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Design, synthesis and antimalarial activity of benzene and isoquinoline sulfonamide derivatives☆

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Abstract—A new series of benzene and isoquinoline sulfonamide derivatives were synthesized by nucleophilic displacement reaction on benzene and isoquinoline sulfonyl chlorides by substituted amines (primary and secondary). The title compounds were evaluated for antimalarial activity against *Plasmodium falciparum* in vitro and showed MIC in the range of 2–50 μg/mL.

Malaria remains major health problem in tropical and subtropical countries.[1,2] The treatment of malaria depends largely on chemotherapeutics and chemoprophylaxis due to the existence of limitations in vaccine development and vector control. Malaria parasite, *Plasmodium falciparum*, the most severe form of malaria, has developed resistance against almost all the drugs available.[3] The design and development of novel drugs for the comprehensive treatment of malaria is highly necessary, intensive research warrants to eradicate this deadly disease.[4]

Sulfonamides represent an important class of medicinally important molecules and are known to possess wide varieties of biological activities which include antimicrobial drugs, saluretics, carbonic anhydrase inhibitors, antithyroid agents, antitumour drugs, etc.[5–14] Sulfonamides remain the most widely used antibacterial agents in the world because of their low cost, low toxicity and excellent activity against common bacterial diseases. Moreover, antimalarial activity of several benzene sulfonamides such as **1** and **2** is also reported,[15,16] Figure 1. Isoquinoline sulfonamide (H-89) **3** is a potent inhibitor of Pfmrk, one of the cyclin dependent protein kinases (CDKs) from *P. falciparum*. Plasmodial CDKs play an essential role in the growth and development of the parasite. Functional conservation among the CDKs suggests a role in cell cycle control of the malaria parasite. Support for an essential role of plasmodial CDKs comes from inhibitor studies in which mammalian CDK inhibitors possessed anti-parasitic activity in vitro.[17]

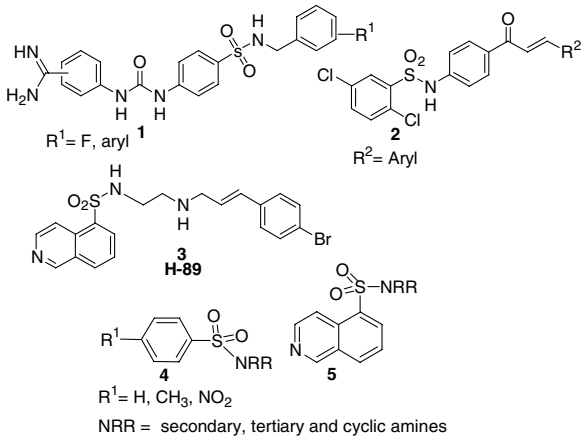

Figure 1.

These results promoted us to synthesize and evaluate a new series of benzene and isoquinoline sulfonamide derivatives for antimalarial efficacy. Our work focused on the design and synthesis of benzene and isoquinoline sulfonamide derivatives and in vitro activity of these compounds against *P. falciparum* growth in culture (Table 1).

