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Original article

# Synthesis and evaluation of sulfonylurea derivatives as novel antimalarials

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**Abstract**

We have synthesized a series of sulfonylureas and have tested their antimalarial activities, including inhibition of in vitro development of a chloroquine-resistant strain of *Plasmodium falciparum*, in vitro hemoglobin hydrolysis, hemozoin formation, and development of *Plasmodium berghei* in murine malaria. The most active antimalarial compound was (*E*)-1-[4′-(3-(2,4-difluorophenyl)acryloyl)phenyl]-3-tosylurea (**22**) with an $IC_{50}$ of 1.2 μM against cultured *P. falciparum* parasites. Biological results suggest a fairly potent antimalarial activity for this derivative, but also imply that its activity may arise from an unknown mechanism. Indeed, these compounds may act against malaria parasites through multiple mechanisms.


*Keywords:* Sulfonylurea; Antimalarial; *Plasmodium falciparum*; *Plasmodium berghei*

## 1. Introduction

Malaria is one of the most prevalent human infections worldwide. Over 40% of the world's population lives in malaria-endemic areas [1]. Exact numbers are unknown, but estimated as 300–500 million cases per year and 1.5–2.7 million deaths occur each year [2]. The majority of these cases are in African children under five years of age. Most severe disease and deaths from malaria are caused by *Plasmodium falciparum*. The control of falciparum malaria is frustrated by increasing resistance of malaria parasites to available antimalarial drugs [3]. Therefore, there is a great need to develop new antimalarial agents. Among potential new targets for antimalarial chemotherapy, proteases hydrolyze hemoglobin in erythrocytic parasites [4,5].

The present work is aimed towards developing novel molecules with improved potential for treating malaria with the hope to decrease the probability for developing drug resistance. We propose to achieve this by generating an α,β-unsaturated keto function in the sulfonylurea moiety which is an important feature for antimalarial activity [6].

Sulfonylureas are used in medicine as potent blood glucose reducing agents for the treatment of diabetes [7]. We have considered these compounds as potential antimalarials because there is evidence that some antimalarial compounds may affect glucose metabolism [8,9]. In addition, sulfonylurea derivatives possess some pharmacophoric groups with antimalarial properties [10] that could exhibit an additive effect when combined with an α,β-unsaturated ketone bridge.

## 2. Chemistry

The sulfonylurea derivatives as the target compounds depicted in Scheme 1 were obtained by allowing ketones **4** or

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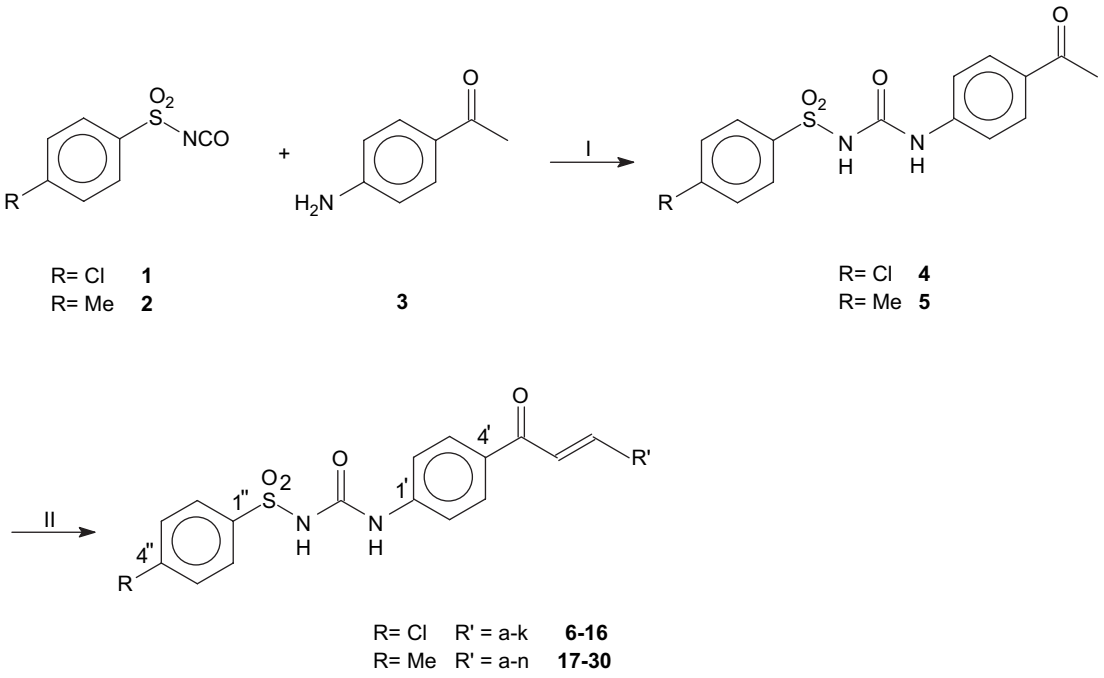



Scheme 1. R′: a – 2,4-diOMeC$_6$H$_3$; b – 4-FC$_6$H$_4$; c – 3,4-OCH$_2$OC$_6$H$_3$; d – 4-ClC$_6$H$_4$; e – 2,4-diClC$_6$H$_3$; f – 2,4-diFC$_6$H$_3$; g – 3,4,5-triOMeC$_6$H$_2$; h – C$_6$H$_5$; i – 4-MeC$_6$H$_4$; j – 4-OMeC$_6$H$_4$; k – C$_5$H$_4$N; l – β-C$_{10}$H$_7$; m – 3-C$_9$H$_5$NCl; n – 6,7-diOMe-3-C$_9$H$_5$NCl. Reagents: I – $CH_2Cl_2$, 3 h; II – MeOH, NaOH, R′-CHO, 8–12 h, r.t.

**5** to react with a variety of aromatic aldehydes by carrying out Claisen–Schmidt condensations under basic aldol conditions to give the α,β-unsaturated ketones **6–30** (Table 1). This procedure afforded various sulfonylureas in good yield. Starting materials were selected to allow an assessment of the biological consequences by varying the substituents on the aromatic ring. Derivatives **4** and **5** have been synthesized as previously reported with some modifications [11–13].

## 3. Biological results and discussion

Twenty five compounds were tested 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 parasitemia with those of untreated controls (Table 2). Ten compounds inhibited parasite development at concentrations at or below 10 μM (Table 2). For the remaining compounds, the $IC_{50}$ for their inhibition of parasite development was >10 μM.

We tested the ability of compounds to inhibit hemozoin formation. Compounds **18**, **22**, **29**, and **30** inhibited this process ($IC_{50} = 1.03$ mM) with activity similar to that of chloroquine ($IC_{50} = 1.4$ mM) (Table 2). Selected compounds that inhibited parasite development were evaluated for the inhibition of hemoglobin hydrolysis (Fig. 1). Compound **22** was the most active, with 90.28% inhibition of hemoglobin degradation at a concentration of 5 mM. Three compounds **7**, **8** and **12** inhibited hemoglobin degradation 34.52, 50.62 and 36.71%, respectively (Table 2).

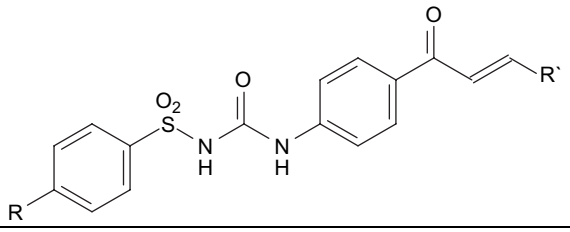
Compounds that were active in vitro (**7**, **8**, **11**, **12** and **22**) were tested for activity in mice infected with *Plasmodium berghei* ANKA, a chloroquine-susceptible strain of murine malaria parasites. The mice were treated with compounds or chloroquine (20 mg/kg, i.p once daily) for four consecutive days (days 0–3 post-infection), and their survival times and parasitemia on day 4 were compared with those of control mice receiving only saline. A number of compounds have significantly inhibited day 4 parasitemia (Fig. 2) and increased their survival times (Table 2).

