrose agar for antifungal activity, respectively. The medium containing the test compound was poured into a petri dish at a depth of 4-5 mm and allowed to solidify under aseptic conditions. A suspension of the respective microorganism of approximately 105 CFU/mL was prepared and applied to plates with serially diluted compounds with concentrations in the range of 3.125-100 µg/mL in dimethyl sulfoxide and incubated at (37±1)°C for 24 hours. The lowest concentration of the substance which prevents the development of visible growth is considered to be the MIC value.

Material & Methodology:

Melting points were determined in open capillaries on a veego electronic apparatus VMP-D and are uncorrected. IR spectra of synthesized compounds were recorded on a shimadzu 8400-S FT-IR spectrometer using KBr pellets. Thin layer chromatography was performed on object glass slides (2×4 cm) coated with silica gel-G and spots were visualized under UV irradiation and also by ninhydrin solution to prove the presence of $-NH_2$ functional group. ^{1}H NMR spectra were recorded on a varian 400 MHz model spectrometer using dimethyl sulfoxide as a solvent and chemical shifts (δ) were reported in parts per million (ppm) with reference to tetramethylsilane as internal standard and coupling constants (*J*) were reported in Hertz (Hz). ^{13}C NMR spectra were obtained on a Bruker 100 MHz AC-300 spectrometer in dimethyl sulfoxide. The log *P* values of the compounds were determined by ChemBioDraw Ultra 12.0 program.

Experimental Section:

Synthesis of Ethyl-2-cyclopropyl-4-(substitutedphenylsulfonyl)quinoline-3-carboxylate (Compounds 11a-j):

This preparation was carried out in the following seven steps:

Step-1: Synthesis of diethyl-2-(cyclopropanecarbonyl) malonate (Compound 3)

A flame-dried 100 mL round bottom flask equipped with septum inlet, magnetic stirrer and mercury bubbler was flushed with argon. Magnessium chloride (26.2 g, 0.275 mol) was weighed in a vial in a glove bag and the contents of the vial were added to the flask. Dry acetonitrile (125 mL) was added to the flask. To the resulting heterogenous mixture (25 mL, 0.163 mol) of diethyl malonate **1** was added. The reaction flask was immersed in an ice-bath and (50 mL, 0.327 mol) of triethylamine was added *via* the septum inlet. The reaction mixture was stirred for 15 min at 0°C, then (25 mL, 0.163 mol) of cyclopropane carbonyl chloride **2** was added. The resulting mixture was stirred for 1 hour at 0°C and 8 hour at room temperature. After being cooled to 0°C the reaction mixture was quinched with 40 mL of 5 M HCl. Progress of the reaction was monitored by TLC using solvent system ethyl acetate: hexane (8:2). The solid obtained was filtered, washed with water, dried and crystallized from ethanol afforded the product diethyl-2-(cyclopropanecarbonyl) malonate compound **3**. Yield= 80%, m.p.= 178-180°C.

Step-2: Synthesis of diethyl-2-(chloro(cyclopropyl)methylene) malonate (Compound 4)

A mixture of compound **3** (25 g, 0.109 mol) and phosphorus oxychloride (110 mL) were placed in 1000 mL two necked round bottom flask equipped with magnetic stirrer, reflux condenser and dropping funnel. Triethylamine (15.3 mL, 0.109 mol) was added with stirring from dropping funnel. During which temperature rises to 60-80°C. When the addition was completed dropping funnel was replaced by glass stopper and the mixture was heated in oil bath at 110°C for 5-6 hours. Excess $POCl_3$ was removed in vacuum on a rotatory evaporator, 30 mL of ether and hexane was added until two phases separates cleanly and the mixture was shaked vigorously. The layers were separated and extraction with ether-hexane was repeated until ether and lower layer separates readily. Ether phase was dried over sodium sulphate, filtered and concentrated on a rotatory evaporator to give crude title compound **4.** Progress of the reaction was monitored by TLC using solvent system methanol: chloroform (4:6). Yiled=82%, m.p.=184°C.

Step-3: Synthesis of diethyl-2-(cyclopropyl(phenylamino)methylene)malonate (Compound 6):

A mixture of aniline (25 g, 0.268 mol), compound **4** (35.3 g, 0.224 mol), Anhydrous K_2CO_3 (74.2 g, 0.536 mol) and DMF (300 mL) was stirred at 100°C temperature in oil bath fir 16 hours. When it was cooled to room temperature, the inorganic material was removed by filtration and washed with ethyl acetate. Rest of the solution was transferred to a separating funnel and added ethyl acetate & water mixture. The organic layer was separated, washed with brine solution, dried and concentrated to give yellow coloured oil, which was further used for the next step. Weight= 60 g, Yield=80%, b.p.=200-202°C.

Step-4: Synthesis of Ethyl-2-cyclopropyl-4-hydroxyquinoline-3-carboxylate (Compound 7):

A solution of diethyl-2-(cyclopropyl(phenylamino)methylene)malonate compound **6** (50 g, 0.165 mol) and diphenyl ether was taken in round bottom flask and the whole system was refluxed at 170-230°C temperature for 1 hour. The resulting light brown solution was poured into the aqueous solution saturated with $NaHCO_3$ (500 mL); the suspension was extracted with ethyl acetate. The organic layer were washed with water, dried and concentrated to give compound **9** oily light yellow liquid (34 mL), Yield=80%, b.p.=280-282°C

Step-5: Synthesis of ethyl-4-chloro-2-cyclopropylquinoline-3-carboxylate (Compound 8):

A mixture of compound **7** (35 g, 0.136 mol) and toluene (60 mL) was taken in 500 mL of round bottom flask and refluxed it. Than (26 mL, 0.277 mol) of phosphorus oxychloride was added drop wise in reaction mixture, After the complete addition of $POCl_3$ the whole system was heated at 80°C temperature for 6 hours. The resulting light brown colour solution was poured into the aqueous solution of saturated with $NaHCO_3$ (500 mL); the suspension was extracted with ethyl acetate. The organic layer were washed with water, dried and concentrated to give compound **8** oily light yellow liquid (34 mL), Yield= 80%, b.p.= 280-282°C.

Step-6: Synthesis of ethyl-2-cyclopropyl-4-(thiophenol)quinoline-3-carboxylate (Compound 10a)

A mixture of compound **8** (2.0 g, 0.00725 mol) and thiophenol **9a** (1.3 g, 0.0088 mol), sodium hydride (1.2 g, 0.0088 mol) and THF (25 mL) were stirred for 18 hours at room temperature. Progress of the reaction was monitored by TLC using solvent system ethyl acetate: hexane (5:5). After the completion of reaction the resulting mixture was transferred to a separating funnel and mixture of 50% ethyl acetate was added. The organic layer was separated,

washed with brine solution, dried and concentrated after dryness to give an yellow coloured solid, which was recrystallized from hexane to afford the title compound **10a** (2.5 g), Yield=82%, m.p.=82°C.

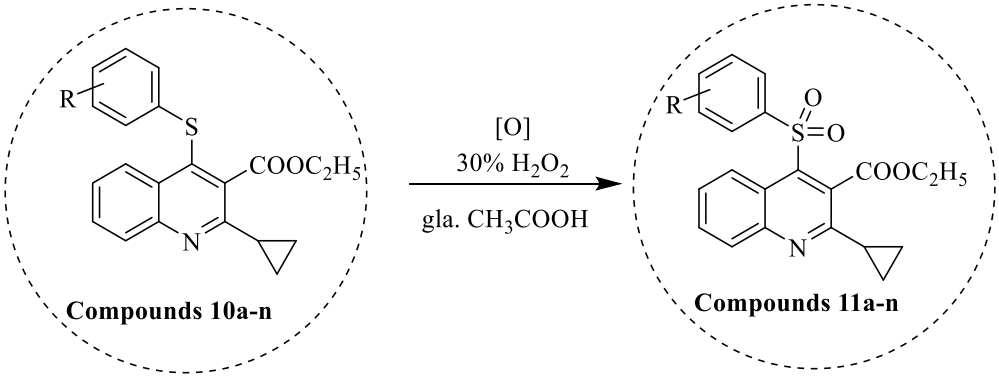
Compounds **10b-n** were prepared in same manner analogues to the method described above.

