RESEARCH ARTICLE

Synthesis of Novel Diarylsulfonylurea-chalcone Hybrid Molecules with Potential *In Vitro* Antimicrobial Activity

M. Akkulu Naidu[1], Y. Rajendra Prasad[2]

[1]Department of Biotechnology, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India, [2]Department of Pharmaceutical Chemistry, A U College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India

Abstract

Introduction: To study the antimicrobial effect of novel diarylsulfonylurea-chalcone hybrids with significant associated morbidity and mortality which is mainly due to the development of microbial resistance to the existing antimicrobial agents. **Materials and Methods:** The antimicrobial effect of novel diarylsulfonylurea-chalcone hybrid molecules was evaluated by agar well diffusion method against various strains of bacteria and fungi. **Results:** Most of the compounds showed promising antibacterial and antifungal activity. **Conclusion:** The results in the present study suggest that novel diarylsulfonylurea-chalcone hybrids can be used in treating diseases caused by the tested organisms.

Key words: Agar well diffusion method, antimicrobial, diarylsulfonylurea-chalcone hybrids, infections, pharmacological agent

INTRODUCTION

Currently, microbial infections have become an important clinical threat, with significant associated morbidity and mortality which is mainly due to the development of microbial resistance to the existing antimicrobial agents. Nowadays, microbial infections are one of the huge concerns because they are main primary causes of death worldwide, especially in health care, where people are generally more susceptible.[1-3] Throughout history, there has been a constant battle between humans and the multitude of microorganisms that cause infections and diseases. The treatment of bacterial and fungal infections is remains a challenging therapeutic problem because of emerging infectious diseases and the elevated number of multidrug-resistant microbial pathogens. Despite the many antibiotics and chemotherapeutics available, the emergence of old and new antibiotic-resistant bacterial strains in the last decades has generated a substantial need for new classes of antibacterial agents.[4] The increasing incidence of infection caused by the rapid development of bacterial resistance to most known antibiotics is a serious health problem. While many factors may be responsible for mutations in microbial genomes, the incorrect use of antibiotics has been thoroughly demonstrated to greatly increase the development of resistant genotypes. The need for effective therapies against multidrug-resistant bacterial strains has stimulated research into the design and synthesis of novel antimicrobial molecules.[5] Diarylsulfonylureas are the structural analogs of urea (NH_2CONH_2) with aromatic sulfonyl group in the position 3 and an aromatic or heteroaromatic ring at the position 1. Diarylsulfonylureas became widely available since 1955 as popular antidiabetic drugs in clinical practice for the treatment of type 2 diabetes, by virtue of their insulin secretagogue properties. The synthesis of compounds containing diarylsulfonylurea moiety has been a subject of extensive research in the recent past because of their enormous biological activities.[6-8] Besides their various pharmacological activities, diarylsulfonylurea has been explored for different optical applications including second harmonic generation materials in non-linear optics, fluorescent probe for sensing different molecules.

Address for correspondence:
M. Akkulu Naidu, Department of Biotechnology, Acharya Nagarjuna University, Nagarjunanagar 522510, Guntur, Andhra Pradesh, India.
E-mail: manaidupharmacy@gmail.com

Received: 06-05-2018
Revised: 17-06-2018
Accepted: 26-06-2018

The objective of this work was to study the novel diarylsulfonylurea evaluated for their applicability in increasing various strains of bacteria and fungi.

MATERIALS AND METHODS

Chemicals and reagents

All chemicals used in this experiment were of highest purity and obtained from Sigma (Bangalore, India) and Merck (Mumbai, India).