Compounds **7**, **8**, **12** and **22** (Table 2) caused an inhibition of hemoglobin degradation by murine parasites. These results suggest that the above derivatives may act as parasite protease inhibitors. Derivatives **18**, **22**, **29** and **30** (Table 2) have a very strong capacity to bind heme and interfered directly with the process of hemozoin formation. This property is very well known for compounds with quinolinyl groups as **29** and **30**. The fluoride atom as substituted in the aromatic ring for compounds **7**, **11**, **18** and **22** may exert some electronegative influence between drug and heme, which may result in a binding interaction. However, only for compound **22** we observe a close relationship between this property and its antimalarial effects in vivo and in vitro.

Parasitemia reduction in mice infected with *P. berghei* was achieved in five compounds **7**, **8**, **11**, **12** and **22**, with inhibition ranging from 53 to 85% compared to control. The most active compound was 1[4′-*N*[*N*′(4″-chlorosulfonyl)urenyl]phenyl]-3(3,4-methylenedioxyphenyl)-2-propen-1-one (**8**). Its activity could be due to some electronic effects between the drug and the biological substrate.

The inhibitory effect for compounds **29** and **30** on hemozoin formation is not a surprise [14], due to the presence of

Table 1
Structure and analytical data of sulfonylurea derivatives




| Compound | R | R′ | Yield[b] (%) | Mp (°C) | Formula | Analyses[a] |
|---|---|---|---|---|---|---|
| **6** | Cl | 2,4-diOMeC$_6$H$_3$ | 53 | 278–280 | $C_{24}H_{21}ClN_2SO_6$ | C, H, N |
| **7** | Cl | 4-FC$_6$H$_4$ | 90 | 316–318 | $C_{22}H_{16}ClN_2SO_4$ | C, H, N |
| **8** | Cl | 3,4-OCH$_2$OC$_6$H$_3$ | 86 | 310 | $C_{23}H_{17}ClN_2SO_6$ | C, H, N |
| **9** | Cl | 4-ClC$_6$H$_4$ | 87 | >350 | $C_{22}H_{16}Cl_2N_2SO_4$ | C, H, N |
| **10** | Cl | 2,4-diClC$_6$H$_3$ | 91 | >350 | $C_{22}H_{15}Cl_3N_2SO_4$ | C, H, N |
| **11** | Cl | 2,4-diFC$_6$H$_3$ | 89 | 326 | $C_{22}H_{15}ClF_2N_2SO_4$ | C, H, N |
| **12** | Cl | 3,4,5-triOMeC$_6$H$_2$ | 63 | 292–294 | $C_{25}H_{23}ClN_2SO_7$ | C, H, N |
| **13** | Cl | C$_6$H$_5$ | 90 | 340 | $C_{22}H_{17}ClN_2SO_4$ | C, H, N |
| **14** | Cl | 4-MeC$_6$H$_4$ | 92 | >350 | $C_{23}H_{19}ClN_2SO_4$ | C, H, N |
| **15** | Cl | 4-OMeC$_6$H$_4$ | 80 | 340 | $C_{23}H_{19}ClN_2SO_5$ | C, H, N |
| **16** | Cl | C$_5$H$_4$N | 85 | >300 | $C_{21}H_{16}ClN_3SO_4$ | C, H, N |
| **17** | Me | 2,4-diOMeC$_6$H$_3$ | 67 | 255–258 | $C_{25}H_{24}N_2SO_6$ | C, H, N |
| **18** | Me | 4-FC$_6$H$_4$ | 90 | 310–314 | $C_{23}H_{19}FN_2SO_4$ | C, H, N |
| **19** | Me | 3,4-OCH$_2$OC$_6$H$_3$ | 88 | 282–283 | $C_{24}H_{20}N_2SO_6$ | C, H, N |
| **20** | Me | 4-ClC$_6$H$_4$ | 86 | 310–312 | $C_{23}H_{19}ClN_2SO_4$ | C, H, N |
| **21** | Me | 2,4-diClC$_6$H$_3$ | 82 | >325 | $C_{23}H_{18}Cl_2N_2SO_4$ | C, H, N |
| **22** | Me | 2,4-diFC$_6$H$_3$ | 91 | 320 | $C_{23}H_{18}F_2N_2SO_4$ | C, H, N |
| **23** | Me | 3,4,5-triOMeC$_6$H$_2$ | 95 | 290–292 | $C_{26}H_{26}N_2SO_7$ | C, H, N |
| **24** | Me | C$_6$H$_5$ | 89 | 284–286 | $C_{23}H_{20}N_2SO_4$ | C, H, N |
| **25** | Me | 4-MeC$_6$H$_4$ | 90 | 301–306 | $C_{24}H_{22}N_2SO_4$. | C, H, N |
| **26** | Me | 4-OMeC$_6$H$_4$ | 79 | 292–294 | $C_{24}H_{22}N_2SO_5$ | C, H, N |
| **27** | Me | C$_5$H$_4$N | 95 | >300 | $C_{22}H_{19}N_3SO_4$ | C, H, N |
| **28** | Me | β-C$_{10}$H$_7$ | 96 | 282–283 | $C_{25}H_{24}N_2SO_6$ | C, H, N |
| **29** | Me | 3-C$_9$H$_5$NCl | 57 | >330 | $C_{25}H_{24}N_2SO_6$ | C, H, N |
| **30** | Me | 6,7-diOMe-3C$_9$H$_5$NCl | 90 | 280 | $C_{25}H_{24}N_2SO_6$ | C, H, N |

[a] C, H and N analyses were within ±0.4% of the theoretical values.
[b] Solvent used for recrystallization: MeOH.

quinolinyl groups. However, further studies with derivatives **18** and **22** will be needed in order to find the mechanisms responsible for their inhibitory activities against hemozoin formation.

## 4. Conclusions

In this study, derivatives (*E*)-1-(4″-chlorophenylsulfonyl)-3-[4′-(3-(2,4-difluorophenyl)acryloyl)phenyl]urea (**11**) and (*E*)-1-[4′-(3-(2,4-difluorophenyl)acryloyl)phenyl]-3-tosylurea (**22**) demonstrated the most potent antimalarial effects, with $IC_{50}$ values of 2.1 and 1.2 μM, respectively (Table 2). Considering this result, we suggest that the 2,4-difluoro substituted derivatives located in the aromatic ring of the α,β-unsaturated ketone system (Scheme 1) play an important role in mediating activity against *P. falciparum*. The presence of difluoride atom in the aromatic ring may cause stronger chemical interaction with the biological substrate.

Compound **11** was also quite active in a *P. berghei* mouse model, with a 77% drop in parasitemia compared to controls 4 days after infection and also an increase in survival.

Our results offer strong support that our best compound is **22**, suggesting that it could be inhibiting hemoglobin degradation and hemozoin formation to exert antimalarial activity in vitro. These results also suggest that it is likely to offer a good antimalarial compound, especially when fluorine substitution is present in the aromatic ring for sulfonylurea derivatives. They maintained an antimalarial efficacy in vitro and moderate activity in vivo. We may speculate that some electronic effect would take place.