Step-7: Synthesis of ethyl-2-cyclopropyl-(4-phenylsulfonyl)quinoline-3-carboxylate (Compound 11a)

A mixture of compound **10a** (2.0 g, 0.0057 mol) and 25 mL of glacial acetic acid were taken in two necked round bottom flask and refluxed it for 15 min at 80-90°C temperature. After that heating was stopped and portion of 10 mL 30% hydrogen peroxide was added. The reaction was again refluxed for 3-4 hours. After the completion of reaction it was poured into crushed ice. Progress of the reaction was monitored by TLC using toluene: acetone (7:3) solvent system. The product thus obtained was filtered, dried and recrystallized from ethanol to afford the title compound **11a**. Yield=75%, m.p.=160°C.

Compounds **11b-n** were prepared by the analogous method. Some of the physical and analytical properties are included in **Table-1**.

Table-1: Physical and analytical data of compound 11a-n



Entry	R	Molecular formula	M.W. (gm/mol)	% Yield	M.P. (°C)	Log *P*
11a	H	$C_{21}H_{19}NO_4S$	381.45	75	160-162	4.26
11b	2-Cl	$C_{21}H_{18}ClNO_4S$	415.89	78	172-174	4.82
11c	3-Cl	$C_{21}H_{18}ClNO_4S$	415.89	80	180-182	4.82
11d	4-Cl	$C_{21}H_{18}ClNO_4S$	415.89	72	158-160	4.82
11e	2-CH_3	$C_{22}H_{21}NO_4S$	395.47	68	174-176	4.74

11f	3-CH_3	$C_{22}H_{21}NO_4S$	395.47	62	184-186	4.74
11g	4-CH_3	$C_{22}H_{21}NO_4S$	395.47	60	180-182	4.74
11h	2-F	$C_{21}H_{18}FNO_4S$	399.44	84	152-154	4.42
11i	3-F	$C_{21}H_{18}FNO_4S$	399.44	80	140-142	4.42
11j	4-F	$C_{21}H_{18}FNO_4S$	399.44	78	160-162	4.42
11k	3-OCH_3	$C_{22}H_{21}NO_5S$	411.17	64	190-192	4.13
11l	4-OCH_3	$C_{22}H_{21}NO_5S$	411.17	66	186-188	4.13
11m	3-NO_2	$C_{21}H_{18}N_2O_6S$	426.44	58	148-150	5.0
11n	4-$CH(CH_3)_2$	$C_{24}H_{25}NO_4S$	423.53	64	178-180	5.49

Results & Discussions:

I) Antimicrobial activity:

The entire tested compounds contains quinoline as the core unit structure substituted with derivatives of various sulfones at 4th position, ethyl acetate at 3rd position and cyclopropane ring at 2nd position. The microbial activities of mono-heterocyclic entity, i.e. quinoline and their derivatives have already been discussed. Urged by their findings and further exploration of the quinoline ring system as a promising nucleus in search of new antimicrobial agent, it was of interest to hybridize this nucleus with various substituted sulfone attach at 4th position of the quinoline ring. The antimicrobial potency in terms of MIC values are summarized in **Table-2**. Results of MIC value of the compounds are observed in the varied range (62.5 to 500 µg/mL) to antibacterial activities against all the tested bacterial strains.

Out of all 14 compounds results suggests that compound bearing electron withdrawing methoxy group at m-position in compound **11k** was the most active (MIC 62.5 µg/mL) against gram +ve *Streptococcus pyogenus* strain and gram –ve *Pseudomonas aeruginosa* & *Echerichia coli* strains at 62.5 µg/mL. A compound having no any substitution **11a** also shows very good activity against gram +ve *Streptococcus pyogenus* with MIC 100 µg/mL and gram –ve *Pseudomonas aeruginosa* with 62.5 µg/mL MIC. Compounds **11b** and **11c** bearing electron withdrawing group like chlorine at 2nd and 3rd position respectively endowed with promising antibacterial activity (MIC 100 µg/mL). However these sets of compounds were found comparatively active showing MIC varying from 100 to 125 µg/mL against gram +ve and gram

–ve strains. On other part, compounds **11e, 11f, 11g** possessing electron donating methyl group shows moderate or inactive against bacterial strains with 200-500 µg/mL MIC value. Furthermore, sulfone derivatives **11h, 11i** and **11j** containing electron withdrawing fluoro group contributed similar efficacy with 62.5 µg/mL MIC value against gram +ve *Staphylococcus aureus* & *Streptococcus pyogenus* strain and 100 µg/mL MIC value against gram –ve *Pseudomonas aeruginosa* & *Echerichia coli* strains. Now, compound **11l** having electron donating methoxy group at *p*-position appeared with 200-250 µg/mL MIC values against all bacterial strains. However, compound **11m** which contain electron withdrawing $–NO_2$ group found active (MIC 100-125 µg/mL) against bacterial strains. So, among mentioned set of compounds compound **11b, 11c, 11h, 11j, 11k & 11m** with electron withdrawing groups H, -Cl, -F, $-OCH_3$, and $–NO_2$ group respectively showed the best inhibition profile of range 62.5-125 µg/mL MIC.

In terms of antifungal activity compound **11a** having no substitution moiety showed good activity against *Aspergillus niger* strain with 100 µg/mL MIC value. Furthermore compound **11k** having methoxy substitution at meta position showed the best activity against all fungal strains with 100 µg/mL MIC value. Which is found to be the highest activity from all set of compounds **11a-n**. With MIC values ranging from 250-1000 µg/mL, compounds tend to be less affective towards all fungal strains. i.e. **11d, 11e, 11f, 11g, 11i, 11j, 11l** and **11n**. However, compounds **11b** & **11c** having electron withdrawing chloro substitution at 2^{nd} and 3^{rd} position respectively appeared with moderate activity. Furthermore, compound **11h** having 2-fluoro group showed similar efficacy against *Candida albicans* and *Aspergillus clavatus* with 200 µg/mL MIC value and against *Aspergillus niger* with 100 µg/mL MIC value. However, compound **11m** having nitro group at meta position showed good efficacy against *Candida albican* & *Aspergillus niger* strains with 200 µg/mL and 100 µg/mL MIC values respectively. Rest of the compounds shows their effect to less extent on the bacterial and fungal strains growth with MIC value ranging from 200-1000 µg/mL. Ciprofloxacin was taken as a standard drug again bacterial growth and Nystatin was taken as a standard drug again fungal growth.

