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ORIGINAL ARTICLE

Synthesis and antimalarial activity evaluation of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one derivatives

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Abstract Some novel derivatives of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one were synthesized and characterized by their physical and spectral data. All the synthesized compounds were subsequently screened for in vitro antimalarial activity against chloroquine sensitive strain of *Plasmodium falciparum* (RKL-2) employing chloroquine as the reference drug. Most of the synthesized compounds exhibited mild to moderate susceptibilities towards the parasite in comparison to the standard. It was found that antimalarial activity of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(4-bromophenyl)-1,3-thiazinan-4-one was marginally superior than all the compounds evaluated.

1. Introduction

Malaria is a life-threatening parasitic disease caused by protozoan parasites of the genus Plasmodium. Four species of the *Plasmodium* viz *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* are responsible for the bulk of human malaria cases globally (http://www.rbm.who.int/) and more recently another species *P. knowlesi* infecting humans has been documented (White, 2008; WHO, 2007). *P. falciparum* is the most widespread, and causes most severe and potentially fatal malaria (Talisuna et al., 2004). Over the years chloroquine (CQ) has remained the drug of choice for the malaria chemotherapy, because it is effective, less toxic and a cheap drug. The rapid spread of resistance of *P. falciparum* towards chloroquine and other available drugs has become a major health concern

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in the tropical and subtropical regions of the world (Sharma, 2007). Therefore, development of novel and effective antimalarial drug is the better approach to circumvent the problem faced by clinically used drugs.

The structure–activity relationship studies on 4-aminoquinoline antimalarial compounds suggested that the 7-chloro-4-aminoquinoline nucleus is obligatory for antimalarial activity, particularly, inhibition of β-haematin formation and accumulation of the drug at the target site (Werbel, 1986; Pandey et al., 2001; Chou et al., 1980). Shortening (2–3 carbon atoms) and lengthening (10–12 carbon atoms) of the carbon side chain in chloroquine (Fig. 1) leads to compounds that remain active against chloroquine-resistant strains of *P. falciparum* (Pandey et al., 2001; De et al., 1998; Solomon et al., 2005; Warhurst, 1981). Solomon et al. (2007) reported a new series of side-chain modified 4-aminoquinolines which was found active against *P. falciparum* (in vitro) and *P. yoelli* (in vivo). They also reported that the basicity of the side chain nitrogen is not very essential for antiplasmodial activity of 4-aminoquinoline, and the derivative having [1,3]-thiazinan-4-one ring system with 4-chlorophenyl- substitution at the C-2 position attached to the terminal side chain amino group of 7-chloro-4-aminoquinoline was 8-fold more potent in antiplasmodial activity as compared to chloroquine.

These findings have given impetus to the concept that side chain modification is an attractive strategy for the development of antimalarial drugs with desirable bioactivity. Encouraged by these evidences, we presumed that selectively modifying the pendent amino group with small heterocyclic systems could modulate the antimalarial activity. Based on this, title analogues were designed wherein, 7-chloro-4-aminoquinoline fragment kept rigid and modifications were made at the C-2 position of a six membered [1,3] thiazinan-4-one ring attached at the terminal propyl side chain of 7-chloro-4-aminoquinoline. Accordingly, seven title molecules of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-substituted 1,3-thiazinan-4-one were synthesized and subsequently screened for their in vitro antimalarial activity against laboratory cultured *P. falciparum*.

2. Materials and methods

2.1. Structural investigation

All chemicals used in the work were procured either from Sigma–Aldrich Corporation, USA or Merck Specialties Pvt. Ltd., Mumbai and were used without further purification. The intermediate was taken in an open capillary on the Veego-MPI melting point apparatus and the melting point of the synthesized compound was calculated. The progress of the reactions was monitored on silica gel-G TLC plate using various solvent combinations. The spots were detected with iodine vapours and illuminated under UV-light. The UV–visible spectra (λ_{max}) of the synthesized compounds were recorded on UV–visible spectrophotometer (Shimadzu UV-1700). Infrared spectra were recorded on an FT-IR Perkin-Elmer spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively on an Avance- 400 Bruker FT-NMR spectrometer using either DMSO-d_6 or $CDCl_3$ as solvent with tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on TOFMS^{+}.