## 5. Experimental

### 5.1. Biological testing

#### 5.1.1. Inhibition of hemozoin formation in vitro

The hemozoin formation assay was performed as previously described [15]. Briefly, a solution of hemin chloride (50 μL, 4 mM), dissolved in DMSO, was distributed in 96-well micro plates. Different concentrations (5–100 mM) of the compounds, dissolved in DMSO, were added in triplicate

Table 2
Antimalarial activities, inhibition of hemozoin formation and hemoglobin hydrolysis of selected compounds

| Compound[a] | FACS [$IC_{50}$][b] μM | Inhibition of hemozoin formation[c] (%) | Inhibition of hemoglobin hydrolysis[d] (%) | Peter's test[e] % P/SD |
|---|---|---|---|---|
| **7** | 10 | <5 | 34.52 ± 2.89 | 10.6 ± 1.66 /1.00 ± 1.09 |
| **8** | 9.7 | <5 | 50.62 ± 2.12 | 3.4 ± 1.44 /2.16 ± 1.27 |
| **11** | 2.1 | <5 | –[f] | 5.2 ± 2.86 /3.00 ± 1.60 |
| **12** | 9.4 | <5 | 36.71 ± 2.79 | 8.0 ± 1.87 /1.83 ± 1.07 |
| **18** | 10 | 87.19 ± 1.56[g] | –[f] | |
| **19** | 9.6 | <5 | –[f] | |
| **22** | 1.2 | 77.52 ± 2.02 | 90.28 ± 1.30 | 15.2 ± 1.08 /1.00 ± 1.09 |
| **23** | 8.8 | <5 | –[f] | |
| **29** | 9.6 | 84.35 ± 1.89[g] | –[f] | |
| **30** | 10 | 85.15 ± 3.56[g] | –[f] | |
| Chloroquine | 0.059 | 86.25 ± 1.15 | | 3.66 ± 0.66 |
| Leupeptin | | | 87.02 ± 0.70 | |
| Pepstatin | | | 91.91 ± 0.66 | |
| Saline | | | | 22.5 ± 4.55[h] |

[a] Only Compounds expressing activity against *P. falciparum* parasites ($IC_{50}$ at 10 μM or below) were expressed their values and those with values of 10 μM have some limited on their solubility.
[b] $IC_{50}$ values (μM) for tested compounds as determined by flow cytometry as inhibitors of cultured *P. falciparum* parasites.
[c] Percentage of inhibition of hemozoin formation.
[d] Percentage of inhibition of globin hydrolysis.
[e] Peter's test results of the most active drugs. P = parasitemia; SD = survival days.
[f] No significant effect on inhibition of hemoglobin hydrolysis, probably due to limited solubility.
[g] The results are expressed by the media ± SEM.
[h] Mice under control died around day 8 ± 1.

to test wells (50 μL) with a final concentration of 1.25 μM–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 solution (200 μL, 0.2 N). The solubilized aggregates were further diluted 1:2 with solution of NaOH (0.1 N) and absorbance recorded at 405 nm (Microplate Reader, BIORAD-550). The results were expressed as a percentage of inhibition of hemozoin formation.

### 5.1.2. Parasite inhibition flow cytometry

Effects of inhibitors on parasite development were determined as follows. Sorbitol synchronized, 0.1% parasitemia, 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 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-1 dye (Molecular Probes). Parasitemia was determined from dot plots (forward scatter vs. fluorescence) acquired on a FACS sort flow cytometer using CellQuest software (Beckton

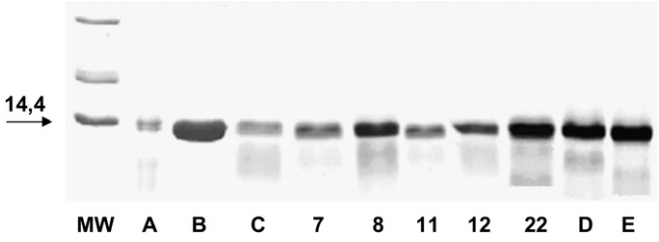



Fig. 1. Effects of hemoglobin hydrolysis on sulfonylurea derivatives. The samples were solubilized in SDS-sample buffer containing β mercapto ethanol and boiled before electrophoresis in 15% SDS-PAGE gels. The gels were stained with Coomassie blue. The positions of molecular weight (MW) standards are shown in kilo Daltons (kDa). Undegraded globin appears at 14 kDa; A = control human hemoglobin; B = control hemoglobin, without enzyme; C = control, enzyme with hemoglobin; D = leupeptin (5 mM); E = pepstatin (5 mM); compounds 7, 8, 11, 12 and 22 (5 mM).

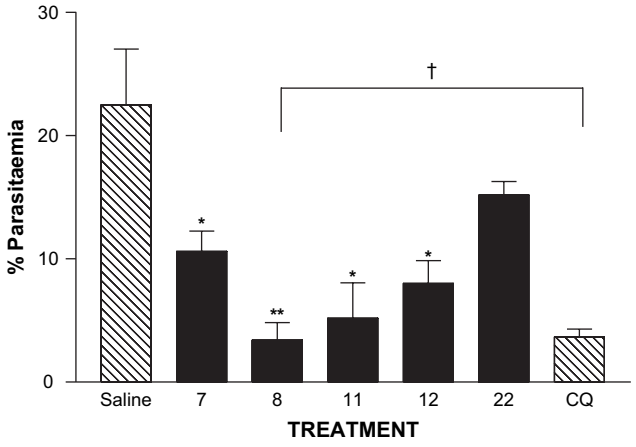



Fig. 2. Percentage of parasitemia at fourth day post-infection. Compounds and controls were administered daily for four days. Compounds **7**, **8**, **11**, **12** and **22** (20 mg/kg); CQ = chloroquine (25 mg/kg). *$p < 0.05$ and **$p < 0.01$ comparing to non-treated mice (Saline group). †$p > 0.05$ comparing to CQ-treated mice. ($n = 6$ mice).

Dickinson). $IC_{50}$ values for growth inhibition were determined from plots of percentage control parasitemia over inhibitor concentration using GraphPad Prism software [16].

*5.1.3. Parasite and experimental host*

Male NIH mice, weighing 18–22 g were maintained on a commercial pellet diet and housed under conditions approved by Ethics Committee. *P. berghei* (ANKA strain), a rodent malaria parasite, was used for infection. Mice were infected by i.p passage of $1 \times 10^6$ infected erythrocytes diluted in phosphate buffered saline solution (PBS, 10 mM, pH 7.4, 0.1 mL). Parasitemia was monitored by microscopic examination of Giemsa stained smears.

*5.1.4. Parasite extracts*

Blood of infected animals, at a high level of parasitemia (30–50%), was collected by cardiac puncture with a heparinized syringe and the blood pool was centrifuged (500*g* × 10 min, 4 °C). Plasma and buffy coat were removed and the red blood cell pellet was washed twice with chilled PBS–glucose (5.4%). The washed pellet was centrifuged on a discontinuous percoll gradient (80–70% percoll in PBS–glucose, 20,000*g* × 30 min × 4 °C) [17]. The upper band (mature forms) was removed by aspiration and washed twice with chilled PBS–glucose, and infected erythrocytes were lysed with saponin (0.1% in PBS × 10 min). Cold PBS (1 mL) was added, and the samples were centrifuged (13,000*g* × 5 min, 4 °C) and washed three times to remove erythrocyte cytoplasm (including erythrocyte hemoglobin). The free parasites were placed in PBS–glucose (5.4%), and subjected to three freeze-thaw cycles (−70 °C/+37 °C). The final homogenate was used in the hemoglobin hydrolysis inhibition assay [18].

*5.1.5. Mouse native hemoglobin*

Native hemoglobin from non-infected mice was obtained by treating one volume of pellet erythrocytes with two volumes of water. The resulting solution was used as the substrate in the hemoglobin hydrolysis assay.

*5.1.6. Hemoglobin hydrolysis assay*

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 μL), parasite extract (50 μL), GSH (10 μL, 10 μM), and acetate buffer (0.2 M, pH 5.4) to a final volume of 200 μL. 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 [18] 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/$mm^2 \pm$ SD.

*5.1.7. 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 four days. At day four, the parasitemia was 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 parasitemia in relation to the control (percentage of parasitemia) and percentage of survival mice [19]. Data were statistically analyzed using one-way ANOVA and *t*-tests for specific group comparisons; assuming 95% of confidence according GraphPad Prism 3.02.