Table-2: *In-vitro* antibacterial and antifungal activities in MIC*(µg/mL) of Compounds 11a-n

Comp. No.	R	Minimum Inhibitory Concentration						
		Antibacterial activity				Antifungal activity		
		Gram Positive		Gram Negative		---		
		S.aureus MTCC 96 µg/ml	*S.pyogenus* MTCC 443 µg/ml	*P.aeruginosa* MTCC 741 µg/ml	*E.coli* MTCC 442 µg/ml	*C.albicans* MTCC 227 µg/ml	*A.niger* MTCC 282 µg/ml	*A.clavatus* MTCC 1323 µg/ml
11a	H	125	100	62.5	250	250	100	200
11b	2-Cl	200	200	100	100	100	100	250
11c	3-Cl	125	100	100	125	200	200	500
11d	4-Cl	125	500	500	200	500	500	250
11e	2-CH_3	250	250	500	200	>1000	1000	1000
11f	3-CH_3	200	500	250	250	500	>1000	500
11g	4-CH_3	200	250	200	500	500	500	>1000
11h	2-F	62.5	62.5	100	100	200	100	200
11i	3-F	500	500	250	250	250	250	500
11j	4-F	125	100	100	100	>1000	1000	500
11k	3-OCH_3	100	62.5	62.5	62.5	100	100	100
11l	4-OCH_3	250	200	250	250	>1000	>1000	>1000
11m	3-NO_2	100	125	100	100	200	100	250
11n	4-$CH(CH_3)_2$	500	500	200	250	>1000	>1000	500
Standard Drug	**Ciprofloxacin**	**50**	**50**	**25**	**25**	**--**	**--**	**--**
	Nystatin	**--**	**--**	**--**	**--**	**100**	**100**	**100**

II) Structural Activity Relation (SAR) study:

The structural similarity in terms of substituents of several of the antimicrobial (Nevirapine, RVT-101, Pitavastatin, Ciprofloxacin and Nystatin) and the synthesized cyclopropyl-quinolinyl-sulfone hybrids derivatives have permitted a systematic comparison of the SAR relationships. The numbers and sites of attachment of the ethyl acetate linkage, various aromatic sulfones and cyclopropane ring substituents profoundly affect the ability of these compounds to inhibit *in vitro* bacterial and fungal infections. SAR reveals the introduction of various groups attached to the aromatic sulfone and, according to the attachment, the activity could be defined where it is increased/decreased. The physiological properties such as lipophilicity or hydrophobicity might be concerned with their activities. Here, we found out some log *P* values of the compounds. The log *P* value of a compound, which is the logarithm of

its partition coefficient between *n*-octanol and water, is a well-established measure of the compound's hydrophobicity and it must be less than 5.0.

$$\log p = \log \frac{c(n-octanol)}{c(water)}$$

In all cases, we observed that the log *P* values of the synthesized compounds were obtained less than 5.0, being around 4.0–5.0, (except= compound **11n**) which is indicated in **Table-1**. From that, we considered that the hydrophobicity of the design molecules are very good and the study of SAR obtained is positive. Halogens are very reactive due to their high electronegativity and high effective nuclear charge. From that we can conclude that sufficient quantities of halogens can be dangerous to microorganisms. However, methyl group substituted compounds **11e, 11f & 11g** (log *P* =4.74) increases the lipophilicity of the compounds and give moderate antimicrobial activity against microorganisms. On the whole, halogen-substituted compounds **11b, 11c, & 11d** (log *P* = 4.82) increases the lipophilicity of the compounds. Hence, it can be concluded that the more hydrophobic the substituent, the more effective is its antimicrobial property. From the results, we can see that compounds which contain –F as substituent **11h, 11i & 11j** (log *P* = 4.42) gave the best absorptions or can be understand to have better hydrophobicity. Compound **11a** is also appeared with the best hydrophobicity because of not having any substituent. On the whole, methoxy group substituted compounds **11k & 11l** (log *P*= 4.13) having lowest value gives highest activity among all the compounds. Furthermore, from the lipophilicity point of view, it can be concluded that compounds with greater lipophilicity (greater log *P* value) displayed higher activities in terms of lower MICs and higher inhibition zones due to their higher lipophilic nature. This clearly demonstrates the importance of lipophilicity for the antimicrobial activities of the resultant scaffolds.

III) HOMO-LUMO study:

To correlate the experimental results, quantum chemical indices such as HOMO (Highest Occupied Molecular Orbital) energies, LUMO (Lowest Unoccupied Molecular Orbital) and HOMO-LUMO energies gap were calculated for compounds **11a, 11b, 11e, 11h, 11k & 11m** according to the literature methodology [38]. The calculated HOMO and LUMO energies shows that charge transfer occurs within the molecule. They are also very important parameters for quantum chemistry. Both HOMO and LUMO are the main orbital taking part in chemical

stability [39]. Results are summarized in **Table-3**. The HOMO and LUMO populations were plotted and show in **Fig. 6**. Positive and negative phases are represented in red and green colour respectively. They determine the way that how molecule-molecule interacts with other species like bacteria and fungi [40]. Thus, the HOMO and LUMO energies are associated respectively with the electron donating and electron accepting abilities of a molecule [41]. Therefore, the high value of HOMO energy indicates a tendency to donate electrons to appropriate acceptor molecule with low energy and empty molecular orbital. As well as the lower value of LUMO energy indicates that this compound would also accept electrons.

Several studies reported correlation between HOMO-LUMO energies and antimicrobial activity [42-44]. This is due to the change in total dipole moment. However, the energies were affected by the presence of electron donating or withdrawing group on the structure, consequently there was a change in energy according to attached groups. In this study, the compounds exhibited different antimicrobial activity; this may be due to the difference in HOMO-LUMO energy gap (ΔE).

i) In the case of compound **11a**, HOMO is located over the N-atom and C-atoms of quinoline ring system and sulfone group and LUMO is located over C-atoms & N-atom of quinoline ring at all C-atoms and cyclopropane ring. So, the HOMO→LUMO transition implies on electron density transfer to quinoline ring from sulfone group to C-atoms & N-atom.

ii) In the case of compound **11b**, HOMO is located over the C-atoms of quinoline ring system and LUMO is located over N-atoms & C-atom of quinoline ring and cyclopropane ring C-atom. So, the HOMO→LUMO transition implies on electron density transfer to quinoline ring from C-atoms to N-atom and cyclopropane ring.

iii) In the case of compound **11e**, HOMO is located over the C-atoms of quinoline ring, sulfone group and –Cl atom of aromatic ring substitution and LUMO is located over N-atom and all C-atoms of quinoline ring and C-atom of cyclopropane ring attached to the quinoline ring. So, the HOMO→LUMO transition implies on electron density transfer to quinoline C-atoms of N-atom and sulfone, -Cl group to cyclopropane ring.

iv) In the case of compound **11h**, HOMO is located over the C-atoms & N-atom of quinoline ring system and sulfone group and LUMO is located over the all C-atoms & N-atom of quinoline ring and C-atom attached to quinoline ring of cyclopropane ring. So, the

HOMO→LUMO transition implies an electron density transfer to the sulfone & C-atoms to N-atom and cyclopropane C-atom.

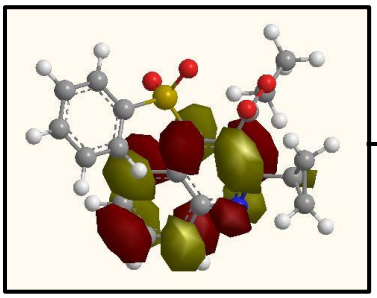
v) In the case of compound **11k**, HOMO is located over the sulfone group & C-atoms, N-atom of quinoline analogues and LUMO is located over the all C-atoms & N-atom of quinoline analogues and cyclopropane ring C-atom. So, the HOMO→LUMO transition implies an electron density transfer to the sulfone to quinoline ring C-atoms & N-atom and on cyclopropane ring.

vi) In the case of compound **11m,** HOMO is located over the sulfone group & C-atoms, N-atom of quinoline motif and LUMO is located over the all C-atom of aromatic substituted thiol ring and on nitro group. So, the HOMO→LUMO transition implies an electron density transfer to the sulfone, quinoline C-atoms & N-atom to nitro group and aromatic carbons.