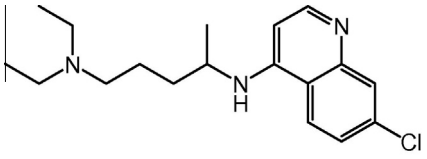


Figure 1 Chloroquine.

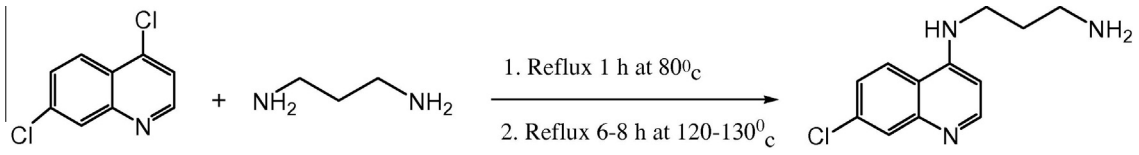
2.2. Antimalarial activity evaluation

All the synthesized compounds were evaluated for in vitro antimalarial activity against chloroquine sensitive strain (RKL-2) of *P. falciparum* (*Pf*) using 96 well-microtitre plates. The laboratory adapted strain of *Pf* was routinely cultured at 37 °C temperature and 5% CO_2 environment in RPMI 1640 medium supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum (Trager and Jensen, 1976). For antimalarial testing the asynchronous parasites of *Pf* were synchronized to obtain only the ring stage parasitized cells by 5% D-sorbitol treatment. For carrying out the assay, the initial ring stage parasitaemia of 0.8–1.5% at 3% haematocrit in a total volume of 200 μL of medium RPMI-1640 was uniformly maintained. A stock solution of 5 mg/ml was prepared by dissolving the test compounds in DMSO and subsequent dilutions were made with the culture medium. Twenty microlitres of the test compounds at 50 μg/ml concentrations in duplicate wells was incubated with parasitized cell preparation at 37 °C and 5% CO_2 in a CO_2 incubator. After an incubation period of 36–40 h, the blood smears were prepared from each well and stained with 3% Giemsa stain. The slides were microscopically observed and the percent dead rings and schizonts were scored against 100 asexual parasites with respect to the control group. Chloroquine was used as the standard reference drug.

3. Results and discussion

In the present study, seven new 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one derivatives were synthesized and their antimalarial activity was evaluated in vitro against chloroquine sensitive *P. falciparum*.

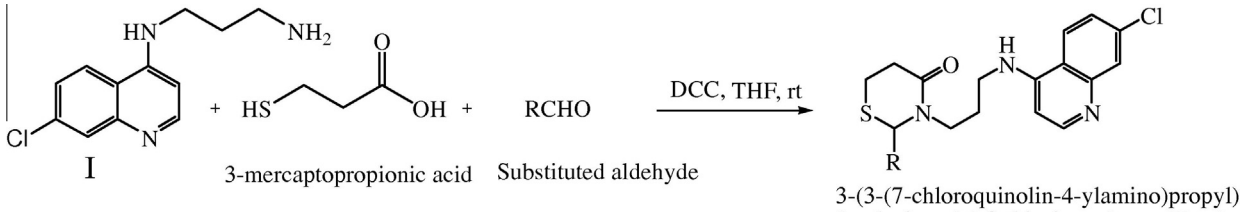
The target compounds were prepared as outlined in Schemes 1 and 2. The N^1-(7-chloroquinolin-4-yl)propan-1,3-diamine was prepared by aromatic nucleophilic substitution on 4,7-dichloroquinoline with excess of 1,3-diaminopropane in neat conditions. The amino group can be transformed to the thiazinan-4-one skeleton by the reaction of aldehyde and 3-mercaptopropionic acid in the presence of *N*,*N*-dicyclohexylcarbodiimide (DCC) whereas, DCC was utilized as a dehydrating agent to accelerate the intramolecular cyclisation, resulting in faster reaction and improved product yield. The 4-aminoquinoline derivatives of 2-substituted [1,3]thiazinan-4-ones were obtained from the N^1-(7-chloroquinolin-4-yl)propan-1,3-diamine, substituted aldehyde and 3-mercaptopropionic acid in the presence of DCC in anhydrous THF at room temperature. After completion of the reaction, the desired products were obtained in excellent yields and purity. Molecular modification of synthesized derivatives was shown in Table 1.



