Trisubstituted Methanes (TRSMs): Synthesis and Bioevaluation as Anti-malarials

Article · January 2014

CITATIONS
0

READS
157

6 authors, including:

Sudipta Kumar Manna
Nagoya University
16 PUBLICATIONS **132** CITATIONS
SEE PROFILE

Priyanka Singh
Université de Montpellier
14 PUBLICATIONS **211** CITATIONS
SEE PROFILE

Sankalan Mondal
Indian Institute of Technology Delhi
18 PUBLICATIONS **165** CITATIONS
SEE PROFILE

Manish Goyal
Indian Institute of Chemical Biology
48 PUBLICATIONS **1,163** CITATIONS
SEE PROFILE

Scientific Online

SOP TRANSACTIONS ON ORGANIC CHEMISTRY
Volume 1, Number 2, November 2014

SOP TRANSACTIONS ON ORGANIC CHEMISTRY

Trisubstituted Methanes (TRSMs): Synthesis and Bioevaluation as Anti-malarials

Sudipta Kumar Manna*[,1], Priyanka Singh[1], Sankalan Mondal[1], Manish Goyal[2], Uday Bandyopadhyay[2], Gautam Panda[1]

[1] *Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, B.S. 10/1, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, UP, India*

[2] *Division of Infectious Diseases and Immunology, CSIR-Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Jadavpur, Kolkata 700032, West Bengal, India*

***Corresponding author**: sudipta.manna09@gmail.com

Abstract:

Focused libraries of Trisubstituted methanes (TRSMs) have been accessed through Grignard reaction of aryl magnesium bromide with various carbaldehydes followed by Friedel-Crafts alkylation of diaryl carbinols with electron rich aryl and heteroaryl thiols. These compounds were investigated to inhibit parasite growth and development and displayed strong anti-malarial activity in vitro against human malaria parasite *Plasmodium falciparum*. The synthesized TRSMs interact well with free heme and form stable TRSM-heme complexes. Furthermore, they also inhibit β-hematin formation (hemozoin formation) in a concentration dependent manner. Measurement of heme binding affinity and hemozoin inhibition for TRSMs revealed strong correlation with anti-malarial potency. Structure activity relationship revealed that TRSMs containing pyridyl and quinoline ring were more efficient to offer anti-malarial activity.

Keywords:

Trisubstituted Methanes; Anti-malarial Agent; Structure-activity Relationship

1. INTRODUCTION

Despite the substantial efforts of industrial and academic research, malaria displays a disturbing social and economic cost across the globe and it is still the most important tropical disease. The disease causes 2-3 million of deaths annually as well as incalculable sufferings [1, 2]. The situation of malaria is getting worse with rapid spread of multi-drug resistant parasite [3–7]. Of the four known human malaria parasites, *Plasmodium falciparum* is the predominant cause of mortality, with 120 million new cases and 1 million deaths per year globally. The treatment of malaria relies solely on chemotherapeutics and chemoprophylaxis due to limitations associated with vaccine development and vector control. Therefore, there is an urgent need for identification and validation of new active anti-malarial agents with improved properties *i.e.*, enhanced and selective activity [8].

Trisubstituted methanes (TRSMs) are of great significance, due to their wide variety of applications in

synthetic, medicinal and industrial chemistry as well as protecting groups [9–15]. TRSMs containing sulfide, sulfoxide or sulfone spacers have been reported to show various biological activities. For example, a series of *a*-(lupinylthio)diphenylmethanes, 9-(lupinylthio) xanthenes and thioxanthenes was found to exhibit diverse pharmacological activities [16]. In addition, arylsulfanyl and arylsulfonyl moieties are essential groups of many anti-malarial agents. For example, several arylacridinyl sulfones have been reported to have anti-malarial activity [17]. Derivatives of furoxan having a sulfone moiety also showed good anti-malarial activity [18]. Furthermore, a series of imidazole-dioxolane compounds displayed potent heme binding and promising anti-plasmodial activity [19]. These findings motivated us to evaluate the anti-malarial activity of a focused library of easily synthesizable TRSMs. Initially, series of TRSMs without sulfur spacer were undertaken and tested to evaluate their inhibitory potency through bioassay based on heme binding, inhibition of hemozoin formation and anti-malarial efficacy. Furthermore, design and synthesis and optimization of functional groups on the TRSMs scaffold and the use of structure activity relationships of the series were established. These studies led to the discovery of TRSM analogues with superior heme binding affinity and anti-malarial potency.

2. RESULTS AND DISCUSSION

Initially syntheses of a series of trisubstituted methanes without sulfur spacer (*i.e.* triarylmethanes) containing substituted aryl groups were undertaken. Grignard reaction of 4-methoxyphenylmagnesium bromide **1a** with substituted aryl aldehydes **2a-c** afforded carbinols **3a-c**. Friedel-Crafts reaction of carbinols **3a-c** with four different electron-rich arenes *i.e.*, N-ethylaniline, N,N-dimethylaniline, aniline and phenol in the presence of a catalytic amount of conc. H_2SO_4 or anhydrous $AlCl_3$ in dry benzene gave the targeted TRSMs **4-9** in good yields (**Figure 1**).

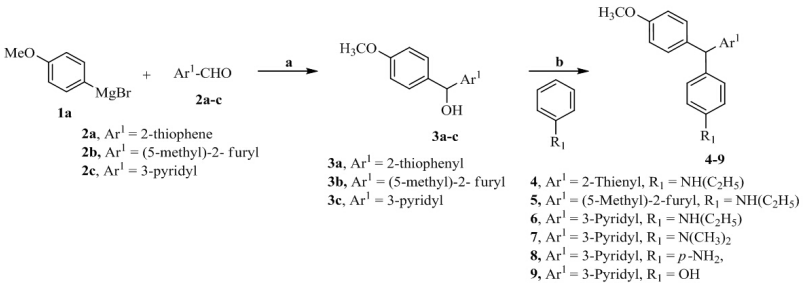

Figure 1. Reagents and conditions: (a) Dry THF, rt, 1 h; (b) conc. H_2SO_4, dry benzene, reflux, 0.5 h or anhyd. $AlCl_3$, dry benzene, rt, 0.5 h.

Prior work from our group related to TRSMs as anti-malarial agents, validate the heme biomineralization (within the malarial parasite digestive vacuole) as the most successful molecular target [20–26]. It has been observed that the free heme released from catabolized host red blood cell hemoglobin is highly toxic in nature [27, 28]. Malarial parasites has develop a novel alternative approach to crystallize this free heme to nontoxic hemozoin [20–26]. It has been well accepted that a number of effective anti-malarial drugs interact with heme and thereby preventing hemozoin formation. Literature studies suggested TRSMs as an active heme interacting scaffold [25], in this regards we screened our initial libraries based on their heme binding affinity and hemozoin inhibition potency. The iitial screening of trisubstituted methanes without sulfur spacer (**4-9**) showed poor heme binding affinity $K_d \geq 12\ \mu M$ to $20 \mu M$), andinhibition of hemozoin formation at very high concentration ($IC_{50} \geq 100\ \mu M$). Furthermore, these compounds

showed poor anti-malarial activity as observed from IC_{50} values of Hypoxanthine uptake, which is greater than 50 μM (**Table 1**).

