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Original article

Synthesis of chlorovinyl sulfones as structural analogs of chalcones and their antiplasmodial activities

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ABSTRACT

The synthesis of novel chlorovinyl sulfone-like chalcone derivatives and their antimalarial activity against cultured *Plasmodium falciparum* parasites, hemozoin formation, hemoglobin hydrolysis and murine malaria model are described. Compounds were prepared via Claisen–Schmidt condensation from available chloromethylphenyl sulfones with substituted aldehydes. Antiplasmodial IC_{50} activity of these compounds ranged between 0.025 and 10 μM, those that blocked *P. falciparum* development at low micro molar concentrations were tested in a murine *Plasmodium berghei* model, and these compounds delayed the progression of malaria but did not eradicate infections. Much effort and attention are needed for discovery and development of new and less toxic antimalarial drugs.

1. Introduction

Malaria remains one of the principal diseases of the developing world with an estimated 500 million cases each year and around two million deaths [1]. In the absence of effective vaccines, chemotherapy represents the mainstay of malarial control. Resistance to currently used antimalarials, particularly chloroquine (Fig. 1) and the antifolates, are seriously impeding efforts to control the disease [2].

In continuation of previous studies [3–5] resulting from our research program directed toward the preparation of new chalcone derivatives and their antimalarial evaluation, we are diversifying our work for pharmaceutically promising analogs of chalcones and we have paid attention to synthesize a series of new vinyl sulfone with a chlorine atom at position 2 (Fig. 1). The compounds could be considered as derivatives of chalcones in which the carbonyl group is replaced by, possessing similar electrophilic character, sulfone group.

Vinyl sulfones have been intensively studied due to their synthetic utility [6,7] and can be obtained by condensation of aromatic aldehydes with various phenyl sulfones [8–13] but their biological activity [14] has not obtained much attention. However, some advances have been made as inhibitors of cysteine protease; such compounds target multiple sites in the parasite as antiplasmodial agents [15–18]. There is a patent claiming anticancer activity [19], their product is under development for treatment of cellular proliferative disorders. The present study was undertaken to evaluate *in vitro* activity in a series of 2-chlorovinyl sulfone derivatives against *Plasmodium falciparum*. An attempt has been made to correlate these *in vitro* data with *in vivo* activities of these compounds against *Plasmodium berghei* infections in mice.

2. Chemistry

We prepare through a facile synthesis of 16 chlorovinyl sulfones derivatives (Table 1), using the Claisen–Schmidt condensation method [20]. One step synthesis protocols, as depicted in Scheme 1, was used to prepare the compounds. Chloromethylphenyl sulfone **1** was condensed with a suitable aldehyde using solid sodium hydroxide as catalyst in methanol at room temperature to yield chlorovinyl sulfones derivatives **3**–**18**. These conditions were found to be satisfactory for the synthesis of chlorovinyl sulfone chalcones in good yields. In most cases, products were formed immediately after the addition of sodium hydroxide pellets to the stirred solution of substituted aldehydes and chloromethylphenyl sulfone. To ensure the formation of solid a minimal amount of methanol was

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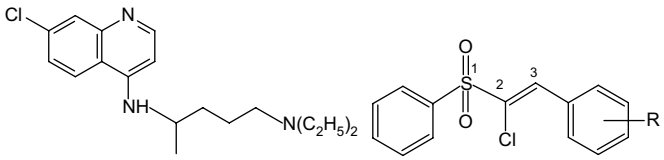


Fig. 1. Structures of chloroquine and 2-chlorovinyl sulfones.

used. The product, α,β-unsaturated vinyl sulfone, is almost always obtained in the trans-alkene form (*E*-form), as judged by ^{1}H NMR spectroscopy, which have been fully characterized by analytical and spectral data. The yields were not optimized and ranged between 36 and 88%.

The homogeneity of the final compounds was ensured by column chromatography (silica, mesh size 60–120) using chloroform as eluent. The R_f of all compounds was recorded in ethyl acetate:hexane (1:1 v/v) as eluant. The antimalarial activities of the compounds are presented in Table 1.

3. Pharmacology

3.1. *Inhibition of hemozoin formation* in vitro

The hemozoin formation assay was performed according to Baelmans et al. [21]. Briefly, a solution of hemin chloride (50 μl, 4 mM), dissolved in DMSO (5.2 mg/mL), was distributed in 96-well micro-plates. Different concentrations (1–100 mM) of the compounds, dissolved in DMSO, were added in triplicate in test wells (50 μl) with a final concentration of 1.25–25 mM/well. Controls contained either water or DMSO. Hemozoin formation was initiated by the addition of acetate buffer (100 μl 0.2 M, pH 4.4). Plates were incubated at 37 °C for 48 h to allow completion of the reaction and centrifuged (4000 rpm × 15 min, IEC-CENTRA, MP4R). After discarding the supernatant, the pellet was washed twice with DMSO (200 μl) and finally dissolved in NaOH (200 μl, 0.2 N). The solubilized aggregates were further diluted 1:2 with NaOH (0.1 N) and absorbance recorded at 405 nm (Micro Plate Reader, BIORAD-550). The results were expressed as a percentage of inhibition of hemozoin formation.

