Article

Synthesis of Unsymmetrical Sulfides and Their Oxidation to Sulfones to Discover Potent Antileishmanial Agents

Ajaz A. Dar, Nagasuresh Enjamuri, Md. Shadab, Nahid Ali, and Abu Taleb Khan

ACS Comb. Sci., **Just Accepted Manuscript** • DOI: 10.1021/acscombsci.5b00044 • Publication Date (Web): 06 Oct 2015

Synthesis of Unsymmetrical Sulfides and Their Oxidation to Sulfones to Discover Potent Antileishmanial Agents

Ajaz A. Dar,[a] *Nagasuresh Enjamuri,*[a] *Md. Shadab, Nahid Ali,*[c,]* *and Abu T. Khan*[a,b,]*

[a]Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, India

[b]Aliah University, IIA/27, New Town, Kolkata-700 156, West Bengal, India.

[c]Infectious Diseases and Immunology Division, Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Kolkata 700 032, India.

ABSTRACT

Unsymmetrical sulfides were first synthesised using combinations of a 1,3-dicarbonyl, an aromatic aldehyde and a thiol in presence of 10 mol% ethanolic piperidine. These sulfides derivatives were subsequently converted into corresponding sulfones *via* oxidation in presence of *m*-chloroperoxybenzoic acid (*m*-CPBA) at ice-bath to room temperature. The former reaction was achieved at room temperature through one-pot three-component. The later was obtained in good yields using mild reaction conditions with flexibility in choice from a range of substrates. The antimicrobial properties of the newly synthesized sulfone derivatives were investigated against the protozoan parasite, *Leishmania donovani*, a

causative agent of visceral leishmaniasis (VL). Nine sulfone derivatives were found to be efficacious and exhibited significant antimicrobial activity. Further, these compounds were nontoxic on murine peritoneal macrophages thus eliminating potential cytoxicity in the host cells. These compounds may be indicated as potential leads in the treatment of visceral leishmaniasis.

KEYWORDS: Knoevenagel-thia-Michael reaction, Unsymmetrical sulfides (β-Mercapto diketones), *m*-Chloroperoxybenzoic acid, Sulfones, protozoan parasite, *Leishmania donovani*, visceral leishmaniasis.

INTRODUCTION

Many sulfur containing compounds particularly dithioacetals,[1a] oxathioacetal, sulfides, sulfoxide, sulfones and sulfonamides have immense importance because of their wide synthetic utility in organic synthesis.[1] In addition, many naturally occurring sulfur based compounds exhibit anticancer activity.[2] A large number of synthetic drugs containing a sulfur atom are used for treatment of various diseases.[3] Moreover, sulfides are usually used for generation of α-metallated sulfide, β-acylvinyl cation, homoenolate anion, equivalents as stabilized carbanion, extensively used for natural and non-natural product synthesis.[4] Additionally, they are the key starting material for the synthesis of other sulfur derivatives like sulfoxides and sulfones.

The synthesis of unsymmetrical sulfides such as β-mercapto diketones are of great interest amongst the synthetic organic chemists. These compounds exhibit remarkable pharmacological activities such as diuretic and HIV protease inhibitory activities.[5] Our research group and others have demonstrated synthesis of unsymmetrical sulfides using multi-component reactions (MCRs) strategy by employing tandem-Knoevenagel-thia-

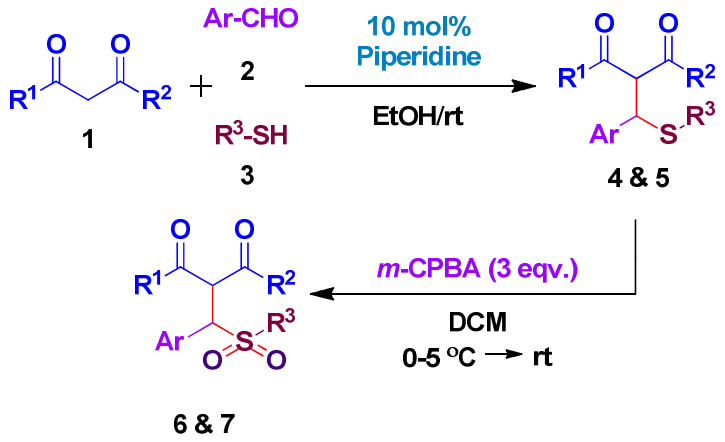
Michael reaction.[6] Nowadays, MCRs are well recognized synthetic strategy for the synthesis of a wide variety of organic compounds due to high atom economy and bond-forming efficiency, mild reaction conditions, ease of handling, no tedious work up and isolation procedures, regio-selectivity and diversity. Recently, we have shown the usefulness of 1,3-dicarbonyl compounds as key starting material for construction of numerous heterocycles through MCRs.[7] They also have been explored by others for the synthesis of many bioactive compounds such as furans,[8] pyrroles,[9] thiophenes[10] and valuable synthetic intermediates.[11] We have realised that a wide variety of unsymmetrical sulfides can be obtained from 1,3-dicarbonyl compounds, aromatic aldehydes and thiols under milder reaction conditions. However, reported methodologies limit the lack of substrate scope, low yield, high temperatures[12] and synthesis of various benzyl sulfides prior to use.[13] Therefore, there is a need to develop a newer methodologies, which works under milder reaction conditions.

Similarly, sulfones are key intermediates[14] in organic synthesis. The sulfonyl group in the sulfone makes it susceptible to the changes in chemical reactivity called as "chemical chameleons"[15] and exhibit interesting chemical properties.[16] The desulfonylation reactions of sulfones gives a sulfinate anion[17] and stabilizes the neighbouring carbanions.[18] The sulfonyl group serves as a possible stereoenriched centre, due to lack of inherent asymmetry.[19] Recently, Chi et al., developed the enantioselective synthesis of β-sulfonyl ketones and the transformation of γ-ketosulfone into cyclopropane with good enantioselectivity.[20] Benzylic sulfones acts as source for the generation of α-sulfonyl carbanions under different reaction conditions owing to carbon-carbon bond formation.[21] Moreover, sulfones play a prominent role in the field of pharmaceuticals,[22] polymers[23] and agrochemicals[24] with an extensive range of biological activities and applications. For instance, sulfone derivatives are potent inhibitors for several enzymes such as HIV-1 reverse transcriptase,[25] γ-secretase,[26]

cyclooxygenase-2[27] and matrix metalloproteinase.[28] They are also biologically active agents for drugs used for the treatment of Alzheimer's disease[29] and cancer related diseases.[30]

Leishmaniasis is a vector-borne protozoan disease. Being one of the world's most neglected diseases, its prevalence is in 98 countries with 350 million people at risk of infection.[31] Clinical manifestations include visceral, cutaneous and mucocutaneous forms. Visceral leishmaniasis caused by *L. donovani* is often fatal if left untreated.[32] There is no licenced *Leishmania* vaccine and current therapy relies on a limited number of drugs including pentavalent antimonials (still used as first line therapy), amphotericin B, pentamidine and miltefosine (the second line therapies), which are also not free from limitations including adverse side effects, requirement of long term treatment regimen and emergence of drug resistant parasites.[33] Consequently, these issues lay emphasis on an urgent need to develop alternative (safer, cheaper and more effective) chemotherapeutic agents with potential antileishmnial activity.[34] Few studies on the activity of sulfonamides and sulfones against *L. major* and *L. donovani* promastigotes and on intracellular amastigotes indicate that these molecules could be promising for the treatment of cutaneous and visceral leishmaniasis, respectively.[35] Infact, studies have shown the efficacy of dapsone in the treatment of cutaneous leishmaniasis.[36] However, to improve case management of severe visceral leishmaniasis (VL) and achieve rapid control of outbreaks, the development of an effective antileishmanial drug is highly desirable. Therefore, much attention has been paid to the synthesis of benzylic sulfones which could be useful in developing potential antileishmanial drug. Although several new methods have recently been reported to improve the synthesis of benzylic sulfones, they require expensive reagents/catalysts and/or harsh reaction conditions.[37] Herein, we report a synthesis of highly substituted unsymmetrical sulfides through one-pot piperidine catalyzed three-component reaction using 1,3-dicarbonyl compounds, aromatic aldehydes and thiols followed by the oxidation of sulfides into the

corresponding sulfones (as shown in scheme 1) and evaluated the activity of sulfones against promastigotes of *L. donovani*.



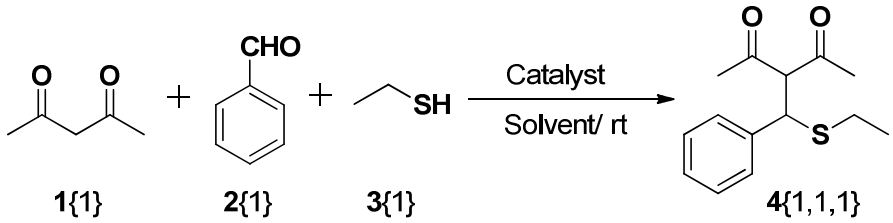
Scheme 1. Synthesis of sulfides through MCR strategy and their oxidation into corresponding sulfones.

RESULTS AND DISCUSSION

Synthesis of Sulfides. For the present study, pentane-2,4-dione **1**{1}, benzaldehyde **2**{1} and ethanethiol **3**{1} were used as the model substrates to find a suitable reaction condition. A trial reaction was carried out in 3 mL ethanol at room temperature in absence of catalyst and a trace amount of desired product was formed (Table 1, entry 1). Then, similar reactions were conducted in presence of 5, 10 and 20 mol% piperidine at room temperature, respectively and the results are summarized in Table 1. It was observed that 10 mol% piperidine in ethanol at room temperature gave the best yield (Table 1, entry 3). Other catalysts, such as pyridine, pyrrolidine, triethylamine (Et_3N) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ethanol were also scrutinized (Table 1, entries 9-12). These catalysts provided lower yields and required longer reaction time. Various other solvents were also examined with 10 mol% of piperidine under identical reaction conditions

(Table 1, entries 5-8) and ethanol proved to be the best solvent as compared to the other tested solvents.