The observed poor anti-malarial activity led to the synthesis of a new series of TRSMs with sulfur spacer (**Figure 2**). Our method for the synthesis of TRSMs with sulfur spacer involved *S*-alkylation of different aryl or heteroaryl thiols using carbinols **3a-d** as alkylating agents. Nucleophilic attack occurred through sulfur giving exclusively **10-16** (**Figure 2**). Depending upon carbinols, S-alkylation reaction was achieved with catalytic amount of conc. H_2SO_4 under reflux condition or with anhydrous $AlCl_3$ at room or reflux temperature. The resulting TRSMs with sulfur spacer showed a modest but improved heme binding affinity (**Table 2**).

Table 1. Synthesized Diarylmethylheteroarenes (**4-9**).

Compound No.	Heme binding K_d (μM)	IC_{50} (μM) Hemozoin formation		IC_{50} Hypoxanthine uptake (μM)
		P. yoelii N-67 MDR	*P. falciparum* NF-54	
4	$\geq$ 20	$\geq$ 100	$\geq$ 100	$\geq$ 80
5	$\geq$ 15	$\geq$ 100	$\geq$ 100	$\geq$ 80
6	$\geq$ 12	$\geq$ 100	$\geq$ 100	$\geq$ 100
7	$\geq$ 14	$\geq$ 100	$\geq$ 100	$\geq$ 90
8	$\geq$ 12	$\geq$ 100	$\geq$ 80	$\geq$ 60
9	$\geq$ 20	$\geq$ 100	$\geq$ 100	$\geq$ 50

However, when we compared potency of inhibition of hemozoin formation with TRSM without sulfur spacer, this new series showed more promising results (IC_{50}= 35-100 μM). The similar remark was observed in case of anti-malarial efficacy, which is in similar (IC_{50} between 15-20 μM) range for most of the compounds (**Table 2**).

Screening of this series of TRSMs (**10-16**) demonstrates that compounds containing thiophene ring **10** and **11** showed poor heme binding affinity ($K_d \geq$16 μM), and inhibition of hemozoin formation at very high concentration ($IC_{50} \geq 100$ μM) in comparison to compounds having furan (**12-14**) and pyridine ring (**15-16**). The comparison of biological activity of compounds having furan and pyridine ring reveals a clear comparable activity (**Table 2**). In the light of these results, we decided to move further with TRSMs having pyridine ring (as furan containing compounds were not very stable at room temperature) and synthesized a new series of TRSMs (**17-22**) (**Figure 2**). These compounds were synthesized in a similar manner as described for compounds of scheme 2. The resulting series of TRSMs containing pyridine rings with sulfur spacer (**17-22**) demonstrates a better biological activity in comparison to previous series (**Table 2**). However, compounds containing 2-pyridine ring (**17-18**) did not exhibit good activity in comparison to compounds having 3-pyridine ring (**20-22**) **Table 2**. In addition to this, quinoline containing TRSM (**19**) also showed better heme binding activity (K_d= 11.25 μM), inhibit hemozoin formation at low concentrations (30-35 μM) and potent anti-malarial activity (IC_{50}= 4.0 μM).

Structure activity relationship

Structure-activity relationship studies resulted in the identification of potent TRSMs, showing better heme affinity, hemozoin inhibitory and anti-malarial potency. Moreover, our study suggested that TRSMs (**4-9)** without sulfur spacer showed poor anti-malarial activity in comparison to TRSMs with sulfur spacer (**10-16**). Among TRSMs with sulfur spacer, compound having thiophene ring (**10-11**) showed poor antimalrial activity than compounds having furan (**12-14)** and pyridine rings **(15-16**).However, among TRSMs having pyridine ring, compound with thiomethoxy benzene ring **(20-22**) showed better antimalrial activity than those having methoxy benzene ring. In addition to this, compound with quinoline ring (**19**) also showed promising anti-malarial activity.

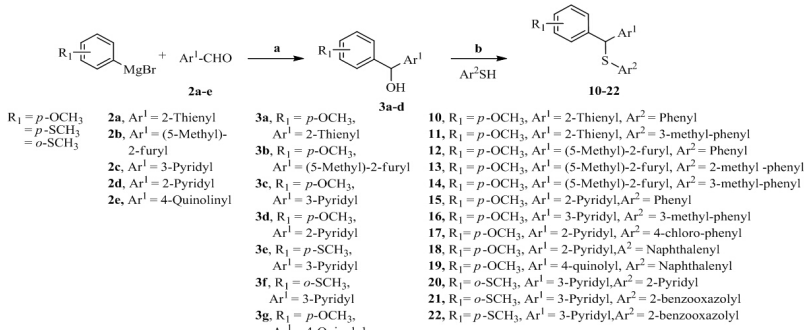

Figure 2. Reagents and conditions: (a) dry THF, rt, 1 h; (b) conc. H_2SO_4, dry benzene, reflux, 0.5 h or anhyd. $AlCl_3$, dry benzene, rt, 0.5 h.

Table 2. Synthesized TRSMs with sulfur spacer (**10-16**).

Compound No.	Heme binding K_d (μM)	IC_{50} ($.\mu$M) Hemozoin formation		IC_{50} Hypoxanthine uptake ($.\mu$M)
		P. yoelii N-67 MDR	*P. falciparum* NF-54	
10	$\geq$12	>100	$\geq$80	$\geq$80
11	$\geq$16	>100	$\geq$100	$\geq$15
12	$\geq$12	>100	$\geq$100	$\geq$14
13	$\geq$16	40±5	40±6	20± 5
14	$\geq$16	40±11	35±5	15±4
15	$\geq$35±8	$\geq$100	$\geq$100	$\geq$18
16	$\geq$16	$\geq$100	$\geq$100	$\geq$20
17	$\geq$35±8	$\geq$100	$\geq$100	$\geq$18
18	$\geq$16	$\geq$100	$\geq$100	$\geq$20
19	11.25±0.9	35±3.1	30±2.1	$\geq$4
20	$\geq$16	50±2.5	47±1.5	$\geq$20
21	$\geq$15	40±2.5	28±7.5	$\geq$18
22	$\geq$14	52±6.5	48±1.5	$\geq$16
Chloroquine [29]	5.1	—	24.4	0.014
Mefloquine [30]	—	—	46.9	0.023

Biology

Parasite culture

P. falciparum was cultured as per the method of Trager and Jensen [31–33]. In short parasite culture was continuously maintained at a level of 5% hematocrit in complete RPMI 1640 medium (supplemented with 25 mM Hepes, 50 μg ml^{-1} gentamycin, 370 μM hypoxanthine, and 0.5% (w/v) AlbuMaxII) in tissue culture flasks with loose screw caps. The medium was repeatedly changed with fresh medium once a day. The growth of *P. falciparum* was tested followed by Giemsa staining of thin blood smears. *In vivo* growth of *P. yoelii* was sustained in BALB/c mice. Male BALB/c mice (20-25 g) were inoculated intra-peritoneally with *P. yoelii* (MDR strain) as described [21, 22]. Parasitemia was monitored by preparing thin smears of blood and subsequent Giemsa staining. Experiments on animals were conducted after obtaining permission from the animal ethics committee and in accordance with the institutional guidelines for the care and the use of laboratory animal.