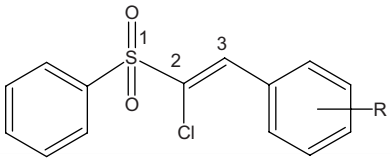
3.2. *Inhibition of globin hydrolysis*

Selected compounds that inhibited parasite development were evaluated for the inhibition of globin hydrolysis (Fig. 2). The proteolytic effect of parasite extracts on the native mouse hemoglobin was assayed in 96-well plates (Greiner Bio-One). The assay mixture contained mouse native hemoglobin (10 mL), parasite extract (50 mL), GSH (10 mL, 10 mM), and acetate buffer (0.2 M, pH 5.4) to a final volume of 200 mL. Compounds, chloroquine, leupeptin and pepstatin (5 mM each) were incorporated in the incubation mixture dissolved in DMSO. The incubations were carried out at 37 °C for 18 h and the reactions were stopped by addition of reduced sample buffer. The degree of digestion was evaluated electrophoretically by SDS-PAGE [22] and densitometric comparison of the globin bands (14 kDa). A DMSO control was electrophoresed at the same time. The band density values were expressed as intensity/mm^2 ± SD.

3.3. *Parasite inhibition flow cytometry*

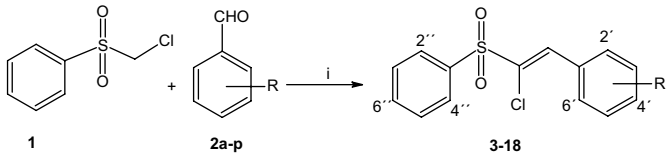
Effects of inhibitors on parasite development were determined as follows. Sorbitol synchronized, 0.1% parasitemias, ring stage *P. falciparum* strain W2 parasites were cultured under the atmosphere of 3% O_2, 6% CO_2 and 91% N_2 in RPMI-1640 medium

Table 1
Antiplasmodial effect for compounds **3**–**18**



Compound	R	Inhibition of hemozoin formation[a] (%)	Inhibition of hemoglobin hydrolysis[b] (%)	Peter's test[c,e] (%P/SD)	FACS[d] (IC_{50}, μM)
Saline				26.2 ± 3.03/10 ± 1.09	
3	2,4-diCl_2	<5	75.3 ± 0.91		0.96
4	4-OMe	<5	<5		0.47
5	2,4,6-triOMe	<5	<5		~10
6	3,4,5-triOMe	<5	<5		~10
7	3,4-OCH_2O-	<5	37.34 ± 1.08		0.053
8	4-Cl	<5	74.92 ± 1.25		0.083
9	4-F	<5	52.72 ± 1.13		>10
10	3,4-diCl_2	<5	95.04 ± 0.78 ***†	(13.4 ± 4.26 *)/(13 ± 1.37)	0.059
11	2-(1-naphthyl)	<5	84.59 ± 1.36‡	(6.25 ± 2.73 **)/(13.2 ± 2.61)	0.058
12	H	<5	59.33 ± 1.23		>10
13	2-Cl-3-quinolyl	<5	28.49 ± 0.53		0.025
14	2-Cl	<5	65.81 ± 0.97		>10
15	4-NO_2	<5	79.19 ± 0.92		0.073
16	1-naphthyl	<5	76.69 ± 1.16		0.075
17	2,4,5-triOMe	<5	11.07 ± 0.59		>10
18	4-CN	<5	44.73 ± 1.15		>10
LEU		[f]	89.75 ± 0.69		
PEP		[f]	93.77 ± 0.66		
CQ		84.16 ± 1.37	26.92 ± 1.85	3 ± 0.6/30	

[a] % of inhibition of hemozoin formation.
[b] Hemoglobin hydrolysis.
[c] Peter's test results of the most active drugs. CQ: chloroquine; LEU: leupeptin, PEP: pepstatin compared to LEU; P = parasitemias, SD = survival days.
[d] IC_{50} for tested compounds as determined by flow cytometry.
[e] The results are expressed by the mean ± standard error of the mean ***$p < 0.001$ compared to LEP, †$p > 0.05$ compared to PEP; ‡$p > 0.05$ compared to LEP.
[f] Unknown.



Scheme 1. Reagents: (i) NaOH, MeOH R: (a) 2′,4′-diCl; (b) 4′-OCH_3; (c) 2′,4′,6′-triOCH_3; (d) 3′,4′,5′-triOCH_3; (e) 3′,4′–OCH_2O–; (f) 4′-Cl; (g) 4′-F; (h) 3′,4′-diCl; (i) 2′-naphtyl; (j) H; (k) 2′-Cl-3′-quinolinyl; (l) 2′-Cl; (m) 4′-NO_2; (n) 1′-naphthyl; (o) 2′,4′,5′-triOCH_3; (p) 4′-CN.

supplemented with 10% human serum in the presence of inhibitors for 48 h without media change. Inhibitors were added from 1000 × DMSO stocks. After 48 h, the culture medium was removed and replaced with 1% formaldehyde in PBS pH 7.4 for an additional 48 h at room temperature to fix cells. Fixed parasites were transferred into 0.1% Triton-X-100 in PBS containing 1 nM YOYO nuclear dye (Molecular Probes). Parasitemias were determined from dot plots (forward scatter vs. fluorescence) acquired on an FACS sort flow cytometer using Cell Quest software (Beckton Dickinson) to count nucleated (parasitized) erythrocytes. IC_{50} values for growth inhibition were determined from plots of percentage control parasitemias over inhibitor concentration using the Prism 3.0 program (Graph Pad Software [23]), with data from duplicate experiments fitted by nonlinear regression, as previously described [24] (Table 1).