Table-3: Energy gap ΔE of the compounds (11a, 11b, 11e, 11h, 11k & 11m)

Compound	E_{HOMO} (eV)	E_{LUMO} (eV)	Energy gap $\Delta E = E_{LUMO-HOMO}$ (eV)
11a	-8.985	-7.197	1.788
11b	-4.384	-3.017	1.367
11e	-8.949	-3.696	5.253
11h	-8.984	-0.794	1.890
11k	-8.983	-8.187	0.796
11m	-8.984	-7.817	1.164

(i) HOMO-LUMO Energy Plot for Compound 11a:

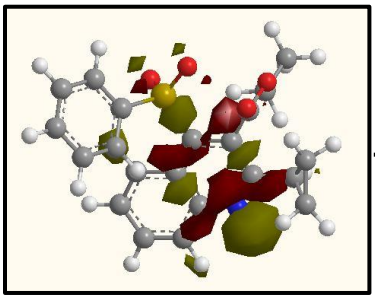


LUMO PLOT

(First excited state)

E_{LUMO}= -7.197 eV

ΔE_{gap}= 1.788 eV



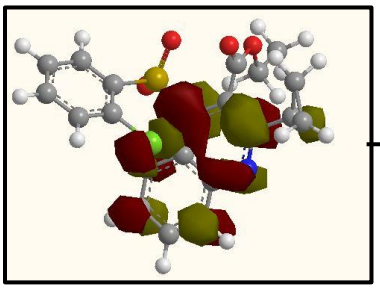
e $^-$

E_{HOMO}= -8.985 eV

HOMO PLOT

(Ground state)

(ii) HOMO-LUMO Energy Plot for Compound 11b:

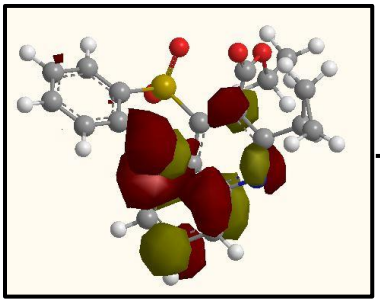


LUMO PLOT

(First excited state)

E_{LUMO}= -3.017 eV

ΔE_{gap}= 1.367 eV



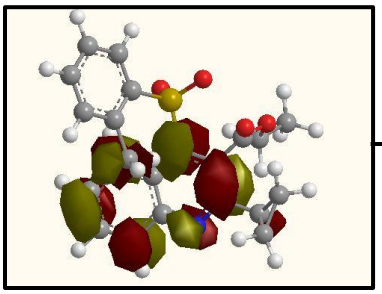
e $^-$

E_{HOMO}= -4.384 eV

HOMO PLOT

(Ground state)

(iii) HOMO-LUMO Energy plot for Compound 11e:



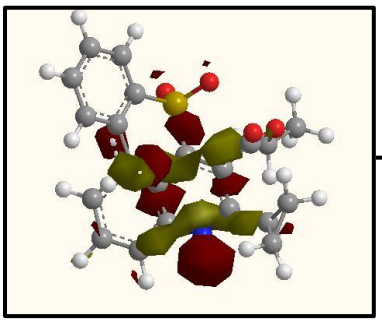
LUMO PLOT

(First excited state)

E_{LUMO}= -3.636 eV

ΔE_{gap}= 5.253 eV

e -

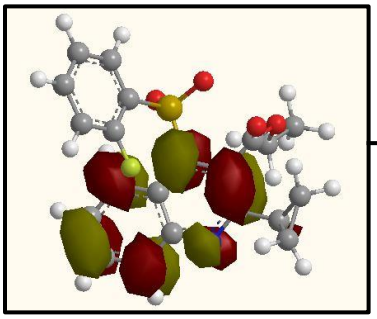


E_{HOMO}= -8.949 eV

HOMO PLOT

(Ground state)

(iv) HOMO-LUMO Energy plot for Compound 11h:



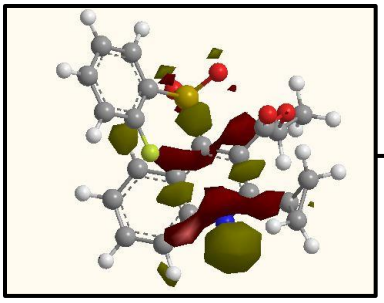
LUMO PLOT

(First excited state)

E_{LUMO}= -7.094 eV

ΔE_{gap}= 1.890 eV

e -

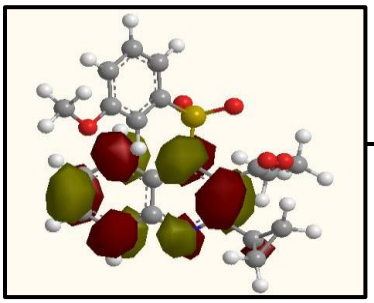


E_{HOMO}= -8.984 eV

HOMO PLOT

(Ground state)

(v) HOMO-LUMO Energy plot for Compound 11k:

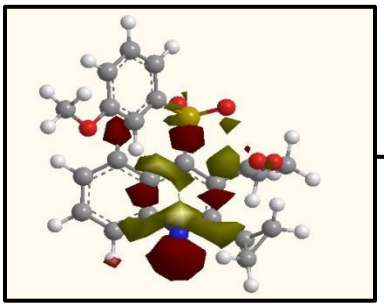


LUMO PLOT

(First excited state)

E_{LUMO}= -8.187 eV

ΔE_{gap}= 0.796 eV



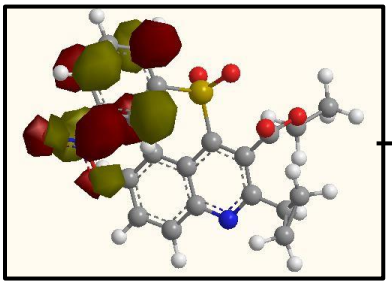
e -

E_{HOMO}= -8.983 eV

HOMO PLOT

(Ground state)

(vi) HOMO-LUMO Energy plot for Compound 11m:

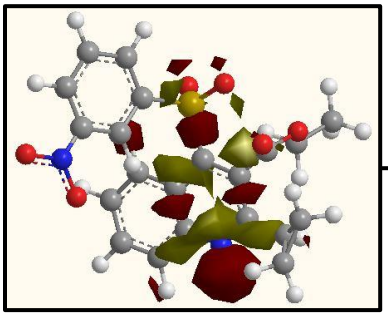


LUMO PLOT

(First excited state)

E_{LUMO}= -7.817 eV

ΔE_{gap}= 1.164 eV



e -

E_{HOMO}= -8.984 eV

HOMO PLOT

(Ground state)

Fig. 6: Atomic orbital compositions of the FMO for Compounds **11a, 11b, 11e, 11h, 11k & 11m**

Conclusion:

Quinoline bearing cyclopropane ring endowed with sulfones have been synthesized in anticipation of augmented biological profile of the said nucleus. The results obtained reveals that the nature of substituent and substitution pattern on the quinoline ring may have a considerate impact on the biological activities of the target product. The variation of antimicrobial activity is related to the chemical structure of the tested compounds having various substituents. Among the synthesized compounds, compound **11a** having no substitution, compound **11b** having –Cl at o-position, compound 11c having –Cl at m-position, compound **11h** having –F at *o*-position, compound **11j** having –F at *p*-position and compound **11m** having $–NO_2$ group at m-position exhibited promising *in-vitro* antibacterial activity inhibitory effects with 100 µg/mL MIC value. Methoxy group shows best biological activity on both bacterial and fungal strains. Likewise, Compound **11k** having 3-OCH_3 group shows good antifungal activity which is equivalent to standard drug Nystatin with 100 µg/mL MIC value. The structural variations such as methoxy group at *m* & *p*-position to the aromatic thiol group resulted different activity due to their electron withdrawing and electron donating effect respectively. Overall, Compounds **11a, 11b, 11c, 11h & 11m** shows better activity against all fungal strains. It may further be concluded that electron withdrawing halo and nitro might be responsible for betterment in biological profile.

Based on a computational study of HOMO-LUMO, it is concluded that the lower the energy gap the better is the biological activity. i.e.,**11a, 11b, 11h, 11k & 11m**. Therefore, the lowest energy gap value of compound **11k** with 0.796 eV of 3-OCH_3 group shows best both antibacterial and antifungal activities compare to the other compounds. So, it is needed in the field of medicinal chemistry to design more compounds having sulfone linkage on quinoline or another analogues with anticipation of betterment in biological profile.