Preparation of parasite lysate

Parasites (*P. falciparum* and *P. yoelii*) were isolated as described [34]. In brief erythrocytes with either ∼10% parasitemia (*P. falciparum*) or 50% parasitemia (*P. yoelii,* from infected mice blood) were centrifuged at 800 *g* for 5 min, washed twice, and suspended in ice cold phosphate-buffered saline (PBS, 137 mM NaCl, 2.7 mM KCl, 5.3 mM Na_2HPO_4, and 1.8 mM KH_2PO_4). For erythrocytes lysis, an equal volume of 0.5% saponin in PBS (final concentration 0.25%) was added to the erythrocyte suspension and kept on ice for 15 min. It was further centrifuged at 1300 g for 5 min to obtain parasite pellet. The pellet was subsequently washed with PBS thrice and either used immediately or kept at -80 ˚C. The isolated parasite was lysed in PBS by mild sonication (30 s pulse, bath-type sonicator) at 4 ˚C and the lysate was then stored at -20 ˚C for further use. Protein content of the parasite lysate was estimated by the method of Lowry *et al.* [35].

Heme interaction studies

The interaction of the synthesized TRSMs with heme was studied by differential optical spectroscopy essentially as described earlier [21, 22]. K_d values of Interaction of TRSMs with heme was calculated by plot of $1/\delta$ 360 nm vs 1/[TRSMs].

Assay of hemozoin (β-hematin) formation

In vitro hemozoin (β-hematin) formation was assayed as described [21, 22]. In brief, the reaction of hemozoin formation assay was assembled in a final volume of 1 ml containing 100 mM sodium acetate buffer, pH 5.2, 100 μM hemin, 20 μg parasite lysate (from *P. yoelli*, N67(MDR) strain and *P. falciparum*, NF54 strain) along with or without different concentrations of TRSMs. The reaction without TRSMs was treated as control. The reaction was started by the addition of hemin and incubated for 12 h at 37 ˚C to allow the conversion of hemin in to hemozoin. The reaction was terminated by centrifugation at 15,000 g for 10 min at room temperature. The reaction pellet was washed thrice with 100 mM Tris buffer, pH 7.8, containing 2.5% SDS and finally with 100 mM bicarbonate buffer, pH 9.2. The resultant insoluble pellet (hemozoin) was then solubilized in 50 μL of 2N NaOH and diluted further to 1 mL with 2.5% SDS. The absorbance of the solution was recorded at 400 nm using a Perkin Elmer Lamda 15 UV/VIS spectrophotometer at 25$\pm$1 ˚C with quartz cells of 1 cm light path. Extinction coefficient of 91 $mM^{-1}cm^{-1}$ was used to quantitate the amount of free heme converted to hemozoin and expressed as nanomole of hemozoin formed per milligram of parasite lysate. Dose-response curves were constructed to obtain the IC_{50} values.

Assay of in vitro anti-malarial potency

The anti-malarial efficacy of synthesized TRSMs was measured using *P. falciparum* culture following TRSMs treatment by following [^{3}H] hypoxanthine uptake [36]. In short, ring synchronized *P. falciparum* (parasitemia 0.5–1%) was cultured in multiwell (200 μL/well) plates in the presence or absence of different concentrations of TRSMs. Parasite culture without any treatment was used as control, whereas DMSO and chloroquine (5 nM–1 μM) were used as negative and positive controls, respectively. After 48 h, [^{3}H] hypoxanthine (0.7μCi/well) was added in each well and further incubated for 48h to monitor parasite viability by measuring incorporation of free [^{3}H] hypoxanthine in parasite nucleic acids. After 48 h, culture was harvested and washed thrice in PBS. Packed RBCs were centrifuged and dissolved in 100 μL 3N NaOH, kept at 37 ˚C for 6 h, and then added in (10 mL/vial) scintillation fluid (PPO, 4 g; POPOP, 200 mg; naphthalene, 60 g; ethylene glycol, 20 ml; methanol 100 ml in 1 liter of 1,4-dioxane). After 12 h of addition, [^{3}H] hypoxanthine uptake was measured using a β-scintillation counter. Dose-response curves were constructed to obtain the IC_{50}values.

3. CONCLUSION

A set of TRSMs with and without sulfur spacer were synthesized and bioevaluated as anti-malarial agents. Furthermore, these compounds were also screened for their heme binding ability, inhibition of hemozoin formation and hypoxanthine uptake. The structure activity relationship study suggested that TRSMs with sulfur spacer showed better anti-malarial activity than TRSMs without sulfur spacer. Substituent on TRSMs with sulfur spacer like pyridyl (**15-16**) and furan ring (**12-14**) were found to be beneficial for potent anti-malarial activity, whereas substituent like thiophene (**10-11**) led to the loss of activity. In addition, TRSMs with sulfur spacer having substituted thiomethoxy benzene (**20-22**) showed better anti-malarial activity than those having methoxy substituent benzene The most active compound of the series having quinoline substitution (**19**) showed IC_{50} value 4.0 μM for hypoxanthine uptake. Series of TRSMs with sulphone derivative has also been synthesized; however it showed poor anti-malarial activity *in vitro* against malaria parasite. These results warrant further investigations of TRSMs as potent anti-malarial agents which are underway in our lab.

4. EXPERIMENTAL SECTION

Chemistry

All reagents and solvents were purchased from commercial sources and used without further purification. Organic solvents were dried by standard methods. Analytical TLC was performed using 2.5x5 cm aluminum plates coated with a 0.25 mm thickness of silica gel (60F-254), visualization was accomplished with iodine and under UV lamp. The spots on TLC were also visualized by warming ceric sulphate (2% $CeSO_4$ in 2N H_2SO_4) sprayed plates in hot plate or in oven at about 100 ^oC. Column chromatography was performed using silica gel (60-120 and 100-200 mesh). ^1H NMR spectra were recorded on 200 and 300 MHz spectrometer in $CDCl_3$(all signals are reported in ppm with the internal chloroform signal at 7.26 ppm as standard) at 25 $^\circ$ C. ^{13}C NMR spectra were recorded on 50 and 75 MHz spectrometer in $CDCl_3$ (all signals are reported in ppm with the internal chloroform signal at 77.00 ppm as standard) at 25 ^oC. In a few cases tetramethylsilane (TMS) at 0.00 ppm was used as the reference standard. Coupling constants (*J* values) are given in hertz (Hz). 1H NMR splitting patterns are designated as singlet (s), doublet (d), double dublet (dd), triplet (t), quartet (q) or multiplet (m). FAB-MS were recorded on a JEOL/SX-102 spectrometer and ES-MS were recorded using a Micromass LC-MS system. IR spectra were recorded using a FTIR spectrophotometer in cm^{-1}. Melting points were determined in capillary tubes on an electrically heated apparatus and were uncorrected.

The spectral data of few compounds were already reported in our previous papers *i.e.* (**3e**, **3g**) [21].

General procedure for the preparation of carbinols (3a-g):

To a suspension of Mg (1.50 g, 61.7 mmol) in dry THF (40 mL) was added drop wise a solution of 4-bromoanisole (6.52 mL, 52.1 mmol) in dry THF (40 mL). After stirring the mixture for 30 min a solution of heteroarylcarbaldehyde (4.21 mL, 45 mmol) in dry THF (30 mL) was added drop wise and the resulting solution was allowed to stir for an additional 30 min. After quenching by adding a saturated solution of NH_4Cl (20 mL), the reaction mixture was extracted with ethyl acetate (100 mL), washed with water (100 mL), brine (2 $\times$ 50 mL) and then dried over Na_2SO_4. The organic layer was removed under reduced pressure. The crude product was purified by column chromatography.