3.4. Activity against murine malaria and data analysis

NIH mice (18–23 g) were infected intraperitoneally with 10^6 *P. berghei*-infected red blood cells. Treatment began 2 h after infection. These compounds were dissolved in DMSO (0.1 M), diluted with saline–Tween 20 solutions (2%). Each compound (20 mg/kg) was administered once daily for 4 days. At day 4, the parasitemias were counted by examination of Giemsa stained smears. Chloroquine (25 mg/kg) was used as a positive control. The survival time beyond the control group (without drug treatment) was recorded. The results were expressed as percentage of parasitemias in relation to the control and percentage of mice survival [25]. Data were statistically analyzed using one way ANOVA and *t*-tests for specific group comparisons; assuming 95% of confidence according to Graph Pad Prism 3.02 (Fig. 2).

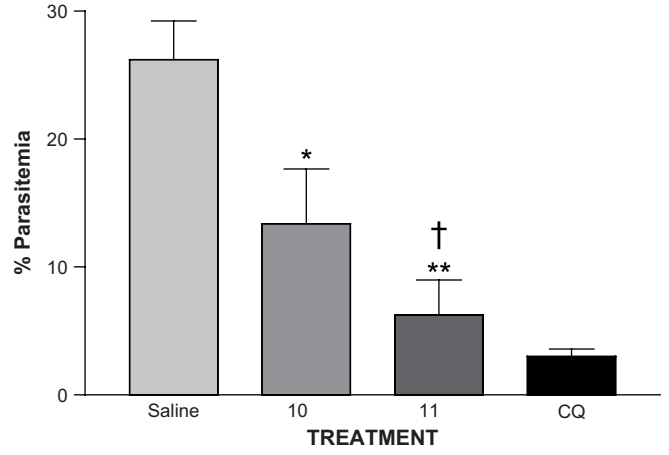


Fig. 2. The % parasitemias at 4th day post-infection and survival days on mice treated with **10**, **11**, $^*p < 0.05$ and $^{**}p < 0.01$ compared to saline-treated mice. $^{\dagger}p > 0.05$ compared to chloroquine-treated mice.

4. Results and discussion

Variation of substituent of aldehydes provided compounds with antimalarial activity against *P. falciparum*. Nine of 16 compounds among the mono- and disubstituted derivatives had IC_{50} of less than 10 μM against *P. falciparum*, but against *P. berghei in vivo* the majority of these compounds were inactive.

On the other hand, activity against *P. berghei* was found in the 3,4-diCl_2 and 2-(1-naphthyl) substitution (compounds **10** and **11**). Within these groups were also active against *P. falciparum*, but placement of trimethoxy groups about the ring imparted inactivity for both *P. falciparum* and *P. berghei* (compounds **5**, **6**, and **17**).

The presence of chlorine (compounds **3**, **8**, **13**), nitro (compound **15**), or naphthyl (compound **16**) maintained antimalarial activity, none of these molecular modifications approached the level of activity of compounds **10** and **11**.

Based on our findings on the *in vitro* antimalarial action of a series of chlorovinyl sulfones against chloroquine-resistant *P. falciparum*, these compounds warrant further definitive investigations.

These analyses of structure–activity relationships should serve as a guide for synthesis and investigations of additional analogs. Newer and more effective drugs are required because of the relentless emergence of strains of human plasmodia (especially *P. falciparum*) resistant to currently available antimalarial drugs.

A total of 16 compounds were identified showing properties for their ability to inhibit parasite development by incubating parasites in different concentrations for 48 h, beginning at the ring stage, counting new ring forms by FACS (Fluorescence activated cell sorting) analysis, and comparing parasitemias with those of untreated controls, nine of those compounds show values ranging from 0.025 to 0.96 μM, derivatives [2(3′,4′-methylendioxyphenyl)-1-chloro]ethenylphenyl sulfone **7** and [2(2′-chloroquinolin-3′-yl)-1-chloro]ethenylphenyl sulfone **13** demonstrated the most potent antimalarial effects against *P. falciparum*, with IC_{50} values of 0.053 and 0.025 μM, respectively, (Table 1). Considering this result, we suggest that the 3′,4′-methylendioxy substituted derivative located in the aromatic ring of the α,β-unsaturated chlorophenyl sulfone, as well as the 2′-chloroquinolinyl group that form part of the aromatic system (Scheme 1), play an important role in mediating activity against *P. falciparum*. These results might be due to some chemical interaction with the biological substrate or involvement of some additional unknown mechanism of action.

The most active compounds for hemoglobin hydrolysis were **10** (95.04%) and **11** (84.59%) also tested for activity in mice infected with *P. berghei* ANKA, a chloroquine susceptible strain of murine malaria parasites. The mice were treated with compounds or chloroquine (20 mg/kg, i.p once daily) for 4 consecutive days, and their survival times and parasitemias on day 4 were compared with those of control mice receiving only saline (Table 1).

The above compounds have significantly inhibited day 4 parasitemias (Fig. 2) and increased their survival times (Table 1). It is well known that *P. falciparum* cysteine proteases hydrolyze hemoglobin in an acidic food vacuole which provide amino acids for erythrocytic malarial parasites and consequently, these results suggest that the above derivatives might act as parasite protease inhibitors. However, only for compounds **10** and **11** we observed a close relationship for their antimalarial effects *in vivo* as *in vitro*. None of the resulting compounds gave good inhibition against hemozoin formation. It should also be noted that inhibitors identified in this study have IC_{50} values in the micro-molar range and thus may not be suitable for use as drugs themselves. However, these compounds do provide much needed drug like non-peptide leads against malaria.