*5.2. Chemistry*

*5.2.1. General*

Melting points were determined in a Thomas micro hot stage apparatus and are uncorrected. Infrared spectra were determined using 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 $\delta$ (ppm) relative to tetramethylsilane. All the exchangeable protons were confirmed by addition of $D_2O$. 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 within ±0.4% of the theoretical values. All solvents were dried and distilled under nitrogen atmosphere. Analytical TLC was carried out on precoated plates (silica gel $60F_{254}$) and visualized with UV light. The progress of the reactions was monitored by TLC with ethyl acetate:hexane (1:1 v/v) as eluant.

*5.2.2. General procedure for the synthesis of sulfonylurea derivatives **6–30***

A series of sulfonylurea derivatives were prepared by Claisen–Schmidt condensation of appropriate acetophenone with suitable aromatic aldehyde. A mixture of 1-(4″-chloro or methylphenylsulfonyl)-3-(4′-acethylphenyl) urea (**4**) or (**5**) (1 mmol), substituted aldehydes (1 mmol) and sodium hydroxide 5 mmol were dissolved in dry methanol (5 mL). The reaction mixture was stirred at room temperature for 4–10 h, the resulting yellow precipitates were filtered off and recrystallized.

*5.2.2.1. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-(2,4-dimethoxyphenyl)acryloyl)phenyl]urea (**6**).* IR 3312 (NH); 1661 (CO). $^1H$ NMR $\delta_H$ 3.83 (s, 3H, OMe); 3.89 (s, 3H, OMe); 6.63 (s, $H_3$); 7.39 (d, $H_\alpha$, $J = 15.77$ Hz); 7.46 (dd, $H_5$, $J_{H_{5-6}} = 8.42$ Hz, $J_{H_{5-3}} = 1.73$ Hz); 7.53 (d, $H_6$, $J = 8.42$ Hz); 7.72 (d, $H_{3''-5''}$, $J = 8.91$ Hz); 7.79 (d, $H_{2''-6''}$, $J = 8.91$ Hz); 7.80 (d, $H_{2'-6'}$, $J = 8.64$ Hz); 7.90 (d, $H_{3'-5'}$, $J = 8.64$ Hz); 7.91 (d, $H_\beta$, $J = 15.77$ Hz); 8.96 (br NH); 8.99 (br NH). $^{13}C$ NMR 55.99 (2-OMe); 56.32 (4-OMe); 106.85 ($C_5$); 116. 66 ($C_{2'-6'}$); 116.87 ($C_1$); 118.10 ($C_\alpha$); 128.20 ($C_{2''-6''}$); 129.02 ($C_6$);

129.19 ($C_{3'-5'}$); 129.79 ($C_{3''-5''}$); 129.98 ($C_{4'}$); 134.73 ($C_{4''}$); 146.16 ($C_{1'}$); 147.73 ($C_\beta$); 158.91 (CO $(NH)_2$); 160.46 ($C_4$); 163.59 ($C_2$); 188.12 (CO). CIMS (*m/z*) 502 [M + H].

*5.2.2.2. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-(4-fluorophenyl)acryloyl)phenyl]urea (**7**).* IR 3312 (NH); 1651 (CO). $^1$H NMR 6.99 (d, $H_{2-6}$, $J = 8.88$ Hz); 7.28 (t, $H_{3-5}$, $J = 8.88$ Hz); 7.46 (d, $H_{3''-5''}$, $J = 8.40$ Hz); 7.59 (d, $H_{2''-6''}$, $J = 8.40$ Hz); 7.70 (d, $H_\alpha$, $J = 14.47$ Hz); 7.80 (d, $H_{2'-6'}$, $J = 8.91$ Hz); 7.81 (d, $H_\beta$, $J = 14.47$ Hz); 7.96 (d, $H_{3'-5'}$, $J = 8.91$ Hz); 8.99 (br NH); 9.01 (br NH). $^{13}$C NMR 114.93 ($C_{3-5}$); 116.83 ($C_{2'-6'}$); 122.76 ($C_\alpha$); 128.19 ($C_{2''-6''}$); 129.22 ($C_{3'-5'}$); 129.48 ($C_{2-6}$); 130.30 ($C_{3''-5''}$); 131.00 ($C_1$); 132.00 ($C_{4'}$); 134.70 ($C_{4''}$); 141.59 ($C_{1''}$); 146.25 ($C_\beta$); 148.15 ($C_{1'}$); 158.94 $(CO(NH)_2)$; 187.71 (CO). CIMS (*m/z*) 460 [M + H].

*5.2.2.3. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-(3,4-methylenedioxyphenyl)acryloyl)phenyl]urea (**8**).* IR 3312 (NH); 1648 (CO). $^1$H NMR 6.09 (s, $-OCH_2O-$); 6.97 (d, $H_5$, $J = 7.91$ Hz); 7.29 (d, $H_6$, $J = 7.91$ Hz); 7.46 (d, $H_{3''-5''}$, $J = 8.91$ Hz); 7.59 (d, $H_{2''-6''}$, $J = 8.91$ Hz); 7.60 (d, $H_\alpha$, $J = 15.58$ Hz); 7.77 (d, $H_\beta$, $J = 15.58$ Hz); 7.80 (d, $H_{2'-6'}$, $J = 8.40$ Hz); 7.96 (d, $H_{3'-5'}$, $J = 8.40$ Hz); 9.01 (br NH). $^{13}$C NMR 102.12 ($-OCH_2O-$); 107.44 ($C_2$); 109.04 ($C_5$); 116.87 ($C_{2'-6'}$); 120.77 ($C_\alpha$); 126.00 ($C_6$); 128.24 ($C_{2''-6''}$); 129.17 ($C_{3'-5'}$); 129.78 ($C_{3''-5''}$); 130.05 ($C_1$); 130.19 ($C_{4'}$); 134.78 ($C_{4''}$); 142.94 ($C_{1''}$); 146.13 ($C_{1'}$); 147.75 ($C_\beta$); 148.61 ($C_3$); 149.77 ($C_4$); 158.93 $(CO(NH)_2)$; 187.43 (CO). CIMS (*m/z*) 486 [M + H].

*5.2.2.4. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-(4-chlorophenyl)acryloyl)phenyl]urea (**9**).* IR 3312 (NH); 1648 (CO). $^1$H NMR 7.50 (d, $H_{3-5}$, $J = 8.67$ Hz); 7.60 (d, $H_{2-6}$, $J = 8.40$ Hz); 7.64 (d, $H_\alpha$, $J = 15.34$ Hz); 7.80 (d, $H_{2''-6''}$, $J = 8.40$ Hz); 7.85 (d, $H_\beta$, $J = 15.34$ Hz); 7.89 (d, $H_{2'-6'}$, $J = 8.67$ Hz); 7.97 (d, $H_{3'-5'}$, $J = 8.67$ Hz); 9.04 (br NH). $^{13}$C NMR 116.92 ($C_{2'-6'}$); 123.54 ($C_\alpha$); 128.25 ($C_{2''-6''}$); 129.17 ($C_{3'-5'}$); 129.44 ($C_{3-5}$); 129.48 ($C_1$); 130.36 ($C_{2-6}$); 130.92 ($C_{3''-5''}$); 134.50 ($C_4$); 134.81 ($C_{4''}$); 135.21 ($C_{4'}$); 141.46 ($C_{1''}$); 146.08 ($C_\beta$); 148.00 ($C_{1'}$); 158.92 $(CO(NH)_2)$; 187.40 (CO). CIMS (*m/z*) 476 [M + H].