Table 1. Optimization of reaction conditions[a]



1{1} **2**{1} **3**{1} **4**{1,1,1}

Entry	Catalyst (mol %)	Solvent	Time (h)	Yield (%)[b]
1	No catalyst (0)	EtOH	24	trace
2	Piperidine (5)	EtOH	5	40
3	**Piperidine (10)**	**EtOH**	**5**	**75**
4	Piperidine (20)	EtOH	5	77
5	Piperidine (10)	DCE	5	64
6	Piperidine (10)	DMF	5	70
7	Piperidine (10)	DCM	5	46
8	Piperidine (10)	CH_3CN	5	50
9	Pyridine (10)	EtOH	12	15
10	Pyrrolidine (10)	EtOH	12	55
11	Et_3N (10)	EtOH	12	40
12	DBU (10)	EtOH	12	35

[a]All the reactions were carried out using **1**{1} (1 mmol), **2**{1} (1 mmol) and **3**{1} (1.2 mmol) in 3 mL of solvent at room temperature. [b]Isolated yield.

After optimization of reaction conditions, the reaction were carried out with various aromatic aldehydes (Figure 1) to generalize the scope of this reaction. In case of aromatic aldehydes

with both electron donating or withdrawing groups, the desired products were obtained with moderate to good yields, such as Me, OMe, 3,4,5-OMe, OH, Br, Cl, CN, F and NO_2 groups. The reaction between pentane-2,4-dione (**1**{1}), benzaldehyde (**2**{1}) with aliphatic or aromatic thiols (**3**) were inspected under optimized reaction conditions. The desired products **4**{1,1,1-5} were obtained in 75-83% yields (Table 2, entries 1–5). The reaction between pentane-2,4-dione (**1**{1}), 4-methoxybenzaldehyde (**2**{2}) with benzylthiol (**3**{3}) or 4-methylthiophenol (**3**{5}) were examined in a similar manner in the presence of the same amount of catalyst. The desired products **4**{1,2,3} and **4**{1,2,5} were obtained in 81% and 85% yields, respectively (Table 2, entries 6 and 7). The reactions between pentane-2,4-dione (**1**{1}), aromatic aldehydes with different electron donating or withdrawing substituents in the aromatic ring, and thiophenol (**3**{4}) were performed under identical conditions, the products **4**{1,3-6,4} were obtained in 57-89% yield (Table 2, entries 8-11). Also, reactions between pentane-2,4-dione (**1**{1}), aromatic aldehydes with various electron donating or withdrawing substituents in the aromatic ring, and 4-methylthiophenol (**3**{5}) were examined under similar conditions, the products **4**{1,7,5}- **4**{1,10,5} were obtained in 57-68% yields (Table 2, entries 12-14). Furthermore, we scrutinised the reactions of pentane-2,4-dione (**1**{1}), 2-napthaldehyde (**2**{12}) with 4-methylthiophenol (**3**{5}) and 2-napthalenethiol (**3**{8}), the reactions proceeded smoothly to give **4**{1,12,5} and **4**{1,12,8}, respectively, in good yields (Table 2, entries 15 and 16). Due to the steric hindrance at *ortho*-position, 2-NO_2 (**2**{13}), 2-Cl (**2**{14}) or 2-OH (**2**{15}) benzaldehyde with pentane-2,4-dione (**1**{1}) and 4-methylthiophenol (**3**{5}) did not give the desired product. However, 2-Me (**2**{16}), 2-OMe (**2**{17}), 2-F (**2**{18}) or 2-Br (**2**{19}) benzaldehyde with pentane-2,4-dione (**1**{1}) and 4-methylthiophenol (**3**{5}) produced the desired product in good yields (Table 2, entries 17–20). Similarly, heterocyclic aldehydes 2-pyridinecarboxaldehyde (**2**{20}) and 2-thiophenecarboxaldehyde (**2**{21}) also worked well with pentane-2,4-dione (**1**{1}) and

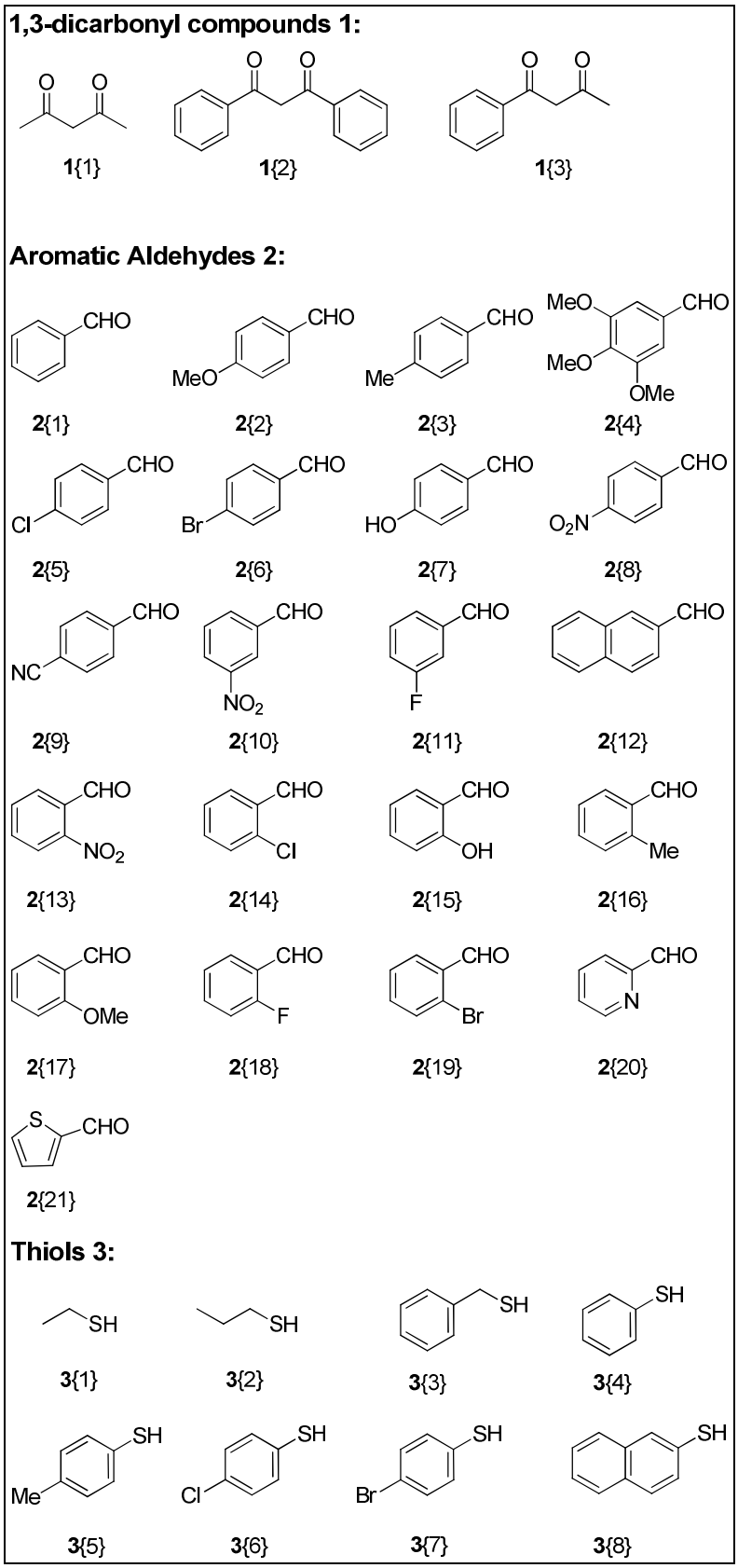


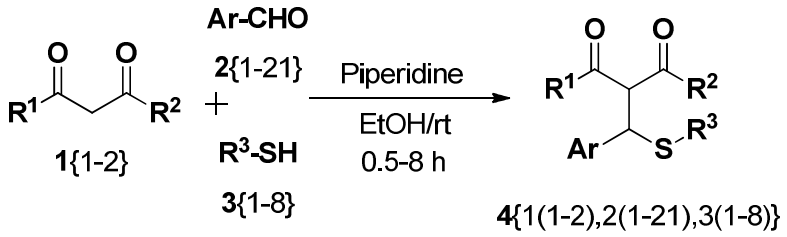
Figure 1. Substrates used in the synthesis of compounds **4** and **5**.

4-methylthiophenol (**3**{5}) to produce the desired products **4**{1,20,5} and **4**{1,21,5}, in good yield respectively (Table 2, entries 21-22). The reactions of 1,3-diphenylpropane-1,3-dione (**1**{2}), benzaldehyde (**2**{1}) with benzylthiol (**3**{3}) or different aromatic thiols (**3**) were examined under the optimized reaction condition. The desired products **4**{2,1,3-7} were obtained in 61-70% yields (Table 2, entries 23–27). Similarly, the reactions of 1,3-diphenylpropane-1,3-dione (**1**{2}), aromatic aldehydes containing various electron donating or withdrawing substituents at the *para* or *meta*-position on the benzene ring, with varied aromatic thiols (**3**) were also carried out. The desired products **4**{2,2,5}- **4**{2,11,7} were isolated in good yields (Table 2, entries 28–32). By these successful results, we also scrutinized the reactions of unsymmetrical 1,3-dicarbonyl, 1-phenyl-1,3-butanedione (**1**{3}), benzaldehyde (**2**{1}), with benzylthiol (**3**{3}), thiophenol (**3**{4}) or 4-methylthiophenol (**3**{5}) by following the same reaction procedure. The desired products **5**{3,1,3-5} were isolated in good yields (Table 3, entries 1–3). Likewise, the reactions of 1-Phenyl-1,3-butanedione (**1**{3}), aromatic aldehydes, which have various electron donating or withdrawing substituents in the aromatic ring, and different aromatic thiols (**3**) were examined, the desired products **5**{3,2,3}- **5**{3,6,5} were obtained in 55-80% yields (Table 3, entries 4–9) .