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References:

1. R. Khan, B. Islam, M. Akram, S. Shakil, A. A. Ahmad, S. M. Ali, M. Siddiqui, A. U. Khan, Molecules **14(2)**, 586-597 (2009) https://doi.org/10.3390/molecules14020586
2. W. Gao, Y. He, F. Li, C. Chai, J. Zhang, J. Guo, C. Chen, J. Wang, H. Zhu, Z. Hu, Y. Zhang, Bioorg. Chem. **83**, 98-104 (2019) https://doi.org/10.1016/j.bioorg.2018.10.020
3. P. M. Chauhan, S. N. Thummar, K. H. Chikhalia, J. Iran. Chem. Soc., **15(6)**, 1261-1277 (2018) https://doi.org/10.1007/s13738-018-1324-0
4. E. D. Brown, G. D. Wright, Chem. Rev. **105(2)**,759-774 (2005) https://doi.org/10.1021/cr030116o
5. P. Y. Chung, Z. X. Bian, H. Y. Pun, D. Chan, A. S. Chan, C. H. Chui, J. C. Tang, K. H. Lam, Future Med. Chem. **7(7)**, 947-967 (2015) https://doi.org/10.4155/fmc.15.34
6. G. C. Dos Santos, A. de Andrade Bartolomeu, V. F. Ximenes, L. C. da Silva-Filho, J. fluorescence **27(1),** 271-280 (2017) https://doi.org/10.1007/s10895-016-1954-5
7. L. Cheng, P. P. Cai, R. R. Zhang, L. Han, C. X. Tan, J. Q. Weng, T. M. Xu, X. H. Liu, J. Hetero. Chem. **56(4),** 1312-1317 (2019) https://doi.org/10.1002/jhet.3502
8. H. Tian, A. F. Hühmer, J. P. Landers, Analyt. Biochem. **283(2),** 175-191 (2000) https://doi.org/10.1006/abio.2000.4577
9. E. Fromm, J. Wittmann, Berichte der deutschen chemischen Gesellschaft **41(2),** 2264-2273 (1908) https://doi.org/10.1002/cber.190804102131
10. N. K. Konduru, S. Dey, M. Sajid, M. Owais, N. Ahmed, Eur. J. Med. Chem. **59**, 23-30 (2013) https://doi.org/10.1016/j.ejmech.2012.09.004
11. Z. H. Wen, C. H. Chao, M. H. Wu, J. H. Sheu, Eur. J. Med. Chem. **45(12)**, 5998-6004 (2010) https://doi.org/10.1016/j.ejmech.2010.09.067
12. V. K. Madduluri, N. Baig, S. Chander, S. Murugesan, A. K. Sah, Cat. Comm. **137**, 105931-105935 (2020) https://doi.org/10.1016/j.catcom.2020.105931
13. A. A. Upare, P. K. Gadekar, H. Sivaramakrishnan, N. Naik, V. M. Khedkar, D. Sarkar, A. Choudhari, S. M. Roopan, Bioorg. Chem. **86**, 507-512 (2019) https://doi.org/10.1016/j.bioorg.2019.01.054
14. Y. Long, M. Yu, P. Li, S. Islam, A. W. Goh, M. Kumarasiri, S. Wang, Bioorg. Med. Chem. Lett. **26(23)**, 5674-5678 (2016) https://doi.org/10.1016/j.bmcl.2016.10.062

15. X. Yu, Y. Liu, Y. Li, Q. Wang, J. Agricul. Food. Chem. **64(15)**, 3034-3040 (2016) https://doi.org/10.1021/acs.jafc.6b00645
16. L. J. Singh, R. H. Singh, R. Chitra, J. Iran. Chem. Soc. **9(4)**, 441-448 (2012) https://doi.org/10.1007/s13738-011-0054-3
17. T. M. Tan, Y. Chen, K. H. Kong, J. Bai, Y. Li, S. G. Lim, T. H. Ang, Y. Lam, Antiviral. Res. **71(1)**, 7-14 (2006) https://doi.org/10.1016/j.antiviral.2006.02.007
18. M. H. Holshouser, L. J. Loeffler, I. H. Hall, J. Med. Chem. **24(7)**, 853-858 (1981) https://doi.org/10.1021/jm00139a017
19. V. L. Rao, M. R. Rao, J. Appl. Polym. Sci. **69(4)**, 743-750 (1998) https://doi.org/10.1002/(SICI)1097-4628(19980725)69:4%3C743::AID-APP12%3E3.0.CO;2-Q
20. X. Nqoro, N. Tobeka, B. A. Aderibigbe, Molecules **22(12)**, 2268-2271 (2017) https://doi.org/10.3390/molecules22122268
21. H. Hamidi, M. M. Heravi, M. Tajbakhsh, M. Shiri, H. A. Oskooie, S. A. Shintre, N. A. Koorbanally, J. Iran. Chem. Soc. **12(12)**, 2205-2212 (2015) https://doi.org/10.1007/s13738-015-0698-5
22. R. Musiol, M. Serda, S. Hensel-Bielowka, J. Polanski, Curr. Med. Chem. **17(18)**, 1960-1973 (2010) https://doi.org/10.2174/092986710791163966
23. S. Rossiter, J. M. Peron, P. J. Whitfield, K. Jones Bioorg. Med. Chem. Lett. **15(21)**, 4806-4808 (2005) https://doi.org/10.1016/j.bmcl.2005.07.044
24. P. Fossa, G. Menozzi, P. Dorigo, M. Floreani, L. Mosti, Bioorg. Med. Chem. **11(22),** 4749-4759 (2003) https://doi.org/10.1016/S0968-0896(03)00528-5
25. L. J. Guo, C. X. Wei, J. H. Jia, L. M. Zhao, Z. S. Quan, Eur. J. Med. Chem. **44(3)**, 954-958 (2009) https://doi.org/10.1016/j.ejmech.2008.07.010
26. S. K. Suthar, V. Jaiswal, S. Lohan, S. Bansal, A. Chaudhary, A. Tiwari, A. T. Alex, A. Joesph, Eur. J. Med. Chem. **63**, 589-602 (2013) https://doi.org/10.1016/j.ejmech.2013.03.011
27. R. Elsayed Khidre, B. Fathy Abdel-Wahab, F. Abdel-Rehem Badria, Lett. Drug. Des. Discov. **8(7)**, 640-648 (2011).
28. C. De la Guardia, D. E. Stephens, H. T. Dang, M. Quijada, O. V. Larionov, R. Lleonart, Molecules **23(3)**, 672-679 (2018) https://doi.org/10.3390/molecules23030672