More work is needed to obtain second-generation version of these interesting compounds to establish meaningful **SAR**. Compounds **7** and **13** could be used as standard precursors for this purpose.

5. Conclusions

In this study, derivatives [2(3′,4′-methylendioxyphenyl)-1-chloro]ethenylphenyl sulfone **7** and [2(2′-chloroquinolin-3′-yl)-1-chloro]ethenylphenyl sulfone **13** demonstrated the most potent antimalarial effects against *P. falciparum*, with IC_{50} values of 0.053 and 0.025 μM, respectively (Table 1). Considering this result, we suggest that the 3′,4′-methylendioxy substituted derivative located in the aromatic ring of the α,β-unsaturated chlorophenyl sulfone, as well as the 2′-chloroquinolinyl group that form part of the aromatic system (Scheme 1), play an important role in mediating activity against *P. falciparum*. These results might be due to some chemical interaction with the biological substrate. Compounds **10** and **11** were also quite active in a *P. berghei* mouse model, with 50 and 72%, respectively, drop in parasitemias compared to control 4 days after infection and also an increase in survival.

Generally speaking, the inhibitory potency of all compounds in the series against the cultured *P. falciparum* parasites did not strongly correlate with inhibitory potency against hemozoin formation for compounds tested, which was very weak, suggesting other mechanisms of inhibition may also be involved. However, good correlation for some compounds was observed for inhibitory potency against hemoglobin hydrolysis that may involve some interaction with some cysteine proteases present in murine model. Compounds maintained an antimalarial efficacy *in vitro* and moderate activity *in vivo*. It should also be noted that inhibitors identified in this study have IC_{50} values in the micro-molar range and thus may not be suitable for use as drugs themselves. However, these compounds do provide much needed drug like non-peptide leads against malaria.

6. Experimental protocols

6.1. Chemistry

Melting points were determined in a Thomas micro-hot stage apparatus and are uncorrected. Infrared spectra were determined as KBr pellets on a Shimadzu model 470 spectrophotometer and are expressed in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL GSX (270 MHz) spectrometer; chemical shifts are expressed in δ (ppm) relative to tetra methyl silane are given. Mass spectral data were obtained with a Varian CP3800 model coupled with Saturn 2000/Gas Chromatograph ionization energy 70 eV, using CIMS (Chemical Ionization Mass Spectrometry). Elemental analyses were performed by Atlantic Microlab; Norcross, GA, USA, results were within ±0.4% of predicted values for all compounds. All solvents were dried and distilled under nitrogen atmosphere. Analytical TLCs were run on commercially pre-coated plates (Merck, silica gel 60 F_{254}) and visualized under UV lamps (254 nm). The progress of the reactions was monitored by TLC with ethyl acetate:hexane (1:1 v/v) as eluant.

6.1.1. General procedure for the synthesis of chlorovinyl sulfones *3*–*18*

A mixture of commercially available chloromethylphenyl sulfone (1 mmol), substituted aldehydes (1 mmol) and pulverized sodium hydroxide (2.5 mmol) were suspended in dry methanol (5 mL). The reaction mixture was stirred at room temperature for 10–24 h and the resulting precipitate was filtered off and crystallized from methanol/water, yields 33–88%.

6.1.2. [2(2′,4′-Dichlorophenyl)-1-chloro] ethenyl phenyl sulfone (*3*)

Yield: 36%; m.p. >270 °C (d), λ_{max} (KBr): 1520, 1331, 1216, 1174 (cm^{-1}). ^1H RMN δ_H: 7.49 (d, 2H, $H_{3''\text{-}5''}$, $J = 8.15$ Hz), 7.67 (d, 1H, $H_{5'}$, $J = 8.64$ Hz), 7.73 (d, 1H, $H_{6'}$, $J = 6.70$ Hz), 7.89 (t, 1H, $H_{4''}$, $J = 7.67$ Hz), 7.94 (s, 1H, H_a), 7.99 (s, 1H, $H_{3'}$), 8.08 (d, 2H, $H_{2'',6''}$, $J = 8.67$ Hz); ^{13}C NMR 121.02 (C-Cl); 128.23 ($C_{2''\text{-}6''}$); 128.57 ($C_{5'}$); 131.03 ($C_{3''\text{-}5''}$); 131.12 ($C_{3'}$); 133.16 ($C_{5'}$); 134.60 ($C_{4''}$); 135.18 (C-Ha); 137.78 ($C_{4'}$); 139.35 ($C_{2'}$); CIMS (*m*/*z*): 349 [M + 1]; Anal. Calculated: C, 48.37%, H, 2.61%. Found: C, 48.34%, H, 2.62%.

6.1.3. [2(4′-Methoxyphenyl)-1-chloro] ethenyl phenyl sulfone (*4*)

Yield: 50%; m.p. 118–120 °C. λ_{max} (KBr): 1507, 1299, 1241, 1178, 1142 (cm^{-1}). ^1H RMN δ_H: 3.71 (s, 3H, 4′-OCH_3), 6.83 (d, 2H, $H_{3',5'}$, $J = 8.40$ Hz), 7.04 (d, 2H, $H_{3''\text{-}5''}$, $J = 8.64$ Hz), 7.59 (d, 2H, $H_{2'\text{-}6'}$, $J = 7.91$ Hz), 7.68 (s, 1H, H_a), 7.69 (d, 2H, $H_{2''\text{-}6''}$, $J = 7.18$ Hz); ^{13}C NMR 55.63 (4′-OMe), 114.24 ($C_{3'\text{-}5'}$), 120.68 (C-Cl), 128.49 ($C_{2''\text{-}6''}$), 129.71 ($C_{3''\text{-}5''}$), 132.75 ($C_{2'\text{-}6'}$), 134.38 ($C_{1'}$), 138.72 (C-Ha), 159.86 ($C_{4'}$); CIMS (*m*/*z*): 310 [M + 1]; Anal. Calculated: C, 58.35%, H, 4.24%. Found: C, 58.37%, H, 4.26%.