Keywords: Benzene and isoquinoline sulfonamides; Antimalarial activity.
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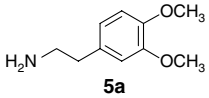
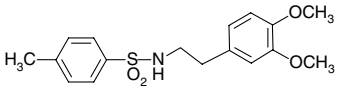
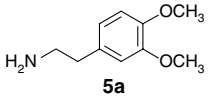
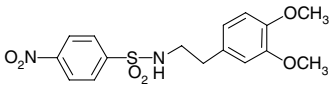
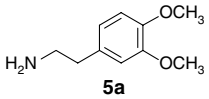
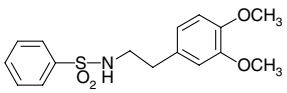
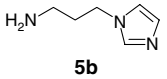
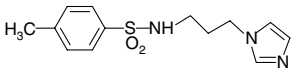
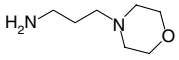
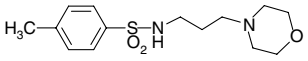
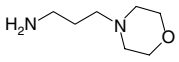
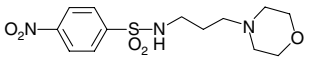
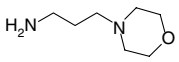
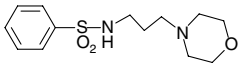
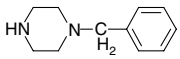
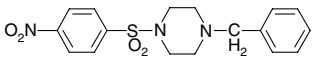
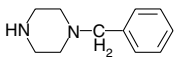
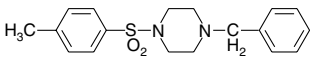
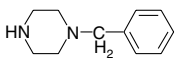
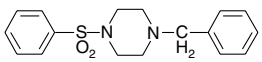
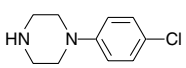
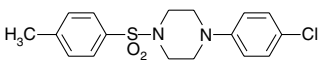
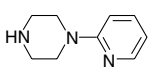
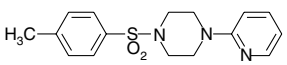
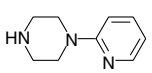
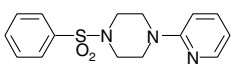
Table 1. Synthesized sulfonamide derivatives with in vitro antimalarial activity[21] against *Plasmodium falciparum*

Serial No.	Compound	R^1	$H_2N-(CH_2)_n-R^2$ **5a-c**	Structures of sulfonamides	Yield[a] (%)	MIC[b] (μg/mL)
1	**8a**	CH_3	 **5a**		84	10
2	**8b**	NO_2	 **5a**		86	10
3	**8c**	H	 **5a**		85	10
4	**8d**	CH_3	 **5b**		75	10
5	**8e**	CH_3	 **5c**		78	10
6	**8f**	NO_2	 **5c**		77	10
7	**8g**	H	 **5c**		87	10
8	**10a**	NO_2	 **7a**		79	10
9	**10b**	CH_3	 **7a**		71	10
10	**10c**	H	 **7a**		73	ND
11	**10d**	CH_3	 **7b**		69	10
12	**10e**	CH_3	 **7c**		75	ND
13	**10f**	H	 **7c**		81	10

(*continued on next page*)

Table 1 (*continued*)