(4-Methoxy-phenyl)-thiophen-2-yl-methanol (3a):

R_f: 0.29 (15% ethyl acetate in hexane). Isolated as yellow oil (yield 68%) by elution with 6% ethyl acetate in hexane on silica gel. IR (Neat): 3416, 3062, 1638, 1611, 1427, 1248, 1175, 1032, 812, 712, 573 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.17-7.05 (m, 3H), 6.78-6.64 (m, 4H), 5.74 (s, 1H), 3.60 (s, 3H), 3.59 (s, 1H). MS (FAB): m/z 220 $[M]^+$, 203 $[M\text{-}OH]^+$. Anal. Cacld. for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49. Found: C, 65.49; H, 5.64.

(4-Methoxy-phenyl)-(5-methyl-furan-2-yl)-methanol (3b):

R_f: 0.32 (15% ethyl acetate in hexane). Isolated as yellow oil (yield 68%) by elution with 10% ethyl acetate in hexane from silica gel. However, due to its high instability alcohol **3b** was stored at 0 ^{o}C and used for the next steps without recording any spectral data.

(4-Methoxy-phenyl)-pyridin-3-yl-methanol (3c):

R_f: 0.28 (ethyl acetate in hexane). Isolated as pale yellow solid (yield 68%, mp 105-106 $^\circ$C) by elution with 45% ethyl acetate in hexane on silica gel. IR (KBr): 3216, 2362, 1608, 1511, 1427, 1248, 1175, 1030, 812, 712, 573 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.42 (d, 1H, *J*= 1.68), 8.29 (dd, 1H, J_1= 1.32, J_2= 4.76), 7.67 (d, 1H, *J*= 7.86), 7.26-7.16 (m, 3H), 6.84 (d, 2H, *J*= 8.62), 5.74 (s, 1H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$+CCl_4, 50 MHz): δ 159.50, 148.22, 148.18, 140.74, 136.18, 134.84, 128.73, 128.30, 123.82, 114.37, 73.60, 55.65. MS (FAB): m/z 216 $[M+H]^+$, 198 $[M\text{-}OH]^+$. Anal. Calcd.for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.59; H, 6.22; N, 6.47.

(4-Methoxy-phenyl)-pyridin-2-yl-methanol (3d):

R_f: 0.43 (ethylacetate in hexane). Isolated as pale yellow solid (yield 80%, mp 126-127 $^\circ$C) by elution with 35% ethylacetate in hexane on silica gel. IR (KBr): 3359, 3270, 2360, 1598, 1510, 1248, 1036, 759, 572 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.56 (d, 1H, *J*= 4.72), 7.59 (dd, 1H, J_1= 1.60, J_2= 7.68), 7.28 (d, 2H, *J*= 8.46), 7.22-7.11 (m, 2H), 6.86 (d, 2H, *J*= 8.4), 5.71 (d, 1H, *J*= 3.6), 5.22 (d, 1H, *J*= 4.10), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 161.70, 159.65, 148.20, 137.21, 135.91, 128.76, 122.73, 121.69, 114.37, 75.00, 55.66. MS (FAB): m/z 216 $[M+H]^+$, 198 $[M\text{-}OH]^+$. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.46; H, 6.14; N, 6.67.

(3-(methylthio)phenyl)(pyridin-3-yl)methanol (3f):

R_f: 0.42 (15 % ethyl acetate in hexane). Isolated as colourless oil (yield 71%) by elution with 5% ethyl acetate in hexane from silica gel. IR (Neat): 3019, 2364, 1584, 1432, 1217, 1028, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, 1H, *J*= 1.58), 8.37 (d, 1H, J_1 = 4.66, J_2 = 1.26), 6.68 (d, 1H, *J*= 7.83), 7.52 (d, 1H, *J*= 7.29), 7.20-7.18 (m, 4H), 6.22 (s, 1H), 4.14 (bs, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.71, 148.31, 141.23, 138.58, 136.00, 134.75, 128.42, 126.93, 126.81, 125.71, 123.28, 70.63, 16.52. MS (FAB): m/z 232 $[M+H]^+$. Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.55; H, 5.70; N, 6.16.

Ethyl-{4-[(4-methoxy-phenyl)-thiophen-2-yl-methyl]-phenyl}-amine (4):

R_f: 0.24 (20% ethyl acetate in hexane). Isolated as black semi-solid (yield 76%) by elution with 4% ethyl acetate in hexane from silica gel. IR (Neat): 3022, 2304, 1552, 1432, 1234, 1028, 771 cm.$^{-1}$ ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.08- 7.01 (m, 3H), 6.90 (d, 2H, *J*= 8.47), 6.81-6.79 (m, 1H), 6.72 (d, 2H, *J*= 8.61), 6.57 (dd, 1H, J_1= 0.88, J_2= 3.43), 6.43 (d, 2H, *J*= 8.47), 5.42 (s, 1H), 3.67 (s, 3H), 3.02 (q, 2H, *J*= 7.12), 1.13 (t, 3H, *J*= 7.11). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.61, 150.04, 147.54, 137.31, 133.37, 130.16, 129.96, 126.87, 126.28, 124.55, 114.08, 113.02, 55.65, 51.02, 38.98, 15.36. MS (FAB): m/z 324 $[M+H]^+$, 323 $[M]^+$. Anal. Calcd for $C_{20}H_{21}NOS$: C, 74.27; H, 6.54; N, 4.33. Found: C, 74.46; H, 6.63; N, 4.24.

Ethyl-{4-[(4-methoxy-phenyl)-(5-methyl-furan-2-yl)-methyl]-phenyl}-amine (5):

R_f: 0.22 (20% ethyl acetate in hexane). Isolated as pale yellow oil (yield 63%) by elution with 4% ethyl acetate in hexane from silica gel. IR (Neat): 3021, 2274, 1584, 1401, 1217, 1058, 760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) : δ 7.09-7.03 (m, 2H), 6.94 (d, 2H, *J*= 8.49), 6.83-6.78 (m, 2H), 6.51 (dd, 2H, J_1= 1.83, J_2= 6.70), 5.84-5.83 (m, 1H), 5.70 (d, 1H, *J*= 2.91), 5.22 (s, 1H), 3.75 (s, 3H), 3.10 (q, 2H, *J*= 7.12), 2.22 (s, 3H), 1.21 (t, 3H, *J*= 7.10). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.56, 156.49, 151.55, 147.49, 135.52, 131.55, 130.07, 129.88, 114.09, 113.10, 108.95, 106.25, 55.64, 49.75, 39.01, 15.36, 14.07. MS (FAB): m/z 321 $[M]^+$. Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.33; H, 7.38; N, 4.45.

