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Research Article

INDANYL ANALOGS AS POTENTIAL ANTIMICROBIAL AGENTS

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ABSTRACT

Objective: The wide variety of biological activities of different indane derivatives makes them an interesting moiety in the field of medicinal chemistry. The objective of the study was to identify and develop novel antimicrobial agents from indanyl analogs.

Methods: Recently synthesized indanyl analogs (4a-c and 5a-o) were examined against various pathogenic microorganisms (Gram-positive and Gram-negative bacteria and fungi) using serial dilution method. These analogs were found to possess antibacterial and antifungal activities with minimum inhibitory concentration values ranging between 1.56 and 100 µg/mL.

Results: The results revealed that the entire compounds showed mild-to-moderate antibacterial activities and moderate-to-excellent antifungal activities against the pathogenic microorganisms as compared to the standard drugs ciprofloxacin and fluconazole, respectively. Compounds 4a, 5a, 5b, 5d, 5e, 5i, and 5j exhibited antifungal activities superior to the reference drug.

Conclusion: Based on the structure-activity relationship, it can conclude that the indan-3-oxo-1-acetic acid moiety is essential for the activities and lipophilic alkoxy substituents on indane ring have enhanced the biological activity. Further, structure-activity relationship studies of the compounds 4a, 5a, and 5b are needful to find the new lead as antimicrobial agent.

Keywords: Indanyl analogs, Minimum inhibitory concentration, Antibacterial, Antifungal.

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INTRODUCTION

The growing incidence of microbial resistance to currently used antibiotics represents a serious medical problem. Therefore, there is an urgent need to develop new classes of therapeutic agents to treat microbial infections. Indanyl derivatives have already drawn some attention as one of the templates for synthesizing compounds of varying biological activities such as antimicrobial [1-7], antitubercular [8-10], antimalarial [11], anti-inflammatory [12-16], anticancer 1 [17,18], antiviral [19], monoamine oxidase inhibitor [20], and anti-Alzheimer [21]. In search of newer antimicrobial agents, I have discovered and evaluated a series of substituted indanyl acids [(5-ethoxy-6-methoxy-3-oxo-2,3-dihydro-1H-inden-l-yl)acetic acid, (5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-l-yl) acetic acid, and (6-chloro-3-oxo -2, 3-dihydro-1H-inden-l-yl) acetic acid] and their esters [(5-ethoxy-6-methoxy-3-oxo-2,3-dihydro-1H-inden-l-yl)acetic acid esters, (5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-l-yl) acetic acid esters, and (6-chloro-3-oxo -2, 3-dihydro-1H-inden-l-yl) acetic acid esters] against various pathogenic microorganisms.

EXPERIMENTAL

Materials and methods

Substituted Indan-3-oxo-1-aceticacids (4a-c) and the corresponding esters (5a-o), outlined in Fig. 1, were synthesized as described earlier [15,16]. Strains used were procured from the microbial type culture collection (MTCC), Institute of Microbial Technology, Chandigarh, and National Chemical Laboratory, Pune, India.

Antimicrobial studies

The *in vitro* antibacterial activities of the synthesized compounds (4a-c and 5a-o) were carried out against various bacterial strains, such as Gram-positive bacteria *Staphylococcus aureus* (NCIM 2901) and *Bacillus subtilis* (MTCC441) and Gram-negative bacteria *Escherichia coli (*MTCC 2810), *Pseudomonas aeruginosa* (NCIM 2036), *Salmonella typhi* (NCIM 2501) and *Klebsiella pneumoniae* (MTCC 3384) by serial dilution method [22,23]. The synthesized compounds were evaluated for various antibacterial activities with MIC values ranging between 1.56 and 100 µg/mL. Ciprofloxacin was used as a standard drug for antibacterial activity of the synthesized compounds.

The synthesized compounds (4a-c and 5a-o) were also screened for their *in vitro* antifungal activity against *Candida albicans* (MTCC 227) and *Aspergillus niger* (NCIM 1056) by serial dilution method [24,25]. The compounds were tested with minimum inhibitory concentration (MIC) values ranging between 6.25 and 50 µg/mL for various antifungal activities. The activity of each compound was compared with fluconazole as standard.

