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Broad spectrum anti-infective properties of benzisothiazolones and the parallels in their anti-bacterial and anti-fungal effects

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ABSTRACT

Various mono- and *bis*-benzisothiazolone derivatives were synthesized and screened against different strains of bacteria and fungi in order to understand the effect of multiple electrophilic sulfur atoms and substitution pattern in the immediate vicinity of reactive sulfur. *Staphyllococcus aureus*-ATCC 7000699, MRSA and *S. aureus*-ATCC 29213 (Quality Control strain) were more susceptible to this class of compounds, and the most potent derivative **1.15** had MIC_{50} of 0.4 μg/mL (cf. Gentamicin = 0.78 μg/mL). CLogP value, optimally in the range of 2.5–3.5, appeared to contribute more to the activity than the steric and electronic effects of groups attached at nitrogen. By and large, their anti-fungal activities also followed a similar trend with respect to the structure and CLogP values. The best potency of IC_{50} = 0.1 μg/mL was shown by N-benzyl derivative (**1.7**) against *Aspergillus fumigatus*; it was also potent against *Candida albicans*, *Cryptococcus neoformans*, *Sporothrix schenckii*, and *Candida parapsilosis* with IC_{50} values ranging from 0.4 to 1.3 μg/mL. Preliminary studies also showed that this class of compounds have the ability to target malaria parasite with IC_{50} values in low micromolar range, and improvement of selectivity is possible through structure optimization.

Introduction

Combating infectious diseases is a major challenge of the present century due to increasing resistance against common therapeutic agents. Among various classes of heterocyclic compounds with anti-infective properties, benzisothiazolones (BITs) are special because of the presence of electrophilic sulfur as part of the bicyclic skeleton.[1,2] Its ability to form disulfide bonds with sulfur nucleophiles in the target cells, or to chelate biologically relevant metals such as zinc from the functional domains of proteins have been correlated with the biological effects.[3–6] Recently we have conducted a series of studies to understand the effect of benzisothiazolones on cancer cells and found that they are capable of inducing apoptosis through intrinsic pathway, and can arrest the cell cycle of HeLa cells at G2/M phase.[7] Although the IC_{50} values were in micromolar range, their ability to induce DNA fragmentation, perturb mitochondrial membrane potential and more importantly, the ability of externally added sulfur nucleophiles like N-acetyl cysteine (NAC) to reverse the inhibitory effects of BITs were indicative of the direct role of sulfur in the biochemical responses.

A literature search revealed that most of the isothiazolones and benzisothiazolones (BITs) investigated thus far are 'monomeric' in the sense that they contain only one electrophilic sulfur atom. These reports showed their effect on whole cell/infectious agent (anti-proliferative effects, inhibition of blood platelet aggregation, antiviral, antibacterial & anti-fungal activities),[7–13] as well as against specific targets like human leukocyte elastase (BIT as 1,1-dioxide),[14–16] RNA polymerase,[5] HIV-NCp-7,[6] macrophage migration inhibitory factor,[17] histone acetyltransferases,[3,18] telomerase[19] and phosphomannose isomerase.[20] Introduction of additional electrophilic sulfur in the molecule could in principle augment the biological response but comparative assessment of their properties remains to be carried out in a systematic manner. The present work primarily aims to compare the activities of monomeric and dimeric BITs (Fig. 1) against different strains of bacteria, fungi and malaria parasite to understand the structural features/molecular properties that are decisive. They were synthesized by reaction of either bromosulfenyl benzoyl chloride or dithiodibenzoyl chloride with appropriate amines in presence of a base such as triethylamine.[7] Experimental procedures and spectral data of these compounds are presented in the supporting material. They differ in the nature of N-substitution and present varying degrees of steric and electronic influences in the vicinity of electrophilic sulfur.