Ethyl-{4-[(4-methoxy-phenyl)-pyridin-3-yl-methyl]-phenyl}-amine (6):

R_f: 0.41 (80% ethyl acetate in hexane). Isolated as light yellow semi-solid (yield 65%) by elution with 4% ethyl acetate in hexane from silica gel. IR (Neat): 3066, 2334, 1588, 1432, 1207, 1028, 765, 665 cm.$^{-1}$ ^1H NMR (200 MHz, $CDCl_3$): δ 8.43-8.41 (m, 2H), 7.34-7.36 (m, 1H), 7.18-7.14 (m, 1H), 7.02-6.98 (m, 2H), 6.89-6.78 (m, 4H), 6.51 (dd, 2H, J_1= 1.89, J_2= 6.68), 5.37 (s, 1H), 3.74 (s, 3H), 3.10 (q, 2H, *J*= 7.13), 1.24 (t, 3H, *J*= 3.77). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.58, 151.17, 147.75, 147.52, 140.93, 137.03, 136.10, 131.97, 130.59, 130.38, 123.55, 114.24, 113.12, 55.64, 53.21, 38.92, 15.30. MS (FAB): m/z 319 $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.34; H, 7.08; N, 8.73.

{4-[(4-Methoxy-phenyl)-pyridin-3-yl-methyl]-phenyl}-dimethyl-amine (7):

R_f: 0.45 (80% ethyl acetate in hexane). Isolated as light yellow semi-solid (yield 70%) by elution with 4% ethyl acetate in hexane from silica gel. IR (Neat): 1612, 1515, 1249, 757 cm.$^{-1}$ ^1H NMR (200 MHz, $CDCl_3$): δ 8.32-8.34 (m, 2H), 7.26-7.27 (m, 1H), 6.93-6.89 (m, 1H), 6.86-6.82 (m, 4H), 6.71 (d, 2H, *J*= 8.70), 6.55 (d, 2H, *J*= 8.71), 5.30 (s, 1H), 3.64 (s, 3H), 2.79 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.58, 151.20, 149.70, 147.80, 140.90, 137.02, 136.10, 131.36, 130.59, 130.23, 123.55, 114.24, 113.01, 55.65, 53.11, 41.01. MS (FAB): m/z 319 $[M+H]^+$, 318 $[M]^+$. Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.42; H, 7.03; N, 8.91.

4-[(4-Methoxy-phenyl)-pyridin-3-yl-methyl]-phenylamine (8):

R_f: 0.3 (ethyl acetate in hexane). Isolated as brown semi-solid (yield 50%) by elution with 4% ethyl acetate in hexane from silica gel. IR (KBr): 3022, 2304, 1552, 1432, 1234, 1028, 771 cm.$^{-1}$ ^1H NMR (200 MHz, $CDCl_3$): δ 8.41 (d, 2H, *J*= 4.21), 7.38 (d, 1H, *J*= 7.87), 7.19-7.13 (m, 1H), 7.04-6.97 (m, 2H), 6.86-6.79 (m, 4H), 6.58 (d, 2H, *J*= 8.36), 5.37 (s, 1H), 3.73 (s, 3H), 3.45 (s, br, 2H). MS (FAB): m/z 291 $[M]^+$. Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.71; H, 6.17; N, 9.79.

4-[(4-Methoxyphenyl)pyridin-3-ylmethyl]phenol (9):

R_f: 0.29 (80% ethyl acetate in hexane). Isolated as colourless semi-solid (yield 55%) by elution with 4% ethyl acetate in hexane from silica gel. IR (KBr): 3428, 1611, 1510, 1458, 1249, 1176, 1033, 823, 768 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.42 (dd, 1H, J_1= 1.49, J_2= 4.82), 8.37 (d, 1H, *J*= 2.03), 7.46-7.42 (m, 1H), 7.27-7.24 (m, 1H), 7.00-6.96 (m, 2H), 6.89-6.73 (m, 6H), 5.41 (s, 1H), 3.76 (s, 3H). MS (FAB): m/z 292 $[M+H]^+$. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.47; H, 6.02; N, 4.98.

General procedure for the preparation of diarylmethylheteroarenes (4-9), TRSMs with sulfur spacer (10-22).

Method a: To a solution of carbinol **3a-g** (2.50 mmol) and electron-rich arene or arylthiol (3.75 mmol) in dry benzene (25 mL), a catalytic amount of conc. H_2SO_4 was added and the mixture was refluxed for half an hour. After adding water, the reaction mixture was extracted with ethyl acetate (25 mL), washed by

brine (25 mL), and dried over Na_2SO_4. The combined organic layer was removed under reduced pressure. The crude product was purified by silica gel column chromatography to furnish diarylmethylheteroarenes **4-9** and TRSMs **10-22.**

Method b: To a solution of carbinol **3a-g** (2.50 mmol) and electron-rich arene or arylthiol (3.75 mmol) in dry benzene, anhydrous $AlCl_3$ (2.52 mmol) was added and the mixture was stirred at room temperature for half an hour. After adding ice-cooled water, the reaction mixture was extracted with ethyl acetate (25 mL), washed by brine (25 mL), and dried over Na_2SO_4. The combined organic layer was removed under reduced pressure. The crude product was purified by silica gel column chromatography to furnish diarylmethylheteroarenes **4-9** and TRSMs **10-22**.

2-[(4-Methoxy-phenyl)-phenylsulfanyl-methyl]-thiophene (10):

R_f: 0.24 (20% ethyl acetate in hexane). Isolated as colourless solid (yield 80%, mp 76-77 °C) by elution with 5% ethyl acetate in hexane from silica gel. IR (KBr): 1603, 1511, 1352, 1251, 1177, 695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.35-7.24 (m, 4H), 7.18-7.14 (m, 4H), 6.88-6.79 (m, 4H), 5.64 (s, 1H), 3.75 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.45, 146.35, 135.95, 133.64, 131.96, 129.76, 129.20, 127.57, 127.07, 126.45, 125.63, 114.36, 55.68, 53.09. MS (FAB): m/z 204 $[M\text{-}C_6H_5S]^+$. Anal. Calcd for $C_{18}H_{16}OS_2$: C, 69.19; H, 5.16. Found: C, 69.45; H, 5.37.

2-[(4-Methoxy-phenyl)-m-tolylsulfanyl-methyl]-thiophene (11):

R_f: 0.24 (20% ethyl acetate in hexane). Isolated as yellow oil (yield 70%) by elution with 4% ethyl acetate in hexane from silica gel. IR (Neat): 2234, 1634, 1519, 1352, 1245, 765 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.33 (dd, 2H, J_1= 2.05, J_2= 6.65), 7.24-7.17 (m, 1H), 7.09-7.06 (m, 3H), 6.89-6.87 (m, 1H), 6.85-6.80 (m, 4H), 5.62 (s, 1H), 3.77 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.43, 146.49, 138.87, 135.68, 133.77, 132.58, 129.76, 128.99, 128.38, 127.02, 126.40, 125.53, 114.31, 55.68, 53.01, 21.66. MS (FAB): m/z 204 $[M\text{-}C_7H_7S]^+$. Anal. Calcd for $C_{19}H_{18}OS_2$: C, 69.90; H, 5.56. Found: C, 70.02; H, 5.42.