From the above results, the reactions were found to be sensitive to the steric and electronic effects of the R^1 and R^2 groups. pentane-2,4-dione (**1**{1}) reacted with benzaldehyde (**2**{1}) and thiophenol (**3**{4}) to provide the product **4**{1,1,4} in 82% yield (Table 2, entry 4), while the 1,3-diphenylpropane-1,3-dione (**1**{2}) and 1-phenyl-1,3-butanedione (**1**{3}) reacted in similar fashion gave the products **4**{2,1,4} and **5**{3,1,4} (68% and 75% yield) respectively (Table 2, entry 24 and Table 3, entry 2). The aromatic aldehydes bearing electron donating groups provided better yield along with shorter reaction time as compared to those aromatic aldehydes having electron withdrawing substituents. It was also observed that the electron

donating substituents in thiophenol increased the yield of the products. Furthermore, it was noted that while replacing the pentane-2,4-dione with 1-phenyl-1,3-butanedione or 1,3-diphenylpropane-1,3-dione provided lower yield of the expected product as well as required longer reaction time, these changes were found to be gradual respectively. This observation can be explained due to the formation of stable Knoevengel intermediate that gives extended conjugation to the system. In addition, when the reaction of unsymmetrical diketone i.e. 1-phenyl-1,3-butanedione (**1**{3}), benzaldehyde (**2**{1}) or 4-methoxybenzaldehyde (**2**{2}) and benzylthiol (**3**{3}), was performed the mixture of two diastereomers were obtained in the ratio of 1:1. The diastereomeric ratio was determined from ^{1}H spectra.

Table 2. Synthesis of unsymmetrical sulfides from symmetrical diketones[a]



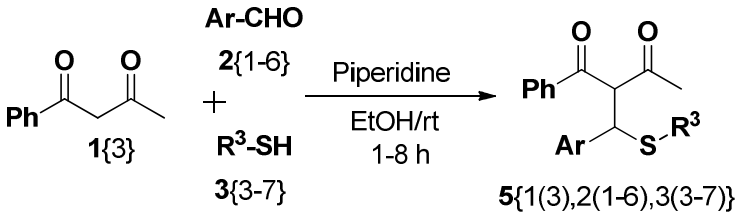
Entry	Product	Yield (%)[b]
1	**4**{1,1,1}	75
2	**4**{1,1,2}	80
3	**4**{1,1,3}	79
4	**4**{1,1,4}	82
5	**4**{1,1,5}	83
6	**4**{1,2,3}	81
7	**4**{1,2,5}	85
8	**4**{1,3,4}	83

9	**4**{1,4,4}	89
10	**4**{1,5,4}	57
11	**4**{1,6,4}	62
12	**4**{1,7,5}	68
13	**4**{1,8,5}	57
14	**4**{1,10,5}	61
15	**4**{1,12,5}	78
16	**4**{1,12,8}	84
17	**4**{1,16,5}	70
18	**4**{1,17,5}	73
19	**4**{1,18,5}	67
20	**4**{1,19,5}	65
21	**4**{1,20,5}	64
22	**4**{1,21,5}	68
23	**4**{2,1,3}	66
24	**4**{2,1,4}	68
25	**4**{2,1,5}	70
26	**4**{2,1,6}	61
27	**4**{2,1,7}	63
28	**4**{2,2,5}	72
29	**4**{2,3,4}	69
30	**4**{2,3,5}	72
31	**4**{2,9,6}	58

32	**4**{2,11,7}	56

[a]All the reactions were carried out using **1**{1} or **1**{2} (1 mmol), **2** (1 mmol) and **3** (1.2 mmol) in 3 mL of solvent at room temperature. [b]Isolated yield.

Table 3. Synthesis of unsymmetrical sulfides from unsymmetrical diketone[a]



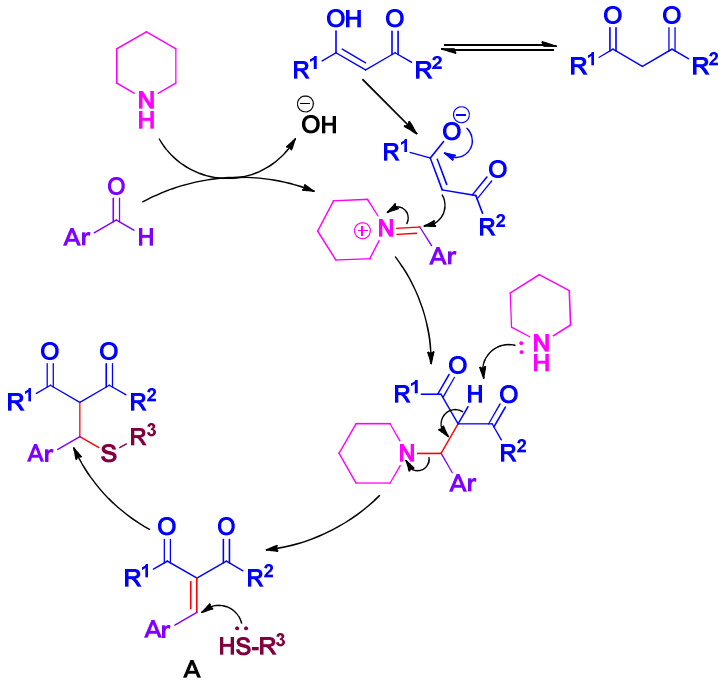
Entry	Product	Yield (%)[b]
1	**5**{3,1,3}	73
2	**5**{3,1,4}	75
3	**5**{3,1,5}	77
4	**5**{3,2,3}	76
5	**5**{3,2,5}	80
6	**5**{3,3,4}	76
7	**5**{3,4,6}	79
8	**5**{3,5,7}	72
9	**5**{3,6,5}	55

[a]All the reactions were carried out using **1**{3}(1 mmol), **2** (1 mmol) and **3** (1.2 mmol) in 3 mL of solvent at room temperature. [b]Isolated yield.

Mechanism. The formation of the product can be explained as follows: Initially piperidine reacts with the aldehyde (**2**) to form iminium ion, the iminium ion is being attacked by the active methylene group of the 1,3-diketone that results in the formation Knoevengel

intermediate **A**. The Knoevengel intermediate **A** subsequently undergoes thia-Michael addition reaction with thiol (**3**) to give desired product as shown in Scheme 2.

The structures of two representative products **4**{1,1,3} and **5**{3,1,4}, one each from both the categories, that is symmetrical diketone and unsymmetrical diketone respectively, have been categorically proved by the single-crystal XRD (Figure S1 in the Supporting Information).

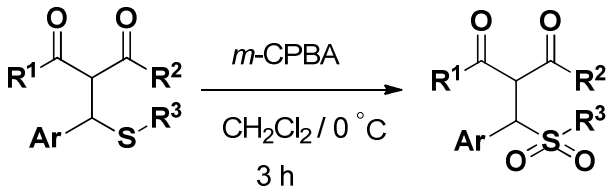


Scheme 2. Plausible mechanism for the formation of unsymmetrical sulfide.

Synthesis of Sulfones. After the successful synthesis of sulfides, the oxidation of unsymmetrical sulfides into sulfone was carried out by using *m*-CPBA as oxidant, because of its outstanding reactivity, availability and easy to handle than hydrogen peroxide, peracid and peracetic acids. It was found that a wide variety of dibenzyl, aryl benzyl and alkyl benzyl sulfides were oxidized to their corresponding sulfones in excellent yields in dichloromethane at 0 ^{o}C to room temperature, the results are summarized in Table 4 and Table 5. The oxidant *m*-chloroperoxybenzoic acid (*m*-CPBA) was used to convert sulfides to sulfones easily under an optimized reaction condition (Table 4 and Table 5) in excellent yields without further

purification. All of the reactions occurred with complete selectivity for sulfone formation, no other products such as sulfoxides and Bayer-Villiger products were obtained in the present study. The selectivity of the present method is fairly wide, as other functionalities remain unaffected under these reaction conditions. Prominent effects of the substituents were not observed in sulfone formation and excellent yields were obtained in all cases (Table 4 and Table 5).

Table 4. One-pot oxidation of sulfides containing symmetric diketones to sulfones[a]



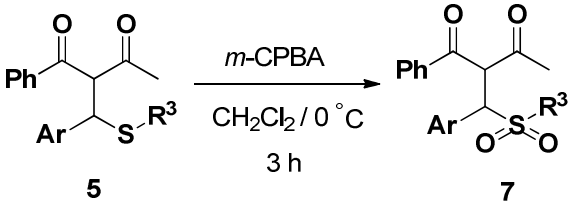
4 **6**

Entry	Substrate	Product	Yield (%)[b]
1	**4**{1,1,1}	**6**{1,1,1}	91
2	**4**{1,1,2}	**6**{1,1,2}	92
3	**4**{1,1,3}	**6**{1,1,3}	88
4	**4**{1,1,4}	**6**{1,1,4}	90
5	**4**{1,1,5}	**6**{1,1,5}	93
6	**4**{1,2,5}	**6**{1,2,5}	94
7	**4**{1,3,4}	**6**{1,3,4}	89
8	**4**{1,4,4}	**6**{1,4,4}	95
9	**4**{1,5,4}	**6**{1,5,4}	87
10	**4**{1,6,4}	**6**{1,6,4}	90
11	**4**{1,7,5}	**6**{1,7,5}	90
12	**4**{1,8,5}	**6**{1,8,5}	86

13	**4**{1,10,5}	**6**{1,10,5}	88
14	**4**{1,12,5}	**6**{1,12,5}	88
15	**4**{1,12,8}	**6**{1,12,8}	88
16	**4**{1,17,5}	**6**{1,17,5}	91
17	**4**{1,18,5}	**6**{1,18,5}	89
18	**4**{1,21,5}	**6**{1,21,5}	87
19	**4**{2,1,4}	**6**{2,1,4}	85
20	**4**{2,1,5}	**6**{2,1,5}	88
21	**4**{2,1,6}	**6**{2,1,6}	83
22	**4**{2,1,7}	**6**{2,1,7}	85
23	**4**{2,2,5}	**6**{2,2,5}	87
24	**4**{2,3,4}	**6**{2,3,4}	89
25	**4**{2,3,5}	**6**{2,3,5}	90

[a]Reaction conditions: substrate (0.5 mmol), *m*-CPBA (1.5 mmol), and dichloromethane (3 mL) at 0 °C for 3 h. [b]Isolated yield.