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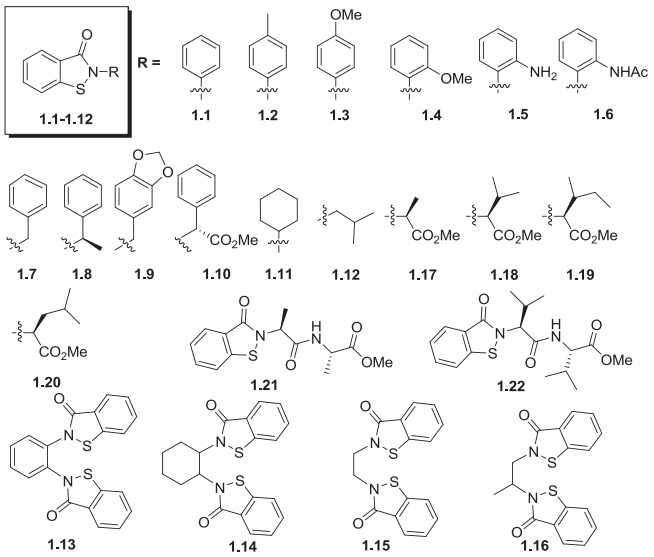

Fig. 1. Benzisothiazolone derivatives used in the present study.

Results and discussion

Antibacterial and antifungal assay results: Compounds **1.1**–**1.22** (Fig. 1) were screened against various bacteria and fungi as per literature protocols. The bacteria were tested by NCCLS method in Mueller Hinton Broth.[21] Gentamicin and Norfloxacin were used as standard drugs to compare antibacterial activity whereas Fluconazole and Amphotericin B were used for antifungal studies as controls. The bacterial strains used were: (1) *Escherichia coli* (ATCC 9637) (2) *Pseudomonas aeruginosa* (ATCC BAA-427) (3) *Klebsiella pneumoniae* (ATCC 27736) (4) *Staphylococcus aureus* (ATCC 25923) (5) *S. aureus* (ATCC 700699, MRSA), and (6) *S. aureus* (ATCC 29213, Quality Control strain).

Compounds **1.1**–**1.22** can be broadly categorized into four groups: (i) N-aryl and N-alkylaryl substituted benzisothiazolone (**1.1**–**1.10**), (ii) those derived from aliphatic or alicyclic amines (**1.11**–**1.12**), (iii) those based on amino acid esters or peptides (**1.17**–**1.22**), and (iv) benzisothiazolone dimers (**1.13**–**1.16**); the alanine-based **1.17** has previously been studied by Dou et al.[10] Among the six bacterial strains tested, *S. aureus* was more sensitive to these compounds (column 4–6, Table 1); for others (strains 1–3, SI), IC_{50} values were >50 μg/mL and are presented in SI. Among *S. aureus* strains, MRSA (ATCC 700699) and the Quality Control strain (ATCC 29213) (Table 1) in general were more susceptible compared to wild type. Although a clear structure-activity relationship in accordance with variation in N-substitution was not obvious, the fact that simple N-aryl benzisothazolones are as active as dimeric systems shows that increase in the number of electrophilic sulfur atoms does not lead to a proportionate increase in activities. Compounds **1.1**–**1.4**, **1.7** and **1.10** had IC_{50} values <2 μg/mL against *S. aureus*, **1.2** being the most potent (0.6 μg/mL). In the case of methicillin resistant *S. aureus*, compounds **1.7** and **1.15** were superior with IC_{50} of 0.4 μg/mL each. Other compounds with IC_{50} value <2 μg/mL against this strain are **1.8**, **1.9**, **1.11**, **1.14**, and **1.16**–**1.19**. The compound **1.15** was found to be the most potent (IC_{50} = 0.3 μg/mL) against the Quality Control *S. aureus* (ATCC 29213), and compounds **1.1**–**1.4**, **1.7** and **1.9** had the IC_{50} value within 2 μg/mL. Simple aryl groups or amino acid units as part of N-substitution gave sub-micro IC_{50} values while introduction of more than one amino acid residue doesn't give any advantage which becomes clear if we compare the activities of **1.17**&**1.18** vs. **1.21**&**1.22**. The fact that a number of these compounds are more active than the standard drugs Gentamycin and Norfloxacin in assays against resistant strains is particularly noteworthy (see Table 2).