2-[(4-Methoxy-phenyl)-phenylsulfanyl-methyl]-5-methyl-furan (12):

R_f: 0.22 (20% ethyl acetate in hexane). Isolated as light yellow semi-solid (yield 60%) by elution with 5% ethyl acetate in hexane from silica gel. IR (KBr): 1602, 1510, 1352, 1250, 760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) : δ 7.32 (d, 2H, J= 6.80), 7.32-7.16 (m, 5H), 6.82 (d, 2H, J= 8.80), 6.01 (d, 1H, J= 3.03), 5.84 (d, 1H, J= 3.02), 5.35 (s, 1H), 3.77 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.42, 152.42, 152.18, 135.71, 132.52, 131.78, 129.91, 129.09, 127.61, 114.30, 109.57, 106.71, 55.67, 51.36, 14.09. MS (FAB): 201 $[M\text{-}SC_6H_5]^+$. Anal. Calcd for $C_{19}H_{18}O_2S$: C, 73.52; H, 5.84. Found: C, 73.71; H, 5.67.

2-[(4-Methoxy-phenyl)-*o*-tolylsulfanyl-methyl]-5-methyl-furan (13):

R_f: 0.22 (22% ethyl acetate in hexane). Isolated as yellow oil (yield 75%) by elution with 5% ethyl acetate in hexane from silica gel. IR (Neat): 2303, 1637, 1515, 1348, 1250, 776, 665 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.31 (d, 2H, J= 8.62), 7.21 (d, 1H, J= 8.02), 7.13-7.02 (m, 3H), 6.81 (d, 2H, J= 8.60), 6.00 (d, 1H, J= 2.82), 5.83 (d, 1H, J= 2.82), 5.30 (s, 1H), 3.76 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.39, 152.38, 152.15, 140.06, 135.00, 133.24, 132.61, 131.76, 130.47, 129.85, 129.44, 128.13, 127.56, 126.67, 114.26, 109.40, 106.71, 55.67, 50.54, 20.94, 14.10. MS (FAB): m/z 324 $[M]^+$, 201 $[M\text{-}C_7H_7S]^+$. Anal. Calcd for $C_{20}H_{20}O_2S$: C, 74.04; H, 6.21. Found: C, 74.21; H, 6.03.

2-[(4-Methoxy-phenyl)-*m*-tolylsulfanyl-methyl]-5-methyl-furan (14):

R_f: 0.23 (20% ethyl acetate in hexane).Isolated as yellow oil (yield 78%) by elution with 5% ethyl

acetate in hexane from silica gel. IR (Neat): 2243, 1593, 1515, 1308, 1226, 776, 664 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.31 (dd, 2H, J_1= 2.03, J_2= 6.69), 7.08-6.97 (m, 4H), 6.81 (dd, 2H, J_1= 1.89, J_2= 6.74), 6.02 (d, 1H, J= 3.06), 5.83-5.82 (m, 1H), 5.33 (s, 1H), 3.75 (s, 3H), 2.24 (s, 3H). MS (FAB): m/z 201 $[M\text{-}C_7H_7S]^+$. Anal. Calcd for $C_{20}H_{20}O_2S$: C, 74.04; H, 6.21. Found: C, 74.15; H, 6.43.

2-((4-methoxyphenyl)(phenylthio)methyl)pyridine (15):

R_f: 0.28 (34% ethyl acetate in hexane). Isolated as colourless oil (yield 75%) by elution with 23% ethyl acetate in hexane from silica gel. IR (Neat): 22673, 1617, 1348, 1278, 765, 660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.53-8.50 (m, 1H), 7.52-6.76 (m, 12H), 5.62 (s, 1H), 3.67 (s, 3H). MS (FAB): m/z 308 $[M+H]^+$. Anal. Calcd for $C_{19}H_{17}NOS$: C, 74.23; H, 5.57; N, 4.56. Found: C, 74.21; H, 5.61; N, 4.48.

3-((4-methoxyphenyl)(*m*-tolylthio)methyl)pyridine (16):

R_f: 0.30 (40% ethyl acetate in hexane).Isolated as brownish oil (yield 68%) by elution with 15% ethyl acetate in hexane from silica gel. IR (Neat): 2263, 1633, 1500, 1353, 1225, 770, 665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.57-8.42 (m, 1H), 7.76-7.72 (m, 1H), 7.32-6.81 (m, 10H), 5.48 (s, 1H), 3.76 (s, 3H), 2.24 (d, J = 5.02, 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ 159.39, 150.09, 148.68, 139.07, 137.72, 136.30, 135.20, 132.33, 129.83, 129.15, 128.61, 128.45, 123.79, 114.53, 55.68, 54.84, 21.65. MS (FAB): m/z 322 $[M+H]^+$. Anal. Calcd for $C_{20}H_{19}NOS$: C, 74.73; H, 5.96; N, 4.36. Found: C, 74.65; H, 5.99; N, 4.42.

2-[(4-Chloro-phenylsulfanyl)-(4-methoxy-phenyl)-methyl]-pyridine (17):

R_f: 0.45 (50% ethyl acetate in hexane). Isolated as colourless semi-solid (yield 78%) by elution with 12% ethyl acetate in hexane from silica gel. IR (KBr): 3034, 2321, 1634, 1348, 1257, 776, 660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.57-8.55 (m, 1H), 7.62-7.57 (m, 1H), 7.41(d, 1H, J= 8), 7.34 (d, 2H, J= 8.6), 7.20-7.10 (m, 5H), 6.82 (d, 2H, J= 8.6), 5.56 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.60, 159.42, 159.82, 137.20, 136.80, 134.45, 133.32, 132.94, 132.12, 130.73, 129.96, 129.27, 122.95, 114.44, 59.19, 55.64. MS (ESI): m/z 342 $[M+H]^+$, 198 $[M\text{-}C_6H_4ClS]^+$. Anal. Calcd for $C_{19}H_{16}ClNOS$: C, 66.75; H, 4.72; N, 4.10. Found: C, 66.64; H, 4.58; N, 4.19.

2-[(4-Methoxy-phenyl)-(naphthalen-2-ylsulfanyl)-methyl]-pyridine (18):

R_f: 0.48 (50% ethyl acetate in hexane). Isolated as pale yellow solid (yield 80%, mp 126-127 ° C) by elution with 12% ethyl acetate in hexane from silica gel. IR (KBr): 2313, 1642, 1556, 1338, 1257, 776, 660 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.55-8.52 (m, 1H), 7.69-7.59 (m, 4H), 7.49-7.47 (m, 2H), 7.42-7.33 (m, 5H), 7.02-7.04 (m, 1H), 6.81-6.77 (m, 2H), 5.75 (s, 1H), 3.68 (s, 3H). MS (ESI): m/z 357 $[M]^+$, 198 $[M\text{-}C_{10}H_7S]^+$. Anal. Calcd for $C_{23}H_{19}NOS$: C, 77.28; H, 5.36; N, 3.92. Found: C, 77.44; H, 5.53; N, 3.98.

4-((4-methoxyphenyl)(phenylthio)methyl)quinoline (19):

R_f: 0.32 (28% ethyl acetate in hexane). Isolated as light brownish oil (yield 67%) by elution with 18% ethyl acetate in hexane from silica gel. IR (Neat): 2259, 1602, 1510, 1352, 1223, 775, 660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) : δ 8.90 (d, 1H, J= 4.58), 8.16-6.79 (m, 16H), 6.24 (s, 1H), 3.74 (s, 3H). MS (FAB): 408 $[M+H]^+$. Anal. Calcd for $C_{27}H_{21}NOS$: C, 79.57; H, 5.19; N, 3.44. Found: C, 79.57; H, 5.25; N, 3.41.