Table 5. One-pot oxidation of sulfides containing unsymmetric diketone to sulfones[a]



5 **7**

Entry	Substrate	Product	Yield (%)[b]
1	**5**{3,1,4}	**7**{3,1,4}	86
2	**5**{3,1,5}	**7**{3,1,5}	88
3	**5**{3,2,5}	**7**{3,2,5}	92

4	**5**{3,3,4}	**7**{3,3,4}	87
5	**5**{3,4,6}	**7**{3,4,6}	94
6	**5**{3,5,7}	**7**{3,5,7}	88
7	**5**{3,6,5}	**7**{3,6,5}	87

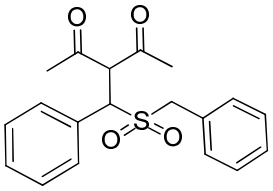
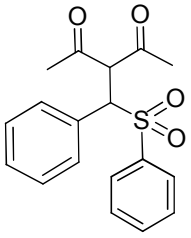
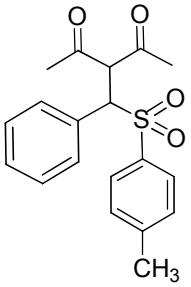
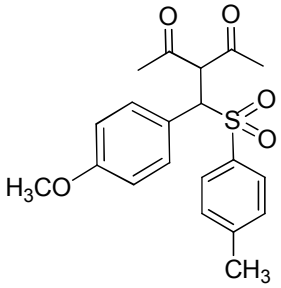
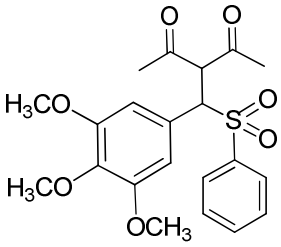
[a]Reaction conditions: substrate (0.5 mmol), *m*-CPBA (1.5 mmol), and dichloromethane (3 mL) at 0 °C for 3 h. [b]Isolated yield.

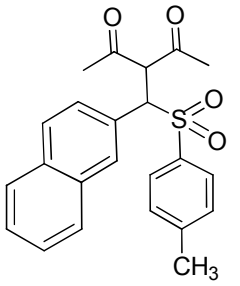
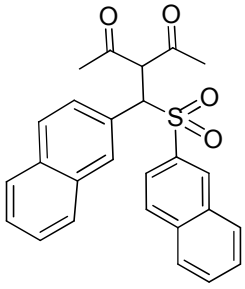
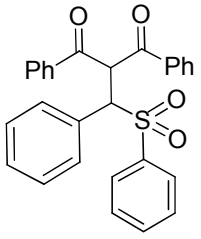
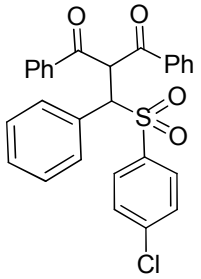
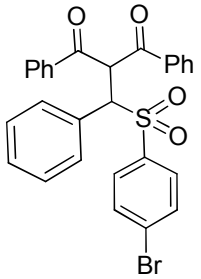
These products were confirmed on the basis of their analytical data (^{1}H NMR, ^{13}C NMR, IR and ESI-MS) and physico-chemical data like melting point. The structures of compounds **6**{1,1,3} and **7**{3,1,4} were further confirmed by X-ray analysis (Figure S2 in the Supporting Information). The crystal structure shows that **6**{1,1,3} forms a dimer through non-covalent weak intermolecular C-H···π interactions (C7-C12···H5A = 2.859 Å). Similarlly, the crystal structure **7**{3,1,4} also forms a dimer through non-covalent weak intermolecular oxygen-hydrogen interactions (O2···H13 = 2.460 Å, ∠O2···H13-C13 = 167.79° and O3···H12 = 2.491 Å, ∠C15-O3···H12 = 168.15°) (Figure S3 in the Supporting Information). In the last few years, these noncovalent interactions involving aromatic rings such as C−H···π, C−H···O−H and C−H···O−S interactions have attracted a great deal of interest among the family of pharmaceutical, optical, functional materials and in biological systems.[38]

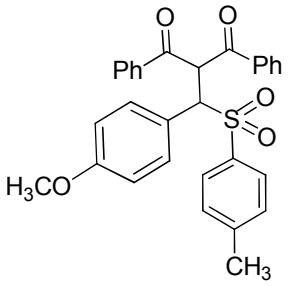
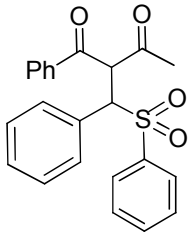
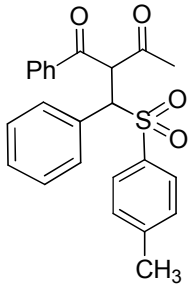
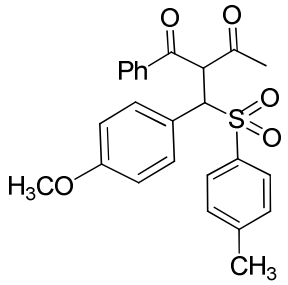
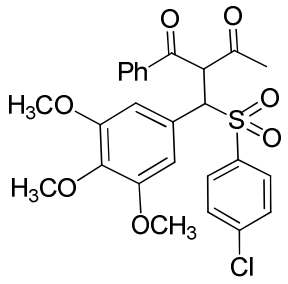
Antimicrobial Activity. In this study, we evaluated the antileishmanial activity of sixteen sulfone derivatives against promastigotes of *L. donovani* and found that most of them displayed significant antileshmanial activity with low cytotoxicity against mammalian cells.

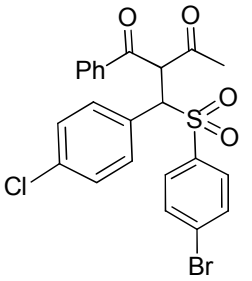
Table 6. Leishmanicidal activity of compounds against *L. donovani* promastigotes

	Activity		**Cytotoxicity**
	L. donovani promastigotes		**Macrophages**
Compounds	**(IC_{50}µg/ml±SD)[a]**	**(IC_{90}µg/ml±SD)[a]**	**(IC_{50}µg/ml±SD)[a]**

 **6**{1,1,3}	4.085±0.7283	7.355±1.308	8.655±2.708
 **6**{1,1,4}	4.485±0.9546	8.075±1.718	10.13±2.949
 **6**{1,1,5}	4.55±0.8202	8.395±1.761	16.75±2.56
 **6**{1,2,5}	5.59±1.329	10.08±2.397	19.24±1.648
 **6**{1,4,4}	4.325±0.7283	7.785±1.308	15.02±2.574

 **6**{1,12,5}	3.99±0.297	7.185±0.5303	11.73±2.157
 **6**{1,12,8}	4.095±0.3323	7.365±0.601	11.17±2.249
 **6**{2,1,4}	4.985±1.69	8.975±2.033	8.73±3.168
 **6**{2,1,6}	3.655±0.2051	6.58±0.3677	15.08±1.188
 **6**{2,1,7}	3.67±0.1131	6.61±0.198	22.79±3.663

 **6**{2,2,5}	3.645±0.2475	6.57±0.4525	22.15±4.943
 **7**{3,1,4}	3.855±0.3041	6.94±0.5515	8.47±1.499
 **7**{3,1,5}	4.455±0.5445	8.02±0.9758	17.25±1.435
 **7**{3,2,5}	6.435±0.859	11.59±1.046	23.04±5.317
 **7**{3,4,6}	4.105±0.7142	7.39±1.287	14.78±1.478



7{3,5,7}	4.045±0.5445	7.29±0.9758	7.335±2.652

[a]n=2

Evaluation of *in vitro* antileishmanial activity (Table 6) are represented as IC_{50} and IC_{90} values of compounds against promastigotes of *L. donovani*. The cytotoxicity of all compounds were evaluated against murine macrophages. Statistical analysis showed that all these sixteen compounds have no significant difference amongst them in exhibiting activity against the promastigotes of *L. donovani*. This means that all these sulfones possess potent to moderate antileishmanial activity. However, the results showed that out of these, seven compounds namely **7**{3,5,7}, **7**{3,1,4}, **6**{1,1,3}, **6**{2,1,4}, **6**{1,1,4}, **6**{1,12,8} and **6**{1,12,5} displayed toxicity towards the mammalian macrophage cells with IC_{50} values of 7.335±2.652 μg/ml, 8.47±1.499 μg/ml, 8.655±2.708 μg/ml, 8.73±3.168 μg/ml, 10.13±2.949 μg/ml, 11.17±2.249 μg/ml, and 11.73±2.157 μg/ml, respectively. These IC_{50} values against macrophages are close to IC_{90} values against promastigoes. Therefore, the efficacy of these compounds is limited due to their toxicity. The compounds **7**{3,4,6}, **6**{1,4,4}, **7**{3,1,5}, **6**{1,1,5}, **6**{1,2,5} and **7**{3,2,5} with IC_{50} values of 4.105±0.7142 μg/ml, 4.325±0.7283 μg/ml, 4.455±0.5445 μg/ml, 4.55±0.8202 μg/ml, 5.59±1.329 μg/ml and 6.435±0.859 μg/ml, respectively could be potent antileishmanial agents as their toxic effect towards macrophage is negligible at the doses used against the parasite (as depicted by their IC_{50} values). Thus, the compounds whose cytotoxicity towards normal murine macrophage cells is low or negligible and at the same time displaying antileishmanial activity at low to moderate doses could have therapeutic prospects. Herein, the compounds **6**{2,2,5}, **6**{2,1,6} and **6**{2,1,7} are found to be most effective against promastigotes with IC_{50} values of 3.645±0.2475 μg/ml,

3.655±0.2051 µg/ml and 3.67±0.1131 µg/ml, respectively. These three compounds (whose IC_{50} values against macrophage are quite high) represent promising lead compounds for antileishmanial therapy. The percent cell viability of *L. donovani* and peritoneal macrophages with increase in concentration from 0.00 to 10.0 mg/mL were also evaluated as shown in Figure 2.