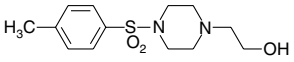
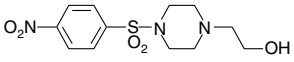
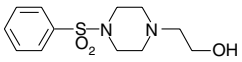
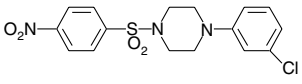
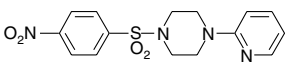
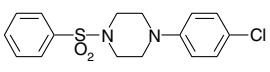
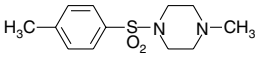
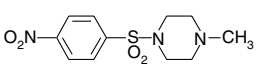
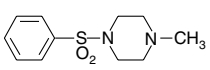
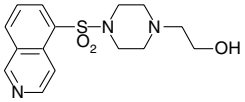
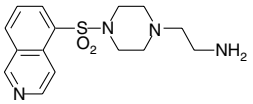
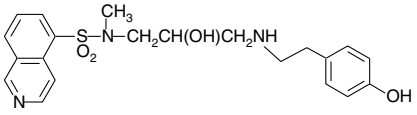
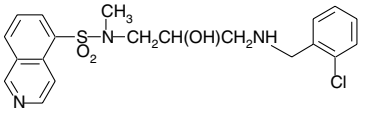
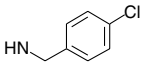
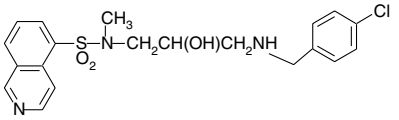
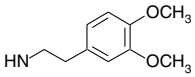
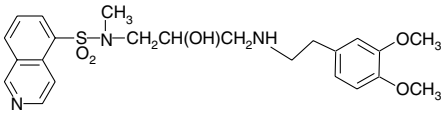
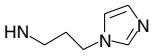
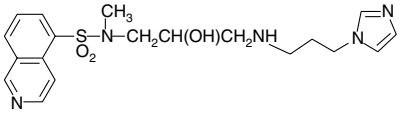
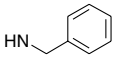
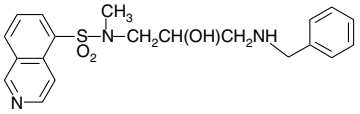
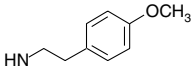
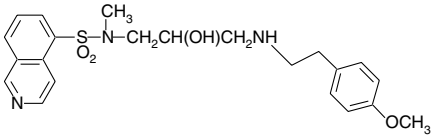
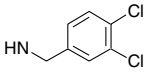
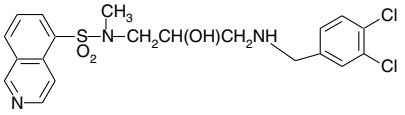
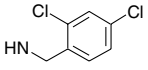
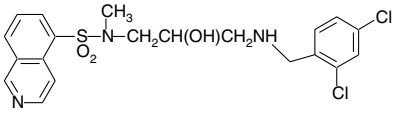
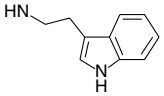
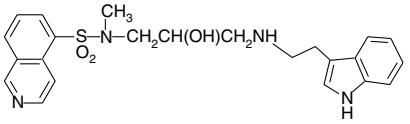
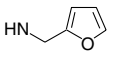
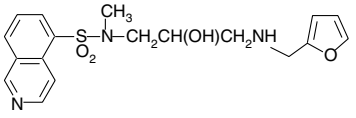
Serial No.	Compound	R^1	H_2N–(CH)$_n$–R^2 **5a-c**	Structures of sulfonamides	Yield[a] (%)	MIC[b] (μg/mL)
14	**10g**	CH_3	**7d**		76	10
15	**10h**	NO_2	**7d**		83	10
16	**10i**	H	**7d**		76	10
17	**10j**	NO_2	**7e**		73	10
18	**10k**	NO_2	**7c**		79	10
19	**10l**	H	**7b**		80	10
20	**10m**	CH_3	**7f**		83	10
21	**10n**	NO_2	**7f**		79	10
22	**10o**	H	**7f**		82	10
23	**12a**	H	**7d**		88	50
24	**12b**	H			84	10
25	**16a**	H			69	50
26	**16b**	H			71	10

Table 1 (*continued*)

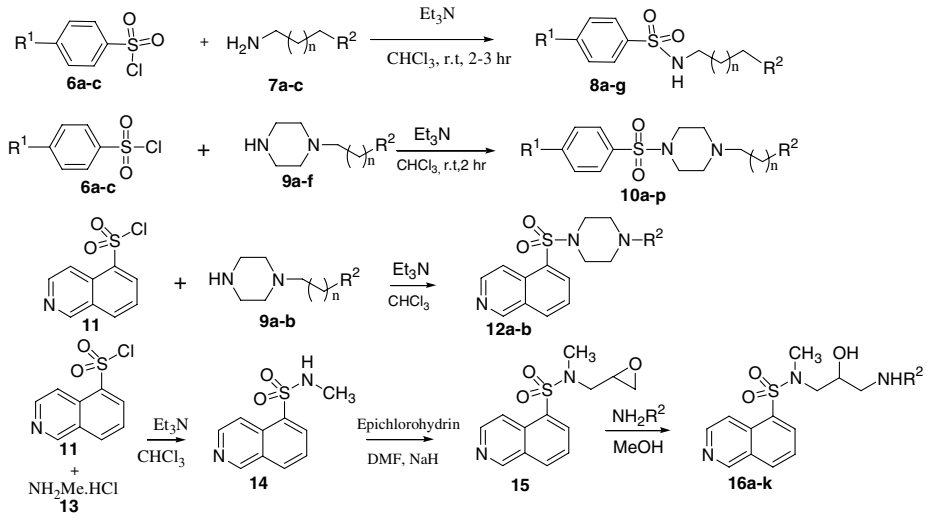
Serial No.	Compound	R^1	H_2N–(CH)$_n$–R^2 **5a-c**	Structures of sulfonamides	Yield[a] (%)	MIC[b] (μg/mL)
27	**16c**	H			66	10
28	**16d**	H			65	10
29	**16e**	H			72	50
30	**16f**	H			67	10
31	**16g**	H			64	10
32	**16h**	H			74	2
33	**16i**	H			69	2
34	**16j**	H			62	10
35	**16k**	H			67	10

[a] Reported yields are optimized.
[b] Standard drug, pyrimethamine; MIC 10 μg/mL.