29. N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran, J. T. Leonard, Biol. Pharm. Bull. **27(10)**, 1683-1687 (2004) https://doi.org/10.1248/bpb.27.1683
30. Y. Zhu, M. Zhang, T. Li, X. Song, Chem. Select **4(36)**, 10838-10842 (2019) https://doi.org/10.1002/slct.201903330
31. R. P. Modh, E. De Clercq, C. Pannecouque, K. H. Chikhalia, J. Enzyme Inhib. Med. Chem. **29(1)**, 100-108 (2014) https://doi.org/10.3109/14756366.2012.755622
32. W. Xu, J. He, M. He, F. Han, X. Chen, Z. Pan, J. Wang, M. Tong, Molecules **16(11)**, 9129-9141 (2011) https://doi.org/10.3390/molecules16119129
33. R. Ragno, M. Artico, G. De Martino, G. La Regina, A. Coluccia, A. Di Pasquali, R. Silvestri, J. Med. Chem. **48(1)**, 213-223 (2005) https://doi.org/10.1021/jm040854k
34. M. W. Rathke, P. J. Cowan, J. Org. Chem. **50(15)**, 2622-2624 (1985) https://doi.org/10.1021/jo00215a003
35. S. S. More, T. K. Mohan, Y. S .Kumar, U. S. Kumar, N. B. Patel, Beilstein J. Org. Chem. **7(1)**, 831-838 (2011) https://doi.org/10.3762/bjoc.7.95
36. S. Zhao, W. Zhou, Bioorg. Med. Chem. **17(23)**, 7915-7923 (2009) https://doi.org/10.1016/j.bmc.2009.10.021
37. Y. Laot, L. Petit, S. Z. Zard, Chem. Comm. **46(31)**, 5784-5786 (2010) https://doi.org/10.1039/C0CC00533A
38. I. Bouabdallah, M. Rahal, T. Harit, A. El Hajbi, F. Malek, D. Eddike, M. Tillard, A. Ramdani, Chem. Phys. Lett. **588**, 208-214 (2013) https://doi.org/10.1016/j.cplett.2013.10.046
39. A. Nakayama, K. Hagiwara, S. Hashimoto, S. Shimoda, QSAR **12(3)**, 251-255 (1993) https://doi.org/10.1002/qsar.19930120306
40. T. Harit, R. Bellaouchi, A. Asehraou, M. Rahal, I. Bouabdallah, F. Malek, J. Mol. Struct. **1133**, 74-79 (2017) https://doi.org/10.1016/j.molstruc.2016.11.051
41. M. Özcan, I. L. Dehri, M. Erbil, Appl. Surf. Sci. **236(1-4)**, 155-164 (2004) https://doi.org/10.1016/j.apsusc.2004.04.017
42. A. Khalafi-Nezhad, M. S. Rad, H. Mohabatkar, Z. Asrari, B. Hemmateenejad, Bioorg. Med. Chem. **13(6)**, 1931-1938 (2005) https://doi.org/10.1016/j.bmc.2005.01.014
43. A. M. Mansour, Inorganica. Chim. Acta. **394**, 436-445 (2013) https://doi.org/10.1016/j.ica.2012.08.025

44. G. M. Reddy, J. R. Garcia, V. H. Reddy, A. M. de Andrade, A. Camilo Jr, R. A. Ribeiro, S. R. de Lazaro, Eur. J. Med. Chem. **123**, 508-513 (2016) https://doi.org/10.1016/j.ejmech.2016.07.

Figures

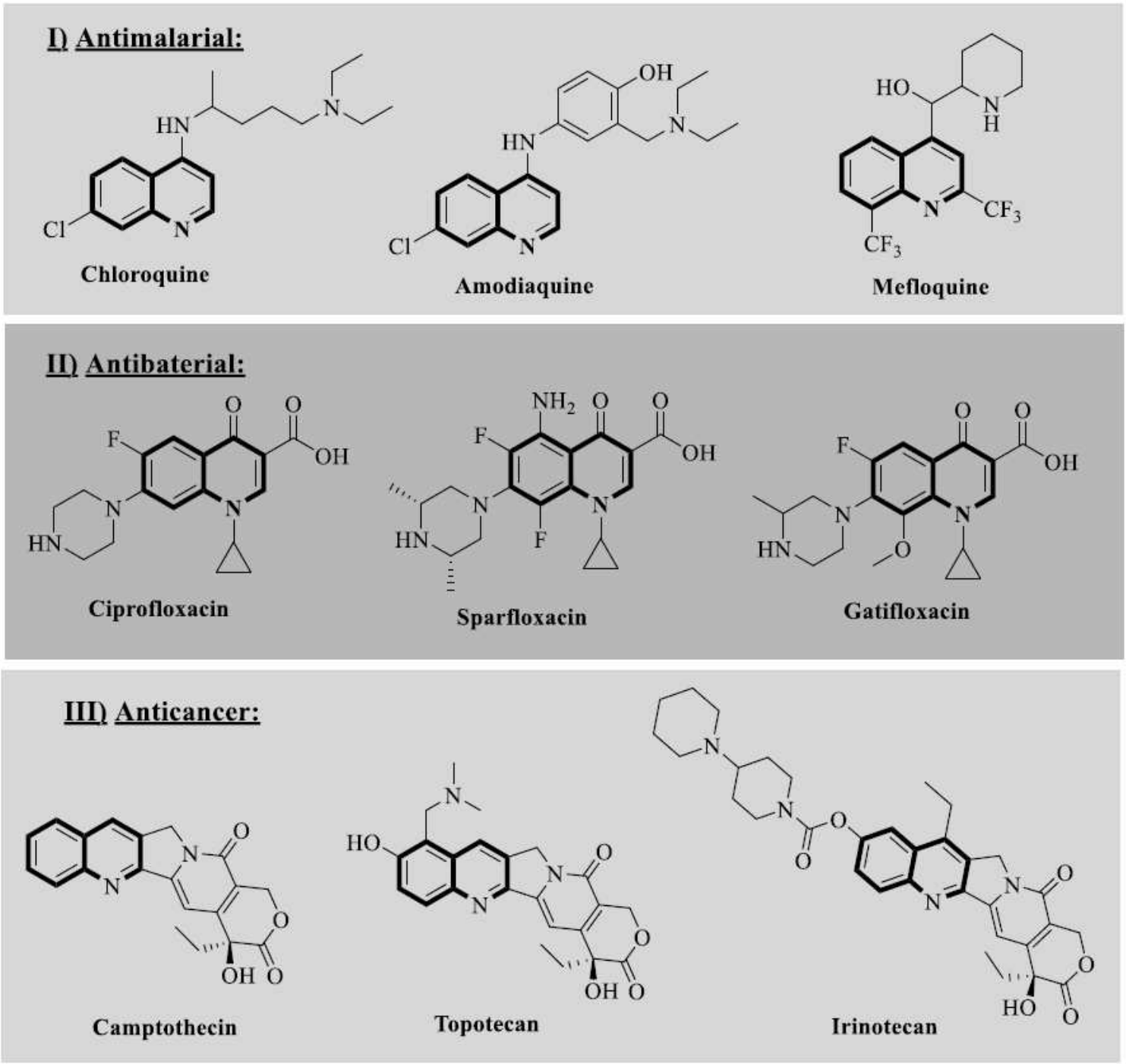


Figure 1

Quinoline containing drugs available in market.