With respect to the antimicrobial activity, the standard strains were procured from the National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratory, Pune, India. The antimicrobial activity of the synthesized compounds was determined by agar well diffusion method as recommended by the National Committee for Clinical Laboratory Standards.[9,10]

Collection of microorganism

All the compounds synthesized in the present study were evaluated for antimicrobial activity against bacteria, namely *Bacillus subtilis* (NCIM 2063), *Bacillus pumilus* (NCIM 2327), *Staphylococcus aureus* (NCIM 2079), *Micrococcus luteus* (NCIM 2155), *Pseudomonas aeruginosa* (NCIM 2036), *Klebsiella pneumonia* (NCIM 5082), *Escherichia coli* (NCIM 2065), *Proteus vulgaris* (NCIM 2813), *Candida albicans* (NCIM 3102), *Aspergillus niger* (NCIM 548), *Aspergillus oryzae* (NCIM 643), and *Penicillium chrysogenum* (NCIM 738). Serial solutions of synthesized compounds were diluted in dimethyl sulfoxide (1% DMSO) to give a final concentration ranging from 16 to 512 µg/mL used for determining minimum inhibitory concentration (MIC) value. The MIC was defined as the lowest concentration of compound required for a complete inhibition of the bacterial and fungal growth after incubation time. For antibacterial activity, nutrient agar was used seeded with 0.1 mL of the respective bacterial culture strains suspension prepared in a sterile saline (0.85%) of 10^5 CFU/mL dilution.

Antifungal activity

For antifungal activity, different fungal spore suspensions in sterile distilled water were adjusted to give a final concentration of 10^6 CFU/mL. An inoculum of 0.1 mL spore suspension of each fungus was spread on potato dextrose agar plates. The wells of 6 mm diameter were filled with 0.1 mL of each compound having different concentrations separately for each test of bacterial and fungi strain. The DMSO (1%) alone was used as a control. The antibiotic chloramphenicol (16 µg/mL) and ketoconazole (16 µg/mL) are used as reference antibacterial and antifungal agents, respectively, for comparison. Inoculated plates in triplicate were then incubated at 37 ± 0.5°C for antibacterial activity for 24 h and 48 h at 28 ± 0.2°C for antifungal activity. After incubation, the MICs were noted.

RESULTS AND DISCUSSION

The antibacterial activity of diarylsulfonylurea-chalcone hybrid molecules against B. subtilis (NCIM 2063), B. pumilus (NCIM 2327), *S. aureus* (NCIM 2079), M. luteus (NCIM 2155), P. aeruginosa (NCIM 2036), K. pneumonia (NCIM 5082), *E. coli* (NCIM 2065), and P. vulgaris (NCIM 2813) was shown in Tables 1 and 2.

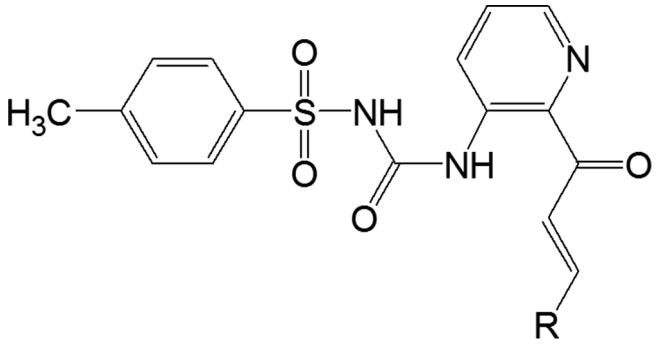
The antifungal activity of diarylsulfonylurea-chalcone hybrid molecules against *C. albicans* (NCIM 3102), *A. niger* (NCIM 548), *A. oryzae* (NCIM 643), and *P. chrysogenum* (NCIM 738) was shown in Table 3.

The results of antimicrobial activity of the synthesized compounds (II.1–28) against selected Gram-positive, Gram-negative bacteria, and fungi are illustrated in Tables 1-3. The compounds II.14 and II.23 were found to be more active than other compounds with MIC 16–32 µg/mL against all tested microorganisms. Compounds II.1, II.2, II.9, II.10, II.11, II.15, II.25, and II.28 showed less antimicrobial activity with MIC 256–512 µg/mL. From the results of antibacterial activity, compounds II.14, II.16, and II.17 were found to be more active against all Gram-positive bacteria with MIC value 16 µg/mL but with less potency against *M. luteus*. Among all the tested compounds, compound II.23 showed significant inhibition against all Gram-negative bacteria with MIC 16 µg/mL except a moderate potency against *E. coli*. A broad spectrum of antifungal activity of the compounds II.14 and II.23 was obtained against all the fungi with MIC 16 µg/mL, while other compounds displayed less antifungal activity.