3-((2-(methylthio)phenyl)(phenylthio)methyl)pyridine (20):

R_f: 0.19 (20% ethyl acetate in hexane). Isolated as colourless oil (yield 71%) by elution with 13% ethyl acetate in hexane from silica gel. ^1H NMR (300 MHz, $CDCl_3$): δ 8.70 (d, 1H, J= 2.03), 8.52-8.34

(m, 2H), 7.78-7.75 (m, 1H), 7.62-7.56 (m, 1H), 7.45-7.39 (m, 1H), 7.34-7.32 (m, 2H), 7.22-7.10 (m, 4H), 6.96-6.92 (m, 1H), 6.34 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.09, 149.75, 149.46, 148.07, 138.01, 137.52, 137.00, 136.82, 136.14, 135.95, 128.85, 126.57, 125.37, 123.25, 122.36, 121.70, 120.78, 49.44, 15.58. MS (FAB): m/z 324 $[M+H]^+$, 214 $[M-C_7H_7S]^+$. Anal. Calcd for $C_{19}H_{17}NS_2$: C, 70.55; H, 5.30; N, 4.33. Found: C, 70.59; H, 5.39; N, 4.37.

2-((2-(methylthio)phenyl)(pyridin-3-yl)methylthio)benzo[*d*]oxazole (21):

R_f: 0.32 (37% ethyl acetate in hexane). Isolated as colourless oil (yield 79%) by elution with 25% ethyl acetate in hexane from silica gel. IR (Neat): 3414, 3023, 2363, 1638, 1217, 768, 672 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (bs, 1H), 8.52 (s, 1H), 7.87 (d, 1H, *J*= 7.98), 7.58-7.17 (m, 9H), 6.87 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.70, 151.82, 148.68, 141.78, 137.74, 137.37, 135.93, 128.83, 128.64, 128.42, 126.10, 124.29, 124.12, 118.89, 109.94, 49.76, 17.23. MS (FAB): m/z 365 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}N_2OS_2$: C, 65.91; H, 4.42; N, 7.69. Found: C, 65.91; H, 4.47; N, 7.65.

2-((4-(methylthio)phenyl)(pyridin-3-yl)methylthio)benzo[d] oxazole (22):

R_f: 0.29 (37% ethyl acetate in hexane). Isolated as light brown oil (yield 64%) by elution with 22% ethyl acetate in hexane from silica gel. IR (Neat): 3419, 3043, 2322, 1638, 1211, 768, 675 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (bs, 1H), 8.49 (bs, 1H), 7.82 (d, 1H, *J*= 7.96), 7.55-7.53 (m, 1H), 7.38-7.35 (m, 3H), 7.25-7.18 (m, 5H), 6.32 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.35, 151.55, 149.56, 148.84, 141.47, 138.83, 135.65, 135.48, 135.00, 128.52, 126.44, 124.22, 124.08, 123.28, 118.60, 109.80, 52.15, 15.29. MS (FAB): m/z 365 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}N_2OS_2$: C, 65.91; H, 4.42; N, 7.69. Found: C, 65.90; H, 4.45; N, 7.68.

ACKNOWLEDGMENTS

This research project was partly supported by CSIR networking project (BSC 0104). S.K.M., P.S. and S.M. thank the Council of Scientific and Industrial Research (CSIR), India for research fellowships. Instrumental facilities from SAIF, CDRI is acknowledged. This is CDRI communication no. 8775.

References

[1] J. Sachs and P. Malaney, "The economic and social burden of malaria," *Nature*, vol. 415, no. 6872, pp. 680–685, 2002.

[2] N. White, "Why is it that antimalarial drug treatments do not always work," *Annals of Tropical Medicine and Parasitology*, vol. 92, no. 4, pp. 449–458, 1998.

[3] M. J. Gardner, N. Hall, E. Fung, O. White, M. Berriman, R. W. Hyman, J. M. Carlton, A. Pain, K. E. Nelson, S. Bowman, *et al.*, "Genome sequence of the human malaria parasite Plasmodium falciparum," *Nature*, vol. 419, no. 6906, pp. 498–511, 2002.

[4] T. J. Egan, "Structure-function relationships in chloroquine and related 4-aminoquinoline antimalarials," *Mini Reviews in Medicinal Chemistry*, vol. 1, no. 1, pp. 113–123, 2001.

[5] T. J. Egan, "Physico-chemical aspects of hemozoin (malaria pigment) structure and formation," *Journal of Inorganic Biochemistry*, vol. 91, no. 1, pp. 19–26, 2002.

[6] L. Musset, O. Bouchaud, S. Matheron, L. Massias, and J. Le Bras, "Clinical atovaquone-proguanil

resistance of Plasmodium falciparum associated with cytochrome b codon 268 mutations," *Microbes and Infection*, vol. 8, no. 11, pp. 2599–2604, 2006.

[7] C. V. Plowe, J. F. Cortese, A. Djimde, O. C. Nwanyanwu, W. M. Watkins, P. A. Winstanley, J. G. E. Franco, R. E. Mollinedo, J. C. Avila, J. L. Cespedes, *et al.*, "Mutations in Plasmodium falciparum dihydrofolate reductase and dihydropteroate synthase and epidemiologic patterns of pyrimethamine-sulfadoxine use and resistance," *Journal of Infectious Diseases*, vol. 176, no. 6, pp. 1590–1596, 1997.

[8] S. Kumar and U. Bandyopadhyay, "Free heme toxicity and its detoxification systems in human," *Toxicology Letters*, vol. 157, no. 3, pp. 175–188, 2005.

[9] V. Nair, S. Thomas, S. C. Mathew, and K. Abhilash, "Recent advances in the chemistry of triaryl-and triheteroarylmethanes," *Tetrahedron*, vol. 62, no. 29, pp. 6731–6747, 2006.

[10] M. Shchepinov and V. Korshun, "Recent applications of bifunctional trityl groups," *Chemical Society Reviews*, vol. 32, no. 3, pp. 170–180, 2003.

[11] D. F. Duxbury, "The photochemistry and photophysics of triphenylmethane dyes in solid and liquid media," *Chemical Reviews*, vol. 93, no. 1, pp. 381–433, 1993.

[12] M. K. Parai, G. Panda, V. Chaturvedi, Y. Manju, and S. Sinha, "Thiophene containing triarylmethanes as antitubercular agents," *Bioorganic & Medicinal Chemistry Letters*, vol. 18, no. 1, pp. 289–292, 2008.

[13] A. Kumar, G. Panda, M. I. Siddiqi, *et al.*, "CoMFA and CoMSIA 3D-QSAR analysis of diaryloxy-methano-phenanthrene derivatives as anti-tubercular agents," *Journal of Molecular Modeling*, vol. 13, no. 1, pp. 99–109, 2007.

[14] G. Panda, M. K. Parai, S. K. Das, M. Sinha, V. Chaturvedi, A. K. Srivastava, Y. Manju, A. N. Gaikwad, S. Sinha, *et al.*, "Effect of substituents on diarylmethanes for antitubercular activity," *European Journal of Medicinal Chemistry*, vol. 42, no. 3, pp. 410–419, 2007.

[15] P. Singh, S. K. Dinda, Shagufta, G. Panda, *et al.*, "Synthetic approach towards trisubstituted methanes and a chiral tertiary-hydroxyaldehyde, a possible intermediate for tetrasubstituted methanes," *RSC Advances*, vol. 3, no. 30, pp. 12100–12103, 2013.