After understanding the antibacterial activities of these compounds we continued our studies by evaluating their effect on various fungal strains namely: 1. *Candida albicans,* 2. *Cryptococcus neoformans,* 3. *Sporothrix schenckii,* 4. *Trichophyton mentagrophytes,* 5. *Aspergillus fumigatus* and 6. *Candida parapsilosis* (ATCC-22019). The MICs of compounds were determined by broth microdilution technique as per the guidelines of the National Committee for Clinical Laboratory Standards using RPMI-1640 media buffered with MOPS [3-(N-morpholino)propanesulfonic acid]. Starting inoculums of test culture was $1–5 \times 10^3$ CFU mL^{-1}. Micro titer plates were incubated at 35 °C. The MIC values were recorded after 48 h of incubation.[22,23] Interestingly, there were some parallels in the antifungal and antibacterial assay results. While, most of them were active with low IC_{50} values (**1.7** being one of the most potent with IC_{50} = 0.1 μg/mL against *Aspergillus fumigatus*), the compounds **1.6**, **1.10**, **1.13, 1.14, 1.21** and **1.22**, which were less potent in antibacterial assays, remained so against fungal strains as well. Among the active ones, IC_{50} value of <1 μg/mL was shown by simple N-aryl (**1.1**–**1.4**), N-alkyl (**1.11**–**1.12**) and N-arylalkyl (**1.7**–**1.9**) derivatives.

Similar trend in their antibacterial and antifungal activity prompted us to look for physicochemical properties that are likely decisive. Of various descriptors, partition coefficients (LogP) which reflects organic/aqueous solubility, seemed important as it affects

Table 1
Antibacterial activities of benzisothiazolones **1.1**–**1.22**.

No	4*		5*		6*		No	4*		5*		6*	
	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}		MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}
1.1	1.6	1.1	0.77	ND	2.1	1.6	**1.13**	18.0	10.0	10.2	4.7	6.5	6.3
1.2	1.07	0.6	0.75	ND	1.0	0.6	**1.14**	3.4	3.2	2.3	1.4	3.7	2.5
1.3	1.6	1.5	0.73	ND	1.9	1.2	**1.15**	16.7	4.1	0.9	0.4	0.4	0.3
1.4	2.0	1.0	1.07	ND	2.4	1.6	**1.16**	12.4	6.1	2.6	1.5	4.1	2.0
1.5	>50	>50	>50	>50	>50	>50	**1.17**	3.0	2.0	0.87	0.84	8.4	6.4
1.6	>50	>50	>50	>50	>50	>50	**1.18**	2.9	2.4	0.97	0.82	4.6	2.6
1.7	1.6	1.5	0.8	0.4	2.3	1.7	**1.19**	4.2	2.0	0.89	0.43	4.3	2.1
1.8	10.2	6.8	1.9	1.0	8.5	4.6	**1.20**	3.5	2.1	3.5	2.1	6.9	2.7
1.9	2.6	2.2	1.0	0.6	2.5	1.9	**1.21**	7.5	3.6	7.5	3.6	5.6	3.5
1.10	1.5	1.1	4.2	2.6	18.7	13.5	**1.22**	>50	>50	>50	>50	>50	>50
1.11	9.8	6.8	2.5	1.0	7.1	4.6	**Std1**[7]	6.25	–	>50	–	0.78	–
1.12	15.4	10.6	5.2	4.7	9.8	6.3	**Std2**[8]	0.39	–	>50	–	0.78	–

* MIC and IC_{50} values in μg/mL, MIC-Minimum inhibitory concentration; (1) *E. coli* (ATCC 9637), (2) *Pseudomonas aeruginosa* (ATCC BAA-427), (3) *Klebsiella pneumoniae* (ATCC 27736); results from assays involving these strains are given in SI; (4) *Staphylococcus aureus* (ATCC 25923), (5) *Staphylococcus aureus* (ATCC 700699, MRSA), (6) *Staphylococcus aureus* (ATCC 29213 Quality control strain for susceptibility testing), (7) Gentamicin and (8) Norfloxacin.

Table 2
Antifungal activities of benzisothiazolones.