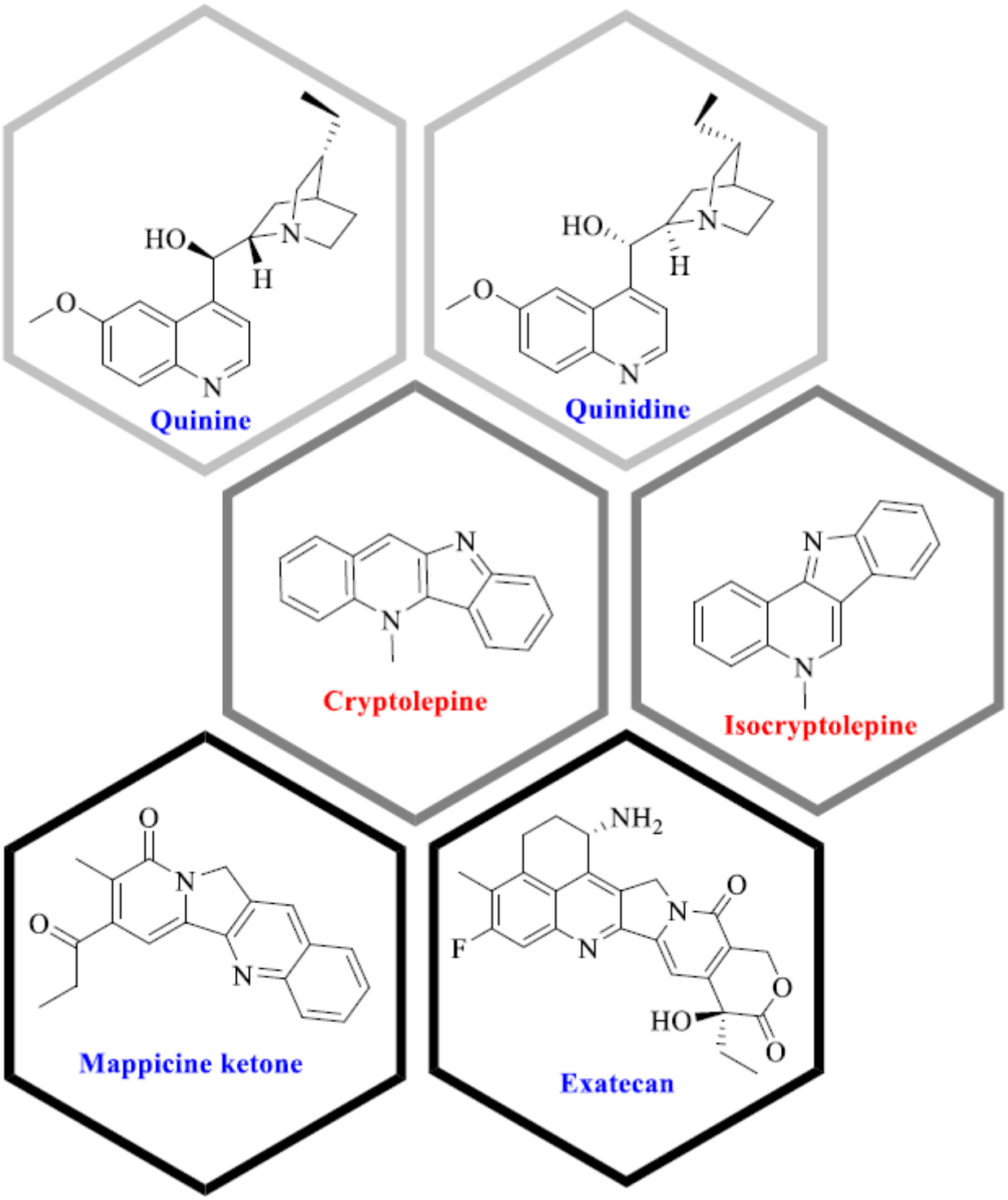


Figure 2

Quinoline containing molecules available in nature

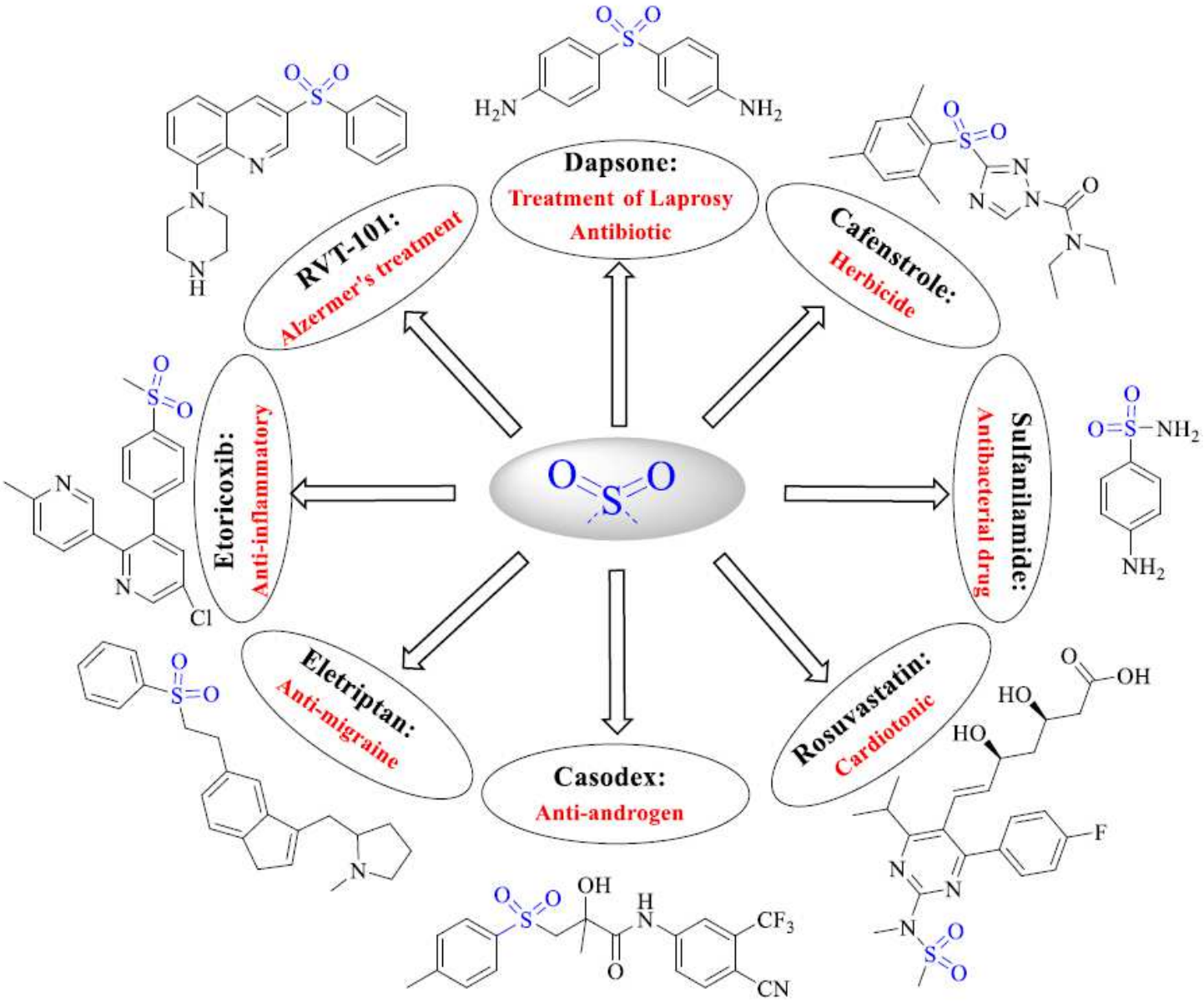


Figure 3

Some available drugs in market contain aryl-sulfone moiety

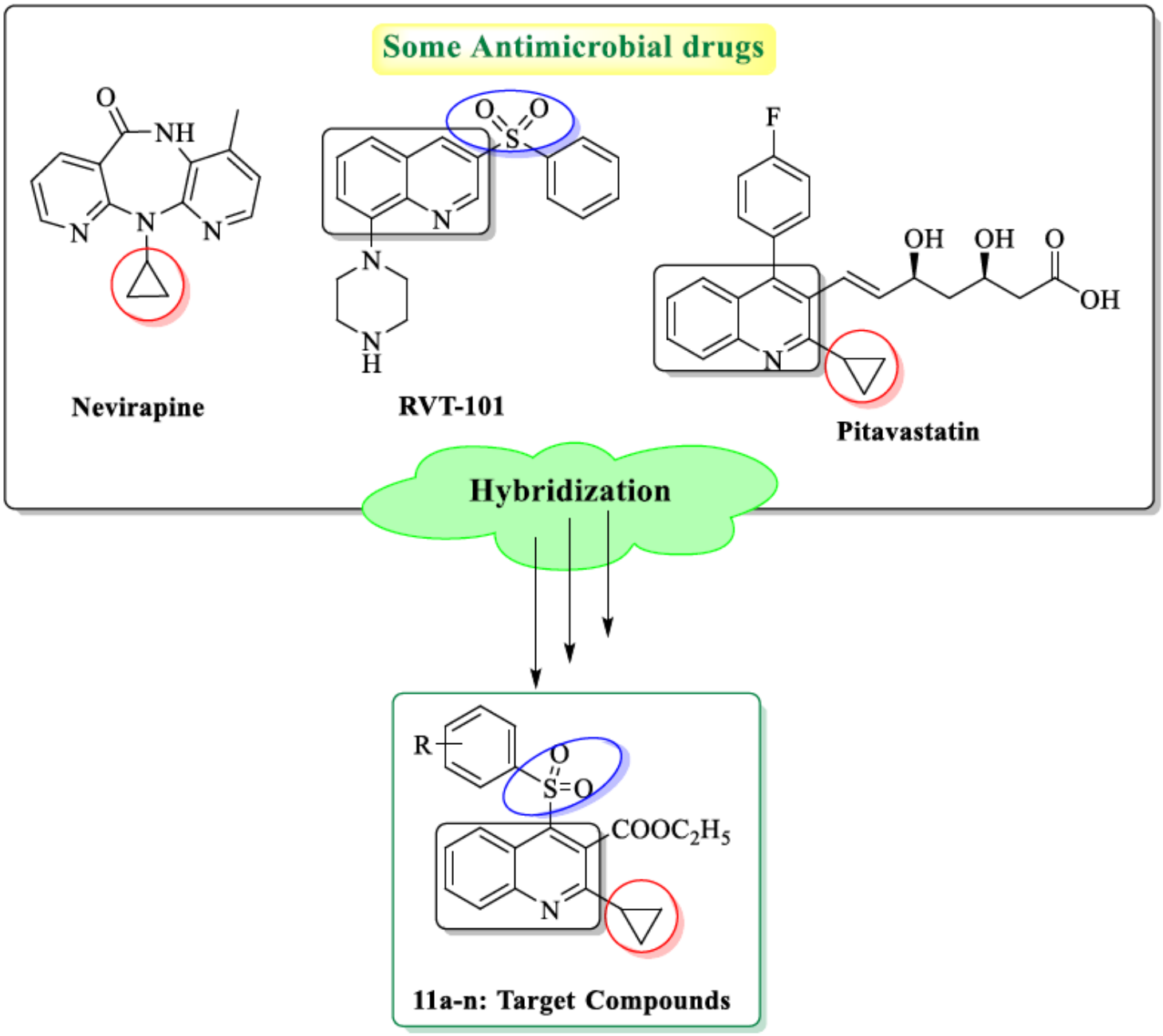
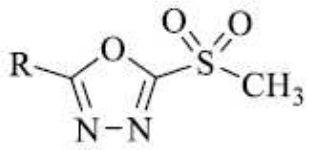


Figure 4

Design of cyclopropyl-quinolinyl-sulfone hybrid derivatives

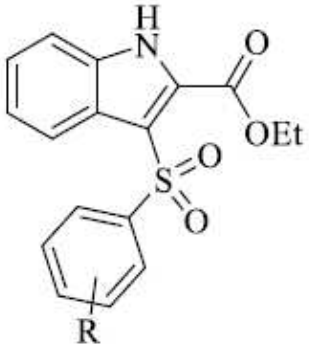
Previous work on 1,3,4-oxadiazole moiety:



⟸ **Weiming et al. (2011)**

Where, R= 2-$CF_3C_6H_4$, 2,3,4-TriFC_6H_2, 2-FC_6H_4, 2,2'-DiFC_6H_3, 2,2'-DiClC_6H_3, 2-$OCH_3C_6H_4$, 2-$CH_3C_6H_4$, 2-BrC_6H_4 etc.