*5.2.2.5. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-(2,4-dichlorophenyl)acryloyl)phenyl]urea (**10**).* IR 3312 (NH); 1648 (CO). $^1$H NMR 7.37 (d, $H_\alpha$, $J = 15.58$ Hz); 7.46 (d, $H_6$, $J = 8.67$ Hz); 7.53 (dd, $H_5$, $J_{H_{5-6}} = 8.67$ Hz, $J_{H_{5-3}} = 1.97$ Hz); 7.60 (d, $H_{3''-5''}$, $J = 8.64$ Hz); 7.74 (d, $H_{2''-6''}$, $J = 8.64$ Hz); 7.88 (d, $H_\beta$, $J = 15.58$ Hz); 7.98 (d, $H_{2'-6'}$, $J = 8.67$ Hz); 8.24 (d, $H_{3'-5'}$, $J = 8.67$ Hz); 9.06 (br NH). $^{13}$C NMR 116.89 ($C_{2'-6'}$); 126.18 ($C_\alpha$); 128.22 ($C_{2''-6''}$); 128.45 ($C_5$); 129.16 ($C_{3'-5'}$); 129.19 ($C_{3''-5''}$); 129.96 ($C_6$); 130.30 ($C_3$); 130.53 ($C_1$); 132.24 ($C_{4'}$); 134.76 ($C_{4''}$); 135.45 ($C_2$); 135.73 ($C_4$); 136.29 ($C_{1''}$); 146.12 ($C_{1'}$); 148.31 ($C_\beta$); 158.83 $(CO(NH)_2)$; 187.06 (CO); 187.40 (CO). CIMS (*m/z*) 511 [M + H].

*5.2.2.6. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-(2,4-difluorophenyl)acryloyl)phenyl]urea (**11**).* IR 3312 (NH); 1648 (CO); 1619 (C═C). $^1$H NMR 6.62 (s, $H_5$); 7.46 (d, $H_{3''-5''}$, $J = 8.42$ Hz); 7.55–7.61 (m, $H_{2''-6''}$, $H_\alpha$); 7.76 (d, $H_\beta$, $J = 14.85$ Hz); 7.82 (d, $H_3$, $J = 1.49$ Hz); 7.86–7.97 (m, $H_{3'-5'}$, $H_{2'-6'}$); 8.98 (br NH); 9.02 (br NH). $^{13}$C NMR 112.00 ($C_5$); 116.95 ($C_{2'-6'}$); 122.00 ($C_1$); 124.24 ($C_\alpha$); 128.25 ($C_{2''-6''}$); 129.18 ($C_{3'-5'}$); 129.99 ($C_6$); 130.23 ($C_{4'}$); 130.39 ($C_{3''-5''}$); 134.82 ($C_{4''}$); 145.99 ($C_{1''}$); 146.09 ($C_{1'}$); 148.18 ($C_\beta$); 158.86 $(CO(NH)_2)$; 163.24–160.19 (d, $C_2$, $J = 207.60$ Hz); 187.36 (CO). CIMS (*m/z*) 478 [M + H].

*5.2.2.7. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-(3,4,5-trimethoxyphenyl)acryloyl)phenyl]urea (**12**).* IR 3312 (NH); 1622 (C═C). $^1$H NMR 3.70 (s, 3H, 4-OMe); 3.85 (s, 6H, 3,5-OMe); 7.19 (s, $H_{2-6}$); 7.46 (d, $H_{3''-5''}$, $J = 8.67$ Hz); 7.55 (d, $H_\alpha$, $J = 15.34$ Hz); 7.62 (d, $H_{2''-6''}$, $J = 8.67$ Hz); 7.74 (d, $H_\beta$, $J = 15.34$ Hz); 7.80 (d, $H_{2'-6'}$, $J = 8.91$ Hz); 7.99 (d, $H_{3'-5'}$, $J = 8.91$ Hz); 8.97 (br NH); 9.02 (br NH). $^{13}$C NMR 56.67 (3,5-OMe); 60.68 (4-OMe); 106.83 ($C_{2-5}$); 116.91 ($C_{2'-6'}$); 121.99 ($C_\alpha$); 128.26 ($C_{2''-6''}$); 129.16 ($C_{3'-5'}$); 129.71 ($C_{3''-5''}$); 130.30 ($C_1$); 131.09 ($C_{4'}$); 134.82 ($C_{4''}$); 143.42 ($C_{1''}$); 146.08 ($C_{1'}$); 147.83 ($C_\beta$); 153.63 ($C_{3-5}$); 158.96 $(CO(NH)_2)$; 187.54 (CO). CIMS (*m/z*) 532 [M + H].

*5.2.2.8. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-phenylacryloyl)phenyl]urea (**13**).* IR 3312 (NH); 1648 (CO); 1619 (C═C). $^1$H NMR 7.43–7.48 (m, $H_{2-6}$, $H_4$, $H_{3-5}$); 7.60 (d, $H_{3''-5''}$, $J = 8.40$ Hz); 7.61 (d, $H_\alpha$, $J = 14.09$ Hz); 7.80 ($H_{2''-6''}$, $J = 8.40$ Hz); 7.83 (d, $H_{2'-6'}$, $J = 8.40$ Hz); 7.89 (d, $H_\beta$, $J = 14.09$ Hz); 7.96 (d, $H_{3'-5'}$, $J = 8.40$ Hz); 9.03 (br NH). $^{13}$C NMR 116.91 ($C_{2'-6'}$); 122.74 ($C_\alpha$); 128.25 ($C_{2''-6''}$); 129.19 ($C_{3'-5'}$); 129.20 ($C_{2-6}$); 129.43 ($C_{3''-5''}$); 129.57 ($C_4$); 130.30 ($C_{3-5}$); 130.80 ($C_{4'}$); 134.80 ($C_1$); 135.48 ($C_{4''}$); 142.95 ($C_{1''}$); 146.07 ($C_{1'}$); 147.92 ($C_\beta$); 158.91 $(CO(NH)_2)$; 187.55 (CO). CIMS (*m/z*) 442 [M + H].

*5.2.2.9. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-(4-methylphenyl)acryloyl)phenyl]urea (**14**).* IR 3312 (NH); 1648 (CO); 1619 (C═C). $^1$H NMR 2.33 (4-Me); 7.25 (d, $H_{3-5}$, $J = 8.67$ Hz); 7.46 (d, $H_{2-6}$, $J = 8.67$ Hz); 7.59 (d, $H_{3''-5''}$, $J = 8.88$ Hz); 7.62 (d, $H_\alpha$, $J = 15.85$ Hz); 7.74 (d, $H_{2''-6''}$, $J = 8.88$ Hz); 7.80 (d, $H_{2'-6'}$, $J = 8.67$ Hz); 7.84 (d, $H_\beta$, $J = 15.85$ Hz); 7.95 (d, $H_{3'-5'}$, $J = 8.67$ Hz); 9.00 (br NH). $^{13}$C NMR 21.62 (4-Me); 116.91 ($C_{2'-6'}$); 121.66 ($C_\alpha$); 128.24 ($C_{2''-6''}$); 129.19 ($C_{2-6}$); 129.24 ($C_{3'-5'}$); 129.67 ($C_{3-5}$); 130.06 ($C_{3''-5''}$); 132.75 ($C_1$); 134.80 ($C_{4''}$); 140.80 ($C_4$); 143.03 ($C_{1''}$); 146.07 ($C_{1'}$); 147.82 ($C_\beta$); 158.90 $(CO(NH)_2)$; 187.57 (CO). CIMS (*m/z*) 456 [M + H].

*5.2.2.10. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-(4-methoxyphenyl)acryloyl)phenyl]urea (**15**).* IR 3312 (NH); 1648 (CO); 1619 (C═C). $^1$H NMR 3.81 (s, 3H, 4-OMe); 6.99 (d, 2H, $H_{3-5}$, $J = 8.67$ Hz); 7.46 (d, 2H, $H_{2-6}$, $J = 8.67$ Hz); 7.59 (d, 2H, $H_{3''-5''}$, $J = 8.91$ Hz); 7.62 (d, 1H, $H_\alpha$, $J = 15.07$ Hz); 7.76 (d, 1H, $H_\beta$, $J = 15.07$ Hz); 7.80 (d, 2H, $H_{2''-6''}$, $J = 8.91$ Hz); 7.95 (d, $H_{3'-5'}$, $J = 8.91$ Hz); 8.99 (br NH). $^{13}$C NMR 55.90 (4-OMe); 114.91 ($C_{3-5}$); 116.90 ($C_{2'-6'}$); 120.25 ($C_\alpha$); 128.14 ($C_1$); 128.25 ($C_{2''-6''}$); 129.16 ($C_{3'-5'}$); 129.84 ($C_{4'}$); 130.13

($C_{3''-5''}$); 131.04 ($C_{2-6}$); 134.79 ($C_{4''}$); 142.89 ($C_{1''}$); 146.12 ($C_{1'}$); 147.69 ($C_{\beta}$); 158.96 ($CO(NH)_2$); 161.59 ($C_4$); 187.48 (CO). CIMS (*m/z*) 472 [M + H].