No	1		2		3		4		5		6	
	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}
1.1	3.02	2.9	1.21	0.9	1.7	0.6	0.8	0.7	6.4	6.1	0.8	0.7
1.2	2.4	1.3	1.5	1.2	1.0	0.9	1.7	ND	13.3	4.1	0.6	0.4
1.3	3.5	2.4	1.1	0.9	0.8	0.4	>50	>50	11.0	6.9	0.7	0.6
1.4	7.2	2.9	3.8	0.9	4.0	0.6	2.6	0.7	>50	>50	3.2	0.7
1.5	4.3	2.6	2.3	1.9	11.7	5.7	3.3	ND	12.5	ND	>50	>50
1.6	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
1.7	1.5	1.3	0.9	0.7	0.5	0.4	>50	>50	1.0	0.1	0.78	0.76
1.8	1.0	0.5	2.9	1.0	1.6	0.4	0.4	0.7	6.5	0.4	2.1	0.7
1.9	0.7	0.56	0.8	0.8	0.5	0.3	1.5	ND	1.7	1.5	>50	ND
1.10	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
1.11	0.5	ND	1.3	1.0	0.6	0.4	1.0	0.7	3.7	0.4	0.9	0.7
1.12	0.6	ND	0.4	ND	1.4	ND	>50	>50	2.6	1.3	1.1	1.0
1.13	25	14.2	14.4	13.7	>50	>50	13.6	12.5	>50	>50	17.1	15.2
1.14	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
1.15	1.54	1.51	2.2	1.4	3.5	2.3	2.9	ND	12.5	ND	>50	>50
1.16	3.1	2.2	1.67	1.61	6.6	3.7	4.3	ND	12.5	ND	>50	>50
1.17	2.7	1.9	2.0	1.4	12.2	2.9	12.0	11.4	25	ND	12.5	ND
1.18	2.3	1.2	4.5	2.5	11.9	2.5	2.4	1.7	12.5	ND	3.1	1.6
1.19	2.5	1.6	8.3	7.3	18.2	4.7	>50	>50	12.5	ND	4.5	3.1
1.20	1.9	1.5	10.5	8.6	20.4	2.9	11.4	6.2	>50	ND	4.9	2.4
1.21	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
1.22	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
Std1[7]	1	–	2	–	2	–	>32	–	>32	–	2	–
Std2[8]	0.016	–	0.125	–	0.25	–	0.25	–	0.5	–	0.016	–

[*] MIC and IC_{50} values in μg/mL, MIC-Minimum inhibitory concentration. 1. *Candida albicans*, 2. *Cryptococcus neoformans*, 3. *Sporothrix schenckii*, 4. *Trichophyton mentagrophytes*, 5. *Aspergillus fumigatus*, 6. *Candida parapsilosis* (ATCC-22019), 7. Fluconazole and 8. Amphotericin-B.

membrane permeation. To make comparison, ClogP values of compounds studied here were first calculated (SI). Among N-aryl & N-alkylaryl substituted benzisothiazolones (**1.1**–**1.10**), compounds **1.5** and **1.6** had ClogP values of 2.13 and 2.37 respectively while that of others were higher, in the range of 2.74–3.85 (SI). Since **1.5** and **1.6** were the least potent in antibacterial assays, their lower partition coefficients appeared as one of the contributory factors. Among dimers, **1.13** with ClogP of 4.56 was least potent while the others (**1.14**–**1.16**) with this value in the range of 3.1–4.1 were relatively more active against S. aureus strains. This suggested that there is a threshold value beyond which ClogP value could adversely affect the potency. In the case of benzisothiazolones having simple hydrophobic groups (**1.11**–**1.12**), aminoacids (**1.17**–**1.20**), and peptides (**1.21**–**1.22**), the alanine-based systems **1.17** and **1.21** had lower ClogP values (1.76 and 1.50 respectively). For others, it was in the range of 2.7–3.6. In the case of **1.17**–**1.19** there is a likelyhood of amino acid transporters also getting involved in cellular uptake. It is important to mention that transporters of amino acids, especially hydrophobic ones are highly functional in *S. aureus*. The transporter BrnQ1, for example is involved in the uptake of Val & Leu where as BrnQ2 is linked with Ileu trasport.[24] In general, a larger fraction of active compounds have partition coefficients in the range of 2.5–3.5 A plot of Log($1/IC_{50}$) vs. ClogP in the case of *S. aureus* (ATCC 700699, MRSA) is given in Fig. 2a.