6.1.4. [2(2′,4′,6′-Trimethoxyphenyl)-1-chloro] ethenyl phenyl sulfone (*5*)

Yield: 52%; m.p. 108–110 °C. λ_{max} (KBr): 1498, 1300, 1232, 1190, 1146 (cm^{-1}). ^1H RMN δ_H: 3.43 (s, 6H, OMe), 3.75 (s, 3H, OMe), 6.12 (s, 2H, $H_{3'\text{-}5'}$), 7.61 (d, 2H, $H_{3''\text{-}5''}$, $J = 8.15$ Hz), 7.67 (d, 2H, $H_{2''\text{-}6''}$, $J = 8.15$ Hz), 7.60 (s, 1H, H_a); ^{13}C NMR 55.83 (OMe), 56.00 (OMe), 91.01 ($C_{3'\text{-}5'}$), 97.81 ($C_{1'}$), 128.45 ($C_{2''\text{-}6''}$), 129.26 ($C_{3''\text{-}5''}$), 133.92 ($C_{4''}$), 140.33 ($C_{1''}$), 159.74 ($C_{2',6'}$), 162.14 ($C_{4'}$); CIMS (*m*/*z*): 370 [M + 1]; Anal. Calculated: C, 55.36%, H, 4.65%. Found: C, 55.39%, H, 4.66%.

6.1.5. [2(3′,4′,5′-Trimethoxyphenyl)-1-chloro] ethenyl phenyl sulfone (*6*)

Yield: 48%; m.p. 106–108 °C. λ_{max} (KBr): 1507, 1302, 1238, 1158, 1123 (cm^{-1}). ^1H RMN δ_H: 3.59 (s, 6H, OMe), 3.62 (s, 3H, OMe), 6.37 (s, 2H, $H_{2'}$, $H_{6'}$), 7.57 (s, 1H, H_a), 7.62 (d, 2H, $H_{3''\text{-}5''}$, $J = 7.16$ Hz), 7.72 (d, 2H, $H_{2''\text{-}6''}$, $J = 7.18$ Hz); ^{13}C NMR 56.29 (OMe), 60.65 (OMe), 108.95 ($C_{2'\text{-}6'}$), 124.50 (C-Cl), 128.73 ($C_{2''\text{-}6''}$), 129.68 ($C_{3''\text{-}5''}$), 134.38 ($C_{4''}$), 138.08 ($C_{1''}$), 138.51 (C-Ha), 152.94 ($C_{3'\text{-}5'}$); CIMS (*m*/*z*): 370 [M + 1]; Anal. Calculated: C, 55.36%, H, 4.65%. Found: C, 55.38%, H, 4.66%.

6.1.6. [2(3′,4′-Methylendioxyphenyl)-1-chloro] ethenyl phenyl sulfone (*7*)

Yield: 62%; m.p. 104–106 °C. λ_{max} (KBr): 1501, 1300, 1254, 1158, 1123 (cm^{-1}). ^1H RMN δ_H: 6.00 (s, 2H, 3′,4′–OCH_2O–), 6.56 (dd, 1H, $H_{6'}$, $J_{H6'\text{-}H2'} = 1.73$ Hz, $J_{H6'\text{-}H5'} = 7.91$ Hz), 6.70 (d, 1H, $H_{2'}$, $J = 1.49$ Hz), 6.81 (d, 1H, $H_{5'}$, $J = 7.94$ Hz), 7.61 (d, 2H, $H_{3''\text{-}5''}$, $J = 7.18$ Hz), 7.70 (s, 1H, H_a), 7.71 (d, 2H, $H_{2''\text{-}6''}$, $J = 7.43$ Hz); ^{13}C NMR 101.69 (–OCH_2O–), 108.61 ($C_{5'}$), 111.49 ($C_{2'}$), 122.43 (C-Cl), 125.36 ($C_{1'}$), 128.56 ($C_{2'',6''}$), 129.70 ($C_{3''\text{-}5''}$), 134.39 ($C_{4''}$), 138.77 ($C_{1''}$), 147.51 ($C_{3'}$), 147.89 ($C_{4'}$); CIMS (*m*/*z*): 324 [M + 1]; Anal. Calculated: C, 55.82%, H, 3.44%. Found: C, 55.81%, H, 3.46%.