*5.2.2.11. (E)-1-(4″-Chlorophenylsulfonyl)-3-[4′-(3-pyridin-3-yl-acryloyl)phenyl]urea (**16**).* IR 3312 (NH); 1651 (CO); 1616 (C═C). $^1$H NMR 7.46 (d, $H_{3''-5''}$, $J = 8.67$ Hz); 7.61 (d, $H_{2''-6''}$, $J = 8.67$ Hz); 7.68 (d, $H_{\alpha}$, $J = 15.58$ Hz); 7.75 (d, $H_{\beta}$, $J = 15.58$ Hz); 7.81 (d, $H_{2'-6'}$, $J = 8.15$ Hz); 7.99 (d, $H_{3'-5'}$, $J = 8.15$ Hz); 8.33 (d, $H_4$, $J = 8.15$ Hz); 8.59 (d, $H_6$, $J = 7.70$ Hz); 8.98 (s, $H_2$); 9.05 (br NH). $^{13}$C NMR 116.99 ($C_{2'-6'}$); 124.54 ($C_{\alpha}$); 124.66 ($C_5$); 128.28 ($C_{2''-6''}$); 129.19 ($C_{3'-5'}$); 129.36 ($C_4$); 130.47 ($C_{3''-5''}$); 131.33 ($C_3$); 134.92 ($C_{4'}$); 135.54 ($C_{4''}$); 139.50 ($C_{1''}$); 145.79 ($C_{\beta}$); 148.00 ($C_{1'}$); 150.62 ($C_2$); 151.16 ($C_6$); 158.87 ($CO(NH)_2$); 187.37 (CO). CIMS (*m/z*) 443 [M + H].

*5.2.2.12. (E)-1-[4′-(3-(2,4-Dimethoxyphenyl)acryloyl)phenyl]-3-tosylurea (**17**).* IR 3312 (NH); 1619 (C═C); 1299 ($SO_2$). $^1$H NMR 2.31 (s, 3H, 4″-Me); 3.83 (s, 3H, OMe); 3.88 (s, 3H, OMe); 6.62 (s, $H_3$); 7.19 (d, $H_5$); 7.49–7.57 (m, $H_{2''-6''}$, $H_{3''-5''}$, $H_6$); 7.63 (d, $H_{\alpha}$, $J = 15.58$ Hz); 7.69 (d, $H_{2'-6'}$, $J = 8.15$ Hz); 7.71 (d, $H_{\beta}$, $J = 15.58$ Hz); 7.90 (d, $H_{3'-5'}$, $J = 8.15$ Hz); 8.92 (br NH). CIMS (*m/z*) 481 [M + H].

*5.2.2.13. (E)-1-[4′-(3-(4-Fluorophenyl)acryloyl)phenyl]-3-tosylurea (**18**).* IR 3312 (NH); 1651 (CO); 1619 (C═C); 1584, 1302 ($SO_2$). $^1$H NMR 2.31 (s, 3H, 4″-Me); 7.19 (d, $H_{2-6}$, $J = 7.91$ Hz); 7.28 (t, $H_{3-5}$, $J = 7.91$ Hz); 7.60 (d, $H_{3''-5''}$, $J = 8.15$ Hz); 7.69 (d, $H_{2''-6''}$, $J = 8.15$ Hz); 7.76 (d, $H_{\alpha}$, $J = 15.82$ Hz); 7.86 (d, $H_{\beta}$, $J = 15.82$ Hz); 7.91–7.98 (m, $H_{2'-6'}$, $H_{3'-5'}$); 8.96 (br NH). CIMS (*m/z*) 439 [M + H].

*5.2.2.14. (E)-1-[4′-(3-(3,4-Methylenedioxyphenyl)acryloyl)-phenyl]-3-tosylurea (**19**).* IR 3312 (NH); 1648 (CO); 1619 (C═C); 1302 ($SO_2$). $^1$H NMR 2.31 (s, 3H, 4″-Me); 6.09 (s, –$OCH_2O$–); 6.97 (d, $H_5$, $J = 8.15$ Hz); 7.19 (d, $H_6$, $J = 8.15$ Hz); 7.28 (d, $H_{3''-5''}$, $J = 8.67$ Hz); 7.37 (d, $H_{\alpha}$, $J = 16.31$ Hz); 7.60 (d, $H_{2''-6''}$, $J = 8.67$ Hz); 7.70 (d, $H_{2'-6'}$, $J = 8.91$ Hz); 7.77 (d, $H_{\beta}$, $J = 16.31$ Hz); 7.96 (d, $H_{3'-5'}$, $J = 8.91$ Hz); 8.94 (br NH). $^{13}$C NMR 21.41 (4″-Me); 102.12 (–$OCH_2O$–); 107.44 ($C_5$); 109.03 ($C_2$); 116.87 ($C_{2'-6'}$); 120.79 ($C_{\alpha}$); 125.97 ($C_6$); 127.10 ($C_{3'-5'}$); 128.68 ($C_{3''-5''}$); 129.71 ($C_{2''-6''}$); 130.06 ($C_1$); 130.18 ($C_{4'}$); 139.80 ($C_{1''}$); 142.89 ($C_{1'}$); 144.40 ($C_{4''}$); 147.86 ($C_{\beta}$); 148.61 ($C_3$); 149.76 ($C_4$); 159.06 ($CO(NH)_2$); 187.40 (CO). CIMS (*m/z*) 465 [M + H].

*5.2.2.15. (E)-1-[4′-(3-(4-Chlorophenyl)acryloyl)phenyl]-3-tosylurea (**20**).* IR 3296 (NH); 1651 (CO); 1619 (C═C); 1302 ($SO_2$). $^1$H NMR 2.31 (s, 3H, 4″-Me); 7.19 (d, $H_{3-5}$, $J = 7.91$ Hz); 7.50 (d, $H_{2-6}$, $J = 7.91$ Hz); 7.61 (d, $H_{3''-5''}$, $J = 8.40$ Hz); 7.66–7.71 (m, $H_{2''-6''}$, $H_{\alpha}$); 7.88–7.90 (m, $H_{2'-6'}$, $H_{\beta}$); 7.97 (d, $H_{3'-5'}$, $J = 8.91$ Hz); 8.98 (br NH). $^{13}$C NMR 21.41 (4″-Me); 116.90 ($C_{2'-6'}$); 123.58 ($C_{\alpha}$); 127.12 ($C_{3'-5'}$); 128.68 ($C_{3-5}$); 129.43 ($C_{2-6}$); 130.34 ($C_{3''-5''}$); 130.91 ($C_{2''-6''}$); 134.52 ($C_{4'}$); 135.20 ($C_4$); 139.81 ($C_{1''}$); 141.39 ($C_{1'}$); 144.40 ($C_{4''}$); 148.13 ($C_{\beta}$); 159.01 ($CO(NH)_2$); 187.35 (CO). CIMS (*m/z*) 456 [M + H].