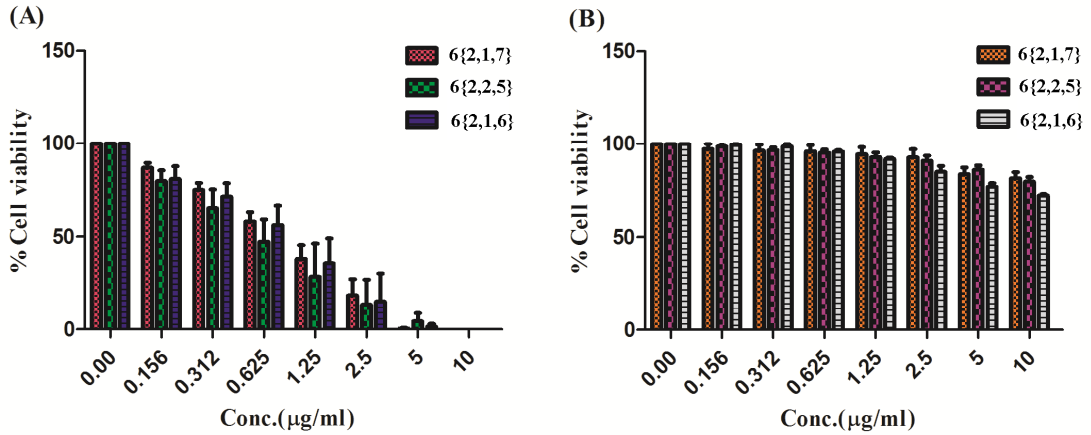


Figure 2: Leishmanicidal effect of **6**{2,1,7}, **6**{2,2,5} and **6**{2,1,6} on promastigotes of *L. donovani* and toxic effect on murine peritoneal macrophages. (A) *L. donovani* promastigotes were treated for 24 h with increasing concentrations of three different compounds **6**{2,1,7}, **6**{2,2,5} and **6**{2,1,6}, and then cell viability was assessed using alarm blue reagent (as described in material and methods). (B) Similarly, peritoneal macrophages were treated for 24 h with increasing concentrations of these three compounds **6**{2,1,7}, **6**{2,2,5} and **6**{2,1,6}, and cell viability was assessed.

Structure–activity relationship (SAR). SAR studies were carried out to identify how the structurural differences, in terms of chemical modifications, in our sulfone derivatives affect their anti-leshmanial activity. We found that in all the structures, the dicarbonyl group in its enol form, which is the interacting moiety, is necessary for their activity. Moreover, the hydrophobic moiety involved in π-cation interaction significantly contributed to maximize

the activity. Although, all these sixteen compounds showed no significant difference amongst them in exhibiting activity against the promastigotes of *L. donovani*, however, SAR studies revealed that the introduction of phenyl rings close to the dicarbonyl group and electron donating groups in the phenyl rings in close proximity to sulfone functionality enhanced the activity of (**6**{2,2,5}, **6**{2,1,6}and **6**{2,1,7}) when used at low to moderate doses and which simultaneously exhibited low or negligible cytotoxicity towards normal murine macrophage cells. Furthermore, sulfone derivatives containing electron donating (**7**{3,4,6}, **6**{1,4,4}, **7**{3,1,5}, **6**{1,1,5}, **6**{1,2,5}and **7**{3,2,5}) substituents in the *meta* and/or *para* position in the phenyl moiety displayed promising anti-leishmanial activity owing to their negligible toxic effect towards macrophages at the doses used against the parasite. Incontrast, the introduction of either electron withdrawing substituents (**7**{3,5,7}) or unsubstituted sulfone derivatives (**7**{3,1,4}, **6**{1,1,3}, **6**{2,1,4}, **6**{1,1,4}, **6**{1,12,8}and **6**{1,12,5}) displayed toxicity towards the mammalian macrophage cells with IC_{50} values close to IC_{90} values against promastigoes.

Molecular Docking Study of Sulfone derivatives against Trypanothione Reductase. Trypanothione reductase (TryR) is a key drug target enzyme involved in the redox metabolism of the parasite and inhibition of TryR may disrupt the redox balance of the parasite leading to parasite death. Thus, sulfone derivatives have been designed which can bind the active site of TryR leading to its inhibition. In order to understand the binding interactions of these sulfones against trypanothione reductase, we have performed the molecular docking study of all the sixteen compounds on *L. infantum* trypanothione reductase by using Glide 5.8 module in maestro 9.3.[39] There is no crystal structure available for trypanothione reductase of *L. donovani* and thus we started our molecular docking studies with trypanothione reductase from *Leishmania infantum* as there is 98% sequence similarity between the trypanothione reductase of *L. donovani* and *L. infantum*. The molecular docking study was carried out using X-ray crystal structures of trypanothione reductase from

Leishmania infantum (PDB code: 2jk6, 2.95 Å).[40] The crystal structure is co-crystallized with cofactor FAD. The enzyme (TryR) is a dimer consisting of two active sites. Active sites are buried at the interface of chains A and B. The molecular docking study suggests that sulfone derivatives bind in the trypanothione reductase binding pocket with hydrogen bonds and hydrophobic contacts with the A-chain and B-chain. The molecular docking of sulfone derivatives showed that the most of the interactions are close to Glu 466, Glu 467, Ser 470, Arg 472 indicating that the binding is preferentially happening in γ–Glutamate and new interacting sites. These residues are found around the active site Cys-52 and Cys-57. Interestingly, some of these derivatives show hydrophobic interaction with His 461 which is a part of catalytic triad (Cys-52- His 461- Cys-57). In all the cases, the 1,3-dicarbonyl group in its enol form is interacting with Glu 467, Ser 470. The phenyl/napthyl moiety involved in π-cation interaction with amino acids which includes mainly Arg 472, His 461. All the sixteen compounds were docked into the active site of TryR. A maximum of 10 docking poses per ligand were generated in each case and analyzed further for the binding mode and intermolecular interactions. The two representative examples revealing the mode of interactions are shown in Figure 3.

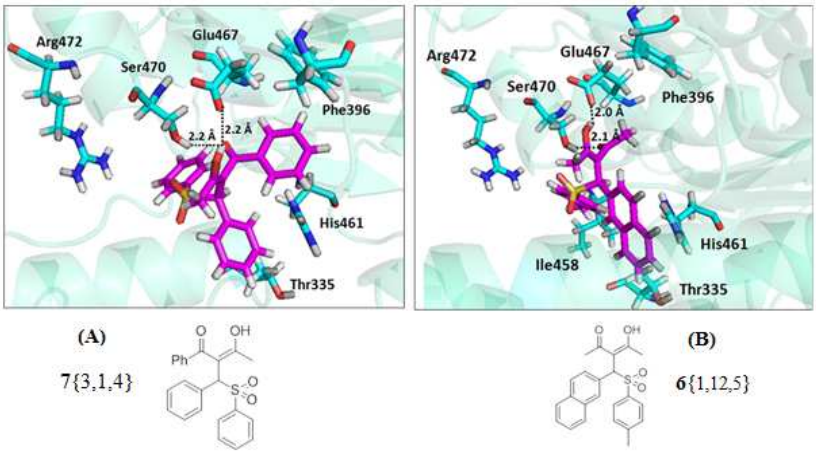


Figure 3: Binding modes of ligands at the interface of homodimer. Ligands are shown in stick models (magenta colour). Hydrogen bonding interactions are shown as black dashes and

residues involved in hydrogen bonding or hydrophobic interactions (π–π, π–cation) are represented in stick models (A) Represent the binding mode of **7**{3,1,4} and (B) Represent the binding mode of **6**{1,12,5}.

CONCLUSION

In conclusion, we have developed an efficient and general method for synthesis of unsymmetrical sulfides which in turn were transformed into alkyl-benzyl and benzyl-aryl sulfones with various functional groups that can also be extended to the preparation of vinyl sulfones. In synthetic organic chemistry, importance of the sulfone functional group provides significant interest in the development of new methodologies related to the introduction of the sulfone functionality into an organic molecule as well as the further synthetic transformation of the sulfone intermediate, and its eventual elimination from the target when needed. Also from evaluation of biological activity as well as docking study, into the active site of trypanothione reductase (TryR) enzyme, against visceral leishmaniasis, it may be concluded from the present study, that most of these newly synthesized sulfone derivatives have promising antileishmanial activity and further study on lead optimisation through *in vitro* and *in vivo* model of visceral leishmaniasis could allow development of new anitleishmanial drug.

EXPERIMENTAL SECTION

Material and Method for Biological Screening.

Cell Culture and Parasite. *L. donovani* strain AG83 (MHOM/IN/1983/AG83), originally isolated from an Indian kala-azar patient was maintained by serial passage in hamsters. *L. donovani* amastigotes periodically recovered from the spleens of infected hamsters were transformed into promastigotes through amastigote culture in M199 supplemented with 10% FCS, 2 mM glutamine, penicillin G (100 U/ml), streptomycin sulfate (100 μg/ml) at 22°C.

Promastigotes were used at the log phase of growth, approximately 2 to 3 days after subculture. Parasites were kept in culture by weekly passaging.

In vitro antipromastigote activity. Antiparasitic activities of compounds against *L. donovani* (AG83) promastigotes were determined using alamarBlue cytotoxicity assays (Thermofisher). Resazurin (7-Hydroxy-3H-phenoxazin-3-one 10-oxide) is the active ingredient of AlamarBlue reagent and is a non-toxic, non-fluorescent and cell permeable compound that is blue in color. Healthy living mamalian cells maintain a reducing environment within their cytosol. Upon entering cells, the "reducing potential" reduces resazurin to resorufin, which is red in colour and highly fluorescent. Viable cells continuously convert resazurin to resorufin, increasing the overall fluorescence and colour of the culture media.

Assays were performed in sterile 96-well plates using 100 µl of log-phase promastigotes adjusted to $2x10^6$ cells/ml. BALB/c mice (8-10 week old) were used for this experiment. Resident peritoneal macrophages were obtained by injecting 5-10 ml RPMI medium supplemented with 10% FCS into the peritoneal cavity of BALB/c mice. The pulled medium containing the peritoneal exudates cells were plated ($1x10^5$ cells /well) in a 96 well culture plate. Non-adherent cells were washed off after 20 h culture. These cells were incubated in control and in presence of 0.1562 µg/ml, 0.3125 µg/ml, 0.625 µg/ml, 1.25 µg/ml, 2.50 µg/ml, 5.0 µg/ml and 10.0 µg/ml compounds and DMSO for 24 h. Next 10 µl of the resazurin dye (0.01%) were added, and plates were further incubated for 4 h at 37 °C. After incubation, cells were analyzed in a microplate reader (SpectraMax spectrofluorometer, Molecular Devices) at a wavelength of 570 nm, using 600 nm as a reference wavelength (normalized to the 600 nm value). Absorbance in the absence of any inhibitor or solvent was set as the control. Cell viability was evaluated based on a comparison between the untreated control

cells, solvent and at inhibitory concentrations of inhibitors necessary to reduce the growth of promastigotes by 50% (IC_{50} values) and 90% (IC_{90} values).

