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EXPLORATION OF [60]FULLERENE-MALEIMIDE DERIVATIVES AS ANTIMICROBIAL AGENTS

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ABSTRACT
The antimicrobial activities of [60]fullerene-Maleimide derivatives were screened against panel of four fungus (C. albicans, C. tropicalis, A. niger and A. clavatus) and two bacteria (S. aureus and E. coli). The minimum inhibitory concentration (MIC) was determined by broth microdilution method. [60]fullerene-Maleimide derivative showed better activity than that of its precursor malonate. Out of compound tested, fullerene derivative **3b** registered significant activity.

KEYWORDS
Fullerene, Maleimide, MIC, antifungal, antibacterial

INTRODUCTION
Since its discovery, fullerenes have been intensely studied for material and biological applications owing to its remarkable physical and chemical properties[i-xv].Fullerene derivatives are known to exhibit a variety of therapeutically interesting utilities such as antibacterial[ii-iv], antioxidant[v], anti-HIV[vi,vii], anti-inflammatory[viii], anticancer[ix], photo induced DNA cleavage[x-xi] and anti-influenza virus[xii]. Recently, some fullerenes derivatives have been incorporated in enzyme inhibitory activities such as hepatitis C virus-polymerase and protease[xiii], HIV-reverse transcriptase[xiv] and HIV-protease[xv]. However, the low solubility of fullerene derivatives in the water or water soluble solvents limits its medical applications.
On the other hand, maleimide derivatives are endowed with several pharmacological activities such as antimicrobial[xvi-xvii], analgesic[xvii] anti-inflammatory[xix], anticancer[xx], antiproliferative activities[xxi]and nematicidalactivities[xxii]. Maleimide are well known in literate as inhibitors of protein kinase[xxiii], monoglyceridelipase[xxiv], glycogen synthase kinase[xxv], etc. In bioconjugate chemistry and biotechnology, maleimides are of great interest for its reaction specificity with the biothiols[xxvi]. Recently, our group has reported the antimicrobial activities of several N-aryl maleimides[xxvii-xxviii].
The aforementioned results suggested that fullerene and maleimides could be useful entities for development of new bioactive molecule. In best of our knowledge, the antimicrobial

activities of [60]fullerene-maleimide derivatives not known in the literature. In this manuscript, the antimicrobial activities of [60]fullerene-maleimide derivatives is reported.