*5.2.2.16. (E)-1-[4′-(3-(2,4-Dichlorophenyl)acryloyl)phenyl]-3-tosylurea (**21**).* IR 3312 (NH); 1651 (CO); 1616 (C═C). $^1$H NMR 2.31 (s, 3H, 4″-Me); 7.19 (d, $H_5$, $J = 8.15$ Hz); 7.52 (d, $H_6$, $J = 8.15$ Hz); 7.61 (d, $H_{3''-5''}$, $J = 8.64$ Hz); 7.69 (d, $H_{2''-6''}$, $J = 8.64$ Hz); 7.87 (d, $H_{\alpha}$, $J = 15.31$ Hz); 7.98 (d, $H_{2'-6'}$, $J = 8.91$ Hz); 7.98 (d, $H_{\beta}$, $J = 15.31$ Hz); 8.22 (d, $H_{3'-5'}$, $J = 8.91$ Hz); 9.01 (br NH). $^{13}$C NMR 21.41 (4″-Me); 116.91 ($C_{2'-6'}$); 126.20 ($C_{\alpha}$); 127.12 ($C_{3'-5'}$); 128.44 ($C_{3''-5''}$); 128.68 ($C_{2''-6''}$); 129.11 ($C_5$); 129.94 ($C_6$); 130.29 ($C_3$); 130.52 ($C_{4'}$); 132.25 ($C_1$); 135.44 ($C_2$); 135.73 ($C_4$); 136.26 ($C_{1''}$); 139.81 ($C_{1'}$); 144.37 ($C_{4''}$); 148.38 ($C_{\beta}$); 158.97 ($CO(NH)_2$); 187.04 (CO). CIMS (*m/z*) 490 [M + H].

*5.2.2.17. (E)-1-[4′-(3-(2,4-Difluorophenyl)acryloyl)phenyl]-3-tosylurea (**22**).* IR 3312 (NH); 1651 (CO); 1616 (C═C). $^1$H NMR 2.31 (s, 3H, 4″-Me); 7.19 (d, $H_5$, $J = 7.91$ Hz); 7.62 (d, $H_{3''-5''}$, $J = 8.67$ Hz); 7.68–7.73 (m, $H_{2''-6''}$, $H_{\alpha}$, $H_6$); 7.92 (d, $H_{\beta}$, $J = 15.34$ Hz); 7.93 (d, $H_{2'-6'}$, $J = 8.64$ Hz); 7.95 (d, $H_{3'-5'}$, $J = 8.64$ Hz); 8.99 (br NH). $^{13}$C NMR 21.41 (4″-Me); 105.09 ($C_3$); 113.00 ($C_5$); 116.91 ($C_{2'-6'}$); 124.66 ($C_{\alpha}$); 127.12 ($C_{3'-5'}$); 128.67 ($C_{3''-5''}$); 129.19 ($C_{2''-6''}$); 129.48 ($C_{4'}$); 130.36 ($C_1$); 133.13 ($C_{\beta}$); 139.78 ($C_{1''}$); 144.39 ($C_{1'}$); 148.27 ($C_{4''}$); 159.00 ($CONH)_2$); 187.12 (CO). CIMS (*m/z*) 457 [M + H].

*5.2.2.18. (E)-1-[4′-(3-(3,4,5-Trimethoxyphenyl)acryloyl)phenyl]-3-tosylurea (**23**).* IR 3296 (NH); 1622 (C═C). $^1$H NMR 2.31 (s, 3H, 4″-Me); 3.71 (s, 3H, 4-OMe); 3.85 (s, 6H, 3,5-OMe); 7.19 (d, $H_{2-6}$, $H_{3''-5''}$, $J = 7.70$ Hz); 7.57–7.71 (m, $H_{2''-6''}$, $H_{\alpha}$, $H_{2'-6'}$); 7.84 (d, $H_{\beta}$, $J = 15.58$ Hz); 7.98 (d, $H_{3'-5'}$, $J = 8.67$ Hz); 8.94 (br NH). $^{13}$C NMR 21.40 (4″-Me); 56.69 (3,5-OMe); 60.68 (4-OMe); 106.86 ($C_{2-6}$); 116.85 ($C_{2'-6'}$); 122.04 ($C_{\alpha}$); 127.12 ($C_{3'-5'}$); 128.66 ($C_{3''-5''}$); 129.58 ($C_{2''-6''}$); 130.28 ($C_1$); 131.10 ($C_{4'}$); 139.74 ($C_{1''}$); 139.99 ($C_{1'}$); 143.33 ($C_{4''}$); 144.45 ($C_{\beta}$); 148.01 ($C_4$); 153.64 ($C_{3-5}$); 158.98 ($CO(NH)_2$); 187.49 (CO). CIMS (*m/z*) 511 [M + H].

*5.2.2.19. (E)-1-[4′-(3-Phenylacryloyl)phenyl]-3-tosylurea (**24**).* IR 3312 (NH); 1651 (CO). $^1$H NMR 2.31 (s, 3H, 4″-Me); 7.19 (d, $H_{3-5}$, $J = 7.67$ Hz); 7.43 (d, $H_{2-6}$, $H_4$, $J = 7.67$ Hz); 7.61 (d, $H_{3''-5''}$, $J = 8.40$ Hz); 7.70 (d, $H_{2''-6''}$, $J = 8.40$ Hz); 7.83–7.87 (m, $H_{2'-6'}$, $H_{\alpha}$); 7.93–7.99 (m, $H_{3'-5'}$, $H_{\beta}$); 8.97 (br NH). $^{13}$C NMR 21.42 (4″-Me); 116.90 ($C_{2'-6'}$); 122.81 ($C_{\alpha}$); 127.12 ($C_{3'-5'}$); 128.68 ($C_{2-6}$); 129.20 ($C_{3''-5''}$); 129.42 ($C_{2''-6''}$); 129.49 ($C_{3-5}$); 130.28 ($C_4$); 130.76 ($C_{4'}$); 135.53 ($C_1$); 139.79 ($C_{1''}$); 142.88 ($C_{1'}$); 144.40 ($C_{4''}$); 148.06 ($C_{\beta}$); 159.04 ($CO(NH)_2$); 187.50 (CO). CIMS (*m/z*) 421 [M + H].

*5.2.2.20. (E)-1-[4′-(3-(4-Methylphenyl)acryloyl)phenyl]-3-tosylurea (**25**).* IR 3312 (NH); 1619 (C═C); 1587 (C═C Ar); 1302 ($SO_2$). $^1$H NMR 2.31 (s, 3H, 4″-Me); 2.34 (s, 3H, 4-Me); 7.19 (d, $H_{2-6}$, $J = 8.15$ Hz); 7.25 (d, $H_{3-5}$, $J = 8.15$ Hz); 7.61 (d, $H_{3''-5''}$, $J = 8.67$ Hz); 7.68 (d, $H_{\alpha}$, $J = 15.34$ Hz); 7.70 (d, $H_{2''-6''}$, $J = 8.67$ Hz); 7.74 (d, $H_{2'-6'}$, $J = 8.91$ Hz); 7.84 (d, $H_{\beta}$, $J = 15.34$ Hz); 7.96 (d, $H_{3'-5'}$, $J = 8.91$ Hz); 8.96 (br NH).

$^{13}$C NMR 21.42 (4-Me); 21.62 (4″-Me); 116.89 ($C_{2'-6'}$); 121.73 ($C_{\alpha}$); 127.12 ($C_{2-6}$); 128.67 ($C_{3'-5'}$); 129.23 ($C_{3''-5''}$); 129.60 ($C_{3-5}$); 130.04 ($C_{2''-6''}$); 130.21 ($C_1$); 132.81 ($C_{4'}$); 139.78 ($C_4$); 140.73 ($C_{1''}$); 142.93 ($C_{1'}$); 144.42 ($C_{4''}$); 147.96 ($C_{\beta}$); 159.05 ($CO(NH)_2$); 187.49 (CO). CIMS (*m/z*) 435 [M + H].