Statistical analysis. Data are expressed as the arithmetic mean±standard deviation values. IC_{50} and IC_{90} values of all sixteen compounds for both promastigotes and macrophages were calculated using dose–response curves in Origin 5.0 software (Microcal Software, Inc., Northampton, MA, USA). These values were compared by 1way ANOVA employing Turkeys multiple comparision test. The p values for all comparisons were determined and $p < 0.05$ was taken as significant difference.

Molecular Docking Study. For the purpose of molecular docking studies, X-ray crystal structure of *L. Infantum* trypanothione redictase was selected (PDB ID: 2jk6, resolution: 2.95 Å).[39] The crystal structure is in dimeric form and it is co-crystalized with cofactor FAD. Both the chains were considered for molecular docking studies because the binding site of trypanothione reductase is at the interface of the chain A and chain B. Protein preparation was done using Maestro. Hydrogen atoms were added during protein preparation wizard. Receptor Grid Generation Panel within Glide suite was used to set up receptor grid for the prepared structures. The grid was defined by 16 Å by considering the amino acids of all the subpockets. Then, this step is followed by restrained minimization using the OPLS 2005 force field to RMSD of 0.3 Å. Three-dimensional structures of these compounds were then prepared using LigPrep module of maestro implementing OPLS_2005 force field and ionic states for the ligands at pH values of 7.0 ± 2.0 were generated. Docking was performed using Glide 5.8 (Grid-based Ligand Docking with Energetics), with the standard precision (SP) mode to estimate protein–ligand binding affinities and static intermolecular interactions.

General Experimental Details.

Melting point was determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra

were recorded on Varian 400 MHz and Bruker 600 MHz spectrometer TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in the order: multiplicity, coupling constant (J value) in hertz (Hz) and no of protons; signals were characterized as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet). Mass spectra were recorded using WATERS MS system, Q-tof premier and data analyzed using Mass Lynx 4.1. Elemental analyses were carried out using Perkin-Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology Guwahati. Column chromatographic separations were performed using Merck silica gel (60-120 mesh). Complete crystallographic data of **4**{1,1,3}, **5**{3,1,4}, **6**{1,1,3} and **7**{3,1,4} for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1019727, 958054, 930603 and 958055 respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

General procedure for synthesis of compounds (**4 and 5**). To a stirred solution of 1,3-diketone (1 mmol) in 3 mL of ethanol were added piperidine (0.1 mmol) and aldehyde (1 mmol) successively and the reaction mixture was kept for stirring for 5-10 min at room temperature. Then, thiol (1.2 mmol) was added either directly if it is a solid or drop-wise through a syringe into the reaction mixture. The solid products namely **4**{1,1,4-5}, **4**{1,2,5} to **4**{1,12,8}, **4**{1,18,5}, **4**{1,21,5}**, 4**{2,1,4} to **4**{2,11,7} and **5**{3,1,4} to **5**{3,1,5}**, 5**{3,2,5} to **5**{3,6,5} were precipitated out during the reaction after appropriate reaction time. Finally, the products were filtered off through a Büchner funnel and dried. The pure product was obtained after recrystallization from methanol. The following work up procedure was followed for the products such as **4**{1,1,1-3}**, 4**{1,2,3}**, 4**{1,16-17,5}, **4**{1,19,5}, **4**{1,20,5}**, 4**{2,1,3}**, 5**{3,1,3} and **5**{3,2,3} because the solid precipitate did not come out during the

reaction time. After completion of reaction as checked by TLC, ethanol was removed in a rotary evaporator and the crude residue was extracted with dichloromethane (2 × 15 mL). The organic layer was washed with water, brine solution (2 x 5 mL) and dried over anhydrous Na_2SO_4. Then, it was concentrated in a rotary evaporator and the crude residue was passed through a silica gel (60-120 mesh) column to get the desired pure product.

3-((ethylthio)(phenyl)methyl)pentane-2,4-dione 4{1,1,1}: Yield: (187.8 mg, 75%); White solid, mp 73-75 °C; IR (KBr): 3396, 3054, 2975, 2956, 1692, 1496, 1454, 1421, 1357, 1270, 1185, 1150, 1099, 717, 700 cm-1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 7.6 Hz, 3H), 1.88 (s, 3H), 2.27-2.35 (m, 2H), 2.37 (s, 3H), 4.26 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 7.24-7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 25.3, 29.5, 30.1, 48.3, 74.8, 128.0, 128.3 (2C), 128.9 (2C), 139.5, 201.6 (2C) ppm; ESI-MS m/z: calcd for $C_{14}H_{18}O_2SNa$: 273.09; Found 273.15 $[M + Na]^+$. Anal Calcd for $C_{14}H_{18}O_2S$ (250.36): C, 67.16; H, 7.25%. Found C, 67.03; H, 7.16%.

General procedure for synthesis of compounds (6 and 7). *m*-Chloroperoxybenzoic acid (*m*-CPBA, 1.5 mmol) was added in portion for a period of 15 min to a stirred solution of corresponding unsymmetrical sulfide (0.5 mmol) in 3 mL of dichloromethane at ice-bath temperature and stirring was continued for 45 min at the same temperature. Then, the reaction mixture was brought to room temperature slowly and it was stirred for another 2 h. After completion of reaction, it was extracted with by adding 18 mL of dichloromethane, which was washed with 5% aqueous $NaHCO_3$ solution (10 mL) and brine solution (10 mL). Finally, the organic layer was dried over anhydrous Na_2SO_4 and it was concentrated in a rotary evaporator. The desired sulfone was obtained after recrystallization from methanol.

3-((ethylsulfonyl)(phenyl)methyl)pentane-2,4-dione 6{1,1,1}: Yield: (257 mg, 91%); White solid, mp 140-142 °C. IR (KBr): 3395, 3048, 2974, 2944, 2659, 2549, 1965, 1908, 1733, 1701, 1596, 1574, 1452, 1424, 1364, 1335, 1308, 1294, 1260, 1246, 1217, 1169, 1134,

1069, 1051, 1036, 877, 851, 795, 707 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.6 Hz, 3H), 1.85 (s, 3H), 2.42 (s, 3H), 2.64-2.81 (m, 2H), 4.88 (d, *J* = 11.6 Hz, 1H), 5.16 (d, *J* = 11.6 Hz, 1H), 7.37 (s, 5H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 6.2, 29.0, 30.7, 45.9, 66.8, 66.9, 129.6 (2C), 129.9, 130.2 (2C), 131.1, 199.1, 200.0 ppm; ESI-MS m/z: calcd for $C_{14}H_{18}O_4SNa$: 305.08; Found 305.16 $[M + Na]^+$. Anal Calcd for $C_{14}H_{18}O_4S$ (282.35): C, 59.55; H, 6.43%. Found C, 59.43; H, 6.35%.

ACKNOWLEDGMENTS

ATK are grateful to Council of Scientific and Industrial Research (CSIR) 02(0181)/14/EMR-II for their financial support. AAD is thankful to IIT Guwahati for providing senior research fellowship. The authors are also grateful to Director, IIT Guwahati for providing the general research facility to carry out this work. We are also thankful to CIF, IIT Guwahati for providing the instrument facilities. We are also grateful to Professor Prasad V. Bharatam and his Ph.D student Deepika Kathuria, National Institute of Pharmaceutical Education and Research, S. A. S Nagar, Mohali for molecular docking study.

Supporting Information

Experimental details and spectroscopic characterization for compounds of chemset **4**, **5**, **6** and **7**. Complete crystallographic description of **4**{1,1,3}, **5**{3,1,4}, **6**{1,1,3} and **7**{3,1,4}. This information is available free of charge via the Internet at http://pubs.acs.org/.

Corresponding Author

*E-mail: atk@iitg.ernet.in (A.T. Khan); nali@iicb.res.in (Nahid Ali).

Tel.: +91 361 2582305; fax: +91 361 2582349.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) (a) Yus, M.; Najera, C.; Foubelo, F. The role of 1,3-dithianes in natural product synthesis. *Tetrahedron* **2003**, *59*, 6147-6212. (b) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis,* Academic Press, London, 1994. (c) Rayner, C. M. Synthesis of thiols, sulfides, sulfoxides and sulfones. *Contemp. Org. Synth.,* **1995**, *2*, 409-440.

(2) (a) Cerella, C.; Kelkel, M.; Viry, E.; Dicato, M.; Jacob, C.; Diederich, M. In *Phytochemicals -Bioactivities and Impact on Health*, Rasooli, I., Ed.; InTech: New York, USA, 2011, Chapter 1, pp 1-42. DOI: 10.5772/26003. (b) Damani, L. A. *Sulfur-Containing Drugs and Related Organic Compounds: Chemistry, Biochemistry, and Toxicology;* Ellis Horwood Ltd.: Chichester, UK, 1989; Vol. 1, Part B: Metabolism of Sulfur Functional Groups.

(3) Singh, R. *Synthetic Drugs*, Mittal Publication, New Delhi, 2002.

(4) (a) Biellmann, J. F.; Ducep, J. B. Synthèse du squalène et d'analogues. *Tetrahedron* **1971**, *27*, 5861-5872. (b) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis,* Academic Press, London, 1994, pp 85-95.