EXPERIMENTAL

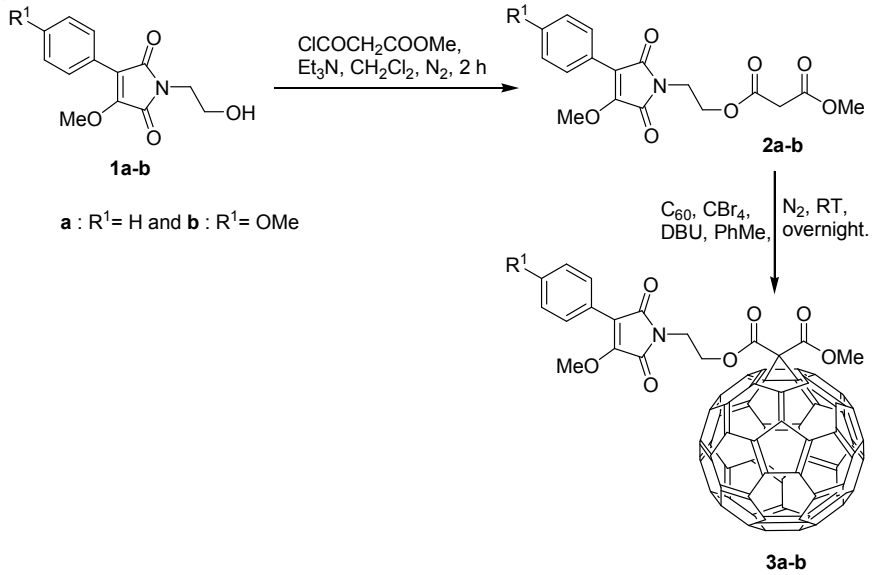
Antimicrobial assay

The antimicrobial activity of malonates **2a-b** and [60]fullerene-maleimide derivatives **3a-b** was carried out by the broth micro dilution method[xxix]. All the MTCC were received from Institute of Microbial Technology Chandigarh, and tested against the standard antibacterial drug ampicillin and antifungal drug griseofulvin. Nutrient medium, Mueller Hinton broth was used to grow the bacterial and fungal strains, and dilutes the drug suspension for the test. The size of inoculum for test the strain was adjusted to 10^8 CFU/ml comparing the turbidity. The primary and secondary screenings were done by serial dilutions. Each synthesized molecule and the reference drugs were diluted so as to obtain 2000 µg/ml concentration as the stock solution. The molecules which were found to be active amid their primary screening (i.e. 500, 250 and 200 µg/ml concentrations) were further subjected to the their screening of second set with dilution at 100, 50, 25 and 12.5 µg/ml concentrations against all microorganisms. 10 µl suspensions were further inoculated on appropriate media and growth was noted after the period of 24 and 48 h. The control tubes with reference drugs were immediately subcultured by evenly spreading a loopful over an area of plate of medium suitable for the growth of the test organism. The tubes were then kept for incubation at 37 °C for 24 h. The highest dilution preventing the appearance of turbidity after spot subculture was considered as the MIC, µg/ml and are given Table 1.

RESULTS AND DISCUSSION

Chemistry

The [60]fullerene-maleimide derivatives**3a-b** have been synthesized as per our recently reported procedure[xxx] and summarized in scheme 1.



Scheme I: Synthesis of [60]fullerene-maleimide derivatives

Antimicrobial activity

The newly synthesized malonates **2a-b** and [60]fullerene derivatives **3a-b** were assessed for their *in vitro* antifungal activity against *Candida albicans MTCC 227, Candida tropicalis MTCC 184, Aspergillus nigerMTCC 282 and Aspergillus clavatus MTCC 1323*) and

antibacterial activity against *Staphylococcus aureus MTCC 96* and *Escherichia coliMTCC 443*). Griseofulvin and ampicillin were used as standard drug respectively. The MICs determined out by broth microdilution method are expressed in µg/ml and are given in Table 1.

Table 1.*In vitro* antimicrobial activity of malonates **2a-b** and [60]fullerene derivative **3a-b**

Compound	Minimum Inhibitory Concentration (MIC) in µg/ml					
	Fungus				Bacteria	
	C. a.	***C. t.***	***A. n.***	***A. c.***	***S. a.***	***E. c.***
2a	1000	>1000	-	-	500	250
2b	1000	500	-	>1000	500	250
3a	1000	250	-	-	500	125
3b	**500**	250	1000	-	**250**	125
Griseofulvin	500	100	100	100	NA	NA
Ampicillin	NA	NA	NA	NA	250	100

C. a. *Candida albicans*; C. t. *Candida tropicalis*; A. n. *Aspergillus niger*; A. c. *Aspergillus clavatus*; S. a. *Staphylococcus aureus;* E. c. *Escherichia coli;* (-): Inactive; NA: Not Applicable

The result of antimicrobial screening (Table 1) revealed that, most of the compounds showed moderate to good antibacterial activity. In case of Gram positive bacteria *Staphylococcus aureus,* fullerene-maleimide derivative **3b** (MIC 250µg/ml) displayed better activity than that of its precursor malonate **2b** (MIC 500µg/ml) which is comparable to standard drug ampicillin(MIC 250 µg/ml). The remaining compounds **2a**, **2b** and **3a** showed moderate activity (MIC 500µg/ml) against same species. While, Gram negative bacteria *E. coli*, compound **3a** & **3b** (MIC 250µg/ml) displayed marginal activity. The compounds showed comparatively better activity for Gram positivebacteria *Staphylococcus aureus*, than Gram negative bacteria *E. coli*. The antifungal activity against *Candida albicans*, screening study reveals that compound **3b** (MIC 500µg/ml) comparable activity to standard drug griseofulvin(MIC 500 µg/ml). The remaining compounds exhibited no significantactivity for rest of the fungal species.

Results of screening clearly illustrated that compounds having [60]fullerene-maleimide derivatives showed better antimicrobial activity in comparison with their corresponding maleimide derivatives. Moreover compounds possessing electron donating methoxy group showed better activity than that their unsubstituted analogue. Amongst all tested compound, fullerene-maleimide derivative **3b** has registered significant antimicrobial activity.

CONCLUSION

All precursor malonates and [60]fullerene-maleimide conjugates were screened for their antifungal and antibacterial activity. The [60]fullerene-maleimide derivatives showed better antimicrobial activity than corresponding maleimide derivatives, indicating the contribution of fullerene moiety towards antimicrobial activity. Electron donating methoxy substituent showed enhanced antimicrobial activity. The compounds showed good activity for Gram positive bacteria,*Staphylococcus aureus* and fungal strain,*Candida albicans*.

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