4,7-dichloroquinoline 1,3-Diaminopropane

N^1-(7-chloroquinolin-4-yl) propane-1,3-diamine (I)

Scheme 1

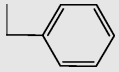
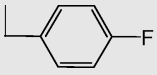
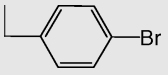
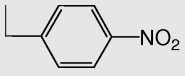
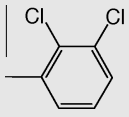
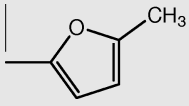
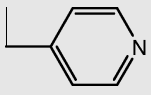


3-mercaptopropionic acid Substituted aldehyde

3-(3-(7-chloroquinolin-4-ylamino)propyl) 2-substituted-1,3-thiazinan-4-one (IIa-g)

Scheme 2

Table 1 Molecular modification and in vitro antimalarial activity evaluation of synthesized compounds (test model: chloroquine sensitive *P. falciparum*, RKL-2 strain).

Compound	R	Dosage (μg/ml)	Percent dead rings + schizonts[a]
IIa		50	12.00
IIb		50	9.00
IIc		50	18.50
IId		50	5.50
IIe		50	10.50
IIf		50	8.00
IIg		50	8.00
Chloroquine (Standard)		0.4	50.50

[a] Mean of two replicates and counted against 100 asexual parasites per replicate.

From the structural investigation, FT-IR spectra showed the stretching frequency range between region 3200–3500 cm^{-1} due to –N–H stretching, 2800–2950 cm^{-1} due to –C–H stretching and 1650–1750 cm^{-1} due to –C═O stretching and ^1H NMR spectra of the compounds showed a singlet at δ (ppm) 1.77–4.56 due to –NH group, a triplet or multiple at δ 1.72–4.46 due to $–CH_2$ group and a doublet or multiple at δ 5.86–8.80 due to –H, quinoline group, further confirmed the formation of this class of derivatives. The analytical and spectral data of the compounds are found in compliance with the structure of the synthesized compounds.

All the seven synthesized compounds (**a–g**) presented mild to moderate activity against chloroquine sensitive *P. falciparum* (RKL-2) strain. Furthermore, these compounds were also found to exhibit significantly inferior activity than chloroquine in the comparison test (Table 1). However, the compounds with phenyl-(**a**), 4-bromophenyl-(**c**), 2,3-dichlorophenyl-(**e**) substitution at 2-position of 1,3-thiazinan-4-one ring system attached with the terminal propyl side chain of 7-chloro-4-aminoquinoline demonstrate slightly better activity than the compounds with 4-fluorophenyl-(**b**), 4-nitrophenyl-(**d**), pyridine-4-yl-(**f**), 5-methylfuryl-(**g**) at the side chain.

4. Conclusion

On the basis of the results, it was established that a lipophilic bulky group at 1,3-thiazinan-4-one ring system attached with the terminal propyl side chain of 7-chloro-4-aminoquinoline may be an essential structural requirement for antimalarial activity of the prepared derivatives. This information will be useful for further studies in terms of toxicity effect and structural activity relationship (SAR) to improve their biological and pharmacological properties in the process of searching for promising agents with utility in the treatment of malaria.

5. Experimental

5.1. Chemistry

The intermediate reaction product (**I**), N^1-(7-chloroquinolin-4-yl)propan-1,3-diamine (Scheme 1) was prepared according to the method reported by Madrid et al. (2004) and obtained as an off-white solid. Seven derivatives (**a–g**) of 3-(3-(7-chloroquinolin-4-ylamino)propyl)-1,3-thiazinan-4-one (Scheme 2) were prepared as per the method designed by Solomon et al. (2007).