[16] F. Novelli, B. Tasso, and F. Sparatore, "Synthesis and pharmacological evaluation of some thiolupinine derivatives," *Il Farmaco*, vol. 54, no. 6, pp. 354–358, 1999.

[17] C. Santelli-Rouvier, B. Pradines, M. Berthelot, D. Parzy, and J. Barbe, "Arylsulfonyl acridinyl derivatives acting on Plasmodium falciparum," *European Journal of Medicinal Chemistry*, vol. 39, no. 9, pp. 735–744, 2004.

[18] U. Galli, L. Lazzarato, M. Bertinaria, G. Sorba, A. Gasco, S. Parapini, and D. Taramelli, "Synthesis and antimalarial activities of some furoxan sulfones and related furazans," *European Journal of Medicinal Chemistry*, vol. 40, no. 12, pp. 1335–1340, 2005.

[19] J. Z. Vlahakis, R. T. Kinobe, K. Nakatsu, W. A. Szarek, and I. E. Crandall, "Anti- Plasmodium activity of imidazole–dioxolane compounds," *Bioorganic & Medicinal Chemistry Letters*, vol. 16, no. 9, pp. 2396–2406, 2006.

[20] M. Goyal, A. Alam, and U. Bandyopadhyay, "Redox regulation in malaria: current concepts and pharmacotherapeutic implications," *Current Medicinal hemistry*, vol. 19, no. 10, pp. 1475–1503, 2012.

[21] M. Goyal, P. Singh, A. Alam, S. Kumar Das, M. Shameel Iqbal, S. Dey, S. Bindu, C. Pal, S. Kumar Das, G. Panda, *et al.*, "Aryl aryl methyl thio arenes prevent multidrug-resistant malaria in mouse by promoting oxidative stress in parasites," *Free Radical Biology and Medicine*, vol. 53, no. 1, pp. 129–142, 2012.

[22] S. Kumar, S. K. Das, S. Dey, P. Maity, M. Guha, V. Choubey, G. Panda, and U. Bandyopadhyay, "Antiplasmodial activity of [(aryl) arylsulfanylmethyl] pyridine," *Antimicrobial Agents and*

Chemotherapy, vol. 52, no. 2, pp. 705–715, 2008.

[23] T. Akompong, N. Ghori, and K. Haldar, "In vitro activity of riboflavin against the human malaria parasite Plasmodium falciparum," *Antimicrobial Agents and Chemotherapy*, vol. 44, no. 1, pp. 88–96, 2000.

[24] D. E. Goldberg, "Hemoglobin degradation in Plasmodium-infected red blood cells," in *Seminars in Cell Biology*, vol. 4, pp. 355–361, Elsevier, 1993.

[25] A. D. Wright, H. Wang, M. Gurrath, G. M. König, G. Kocak, G. Neumann, P. Loria, M. Foley, and L. Tilley, "Inhibition of heme detoxification processes underlies the antimalarial activity of terpene isonitrile compounds from marine sponges," *Journal of Medicinal Chemistry*, vol. 44, no. 6, pp. 873–885, 2001.

[26] R. Kannan, K. Kumar, D. Sahal, S. Kukreti, and V. Chauhan, "Reaction of artemisinin with haemoglobin: implications for antimalarial activity," *Biochem. J*, vol. 385, pp. 409–418, 2005.

[27] T. H. Schmitt, W. Frezzatti, and S. Schreier, "Hemin-induced lipid membrane disorder and increased permeability: a molecular model for the mechanism of cell lysis," *Archives of Biochemistry and Biophysics*, vol. 307, no. 1, pp. 96–103, 1993.

[28] S. Vincent, "Oxidative effects of heme and porphyrins on proteins and lipids," in *Seminars in Hematology*, vol. 26, pp. 105–113, 1989.

[29] J. Xu Kelly, R. Winter, M. Riscoe, and D. H. Peyton, "A spectroscopic investigation of the binding interactions between 4, 5-dihydroxyxanthone and heme," *Journal of Inorganic Biochemistry*, vol. 86, no. 2, pp. 617–625, 2001.

[30] C. Pal and U. Bandyopadhyay, "Redox-active antiparasitic drugs," *Antioxidants & Redox Signaling*, vol. 17, no. 4, pp. 555–582, 2012.

[31] W. Trager and J. B. Jensen, "Human malaria parasites in continuous culture," *Science*, vol. 193, no. 4254, pp. 673–675, 1976.

[32] V. Choubey, M. Guha, P. Maity, S. Kumar, R. Raghunandan, P. R. Maulik, K. Mitra, U. C. Halder, and U. Bandyopadhyay, "Molecular characterization and localization of Plasmodium falciparum choline kinase," *Biochimica et Biophysica Acta (BBA)-General Subjects*, vol. 1760, no. 7, pp. 1027–1038, 2006.

[33] W. Trager and J. B. Jensen, "Human malaria parasites in continuous culture," *Journal of Parasitology*, vol. 91, no. 3, pp. 484–486, 2005.

[34] V. Choubey, P. Maity, M. Guha, S. Kumar, K. Srivastava, S. K. Puri, and U. Bandyopadhyay, "Inhibition of Plasmodium falciparum choline kinase by hexadecyltrimethylammonium bromide: a possible antimalarial mechanism," *Antimicrobial Agents and Chemotherapy*, vol. 51, no. 2, pp. 696–706, 2007.

[35] O. H. Lowry, N. J. Rosebrough, A. L. Farr, R. J. Randall, *et al.*, "Protein measurement with the Folin phenol reagent," *J Biol Chem*, vol. 193, no. 1, pp. 265–275, 1951.

[36] R. E. Desjardins, C. Canfield, J. Haynes, and J. Chulay, "Quantitative assessment of antimalarial activity in vitro by a semiautomated microdilution technique," *Antimicrobial Agents and Chemotherapy*, vol. 16, no. 6, pp. 710–718, 1979.

About This Journal

STOC is an open access journal published by Scientific Online Publishing. This journal focus on the following scopes (but not limited to):

- Bioorganic Chemistry
- Chemical Biology
- Medical Chemistry
- Natural Products Chemistry
- Organic Reactions
- Organic Synthesis
- Organometallic & Microwave Chemistry
- Physical Organic Chemistry
- Supramolecular Chemistry
- Synthesis of Functional Materials
-

Welcome to submit your original manuscripts to us. For more information, please visit our website: http://www.scipublish.com/journals/STOC/

You can click the bellows to follow us:

- Facebook: https://www.facebook.com/scipublish
- Twitter: https://twitter.com/scionlinepub
- LinkedIn: https://www.linkedin.com/company/scientific-online-publishing-usa
- Google+: https://google.com/+ScipublishSOP

SOP welcomes authors to contribute their research outcomes under the following rules:

- Although glad to publish all original and new research achievements, SOP can't bear any misbehavior: plagiarism, forgery or manipulation of experimental data.
- As an international publisher, SOP highly values different cultures and adopts cautious attitude towards religion, politics, race, war and ethics.
- SOP helps to propagate scientific results but shares no responsibility of any legal risks or harmful effects caused by article along with the authors.
- SOP maintains the strictest peer review, but holds a neutral attitude for all the published articles.
- SOP is an open platform, waiting for senior experts serving on the editorial boards to advance the progress of research together.