(5) (a) Bicking, J. B.; Holtz, W. J.; Watson, L. S.; Cragoe, Jr. E. J. (Vinylaryloxy)acetic acids. A new class of diuretic agents. 1. (Diacylvinylaryloxy) acetic acids. *J. Med. Chem.* **1976**, *19*, 530-535. (b) Ding, Y.; Vara Prasad, C. V. N. S.; Smith, K. L.; Chang, E.; Hong, J.; Yao, N. Synthesis of Tipranavir Analogues as Non-Peptidic HIV Protease Inhibitors. *Lett. Org. Chem.* **2009**, *6*, 130-133. (c) Inomata, K.; Barrague, M.; Paquette, L. A. Diastereoselectivities Realized in the Amino Acid Catalyzed Aldol Cyclizations of Triketo Acetonides of Differing Ring Size. *J. Org. Chem.* **2005**, *70*, 533-539. (d) Yamauchi, M.; Katayama, S.; Watanabe, T. 2-Methylthiomethylation of 1,3-Dicarbonyl Compounds and Synthesis of 2-Methylene-1,3-dicarbonyl Compounds. *Synthesis* **1982**, 935-937.

(6) (a) Khan, A.T.; Ali, S.; Dar, A. A.; Lal, M. New three-component condensation reaction: synthesis of 1-[(alkylthio)(phenyl)methyl]-naphthalene-2-ol catalyzed by bromodimethylsulfonium bromide (BDMS). *Tetrahedron Lett.* **2011**, *52*, 5157-5160. (b) Sarkar, S.; Das, D. K.; Khan, A. T. Sodium-Hydroxide-Mediated Synthesis of Highly Functionalized [1,6]-Naphthyridines in a One-Pot Pseudo Five-Component Reaction. *Eur. J. Org. Chem.* **2013**, 6823-6830. (c) Bhattacharjee, S.; Das, D. K.; Khan, A. T. Ammonium Chloride-Catalyzed Three-Component Reaction for the Synthesis of Fused 4H-Chromene Derivatives in Aqueous Medium. *Synthesis* **2014**, *46,* 73-80. (d) Parnes, R.; Narute, S.; Pappo, D. Thiol-Promoted Selective Addition of Ketones to Aldehydes. *Org. Lett.* **2014**, *16*, 5922−5925. (e) Abaee, M. S.; Cheraghi, S.; Navidipoor, S.; Mojtahedi, M. M.; Forghani, S. An efficient tandem aldol condensation-thia-Michael addition process. *Tetrahedron Lett*. **2012**, *53*, 4405–4408.

(7) (a) Khan, A. T.; Das, D. K. Michael Initiated Ring Closure (MIRC) reaction on in situ generated benzylidenecyclohexane-1,3-diones for the construction of chromeno[3,4-b]quinoline derivatives. *Tetrahedron Lett.* **2012**, *53*, 2345-2351. (b) Khan, A. T.; Lal. M.; Ali, S.; Khan, M. M. One-pot three-component reaction for the synthesis of pyran annulated heterocyclic compounds using DMAP as a catalyst. *Tetrahedron Lett.* **2011**, *52*, 5327-5332. (c) Khan, A. T.; Lal, M.; Khan, M. M. Synthesis of highly functionalized piperidines by one-pot multicomponent reaction using tetrabutylammonium tribromide (TBATB). *Tetrahedron Lett.* **2010**, *51*, 4419-4424.

(8) Cao, H.; Zhan, H.; Cen, J.; Lin, J.; Lin, Y.; Zhu, Q.; Fu, M.; Jiang, H. Copper-Catalyzed C–O Bond Formation: An Efficient One-Pot Highly Regioselective Synthesis of Furans from (2-Furyl)Carbene Complexes. *Org. Lett.* **2013,** *15*, 1080-1083.

(9) Maiti, S.; Biswas, S.; Jana, U. Iron (III)-Catalyzed Four-Component Coupling Reaction of 1,3-Dicarbonyl Compounds, Amines, Aldehydes, and Nitroalkanes: A Simple and Direct Synthesis of Functionalized Pyrroles. *J. Org. Chem.* **2010**, *75*, 1674-1683.

(10) Wang, Y.; Huang, J.; Chai, Y.; Liu, Q.; Liang, Y.; Dong, D. Efficient One-Pot Synthesis of Highly Substituted Thiophene Library from 1,3-Dicarbonyl Compounds. *J. Comb. Chem.* **2008**, *10*, 511-516.

(11) Krylov, I. B.; Terent'ev, A. O.; Timofeev, V. P.; Shelimov, B. N.; Novikov, R. A.; Merkulova, V. M.; Nikishin, G. I. Iminoxyl Radical-Based Strategy for Intermolecular C-O Bond Formation: Cross-Dehydrogenative Coupling of 1,3-Dicarbonyl Compounds with Oximes *Adv. Synth. Catal.* **2014**, *356*, 2266-2280.

(12) Li, L.; Liu, B.; Wu, Q.; Lin, X. Catalyst-free Multicomponent Synthesis of β-Mercapto Diketones in Water. *Chin. J. Chem.* **2011**, *29*, 1856-1862.

(13) Li, Z.; Li, H.; Guo, X.; Cao, L.; Yu, R.; Li, H.; Pan, S. C−H Bond Oxidation Initiated Pummerer- and Knoevenagel-Type Reactions of Benzyl Sulfide and 1,3-Dicarbonyl Compounds. *Org. Lett.* **2008**, *10*, 803-805.

(14) (a) Simpkins, N. S. *Sulfones in Organic Synthesis; Pergamon Press: Oxford*, 1993. (b) Block, E. *Reaction of OrganosuIfur Compounds; Academic Press: New York*, 1978. (c) Liu, Y.; Jacobs, H. K.; Gopalan, A. S. A new approach to fused furan ring systems and benzofurans: intramolecular cyclization reactions of unsaturated acyloxy sulfone derivatives. *Tetrahedron Lett.* **2011,** *52*, 2935-2939. (d) Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y. Sulfonylation of Quinoline N-Oxides with Aryl Sulfonyl Chlorides via Copper-Catalyzed C–H Bonds Activation. *Org. Lett.* **2013**, *15*, 1270-1273.

(15) Trost, B. M.; Ghadiri, M. R. Sulfones as chemical chameleons. Cyclization via 1,1-dipole synthons. *J. Am. Chem. Soc.* **1984**, *106*, 7260-7261.

(16) (a) Zhang, Q.; Li, J.; Shizu, K.; Huang, S.; Hirata, S. ; Miyazaki, H.; Adachi, C. Design of Efficient Thermally Activated Delayed Fluorescence Materials for Pure Blue Organic Light Emitting Diodes. *J. Am. Chem. Soc.* **2012**, *134*, 14706-14709. (b) Kiren, S.; Padwa, A. A Benzannulation Protocol To Prepare Substituted Aryl Amines Using a Michael-Aldol Reaction of β-Keto Sulfones. *J. Org. Chem.* **2009**, *74*, 7781-7789.

(17) (a) Baidya, M.; Kobayashi, S.; Mayr, H. Nucleophilicity and Nucleofugality of Phenylsulfinate ($PhSO_2^-$): A Key to Understanding its Ambident Reactivity. *J. Am. Chem. Soc* **2010**, *132*, 4796-4805. (b) Palmieri, A.; Petrini, M. Ketosulfonyl indoles in the regiodefined synthesis of tryptophols and related indole derivatives. *Org. Biomol. Chem.* **2012**, *10*, 3486-3493.

(18) (a) Chen, Z.; Zhang, J.; Chen, J.; Deng, H.; Shao, M.; Zhang, H.; Cao, W. Highly stereoselective synthesis of *trans*-4-trifluoromethylsulfonyl-2,3-dihydrofurans from arsonium ylides and (E)-α-trifluoromethylsulfonyl-α,β-unsaturated ketones. *Tetrahedron* **2010**, *66*, 6181-6187. (b) Zhang, L.; Ding, M. H.; Guo, H. Y. One-step synthesis of α,β-unsaturated arylsulfones by a novel multicomponent reaction of aromatic aldehydes, chloroacetonitrile, benzenesulfinic acid sodium salt. *Chinese Chemical Lett.* **2012**, *23*, 1352-1354.

(19) Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixao, M. W.; Jørgensen, K. A. Asymmetric Organocatalysis with Sulfones. *Angew. Chem. Int. Ed.* **2010**, *49*, 2668-2679.

(20) Jin, Z.; Xu, J.; Yang, S.; Song, B.; Chi, Y. R. Enantioselective Sulfonation of Enones with Sulfonyl Imines by Cooperative N-Heterocyclic-Carbene/Thiourea/Tertiary-Amine Multicatalysis. *Angew. Chem. Int. Ed.* **2013**, *52*, 12354-12358.

(21) (a) Hellmann, G.; Hack, A.; Thiemermann, E.; Luche, O.; Raabe, G.; Gais, H-J. Chiral Fluorinated α-Sulfonyl Carbanions: Enantioselective Synthesis and Electrophilic Capture, Racemization Dynamics, and Structure. *Chem. Eur. J.* **2013**, *19*, 3869-3897. (b) Řehová, L.; Císařová, I.; Jahn, U. Divergent Reactivity of Alkyl Aryl Sulfones with Bases: Selective Functionalization of *ortho*-Aryl and α-Alkyl Units Enabled by a Unique Carbanion Transmetalation. *Eur. J. Org. Chem.* **2014**, 1461-1476.

(22) Fang, S-H.; Padmavathi, V.; Rao, Y. K.; Subbaiah, D. R. C. V.; Thriveni, P.; Geethangili, M.; Padmaja, A.; Tzeng, Y-M. Biological evaluation of sulfone derivatives as anti-inflammatory and tumor cells growth inhibitory agents. *International Immunopharmacology* **2006**, *6*, 1699-1705.

(23) (a) Takamuku, S.; Jannasch, P. Multiblock Copolymers Containing Highly Sulfonated Poly (arylenesulfone) Blocks for Proton Conducting Electrolyte Membranes. *Macromolecules* **2012**, *45*, 6538-6546. (b) Suzuki, Y.; Higashihara, T.; Ando, S.; Ueda, M. Synthesis and Characterization of High Refractive Index and High Abbe's Number Poly(thioether sulfone)s based on Tricyclo[5.2.1.$0^{2,6}$] decane Moiety. *Macromolecules* **2012**, *45*, 3402-3408.