Compound **I**: N^1-(7-chloroquinolin-4-yl)propan-1,3-diamine: yield 77.40%, mp 96–98 °C, R_f value: 0.13 (acetone**:**ethanol = 1:1) spectroscopic analysis: λ_{max}: 263 nm (DMSO); IR (KBr, υ_{max}, cm^{-1}): 3346, 3333, 3253 (N–H str.), 1190 (C–N str.), 1090 (C–Cl str.); ^1H NMR (DMSO-d_6) δ (ppm): 1.82 (m, 2H, CH_2), 2.65 (t, J = 19.2 Hz, 2H, CH_2), 2.76 (br s, 2H, NH_2), 3.27–3.32 (t, J = 9.6 Hz, 2H, CH_2), 4.32 (br, s, 1H, NH), 6.41–6.44 (d, J = 5.30 Hz, 1H, 3H quinoline), 7.51–7.56 (dd, J = 18.00, 18.00 Hz, 1H, 6H quinoline), 7.61 (d, J = 6.0 Hz, 1H, 5H quinoline), 8.02–8.04 (d, J = 9.20 Hz, 1H, 8H quinoline), 8.14–8.29 (m, 1H, 2H quinoline); ^{13}C NMR (DMSO-d_6) δ (ppm): 39.59, 44.67, 118.47, 127.59, 134.38, 146.89, 151.72, 152.53; MS (m/z): 236.12 $[M+H]^+$.

Compound $\mathbf{II_a}$: 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-phenyl-1,3-thiazinan-4-one: yield 80.35%, R_f value: 0.75 (acetone:ethanol = 3:1): semi-solid; spectroscopic analysis: λ_{max}: 262.00 nm (DMSO); IR ($CHCl_3$, cm^{-1}): 3423 (N–H str.), 1616.6 (C═O str.), 1090.9 (C–Cl str.); ^1H NMR (DMSO-d_6) δ (ppm): 1.50–1.86 (m, 2H, CH_2), 2.65 (t, J = 19.2 Hz, 2H, CH_2), 2.79–2.84 (m, 2H, CH_2), 4.56 (br, s, 1H, NH), 5.53 (s, 1H, CH), 6.24–6.25 (d, J = 4.80 Hz, 1H, 3H quinoline), 7.16–7.18 (d, J = 7.20 Hz, 1H, Ar–H), 7.29–7.34 (d, J = 8.00 Hz, 1H, 6H quinoline), 7.59 (br, s, 1H, 5H quinoline), 8.00–8.02 (d, J = 8.80 Hz, 1H, 8H quinoline), 8.30 (m, 1H, 2H quinoline); ^{13}C NMR (DMSO-d_6) δ (ppm): 26.20, 36.85, 39.79, 116.79, 123.01, 127.18, 128.79, 129.75, 134.53, 148.30, 151.91, 170.78; MS (m/z): 412.1 $[M+H]^+$.

Compound $\mathbf{II_b}$: 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(4-fluorophenyl)-1,3-thiazinan-4-one: yield 96.20%, R_f value: 0.79 (acetone:ethanol = 3:1): semi-solid; spectroscopic analysis: λ_{max}: 261.00 nm (DMSO); IR ($CHCl_3$, cm^{-1}): 3277.1 (N–H str.), 2930.2, (C–H str.), 1611.9 (C═O str.),1157.7 (C–F str.), 1091.4 (C–Cl str.); 1H NMR (DMSO-d_6) δ (ppm): 1.77–1.86 (dd, J = 10.80,5.60, 2H, CH_2), 2.61–2.65 (t, J = 8.40 Hz, 2H, CH_2), 2.82–2.85 (t, J = 6.80 Hz, 2H, CH_2), 3.44 (s, 2H, CH_2), 4.67 (br, s, 1H, NH), 5.90 (s, 1H, CH), 6.42 (br, s, 1H, 3H quinoline), 7.06–7.15 (m, 1H, Ar–H), 7.36–7.41 (m, 1H, 6H quinoline), 7.77 (s, 1H, 5H quinoline), 7.88–7.90 (m, 1H, 8H quinoline), 8.20–8.30 (d, J = 49.60 Hz, 1H, 2H quinoline); ^{13}C NMR (DMSO-d_6) δ (ppm): 26.30, 36.84, 40.64, 60.91, 117.35, 124.69, 125.14, 129.44, 129.98, 151.75, 160.74, 170.80; MS (m/z): 430.1 $[M+H]^+$.