6.1.7. [2(4′-Chlorophenyl)-1-chloro] ethenyl phenyl sulfone (*8*)

Yield: 59%; m.p. 114–116 °C. λ_{max} (KBr): 1520, 1315, 1277, 1174, 1130 (cm^{-1}). ^1H RMN δ_H: 7.28 (d, 2H, $H_{3'\text{-}5'}$, $J = 7.80$ Hz); 7.57 (m, 2H, $H_{3''\text{-}5''}$); 7.63 (d, 2H, $H_{2'\text{-}6'}$, $J = 7.80$ Hz); 7.67–7.71 (m, 1H, $H_{4''}$), 7.73 (s, 1H, Ha), 7.99–8.03 (m, 2H, $H_{2''\text{-}6''}$); ^{13}C NMR 118.67 (C-Cl); 128.23 ($C_{2''\text{-}6''}$); 130.11 ($C_{3'\text{-}5'}$); 130.99 ($C_{3''\text{-}5''}$); 133.03 ($C_{2'\text{-}6'}$); 134.52 ($C_{4''}$); 135.46 ($C_{1'}$); 137.97 ($C_{4''}$); 139.10 ($C_{1''}$); 140.36 (C-Ha); CIMS (*m*/*z*): 314 [M + 1]; Anal. Calculated: C, 53.69%, H, 3.22%. Found: C, 53.72%, H, 3.24%.

6.1.8. [2(4′-Fluorophenyl)-1-chloro] ethenyl phenyl sulfone (*9*)

Yield: 36%; m.p. 117–118 °C. λ_{max} (KBr): 1507, 1293, 1235, 1152 (cm^{-1}). ^1H RMN δ_H: 7.31 (d, 2H, $H_{3''\text{-}5''}$, $J = 8.91$ Hz), 7.35 (s, 1H, H_a), 7.60 (d, 1H, $H_{4''}$, $J = 7.93$ Hz), 7.70 (d, 2H, $H_{2'\text{-}6'}$, $J = 7.42$ Hz), 7.99 (d, 2H, $H_{3'\text{-}5'}$, $J = 8.66$ Hz), 8.01 (d, 2H, $H_{2''\text{-}6''}$, $J = 8.64$ Hz); ^{13}C NMR 114.24 (C-Cl); 116.02 ($C_{3'\text{-}5'}$); 116.34 ($C_{2''\text{-}6''}$); 121.13 ($C_{1'}$); 127.91 ($C_{4''}$); 128.57 ($C_{1''}$); 129.65 (C-Ha); 132.59 ($C_{3''\text{-}5''}$); 132.73 ($C_{2'\text{-}6'}$); 166.91 ($C_{4'}$); CIMS (*m*/*z*): 298 [M + 1]; Anal. Calculated: C, 56.67%, H, 3.40%. Found: C, 56.65%, H, 3.41%.

*6.1.9. [2(3′,4′-Dichlorophenyl)-1-chloro] ethenyl phenyl sulfone (**10**)*

Yield: 72%; m.p. 150–152 °C. λ_{max} (KBr): 1555, 1315, 1248, 1152, 1114 (cm^{-1}). ^1H RMN δ_H: 7.58 (d, 2H, $H_{3''\text{-}5''}$, $J = 8.41$ Hz), 7.61–7.65 (m, 1H, $H_{4''}$); 7.68–7.70 (m, 1H, $H_{6'}$); 7.72 (d, 1H, $H_{5'}$, $J = 8.80$ Hz); 7.79 (s, 1H, Ha); 7.85 (d, 1H, $H_{2'}$, $J = 1.24$ Hz); 7.94 (d, 2H, $H_{2''\text{-}6''}$, $J = 8.66$ Hz); ^{13}C NMR 118.97 (C-Cl); 129.31 ($C_{2''\text{-}6''}$); 130.24 ($C_{5'}$); 131.70 ($C_{3''\text{-}5''}$); 131.32 ($C_{5'}$); 131.77 ($C_{6'}$); 132.05 ($C_{2'}$); 133.25 ($C_{1'}$); 133.58 ($C_{3'}$); 133.98 ($C_{4''}$); 135.11 ($C_{4'}$); 140.01 ($C_{1''}$); 141.76 (C-Ha); CIMS (m/z): 349 [M + 1]; Anal. Calculated: C, 48.37%, H, 2.61%. Found: C, 48.36%, H, 2.60%.

*6.1.10. [2(2′-Naphthyl)-1-chloro] ethenyl phenyl sulfone (**11**)*

Yield: 51%; m.p. 150–152 °C. λ_{max} (KBr): 1520, 1302, 1235, 1155, 1133 (cm^{-1}). ^1H RMN δ_H: 7.59 (dd, 1H, $H_{5'}$, $J_{H5'\text{-}H6'} = 6.78$ Hz, $J_{H5'\text{-}H7'} = 1.49$ Hz); 7.63 (td, 1H, $H_{7'}$, $J_{H7'\text{-}H6'} = 8.10$ Hz, $J_{H7'\text{-}H5'} = 1.49$ Hz); 7.67 (dd, 1H, $H_{8'}$, $J_{H8'\text{-}H7'} = 6.94$ Hz, $J_{H8'\text{-}H6'} = 1.49$ Hz); 7.96 (d, 1H, $H_{1'}$, $J = 1.49$ Hz); 7.99–8.03 (m, 6H, $H_{2''\text{-}6''}$, $H_{3''\text{-}5''}$, $H_{4''}$, Ha); 8.12 (dd, 1H, $H_{3'}$, $J_{H3'\text{-}H4'} = 9.15$ Hz, $J_{H3'\text{-}H1'} = 1.49$ Hz); 8.61 (br, 1H, $H_{4'}$); ^{13}C NMR 114.10 ($C_{4'}$); 118.36 (C-Cl); 127.02 ($C_{6'}$); 128.26 ($C_{2''\text{-}6''}$); 128.38 ($C_{7'}$); 129.00 ($C_{5'}$); 129.22 ($C_{3'}$); 129.53 ($C_{1'}$); 130.12 ($C_{3''\text{-}5''}$); 131.24 ($C_{8'}$); 132.99 ($C_{1'}$); 133.78 ($C_{4''}$); 138.35 (C_{8a}); 139.33 ($C_{1''}$); 141.42 (C-Ha); CIMS (m/z): 330 [M + 1]; Anal. Calculated: C, 65.75%, H, 3.98%. Found: C, 65.77%, H, 3.96%.