MICs were determined to evaluate the antimicrobial activity of synthesized compounds [26,27]. A pure culture of a single microorganism was grown in Mueller-Hinton broth (MHB). The antimicrobial agents were diluted a number of times, 1:1, through a sterile diluents (MHB). Test compounds were dissolved in 10% dimethyl sulfoxide, to produce a 2000 g/mL stock solution. These test tubes were serially diluted to give a concentration of 100, 50, 25, 12.5, 6.25, 3.125, 1.56, and 0.78 µg/mL. MHB was used for bacteria and Sabouraud dextrose broth was used for fungus. The cell density of each inoculum was adjusted in sterile water of a McFarland standard. A final concentration was ~107 CFU/mL and ~106 CFU/mL for bacteria and fungi, respectively. Microbial inoculums were added to the two-fold diluted samples. The test tubes were incubated 18–24 h at 37°C±1°C for bacteria and 2–5 days at 25°C±1°C for fungi. The highest dilution of the test compound that completely inhibited the growth of test organism was considered as the MIC value of the test compound and was expressed in µg/mL.

RESULTS AND DISCUSSION

Antimicrobial studies

Antibacterial activities

Marketed antimicrobials have various drawbacks such as toxicity and narrow spectrum of activity and few of them show drug-drug interactions.

Table 1: MIC of test compounds (4a-c and 5a-o) against *S. aureus, B. subtilis, S. typhi, E. coli, P. aeruginosa*, and *K. pneumoniae*

Compound	MIC (µg/mL)					
	S. aureus	*B. subtilis*	*S. typhi*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
4a	1.56	1.56	6.25	6.25	6.25	3.125
5a	6.25	1.56	6.25	25	6.25	3.125
5b	6.25	1.56	6.25	6.25	12.5	6.25
5c	3.125	6.25	1.56	6.25	12.5	1.56
5d	6.25	50	6.25	12.5	50	12.5
5e	12.5	6.25	6.25	12.5	6.25	3.125
4b	25	25	25	25	25	25
5f	6.25	12.5	1.56	12.5	3.125	12.5
5g	6.25	12.5	6.25	50	12.5	50
5h	50	25	25	25	25	25
5i	50	25	25	50	25	12.5
5j	12.5	12.5	12.5	12.5	12.5	12.5
4c	12.5	12.5	12.5	50	100	100
5k	25	50	25	25	50	25
5l	6.25	6.25	3.125	6.25	3.125	3.125
5m	25	12.5	25	50	12.5	100
5n	12.5	12.5	12.5	12.5	12.5	12.5
5o	12.5	12.5	12.5	50	100	100
Ciprofloxacin	0.78	0.78	0.78	0.78	0.78	0.78

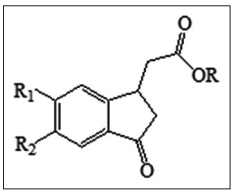
MIC: Minimum inhibitory concentration, *S. aureus: Staphylococcus aureus, B. subtilis: Bacillus subtilis, E. coli*: *Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa, S. typhi: Salmonella typhi, K. pneumonia: Klebsiella pneumonia*

Table 2: MIC of test compounds (4a-c and 5a-o) against *C. albicans* and *A. niger*

Compound	MIC (µg/mL)	
	C. albicans	*A. niger*
4a	6.25	6.25
5a	6.25	6.25
5b	6.25	6.25
5c	12.5	12.5
5d	12.5	6.25
5e	6.25	6.25
4b	12.5	12.5
5f	25	50
5g	12.5	12.5
5h	25	50
5i	12.5	6.25
5j	6.25	12.5
4c	25	25
5k	12.5	12.5
5l	25	12.5
5m	50	25
5n	12.5	12.5
5o	12.5	50
Fluconazole	12.5	12.5

MIC: Minimum inhibitory concentration, *C. albicans: Candida albicans, A. niger: Aspergillus niger*