Compound $\mathbf{II_c}$: 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(4-bromophenyl)-1,3-thiazinan-4-one: yield 69.11%, R_f value: 0.75 (acetone:ethanol = 3:1): semi-solid; spectroscopic analysis: λ_{max}: 261.00 nm (DMSO); IR ($CHCl_3$, cm^{-1}): 3297.1 (N–H str.), 2929.4, (C–H str.), 1696.9 (C═O str.), 1092.9 (C–Cl str.); 1H NMR (DMSO-d_6) δ (ppm): 1.87 (m, 2H, CH_2), 2.20–2.86 (m, 2H, CH_2), 3.22–3.40 (d, J = 72.80 Hz, 2H, CH_2), 4.35 (br, s, 1H, NH), 5.79 (s, 1H, CH), 6.72–6.75 (d, J = 12.80 Hz, 1H, 3H quinoline), 6.83 (s, 1H, Ar–H), 7.46 (m, 1H, 6H quinoline), 7.38–7.76 (dd, J = 106.40, 86.40 Hz, 1H, 5H quinoline), 8.03 (m, 1H, 8H quinoline), 8.33–8.59 (d, J = 96.80 Hz, 1H, 2H quinoline); ^{13}C NMR (DMSO-d_6) δ (ppm): 26.35, 35.29, 40.33, 60.83, 117.84, 121.28, 127.35, 129.06, 143.14, 148.83, 151.78, 169.01; MS (m/z): 492.0 $[M+H]^+$.

Compound $\mathbf{II_d}$: 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(4-nitrophenyl)-1,3-thiazinan-4-one: yield 89.03%, R_f value: 0.80 (acetone:ethanol = 3:1): semi-solid; spectroscopic analysis: λ_{max}: 261.00 nm (DMSO); IR ($CHCl_3$, cm^{-1}): 3264.1 (N–H str.), 1706.9 (C═O str.), 1520.1, 1346 $(N═O)_2$ str., 1215.8, (C–Cl str.); 1H NMR (DMSO-d_6) δ (ppm): 1.76 (m, 2H, CH_2), 2.80–2.92 (m, 2H, CH_2), 3.94–3.97 (t, J = 10.40 Hz, 2H, CH_2), 4.34 (br, s, 1H, NH), 5.86 (s, 1H, CH), 6.47–6.49 (d, J = 9.20 Hz, 1H, 3H quinoline), 6.89 (s, 1H, Ar–H), 7.44 (m, 1H, 6H quinoline), 7.78–7.79 (d, J = 8.00 Hz, 1H, 5H quinoline), 8.07–8.14 (m, 1H, 8H quinoline), 8.32–8.30 (d, J = 8.40 Hz, 1H, 2H quinoline); ^{13}C NMR (DMSO-d_6) δ (ppm): 26.34, 35.48, 40.66, 60.64, 117.30, 123.77, 129.21, 146.32, 146.98, 149.55, 151.97, 173.33; MS (m/z): 457.1 $[M+H]^+$.

Compound **II_e**: 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(2,3-dichlorophenyl)-1,3-thiazinan-4-one: yield 79.95%, R_f value: 0.43 (acetone:ethanol = 3:1): semi-solid; spectroscopic analysis: λ_{max}: 262.00 nm (DMSO); IR ($CHCl_3$, cm^{-1}): 3270.2 (N–H str.), 1711.9 (C═O str.), 1093.1 (C–Cl str.); ^1H NMR (DMSO-d_6) δ (ppm): 1.79 (m, 2H, CH_2), 2.46–2.63 (m, 2H, CH_2), 2.85–2.90 (d, J = 16.80 Hz, 2H, CH_2), 4.63 (br, s, 1H, NH), 5.59 (s, 1H, Ar–H), 6.41–6.46 (d, J = 37.60 Hz, 1H, 3H quinoline), 6.90 (s, 1H, Ar–H), 7.40–7.42 (d, J = 10.80 Hz, 1H, 6H quinoline), 7.60–7.62 (dd, J = 8.00, 12.00 Hz, 1H, 5H quinoline), 7.98–8.14 (m, 1H, 8H quinoline), 8.30–8.34 (d, J = 16.80 Hz, 1H, 2H quinoline); ^{13}C NMR (DMSO-d_6) δ (ppm): 26.10, 34.64, 36.84, 46.08, 59.59, 98.84, 117.19, 123.48, 128.51, 129.69, 135.91, 145.82, 149.12, 152.47, 170.82, 173.57; MS (m/z): 482.1 $[M+H]^+$.