From the obtained data, the following conclusions on antimicrobial activity can be made: The compounds substituted with halogens on the phenyl ring at ortho, meta, and para positions enhanced the antibacterial activity (F > Cl > Br) as seen in the case of compounds II.17–22. It is also interesting to observe an increase in activity when the nitro group is present at the ortho position of the phenyl ring when compared to the substitution at meta position as seen in the case of compounds II.14 and II.15. The compound II.16 having nitro group at position 2 and hydroxyl group at position 5 of the phenyl ring also contributed favorably to the antibacterial activity. It is noteworthy that compounds II.2–8 having electron donating substituents (OCH_3 > $N(CH_3)_2$ > CH_3) on the phenyl ring at ortho, meta, and para positions were found to enhance the antibacterial activity.

A decrease in the antimicrobial activity is attributed to the presence of hydroxyl group on the phenyl ring at ortho,

Table 1: Antibacterial activity of diarylsulfonylurea-chalcone hybrids (II.1–28)

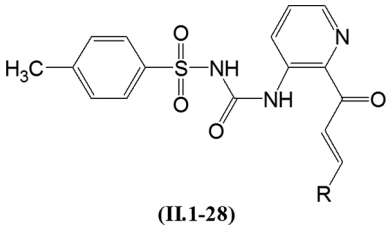


(II.1-28)

Compound	R	MIC µg/mL			
		Gram-positive bacteria			
		Bs	Bp	Sa	Ml
II.1	C_6H_5	512	512	512	512
II.2	4-MeC_6H_4	256	256	128	256
II.3	4-$NMe_2C_6H_4$	64	64	64	128
II.4	3-$OMeC_6H_4$	128	128	128	128
II.5	4-$OMeC_6H_4$	64	128	128	128
II.6	3,4-di$OMeC_6H_3$	32	64	64	128
II.7	2,4-di$OMeC_6H_3$	32	32	32	128
II.8	3,4,5-tri$OMeC_6H_2$	32	32	32	256
II.9	2-OHC_6H_4	512	512	256	256
II.10	3-OHC_6H_4	512	512	512	512
II.11	4-OHC_6H_4	256	128	256	128
II.12	3-OEt, 4-OHC_6H_3	128	64	128	512
II.13	3-OMe, 4-OHC_6H_3	64	64	128	128
II.14	2-$NO_2C_6H_4$	16	16	16	32
II.15	3-$NO_2C_6H_4$	256	256	256	256
II.16	5-OH,2-$NO_2C_6H_3$	16	16	16	64
II.17	3-FC_6H_4	16	16	16	64
II.18	4-FC_6H_4	16	32	32	64
II.19	2-ClC_6H_4	64	64	64	128
II.20	4-ClC_6H_4	32	32	32	64
II.21	2,4-diClC_6H_3	16	32	32	64
II.22	3-BrC_6H_4	16	16	64	16
II.23	4-Allyl-OC_6H_4	32	16	16	32
II.24	Phenylethene-yl	128	128	128	256
II.25	Pyrrol-2-yl	256	128	128	256
II.26	Pyridin-3-yl	128	128	128	128
II.27	Pyridin-4-yl	128	64	64	64
II.28	Anthracen-9-yl	512	512	512	512
Chloramphenicol	-	16	16	16	16

MIC: Minimum inhibitory concentration, *Bs: Bacillus subtilis (NCIM 2063), Sa*: *Staphylococcus aureus (NCIM 2079),* Bp: *Bacillus pumilus (NCIM 2327)*, ML: *Micrococcus luteus (NCIM 2155)*

Table 2: Antibacterial activity of diarylsulfonylurea-chalcone hybrids (II.1-28)