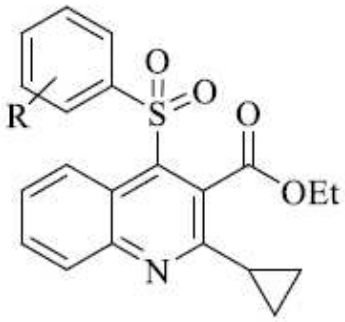
Previous work on Indole moiety:



⟸ **Ragno et al. (2005)**

Where, R= H, 2-NH_2, 5-Cl, 2-CH_3, 4-CH_3, 4-F, 4-Cl, 4-isoPr, 2,6-diCl

This work on Quinoline moeity:



⟸ **Compounds 11a-n**

Where, R= H, 2-Cl, 3-Cl, 4-Cl, 2-CH_3, 3-CH_3, 4-CH_3, 2-F, 3-F, 4-F, 3-OCH_3, 4-OCH_3, 3-NO_2, 4-$CH(CH_3)_2$

Figure 5

Sulfone linkage between three different pharmacophores expected to appear with better antimicrobial activity

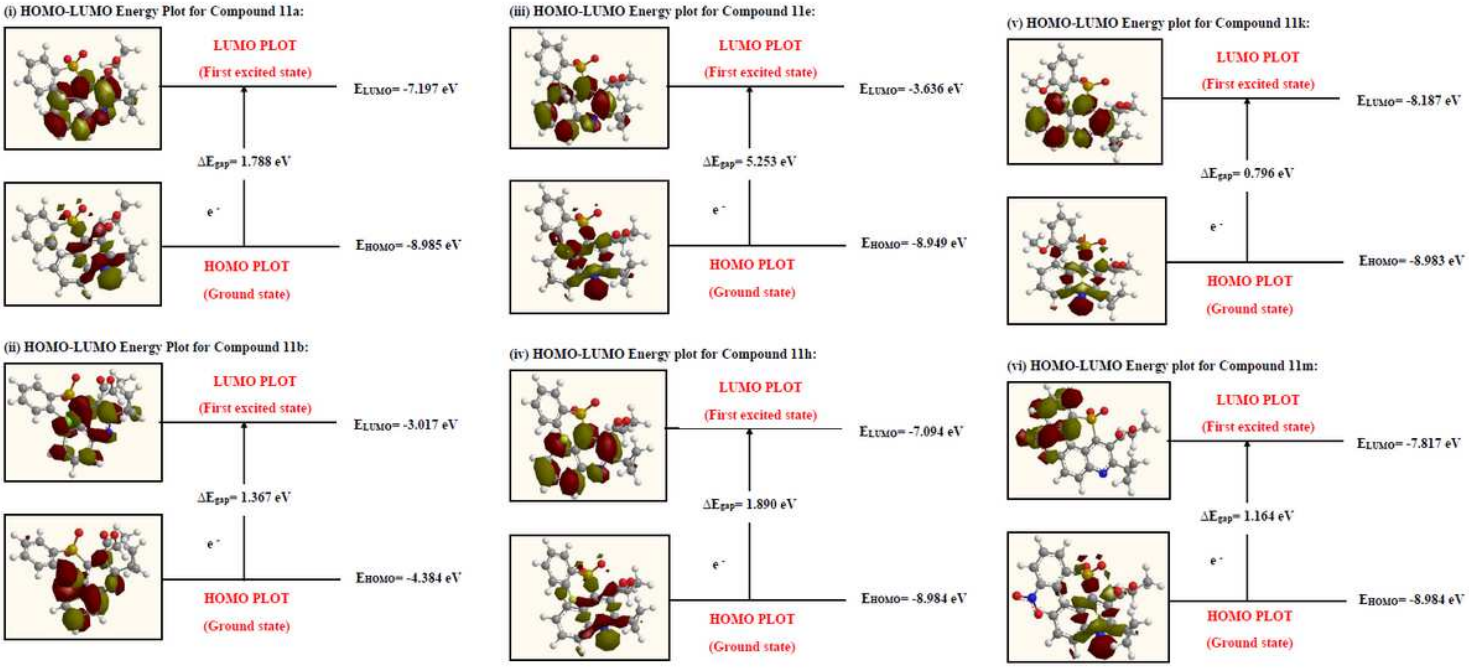


Figure 6

Atomic orbital compositions of the FMO for Compounds 11a, 11b, 11e, 11h, 11k & 11m