Compound **II_f**: 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(5-methylfuran-2-yl)-1,3-thiazinan-4-one: yield 83.66%, R_f value: 0.76 (acetone:ethanol = 3:1): semi-solid; spectroscopic analysis: λ_{max}: 261.00 nm (DMSO); IR ($CHCl_3$, cm^{-1}): 3263.9 (N–H str.), 2926.7 (C–H str.), 1612.7 (C═O str.), 1091.5 (C–Cl str.); ^1H NMR (DMSO-d_6) δ (ppm): 1.76 (m, 2H, CH_2), 2.18–2.19 (d, J = 6.40 Hz, 2H, CH_2), 3.83–3.85 (m, 2H, CH_2), 4.39 (br, s, 1H, NH), 6.47–6.49 (d, J = 5.60 Hz, 1H, 3H quinoline), 7.45–7.48 (d, J = 12.80 Hz, 1H, 6H quinoline), 7.77 (s, 1H, 5-methylfuran-2-yl), 8.20–8.23 (d, J = 9.20 Hz, 1H, 8H quinoline), 8.36–8.37 (d, J = 5.60 Hz, 1H, 2H quinoline); ^{13}C NMR (DMSO-d_6) δ (ppm): 26.99, 34.32, 40.67, 47.99, 56.26, 79.66, 99.03, 117.43, 125.86, 146.95, 151.95, 157.23, 159.92, 168.82, 173.61; MS (m/z): 416.1 $[M+H]^+$.

Compound **II_g**: 3-(3-(7-chloroquinolin-4-ylamino)propyl)-2-(2-pyridin-4-yl)-1,3-thiazinan-4-one: yield 35.88%, R_f value: 0.56 (acetone:ethanol = 3:1): semi-solid; spectroscopic analysis: λ_{max}: 262.00 nm (DMSO); IR ($CHCl_3$, cm^{-1}): 3334.3 (N–H str.), 1728.7 (C═O str.), 1090.9 (C–Cl str.); 1H NMR (DMSO-d_6) δ (ppm): 1.88–1.90 (d, J = 8.40 Hz, 2H, CH_2), 2.57–2.58 (d, J = 5.20 Hz, 2H, CH_2), 3.29 (m, 2H, CH_2), 4.71 (br, s, 1H, NH), 5.99 (s, 1H, CH), 6.44 (m, 1H, 3H quinoline), 6.50–6.52 (m, 1H, pyridin-4-yl), 7.20–7.22 (d, J = 5.20 Hz, 1H, pyridin-4-yl), 7.44–7.46 (dd, J = 2.00, 2.40 Hz, 1H, pyridin-4-yl), 7.77–7.87 (m, 1H, pyridin-4-yl), 7.82–7.83 (d, J = 2.80 Hz, 1H, 5H quinoline), 8.06–8.10 (dd, J = 8.00, 6.00 Hz, 1H, 8H quinoline), 8.64–8.63 (d, J = 4.80 Hz, 1H, 2H quinoline); ^{13}C NMR (DMSO-d_6) δ (ppm): 28.10, 34.39, 40.79, 60.23, 79.64, 117.15, 121.87, 122.66, 129.47, 142.76, 149.65, 151.47, 169.03, 170.72, 173.38; MS (m/z): 413.1 $[M+H]^+$.

Declaration of interest

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Conflict of Interest

Author declares no conflict of interest.

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