*6.1.11. 2-Phenyl-1-chloroethenyl phenyl sulfone (**12**)*

Yield: 33%; m.p. 132–134 °C. λ_{max} (KBr): 1510, 1312, 1254, 1171, 1110 (cm^{-1}). ^1H RMN δ_H: 7.47–7.50 (m, 4H, $H_{3''\text{-}5''}$, $H_{3'\text{-}5'}$); 7.53 (s, 1H, Ha); 7.58–7.71 (m, 4H, $H_{4''}$, $H_{4'}$, $H_{2'\text{-}6'}$); 7.94 (d, 2H, $H_{2''\text{-}6''}$, $J = 8.40$ Hz); ^{13}C NMR 118.77 (C-Cl); 128.63 ($C_{2''\text{-}6''}$); 129.10 ($C_{3'\text{-}5'}$); 130.03 ($C_{3''\text{-}5''}$); 131.22 ($C_{2'\text{-}6'}$); 132.78 ($C_{4'}$); 133.67 ($C_{4''}$); 136.67 ($C_{1'}$); 138.54 ($C_{1''}$); 140.89 (C-Ha); CIMS (m/z): 280 [M + 1]; Anal. Calculated: C, 60.32%, H, 3.98%. Found: C, 60.33%, H, 3.98%.

*6.1.12. [2(2′-Chloroquinolin-3′-yl)-1-chloro] ethenyl phenyl sulfone (**13**)*

Yield: 56%; m.p. 250 °C (d). λ_{max} (KBr): 1549, 1302, 1254, 1142 (cm^{-1}). ^1H RMN δ_H: 7.25 (t, 2H, $H_{3''\text{-}5''}$, $J = 7.67$ Hz); 7.38 (t, 1H, $H_{4''}$, $J = 8.15$ Hz); 7.44 (s, 1H, Ha); 7.52 (d, 1H, $H_{8'}$, $J = 8.66$ Hz); 7.66 (t, 1H, $H_{7'}$, $J = 7.42$ Hz); 7.78 (t, 1H, $H_{6'}$, $J = 8.40$ Hz); 7.92 (d, 2H, $H_{2''\text{-}6''}$, $J = 7.67$ Hz); 8.05 (d, 1H, $H_{5'}$, $J = 7.92$ Hz); 8.51 (s, 1H, $H_{4'}$); ^{13}C NMR 118.34 (C-Cl); 121.90 ($C_{2'}$); 128.26 ($C_{2''\text{-}6''}$); 128.50 ($C_{6'}$); 129.98 ($C_{7'}$); 131.00 ($C_{3''\text{-}5''}$); 131.10 ($C_{5'}$); 133.98 ($C_{8'}$); 134.23 ($C_{4''}$); 135.02 (C-Ha); 138.77 ($C_{1'}$); 141.11 ($C_{1''}$); 145.55 ($C_{3'}$); CIMS (m/z): 365 [M + 1]; Anal. Calculated: C, 56.06%, H, 3.04%, N, 3.85%. Found: C, 56.07%, H, 3.01%, N, 3.88%.

*6.1.13. [2(2′-Chlorophenyl)-1-chloro] ethenyl phenyl sulfone (**14**)*

Yield: 88%; m.p. 118–122 °C. λ_{max} (KBr): 1540, 1312, 1264, 1152 (cm^{-1}). ^1H RMN data: δ_H: 7.39–7.50 (m, 5H, $H_{3''\text{-}5''}$, $H_{4''}$, $H_{4'}$, $H_{5'}$); 7.54 (d, 1H, $H_{3'}$, $J = 7.70$ Hz); 7.78 (s, 1H, Ha); 8.08 (d, 2H, $H_{2''\text{-}6''}$, $J = 7.16$ Hz); ^{13}C NMR 119.70 (C-Cl); 128.17 ($C_{2''\text{-}6''}$); 129.32 ($C_{5'}$); 130.35 ($C_{3''\text{-}5''}$); 130.41 ($C_{3'}$); 131.12 ($C_{1'}$); 132.00 ($C_{6'}$); 133.22 ($C_{4'}$); 133.98 ($C_{4''}$); 134.60 (C-Ha); 138.54 ($C_{2'}$); 139.13 ($C_{1''}$); CIMS (m/z): 314 [M + 1]; Anal. Calculated: C, 53.69%, H, 3.22%. Found: C, 53.70%, H, 3.21%.