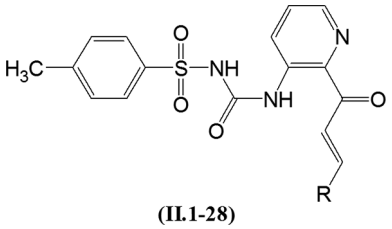
(II.1-28)

Compound	R	MIC µg/mL			
		Gram-negative bacteria			
		Pa	Kp	Ec	Pv
II.1	C_6H_5	512	512	512	512
II.2	4-MeC_6H_4	256	256	256	256
II.3	4-$NMe_2C_6H_4$	64	128	64	128
II.4	3-$OMeC_6H_4$	128	128	128	128
II.5	4-$OMeC_6H_4$	64	128	128	128
II.6	3,4-di$OMeC_6H_3$	32	128	64	128
II.7	2,4-di$OMeC_6H_3$	32	128	32	128
II.8	3,4,5-tri$OMeC_6H_2$	32	256	32	256
II.9	2-OHC_6H_4	512	256	512	256
II.10	3-OHC_6H_4	512	512	512	512
II.11	4-OHC_6H_4	256	128	128	128
II.12	3-OEt, 4-OHC_6H_3	128	512	64	512
II.13	3-OMe, 4-OHC_6H_3	64	128	64	128
II.14	2-$NO_2C_6H_4$	16	32	32	32
II.15	3-$NO_2C_6H_4$	256	256	256	256
II.16	5-OH,2-$NO_2C_6H_3$	16	64	16	64
II.17	3-FC_6H_4	16	64	16	64
II.18	4-FC_6H_4	32	16	32	16
II.19	2-ClC_6H_4	64	128	64	128
II.20	4-ClC_6H_4	32	64	32	64
II.21	2,4-diClC_6H_3	16	64	32	64
II.22	3-BrC_6H_4	32	128	16	16
II.23	4-Allyl-OC_6H_4	16	16	32	16
II.24	Phenylethene-yl	128	256	128	256
II.25	Pyrrol-2-yl	256	256	128	256
II.26	Pyridin-3-yl	128	128	128	128
II.27	Pyridin-4-yl	128	64	64	64
II.28	Anthracen-9-yl	512	512	512	512
Chloramphenicol	-	16	16	16	16

Pa*: Pseudomonas aeruginosa (NCIM 2036)*, Ec: *Escherichia coli (NCIM 2065)*, Kp: *Klebsiella pneumonia (NCIM 5082)*, Pv: *Proteus vulgaris (NCIM 2813), MIC:* Minimum inhibitory concentration

meta, and para positions as seen in the case of compounds II.9–13. Similarly, the presence of allyloxy group at the para position of the phenyl ring as seen in the case of compound II.23 also enhanced the antibacterial activity. An increase in the antifungal activity was also observed for the compounds having halogen substitution, but the level of activity in many cases is found to be less than that of the antibacterial activity. To explore the antibacterial activity of differentially substituted chalcones[11] synthesized two sets of chalcones using conventional and microwave-assisted synthesis

Table 3: Antifungal activity of diarylsulfonylurea-chalcone hybrids (II.1-28)



(II.1-28)