*5.2.2.21. (E)-1-[4′-(3-(4-Methoxyphenyl)acryloyl)phenyl]-3-tosylurea (**26**).* IR 3312 (NH); 1651 (CO); 1587 (C=C); 1299 ($SO_2$). $^1$H NMR 2.31 (s, 3H, 4″-Me); 3.80 (s, 3H, 4-OMe); 6.99 (d, $H_{3-5}$, $J = 8.64$ Hz); 7.19 (d, $H_{2-6}$, $J = 8.64$ Hz); 7.60 (d, $H_{3''-5''}$, $J = 8.15$ Hz); 7.65–7.73 (m, $H_{2''-6''}$, $H_{\alpha}$, $H_{\beta}$); 7.80 (d, $H_{2'-6'}$, $J = 8.67$ Hz); 7.95 (d, $H_{3'-5'}$, $J = 8.67$ Hz); 8.95 (br NH). $^{13}$C NMR 21.41 (4″-Me); 55.90 (4-OMe); 114.91 ($C_{3-5}$); 116.89 ($C_{2'-6'}$); 120.28 ($C_{\alpha}$); 127.09 ($C_{3'-5'}$); 128.16 ($C_1$); 128.69 ($C_{3''-5''}$); 129.77 ($C_{4'}$); 130.12 ($C_{2''-6''}$); 131.03 ($C_{2-6}$); 139.78 ($C_{1''}$); 142.85 ($C_{1'}$); 144.33 ($C_{4''}$); 147.76 ($C_{\beta}$); 159.06 ($CO(NH)_2$); 161.59 ($C_4$); 187.45 (CO). CIMS (*m/z*) 451 [M + H].

*5.2.2.22. (E)-1-[4′-(3-Pyridin-3-yl-acryloyl)phenyl]-3-tosylurea (**27**).* IR 3312 (NH); 1651 (CO). $^1$H NMR 2.31 (s, 3H, 4″-Me); 7.19 (d, $H_{3''-5''}$, $J = 8.91$ Hz); 7.44–7.49 (m, $H_5$); 7.62 (d, $H_{2''-6''}$, $J = 8.91$ Hz); 7.68 (d, $H_{\alpha}$, $J = 16.09$ Hz); 7.70 (d, $H_{2'-6'}$, $J = 8.15$ Hz); 7.78 (d, $H_{\beta}$, $J = 16.09$ Hz); 7.99 (d, $H_{3'-5'}$, $J = 8.15$ Hz); 8.33 (d, $H_4$, $J = 8.15$ Hz); 8.58 (d, $H_6$, $J = 7.60$ Hz); 8.98 (s, $H_2$); 9.01 (br NH). $^{13}$C NMR 21.39 (4″-Me); 116.97 ($C_{2'-6'}$); 124.52 ($C_{\alpha}$); 124.66 ($C_5$); 127.12 ($C_{3'-5'}$); 128.73 ($C_{3''-5''}$); 129.29 ($C_4$); 130.45 ($C_{2''-6''}$); 131.32 ($C_1$); 135.53 ($C_{4'}$); 139.48 ($C_{1''}$); 139.99 ($C_{\beta}$); 144.09 ($C_{1'}$); 148.09 ($C_{4''}$); 150.62 ($C_2$); 151.19 ($C_6$); 158.98 ($CO(NH)_2$); 187.33 (CO). CIMS (*m/z*) 422 [M + H].

*5.2.2.23. (E)-1-[4′-(3-Naphtalen-2-yl-acryloyl)phenyl]-3-tosylurea (**28**).* IR 3312 (NH); 1651 (CO). $^1$H NMR 2.31 (s, 3H, 4″-Me); 7.18 (d, $H_6$, $J = 8.42$ Hz); 7.54–7.58 (m, $H_{3''-5''}$, $H_{\alpha}$, $H_7$); 7.61 (d, $H_{2''-6''}$, $J = 8.91$ Hz); 7.68 (d, $H_{2'-6'}$, $J = 7.91$ Hz); 7.81 (d, $H_{\beta}$, $J = 15.34$ Hz); 7.93–8.01 (m, $H_{3'-5'}$, $H_1$, $H_3$, $H_5$); 8.09 (dd, $H_8$, $J_{H_{8-7}} = 10.13$ Hz, $J_{H_{8-6}} = 2.62$ Hz); 8.29 (s, $H_4$); 8.92 (br NH). $^{13}$C NMR 21.42 (4″-Me); 116.90 ($C_{2'-6'}$); 123.09 ($C_{\alpha}$); 125.03 ($C_3$); 127.16 ($C_{3'-5'}$); 127.29 ($C_{4a}$); 127.82 ($C_1$); 128.26 ($C_6$); 128.69 ($C_{3''-5''}$); 128.99 ($C_8$); 129.53 ($C_7$); 130.78 ($C_{2''-6''}$); 133.20 ($C_5$); 133.56 ($C_2$); 134.32 ($C_{4'}$); 139.81 ($C_{8a}$); 142.94 ($C_{1''}$); 144.39 ($C_{\beta}$); 148.12 ($C_{4''}$); 159.00 ($CO(NH)_2$); 187.46 (CO). CIMS (*m/z*) 472 [M + H].

*5.2.2.24. (E)-1-[4′-(3-(2-Chloroquinolin-3-yl)acryloyl)phenyl]-3-tosylurea (**29**).* IR 3456 (NH); 1667 (CO). $^1$H NMR 2.31 (s, 3H, 4″-Me); 7.10–7.35 (m, $H_{3''-5''}$, $H_{\alpha}$); 7.49–7.95 (m, $H_{2''-6''}$, $H_{2'-6'}$, $H_{3'-5'}$, $H_{\beta}$, $H_6$, $H_7$); 8.23 (s, $H_8$); 8.37 (s, $H_4$); 8.57 (s, $H_5$); 8.93 (br NH). $^{13}$C NMR 21.42 (4″-Me); 116.63 ($C_{2'-6'}$); 122.91 ($C_{\alpha}$); 125.95 ($C_3$); 127.19 ($C_{3'-5'}$); 128.65 ($C_{3''-5''}$); 131.37 ($C_{2''-6''}$); 134.03 ($C_4$); 139.74 ($C_{\beta}$); 142.63 ($C_{1''}$); 142.76 ($C_2$); 144.42 ($C_{4''}$); 158.91 ($CO(NH)_2$); 190.68 (CO). CIMS (*m/z*) 507 [M + H].

*5.2.2.25. (E)-1-[4′-(3-(2-Chloro-6,7-dimethoxyquinolin-3-yl)-acryloyl)phenyl]-3-tosylurea (**30**).* IR 3328 (NH); 1619 (C=C); 1350, 1293 ($SO_2$). $^1$H NMR 2.31 (s, 3H, 4″-Me); 3.94 (s, 3H, OMe); 3.96 (s, 3H, OMe); 7.18 (d, $H_{3''-5''}$, $J = 8.91$ Hz); 7.38 (s, $H_5$, $H_8$); 7.44 (d, $H_{\alpha}$, $J = 15.34$ Hz); 7.62 (d, $H_{2''-6''}$, $J = 8.91$ Hz); 7.67 (d, $H_{2'-6'}$, $J = 8.67$ Hz); 7.96 (d, $H_{\beta}$, $J = 15.34$ Hz); 7.99 (d, $H_{3'-5'}$, $J = 8.67$ Hz); 8.95 (br NH); 9.04 (br NH). $^{13}$C NMR 21.40 (4″-Me); 56.33 (OMe); 56.63 (OMe); 106.25 ($C_5$); 107.24 ($C_8$); 116.88 ($C_{2'-6'}$); 123.24 ($C_{\alpha}$); 125.18 ($C_3$); 125.56 ($C_4$); 127.16 ($C_{3'-5'}$); 128.65 ($C_{3''-5''}$); 129.14 ($C_{4a}$); 130.42 ($C_{2''-6''}$); 135.74 ($C_{4'}$); 137.08 ($C_{5a}$); 139.75 ($C_{\beta}$); 144.34 ($C_{1''}$); 145.23 ($C_{1'}$); 147.82 ($C_{4''}$); 148.37 ($C_2$); 150.69 ($C_7$); 154.70 ($C_6$); 158.77 ($CO(NH)_2$); 186.80 (CO). CIMS (*m/z*) 567 [M + H].

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