*6.1.14. [2(4′-Nitrophenyl)-1-chloro] ethenyl phenyl sulfone (**15**)*

Yield: 65%; m.p. 152–156 °C. λ_{max} (KBr): 1520, 1344, 1286, 1171, 1123 (cm^{-1}). ^1H RMN δ_H: 8.11 (d, 2H, $H_{3''\text{-}5''}$, $J = 7.16$ Hz); 8.17 (d, 2H, $H_{3'\text{-}5'}$, $J = 7.67$ Hz); 8.22 (s, 1H, Ha); 8.26 (d, 1H, $H_{4''}$, $J = 8.91$ Hz); 8.33 (d, 2H, $H_{2'\text{-}6'}$, $J = 7.61$ Hz); 8.39 (d, 2H, $H_{2''\text{-}6''}$, $J = 7.67$ Hz); ^{13}C NMR 118.78 (C-Cl); 121.98 ($C_{3'\text{-}5'}$); 127.35 ($C_{2''\text{-}6''}$); 130.18 ($C_{3''\text{-}5''}$); 133.56 ($C_{2'\text{-}6'}$); 134.02 ($C_{4''}$); 138.75 ($C_{1''}$); 140.89 (C-Ha); 141.88 ($C_{1'}$); 149.68 ($C_{4'}$); CIMS (m/z): 325 [M + 1]; Anal. Calculated: C, 51.94%, H, 3.11%, N, 4.33%. Found: C, 51.94%, H, 3.12%, N, 4.32%.

*6.1.15. [2(1′-Naphtyl)-1-chloro] ethenyl phenyl sulfone (**16**)*

Yield: 67%; ^1H RMN δ_H: 7.42–7.94 (m, 6H, $H_{3''\text{-}5''}$, $H_{4''}$, $H_{6'}$, Ha, $H_{3'}$); 8.02 (d, 1H, $H_{2'}$, $J = 7.91$ Hz); 8.09 (d, 2H, $H_{2''\text{-}6''}$, $J = 7.67$ Hz); 8.19 (t, 1H, $H_{7'}$, $J = 7.67$ Hz); 8.29 (d, 1H, $H_{5'}$, $J = 8.40$ Hz); 8.86 (d, 1H, $H_{4'}$, $J = 8.40$ Hz); 9.16 (d, 1H, $H_{8'}$, $J = 8.42$ Hz); ^{13}C NMR 120.95 (C-Cl); 124.99 ($C_{8'}$); 126.16 ($C_{6'}$); 128.03 ($C_{2''\text{-}6''}$); 128.85 ($C_{3'}$); 129.67 ($C_{5'}$); 130.24 ($C_{3''\text{-}5''}$); 132.78 ($C_{4'}$); 133.21 ($C_{4''}$); 134.93 ($C_{2'}$); 136.59 (C_{4a}); 139.56 ($C_{1'}$); 142.02 ($C_{1''}$); 142.14 (C-Ha); CIMS (m/z): 330 [M + 1]; Anal. Calculated: C, 65.75%, H, 3.98%. Found: C, 65.76%, H, 3.98%.

*6.1.16. [2(2′,4′,5′-Trimethoxyphenyl)-1-chloro] ethenyl phenyl sulfone (**17**)*

Yield: 68%; m.p. 150–152 °C. λ_{max} (KBr): 1517, 1299, 1245, 1149, 1114 (cm^{-1}). ^1H RMN data: δ_H 3.43 (s, 3H, OMe); 3.56 (s, 3H, OMe); 3.75 (s, 3H, OMe); 6.53 (s, 1H, $H_{3'}$); 6.62 (s, 1H, $H_{6'}$); 7.58 (d, 2H, $H_{3''\text{-}5''}$, $J = 6.91$ Hz); 7.60 (s, 1H, Ha); 7.62 (d, 1H, $H_{4''}$, $J = 6.43$ Hz); 7.69 (d, 2H, $H_{2''\text{-}6''}$, $J = 7.43$ Hz); ^{13}C NMR 55.43 (OMe); 55.70 (OMe); 56.17 (OMe); 97.99 ($C_{3'}$); 112.65 ($C_{1'}$); 118.02 (C-Cl); 121.12 ($C_{6'}$); 128.6 ($C_{2''\text{-}6''}$); 131.22 ($C_{3''\text{-}5''}$); 134.45 ($C_{4''}$); 140.11 ($C_{1''}$); 142.00 (C-Ha); 143.54 (OMe); 152.55 (OMe); 155.36 (OMe); CIMS (m/z): 370 [M + 1]; Anal. Calculated: C, 55.36%, H, 4.65%. Found: C, 55.38%, H, 4.66%.

*6.1.17. [2(4′-Cyanophenyl)-1-chloro] ethenyl phenyl sulfone (**18**)*

Yield: 60%; m.p. 134–136 °C. λ_{max} (KBr): 1504, 1321, 1286, 1155, 1129 (cm^{-1}). ^1H RMN data: δ_H 7.50–7.74 (m, 6H, $H_{3''\text{-}5''}$, $H_{4''}$, Ha, $H_{3'\text{-}5'}$); 7.98 (d, 2H, $H_{2''\text{-}6''}$, $J = 8.91$ Hz); 8.08 (d, 2H, $H_{2'\text{-}6'}$, $J = 8.64$ Hz); ^{13}C NMR 116.48 ($C_{4'}$); 118.19 (C-Cl); 119.88 (CN); 128.19 ($C_{2''\text{-}6''}$); 129.96 ($C_{3''\text{-}5''}$); 132.03 ($C_{2'\text{-}6'}$); 132.99 ($C_{3'\text{-}5'}$); 134.22 ($C_{4''}$); 140.44 ($C_{1''}$); 140.78 (C-Ha); 144.69 ($C_{1'}$); CIMS (m/z): 305 [M + 1]; Anal. Calculated: C, 59.31%, H, 3.32%, N, 4.61%. Found: C, 59.29%, H, 3.30%, N, 4.63%.

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