Compound	R	MIC µg/mL			
		Fungi			
		Ca	An	Ao	Pc
II.1	C_6H_5	512	512	512	512
II.2	4-MeC_6H_4	256	256	256	256
II.3	4-$NMe_2C_6H_4$	128	256	256	256
II.4	3-$OMeC_6H_4$	128	128	128	128
II.5	4-$OMeC_6H_4$	128	128	128	128
II.6	3,4-di$OMeC_6H_3$	128	128	128	128
II.7	2,4-di$OMeC_6H_3$	128	128	128	128
II.8	3,4,5-tri$OMeC_6H_2$	256	256	256	256
II.9	2-OHC_6H_4	256	256	256	256
II.10	3-OHC_6H_4	512	512	512	512
II.11	4-OHC_6H_4	128	128	128	128
II.12	3-OEt, 4-OHC_6H_3	512	512	512	512
II.13	3-OMe, 4-OHC_6H_3	128	128	128	128
II.14	2-$NO_2C_6H_4$	16	16	16	16
II.15	3-$NO_2C_6H_4$	256	256	256	256
II.16	5-OH,2-$NO_2C_6H_3$	32	64	64	64
II.17	3-FC_6H_4	64	64	64	64
II.18	4-FC_6H_4	64	64	64	64
II.19	2-ClC_6H_4	128	128	128	128
II.20	4-ClC_6H_4	64	64	64	64
II.21	2,4-diClC_6H_3	64	64	64	64
II.22	3-BrC_6H_4	128	64	128	128
II.23	4-Allyl-OC_6H_4	16	16	16	16
II.24	Phenylethene-yl	256	256	256	256
II.25	Pyrrol-2-yl	256	256	256	256
II.26	Pyridin-3-yl	128	128	128	128
II.27	Pyridin-4-yl	64	64	64	64
II.28	Anthracen-9-yl	512	512	512	512
Ketoconazole	-	16	16	16	16

MIC: Minimum inhibitory concentration, Ca*: Candida albicans* (NCIM 3102) Ao: *Aspergillus oryzae* (NCIM 643), An: *Aspergillus niger* (NCIM 548), Pc: *Penicillium chrysogenum* (NCIM 738)

methods. The compounds II.14 and II.16 having nitro group at ortho position also contributed favorably to the antifungal activity.

It is concluded that the diarylsulfonylurea-chalcone hybrids possess antibacterial and antifungal activity against tested organisms.

REFERENCES

1. Ventola CL. The antibiotic resistance crisis: Part 1: Causes and threats. P T 2015;40:277-83.
2. Siedenbiedel F, Tiller JC. Antimicrobial polymers in solution and on surfaces: Overview and functional principles. Polymers 2012;4:46-71.
3. Muñoz-Bonilla A, Fernández-García M. Polymeric materials with antimicrobial activity. Prog Polym Sci 2012;37:281-339.
4. Yurttaş L, Özkay Y, Kaplancıklı ZA, Tunalı Y, Karaca H. Synthesis and antimicrobial activity of some new hydrazone-bridged thiazole-pyrrole derivatives. J Enzyme Inhib Med Chem 2013;28:830-5.
5. Gavade SN, Markad VL, Kodam KM, Shingare MS, Mane DV. Synthesis and biological evaluation of novel 2,4,6-triazine derivatives as antimicrobial agents. Bioorg Med Chem Lett 2012;22:5075-7.
6. Winters MP, Crysler C, Subasinghe N, Ryan D, Leong L, Zhao S, *et al.* Carboxylic acid bioisosteres acylsulfonamides, acylsulfamides, and sulfonylureas as novel antagonists of the CXCR2 receptor. Bioorg Med Chem Lett 2008;18:1926-30.
7. León C, Rodrigues J, Gamboa de Domínguez N, Charris J, Gut J, Rosenthal PJ, *et al.* Synthesis and evaluation of sulfonylurea derivatives as novel antimalarials. Eur J Med Chem 2007;42:735-42.
8. Ameya A, Chavan C, Nandini RP. Sulfonylureas as dual acting agents-synthesis and biological activity. J Chin Chem Soc 2007;54:771-7.
9. National Committee for Clinical Laboratory Studies, Performance Standards for Antimicrobial Susceptibility; 1998.
10. NCCLS. National Committee for Clinical Standards. 5th ed. Villanova, PA: NCCLS; 2000.
11. Ansari FL, Baseer M, Iftikhar F, Kulsoom S, Ullah A, Nazir S, *et al*. Microwave assisted synthesis, antibacterial activity against Bordetella bronchiseptica of a library of 3-hydroxylaryl and heteroaryl chalcones and molecular descriptors-based SAR. Gen Pap 2009;2009:318-32.

Source of Support: Nil. **Conflict of Interest:** None declared.