With regard to antifungal assay results, the compounds **1.6**, **1.10**, **1.13**, **1.14**, **1.21** and **1.22** remained less potent compared to others. As in the case of antibacterial assay results, CLogP values in the range of 2.5–3.5 seem to favour antifungal activities which is more pronounced in the case of Candida albicans, *Cryptococcus neoformans* and *Trichophyton mentagrophytes* as shown in Figs. 2b–d. Relatively lower activities of dipeptide derivatives **1.21**–**1.22** compared to their lower homologues **1.17**–**1.18**, lower potencies of dimers **1.13** and **1.14** (ClogP > 4) compared to **1.15** & **1.16** (ClogP 2.78–3.1) were also consistent. Since antibacterial and antifungal activities of the simple N-phenyl derivative **1.1** was comparable to that of other potent ones listed in Fig. 1, we prepared a subset of compounds (**1.23**–**1.31**, Fig. 3) with halogen or CF_3 groups on the aromatic ring to see whether any structure-activity relationship would emerge. Since the N-aryl derivatives listed in Fig. 1 all carry electron-donating substituents, these new compounds were expected to reveal the effect of electron withdrawing groups and the influence of steric effects. They were synthesized and screened against bacteria and fungi as per the protocol described earlier. To our surprise, these compounds were less potent in antibacterial and antifungal assays. Their MIC values were >50 μg/mL against *E. coli* (ATCC 9637), *Pseudomonas aeruginosa* (ATCC BAA-427) and *Klebsiella pneumoniae* (ATCC 27736), whereas that against *S. aureus* strains were between 3.12 and 25 μg/mL. Their MIC values against fungal strains were also low

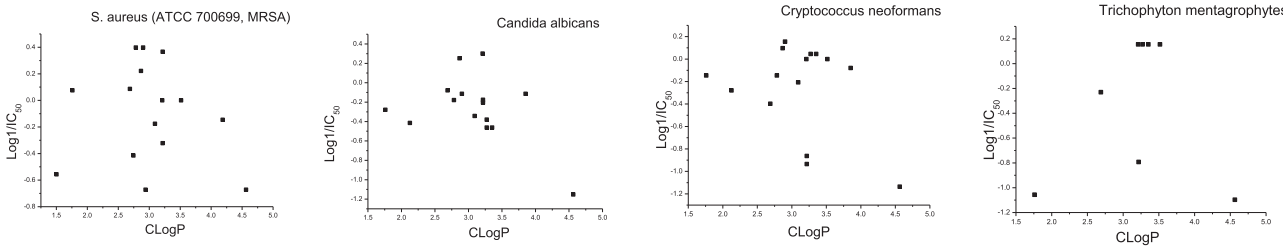

Fig. 2. Log $1/IC_{50}$ vs. CLogP plot for antibacterials and antifungal activities of various compounds showing the importance of optimal partition coefficient for better activity.

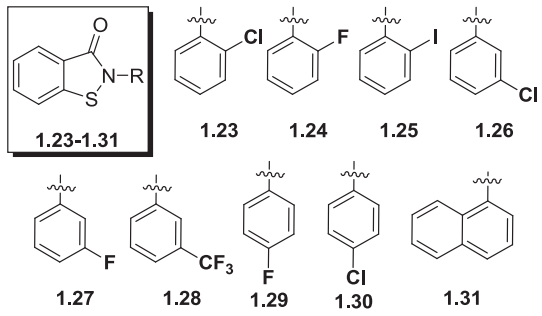

Fig. 3. A subset of benzisothiazolones derivatives synthesized to understand the effect of halogen substitution around the aromatic ring.

and ranged between 12.5 and 50 μg/mL (SI). Importance of correct lipophilicity/hydrophilicity balance for better activity was evident in these cases also. Compounds **1.23**, **1.26** and **1.30** contain additional chlorine atom compared to compound **1.1**, which led to increase in ClogP from 3.353 to 4.066 (increase of 0.713). Similarly compounds **1.25**, **1.28**, and **1.31** had ClogP values of 4.476, 4.236 and 4.527 respectively, which is outside the favorable limit as per the previous observations. The fluorine analogues **1.24**, **1.27** and **1.29** were the exceptions, which, despite having ClogP value of 3.5, were not superior in their potencies (3.12–25 μg/mL). Influence of factors other than partition coefficient in the potencies of these compounds need to be investigated in detail and will be the subject of our future investigations.