The structures of the target molecules **4** and **5** are given. Benzene and isoquinoline sulfonyls are attached to secondary, tertiary and cyclic amines. Substitution of benzene and isoquinoline sulfonyl chlorides with various amines is expected to give the target molecule (Scheme 1).

Reaction of commercially available benzene sulfonyl chlorides **6a**–**c** with primary amine **7a**–**c** in the presence of triethylamine and chloroform at room temperature furnished **8a**–**g** in 75–87% yield. Similarly **6a**–**c** and isoquinoline sulfonyl chloride **11** with secondary amine **9a**–**f** under similar reaction condition gave **10a**–**p** and **12a**–**b**, respectively. To synthesize the β-amino alcohol derivatives **16a**–**k** of isoquinoline sulfonamide, **11** was reacted with methylamine hydrochloride **13** to furnish **14**. The hydrogen atom attached to nitrogen in **14** is acidic and thus reaction of **14** with NaH/DMF followed by epichlorohydrin furnished the epoxide **15**. Nucleophilic addition reaction of **15** with primary amines in MeOH gave a series of β-amino alcohol derivatives **16a**–**k** regioselectively.

All sulfonamide derivatives displayed activity against *P. falciparum* with minimum inhibitory concentrations (MIC) ranging from 2 to 50 μg/mL. The analysis of



Scheme 1.

the structures and antimalarial activity reveals that substitution in the benzene ring among the series of benzene sulfonamides did not have any effect on activity. However, isoquinoline derivatives showed better activity. Between **12a** and **12b**, compound containing amino group is more active than the hydroxyl group.

Isoquinoline sulfonamides with 2-hydroxy-propyl amines exhibited lower inhibitory activity than benzene sulfonamides. The analysis reveals that isoquinoline sulfonamide derivatives with disubstituted phenyl ring showed better inhibitory activity than other monosubstituted phenyl derivatives. Increasing hydrophilic moiety on propyl amine did not exhibit better activity. Isoquinoline sulfonamides **12a**, **16a**, **16e** containing piperazine, 4-(2-amino-ethyl)-phenol and 3-imidazol-1-yl-propylamine group, respectively, did not show good activity. Thus, 2-hydroxy propyl amines with isoquinoline on one side and dichloro phenyl ring on another side showed better antimalarial activity.

In conclusion, a series of benzene and isoquinoline sulfonamides were synthesized from corresponding sulfonyl chlorides using nucleophilic addition reaction. While benzene sulfonamides did not exhibit good activity, some of the isoquinoline derivatives showed good activity in vitro. Further optimization on the lead obtained might result into potent antimalarial agents.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.11.038.

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21. Procedure for in vitro antimalarial activity evaluation: the in vitro antimalarial assay was carried out in 96-well microtitre plates according to the micro assay of Rieckmann et al.[18] The culture of *P. falciparum* NF-54 strain is routinely being maintained in the RPMI-1640 medium supplemented with 25 mM Hepes, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat-inactivated human serum.[19] The asynchronous parasite of *P. falciparum* was synchronized after 5% D-sorbitol treatment to obtain parasitized cells harbouring only the ring stage.[20] For carrying out the assay, an initial ring-stage parasitaemia of ≈1% at 3% haematocrit in total volume of 200 μL of RPMI-1640 medium was uniformly maintained. The test compound in 20 μL volume at required concentration (ranging between 1.0 and 10 μg/mL) in duplicate wells was incubated with parasitized cell preparation at 37 °C in candle jar. After 36–40 h of incubation, the blood smears from each well were prepared and stained with Giemsa stain. The slides were microscopically observed to record maturation of ring-stage parasites into trophozoites and schizonts in the presence of different concentrations of compounds. The test concentration, which inhibits the complete maturation into schizonts, was recorded as the minimum inhibitory concentration (MIC). Pyrimethamine was used as the standard reference drug. Activity of all the tested compounds is given in Table 1.