Demands for new antimicrobial agents with a broad spectrum of activity and less adverse effects have been increased, due to the high incidence of infections in immunocompromised patients. Most of the tested compounds (4a-c and 5a-o) exhibited mild to moderately good *in vitro* antibacterial activity against both the Gram-positive (*S. aureus* and *B. subtilis*) and the Gram-negative (*E. coli*, *P. aeruginosa*, *S. typhi,* and *K. pneumonia*) bacteria. The antibacterial data indicated that compounds 5e, 5f, and 5l exhibited moderate and compounds 4a, 5a, 5b, and 5c illustrated appreciable antibacterial activity against various strains but lower than that of standard ciprofloxacin. Among the synthesized series, 4a showed the overall best activity and the highest inhibition against *S. aureus* and *B. subtilis* and 5c showed the highest inhibition against *S. typhi* and *K. pneumoniae*. Compounds 4a and 5c both contain ethoxy and methoxy groups in 5 and 6 positions of the indan-3-oxo-1-acetic acid moiety, respectively, though 1 position of 5c was esterified by n-propyl alcohol. Results of antibacterial studies have been presented in Table 1.



Compound	R_1	R_2	R	Compound	R_1	R_2	R
4a	OCH_3	OC_2H_5	H	5g	OCH_3	OCH_3	Et
4b	OCH_3	OCH_3	H	5h	OCH_3	OCH_3	Pr
4c	Cl	H	H	5i	OCH_3	OCH_3	i-Pr
5a	OCH_3	OC_2H_5	Me	5j	OCH_3	OCH_3	Bu
5b	OCH_3	OC_2H_5	Et	5k	Cl	H	Me
5c	OCH_3	OC_2H_5	Pr	5l	Cl	H	Et
5d	OCH_3	OC_2H_5	i-Pr	5m	Cl	H	Pr
5e	OCH_3	OC_2H_5	Bu	5n	Cl	H	i-Pr
5f	OCH_3	OCH_3	Me	5o	Cl	H	Bu

Fig. 1: Indan-1-acetic acids and their ester derivatives

Antifungal activities

Antifungal activities of all compounds (4a-c and 5a-o) were evaluated against *C. albicans* and *A. niger*. Most of the compounds exhibited moderate-to-excellent antifungal activities. Among the synthesized compounds, 4b, 5c, 5g, 5k, 5l, and 5n showed comparable antifungal activities and 4a, 5a, 5b, 5d, 5e, 5i, and 5j showed higher antifungal activities than fluconazole. Hence, these compounds were found to be potent antifungal agents. Few of the tested compounds 4c, 5f, 5h, 5m, and 5n showed less inhibition against the microorganisms as compared to the standard drug. Majority of the tested compounds showed comparable to high *in vitro* antifungal activities, contain alkoxy groups in 5 and 6 positions of the indane moiety, which has accounted for their enhanced activity. Results of antibacterial studies have been presented in Table 2.

CONCLUSION

Substituted indanyl acids (4a-c) and esters (5a-o) were investigated for their *in vitro* antibacterial and antifungal activities by well plate method. Among the screened samples, 4a, 5a, 5b, and 5c illustrated appreciable inhibition of bacterial growth. Compounds 4a, 5a, 5b, 5d, 5e, 5i, and 5j showed higher inhibition of fungal strain as compared with standard

drug fluconazole. Based on the relationships between the structure of the substituted indanyl derivatives and their detected antimicrobial properties, it can be said that substituted indanyl derivatives showed varied biological activities. From *in vitro* antibacterial and antifungal studies (Tables 1 and 2), it was observed that a total of three compounds (4a, 5a, and 5b) showed excellent results in both cases. Moreover, the presence of 5 and 6 position substituents causes a certain change of activity. Lipophilic alkoxy groups (methoxy and ethoxy) present on 5 and 6 positions of indane ring have enhanced the biological activity. Finally, it can be concluded that compounds 4a, 5a, and 5b have great potential as lead compounds for further structure-activity relationship studies in the search for a new antimicrobial agent.

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