Previously, Lu and coworkers have reported the inhibition of trypanothione reductase by benzisothiazolones. In this study, they also demonstrated their anti-trypanosomial activity through effect on ROS detoxification.[25] Malaria is another parasitic disease posing threat due to decreasing clinical efficacy of existing drugs, and there is lot of interest to identify new drug candidates against the plasmodium parasites.[26] Since parasite survival in the host relies on the action of cysteine-containing proteins like falcipain (in *P. falciparum*), we envisioned that benzisothiazolone derivatives will be interesting candidates to look at, and *in vitro* anti-malarial assays involving the monomeric and dimeric BITs in our hand were performed following literature protocol (SI). During the course of publication of these results, a very relevant publication has come from the group of Odom John and coworkers which highlight ability of this class of compounds to interfere with methylerythritol pathway (MEP) in malaria parasites by targeting IspD (2-C-methyl-D-erythritol-4-phosphate cytidyltransferase) which catalyzes the condensation of methylerythritol phosphate (MEP) with cytidine triphosphate (CTP).[27] Although the initial leads were identified through high throughput screening, detailed structure activity relationship studies were performed and a clear understanding on their affinity towards this target was confirmed through molecular modeling, site-directed mutagenesis and crystallographic studies. These results also point towards an initial non-covalent recognition of BITs in the active site of IspD followed by disulfide formation with its Cys202. More focused experiments to understand the specificity towards MEP pathway by supplementing the isoprenoid precursor IPP however showed that off-target effects could also contribute to their anti-parasitic effects. These observations make comparative assessment of the activities of monomeric and dimeric BITs more relevant and the results we have obtained are discussed below.

Among the compounds tested against *Plasmodium falciparum* (Strain 3D7), the simple N-phenyl derivative (**1.1**) was the most potent with an IC_{50} value of 0.74 μM while the corresponding value for the tolyl derivative **1.2** was 1.66 μM (Table 3). The CC_{50} values of these two compounds against Verona cells were 19.43 and 19.95 μM with the selectivity indices of 26 and 12 μM respectively.

Table 3
Antimalarial activities of benzisothiazolones against *Plasmodium falciparum* (Strain 3D7; CQ sensitive).

No.	IC_{50} μM	CC_{50} μM	SI
1.1	0.74	19.43	26.256
1.2	1.66	19.95	12.018
1.3	>2.0	32.59	na
1.4	>2.0	24.49	na
1.5–1.28	>2.0	ND	na
1.29	0.97	85.4	84.43
1.30	0.92	71.7	70.78
1.31	2.64	90.8	34.39
Chloroquine diphosphate	0.0054 ± 0.0001	–	125.85

IC_{50} values of other compounds (**1.5**–**1.28** and **1.31**) were above 2.0 μM (SI). This includes benzisothiazolone dimers as well and shows that the presence of multiple electrophilic sulfur atoms need not give an advantage in this case. Interestingly, compounds **1.29** and **1.30** with fluorine or chlorine at the para position exhibit comparable activity as that of **1.1** with ~3-fold increase in the selectivity index which is remarkable.

These observations have lot of significance because of the increasing need to identify new anti-plasmodial agents from new structural classes. Apart from making a comparative assessment of antibacterial and antifungal activities of benzisothiazolones, our studies show that the bioactivities of benzisothiazolones can be modulated by fine-tuning the substitution pattern around the core. This can be used favourably to improve the selectivity profile as in the case of halo-substituted derivatives mentioned above.

Conclusion

In this study, we have compared the antibacterial and antifungal activities of a selected group of benzisothiazolones in both monomeric and dimeric forms. A number of derivatives with sub-micromolar IC_{50} values against these infectious agents were identified. Drug resistant *S. aureus* (ATCC 700699) and the Quality Control *S. aureus* (ATCC 29213) were more susceptible to these compounds, and the most active compounds **1.7** and **1.15** had IC_{50} values of 0.4 μg/mL each against *S. aureus* (ATCC 700699, MRSA; cf. Gentamicin = 0.78 μg/mL). Interestingly, CLogP value, optimally in the range of 2.5–3.5, was found to exert more influence on the activity than steric and electronic effects from groups attached to nitrogen. Dimeric benzisothiazolones, despite having two electrophilic súlfur atoms, did not exhibit a proportionate increase in potency. Preliminary antimalarial evaluation led to the identification of a few simple N-aryl derivatives with sub-micromolar IC_{50} values. Significant improvement in selectivity index on introducing halo-substituents on this aromatic ring is noteworthy since such structure optimization would enable us to identify candidates with acceptable safety profile for further development.

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A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2017.01.027.

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