(24) Xu, W.; Yang, S.; Bhadury, P.; He, J.; He, M.; Gao, L.; Hu, D.; Song, B. Synthesis and bioactivity of novel sulfone derivatives containing 2,4-dichlorophenyl substituted 1,3,4-oxadiazole/thiadiazole moiety as chitinase inhibitors. *Pesticide Biochemistry and Physiology* **2011**, *101*, 6-15.

(25) Regina, G. L.; Coluccia, A.; Brancale, A.; Piscitelli, F.; Gatti, V.; Maga, G.; Samuele, A.; Pannecouque, C.; Schols, D.; Balzarini, J.; Novellino, E.; Silvestri, R. Indolylarylsulfones as HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors: New Cyclic Substituents at Indole-2-carboxamide. *J. Med. Chem*. **2011**, *54*, 1587-1598.

(26) Wu, W-L.; Asberom, T.; Bara, T.; Bennett, C.; Burnett, D. A.; Clader, J.; Domalski, M.; Greenlee, W. J.; Josien, H.; McBriar, M.; Rajagopalan, M.; Vicarel, M.; Xu, R.; Hyde, L. A.; Del Vecchio, R. A.; Cohen-Williams, M. E.; Song, L.; Lee, J.; Terracina, G.; Zhang, Q.; Nomeir, A.; Parker, E. M.; Zhang, L. Structure activity relationship studies of tricyclic bispyran sulfone γ-secretase inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 844-849.

(27) Assadieskandar, A.; Amirhamzeh, A.; Salehi, M.; Ozadali, K.; Ostad, S, N.; Shafiee, A.; Amini, M. Synthesis, cyclooxygenase inhibitory effects, and molecular modeling study of 4-aryl-5-(4-(methylsulfonyl)phenyl)-2-alkylthio and -2-alkylsulfonyl-1H-imidazole derivatives. *Bioorg. Med. Chem.* **2013**, *21*, 2355-2362.

(28) (a) Becker, D. P.; Barta, T. E.; Bedell, L. J.; Boehm, T. L.; Bond, B. R.; Carroll, J.; Carron, C. P.; DeCrescenzo, G. A.; Easton, A. M.; Freskos, J. N.; Funckes-Shippy, C. L.; Heron, M.; Hockerman, S.; Howard, C. P.; Kiefer, J. R.; Li, M. H.; Mathis, K. J.; McDonald, J. J.; Mehta, P. P.; Munie, G. E.; Sunyer, T.; Swearingen, C. A.; Villamil, C. I.; Welsch, D.; Williams, J. M.; Yu, Y.; Yao, J. Orally Active MMP-1 Sparing α-Tetrahydropyranyl and α-Piperidinyl Sulfone Matrix Metalloproteinase (MMP) Inhibitors with Efficacy in Cancer, Arthritis, and Cardiovascular Disease. *J. Med. Chem.* **2010**, *53*, 6653-6680. (b) Kolodziej, S. A.; Hockerman, S. L.; DeCrescenzo, G. A.; McDonald, J. J.; Mischke, D. A.; Munie, G. E.; Fletcher, T. R.; Stehle, N.; Swearingen, C.; Becker, D. P. MMP-13 selective isonipecotamide α-sulfone hydroxamates. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3561-3564. (c) Sasikumar, T. K.; Qiang, L.; Burnett, D. A.; Cole, D.; Xu, R.; Li, H. M.; Greenlee, W. J.; Clader, J.; Zhang, L. L.; Hyde, L. Tricyclic sulfones as orally active γ-secretase inhibitors: Synthesis and structure–activity relationship studies. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3632-3635.

(29) Churcher, I.; Beher, D.; Best, J. D.; Castro, J. L.; Clarke, E. E.; Gentry, A.; Harrison, T.; Hitzel, L.; Kay, E.; Kerrad, S.; Lewis, H. D.; Morentin-Gutierrez, P.; Mortishire-Smith, R.;

Oakley, P. J.; Reilly, M.; Shaw, D. E.; Shearman, M. S.; Teall, M. R.; Williams, S.; Wrigley, J. D. J. 4-Substituted cyclohexyl sulfones as potent, orally active γ-secretase inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 280-284 and references therein.

(30) Richards-Taylor, C. S.; Blakemore, D. C.; Willis, M. C. One-pot three-component sulfone synthesis exploiting palladium-catalysed aryl halide aminosulfonylation. *Chem. Sci.* **2014**, *5*, 222-228 and references therein.

(31) WHO Control of the Leishmaniasis. Report of a meeting of the WHO expert committee on the control of Leishmaniasis; Geneva 3, 2010, 22-26.

(32) (a) Sundar, S.; Chatterjee, M. Visceral leishmaniasis - current therapeutic modalities. *Ind. J. Med. Res.* **2006**, *123*, 345–352. (b) Shadab, M.; Ali, N. Evasion of Host Defence by Leishmania donovani: Subversion of Signaling Pathways. *Mol. Biol. Int.* **2011**, *2011*, Article ID: 343961. doi:10.4061/2011/343961

(33) Chappuis, F.; Sundar, S.; Hailu, A.; Ghalib, H.; Rijal, S.; Peeling, R.W.; Alvar, J.; Boelaert, M. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control?. *Nat. Rev. Microbiol.* **2007**, *5*, 873–882.

(34) (a) Oliveira-Silva, F. de.; Morais-Teixeira, E. de.; Rabello, A. Antileishmanial Activity of Azithromycin Against *Leishmania* (*Leishmania*) *amazonensis*, *Leishmania* (*Viannia*) *braziliensis*, and *Leishmania* (*Leishmania*) *chagasi*. *Am. J. Trop. Med. Hyg.* **2008**, *78,* 745–749. (b) Nagle, A. S.; Khare, S.; Kumar, A. B.; Supek, F.; Buchynskyy, A.; Mathison, C. J. N.; Chennamaneni, N. K.; Pendem, N.; Buckner, F. S.; Gelb, M. H.; Molteni, V. Recent Developments in Drug Discovery for Leishmaniasis and Human African Trypanosomiasis. *Chem. Rev.* **2014**, *114*, 11305−11347.

(35) (a) Peixoto, M. P.; Beverley, S. M. In Vitro Activity of Sulfonamides and Sulfones against *Leishmania major* Promastigotes. *Antimicrob. Agents Chemother.* **1987**, *31*, 1575-1578. (b) Wyllie, S.; Patterson, S.; Stojanovski, L.; Simeons, F. R. C.; Norval, S.; Kime, R.; Read, K. D.; Fairlamb, A. H. The anti-trypanosome drug fexinidazole shows potential for treating visceral leishmaniasis. *Sci Transl Med.* **2012**, *4*, 119re1. (c) Wyllie, S.; Patterson, S.; Fairlamb, A. H. Assessing the Essentiality of *Leishmania donovani* Nitroreductase and Its Role in Nitro Drug Activation. *Antimicrob. Agents Chemother.* **2013**, *57*, 901-906.

(36) (a) Dogra, J. Current Therapies for Treatment of Cutaneous Leishmaniasis in India. *Infection* **1992**, *20*, 189-191. (b) Dogra J. A double-blind study on the efficacy of oral dapsone in cutaneous leishmaniasis. *Trans. R Soc. Trop. Med. Hyg.* **1991**, *85*, 212-213. (c) Dogra, J.; Beharilal, B.; Misra, S. N. Dapsone in the Treatment of Cutaneous Leishmaniasis. *Pharmacology and Therapeutics* **1986**, *25*, 398-400.

(37) (a) Solladie, G. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 133. (b) Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. An Unexpected Reaction of Arenesulfonyl Cyanides with Allylic Alcohols: Preparation of Trisubstituted Allyl Sulfones. *Angew. Chem., Int. Ed.* **2009**, *48*, 172-174. (c) Jegelka, M.; Plietker, B. Selective C−S Bond Formation via Fe-Catalyzed Allylic Substitution. *Org. Lett.* **2009**, *11*, 3462-3465. (d) Liu, C.-R.; Li, M.-B.; Cheng, D.-J.; Yang, C.-F.; Tian, S.-K. Catalyst-Free Alkylation of Sulfinic Acids with Sulfonamides via sp^3 C−N Bond Cleavage at Room Temperature. *Org. Lett.* **2009**, *11*, 2543-2545.

(38) (a) Muralikrishna, A.; Kannan, M.; Padmavathi, V.; Padmaja, A.; Krishna, R. "N-(4-Chloro-phen-yl)-1-(5-{[(2-phenyl-ethen-yl)sulfon-yl]meth-yl}-1,3,4-oxadiazol-2-yl)methane-sulfonamide." *Acta Cryst.* **2012**, *E68*, o2954. (b) Alonso, M.; Woller, T.; Martín-Martínez, F. J.; Contreras-García, J.; Geerlings, P.; De Proft, F. Understanding the Fundamental Role of

π/π, σ/σ, and σ/π Dispersion Interactions in Shaping Carbon-Based Materials. *Chem. Eur. J.* **2014**, *20*, 4931–4941.

(39) (a) Friesner, R. A.; Murphy, R. B.; Repasky, M. P.; Frye, L. L.; Greenwood, J. R.; Halgren, T. A.; Sanschagrin, P. C.; Mainz, D. T. Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein-Ligand Complexes. J. *Med. Chem.* **2006**, *49*, 6177−6196. (b) Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J. Med. Chem.* **2004**, *47*, 1739−1749.

(40) (a) Baiocco, P.; Colotti, G.; Franceschini, S.; Ilari, A. Molecular basis of antimony treatment in leishmaniasis. *J. Med. Chem.* **2009**, *52*, 2603−2612. (b) Verma, R. K.; Prajapati, V. K.; Verma, G. K.; Chakraborty, D.; Sundar, S.; Rai, M.; Dubey, V. K.; Singh, M. S. Molecular Docking and in Vitro Antileishmanial Evaluation of Chromene-2-thione Analogues. *ACS Med. Chem. Lett.* **2012**, *3*, 243−247.

"For Table of Contents Use Only"

Graphical abstract

Synthesis of Unsymmetrical Sulfides and Their Oxidation to Sulfones to Discover Potent Antileishmanial Agents

Ajaz A. Dar, Nagasuresh Enjamuri, Md. Shadab, Nahid Ali* and Abu T. Khan*