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Short communication

Synthesis, stereochemistry, antimicrobial evaluation and QSAR studies of 2,6-diaryltetrahydropyran-4-one thiosemicarbazones

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ABSTRACT

A series of 2,6-diaryltetrahydropyran-4-one thiosemicarbazones (**11**–**27**) were synthesized and characterized for evaluation of potential antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Bacillus subtilis* and *Klebsiella pneumonia* and antifungal activity against *Cryptococcus neoformans*, *Candida albicans*, *Rhizopus* sp., *Aspergillus niger* and *Aspergillus flavus* were evaluated. Compounds **21** and **22** showed maximum inhibition potency at low concentration (6.25 μg/ml) against *P. aeruginosa*. For antifungal activity, **20** and **21** were effective against *C. neoformans* and **22**–**24** against *C. albicans* at minimum concentration. Further, the results of QSAR studies of these synthesized compounds indicated the importance of weakly polar component of surface area, hydrophobicity and ionization potential parameters in defining their antimicrobial activity.

1. Introduction

Since resistance of pathogenic microorganisms towards available antibiotics is rapidly becoming a worldwide problem, the design of new compounds to deal with these resistant strains has become a major area of research today. Additionally, the biochemical similarity of the human and fungi cells is a significant handicap for development of new antifungal agents because of problems of toxicity and easily gained resistance [1,2]. The present work is aimed towards developing novel molecules with potent antimicrobial activity to tackle this problem of resistance.

Thiosemicarbazones are a class of small molecules that have been evaluated against various diseases such as those caused by *Plasmodium falciparum*, *Trypanosoma brucei* and *Trypanosoma cruzi*. The effectiveness of thiosemicarbazone analogues in treating these diseases is reported due to their activity against cysteine proteinases including rhodesain [3–6]. Thiosemicarbazones are also known to possess tranquilizing, muscle relaxing, psychoanaleptic, hypnotic, ulcerogenic, antidepressant, antibacterial, antifungal, analgesic and anti-inflammatory properties [7–14].

Heterocyclic compounds carrying pyran skeleton are attractive targets of organic synthesis owing to their presence in numerous naturally occurring carbohydrates and synthetic compounds with interesting biological and pharmacological properties [15–18]. Additionally, a careful analysis of literature on antimicrobial agents concerning our ongoing research program in this field has been performed [19]. Therefore in the present study, we have synthesized 2,6-diarylpyran-4-one thiosemicarbazones as potential antimicrobial molecules and performed Quantitative Structure Activity Relationship (QSAR) studies on them.

2. Chemistry

The general schematic representation describing the routes of syntheses is furnished in Scheme 1. 3-Alkyl-2,6-diphenyltetrahydropyran-4-ones (**1** and **2**) were prepared by the condensation reaction of benzaldehyde with respective ketones (2-butanone for **1** and 2-pentanone for **2**) in the presence of potassium hydroxide in water–ethanol medium stirred for 15 days [20]. Thiosemicarbazones (**11**, **12**, **18** and **19**) are synthesized by refluxing 3-alkyl-2,6-diphenyltetrahydropyran-4-ones (**1** or **2**) with respective thiosemicarbazides (thiosemicarbazide or 4′-phenylthiosemicarbazide) in the presence of concentrated hydrochloric acid in methanol medium for 3 h. 3,5-Dimethyl-2,6-diaryltetrahydropyran-4-ones (**3**–**10**) were obtained through condensation reaction of *para*-substituted benzaldehyde with 3-pentanone in the presence of potassium hydroxide in water–ethanol medium stirred for 2–96 h in mechanical stirrer. The ketones (**3**–**10**) were further converted

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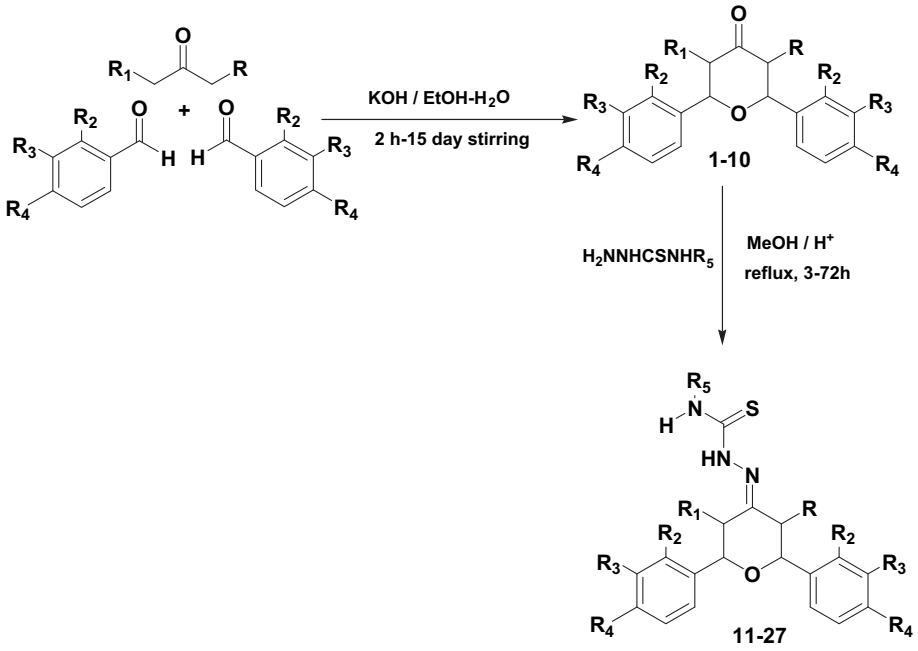

Scheme 1. Schematic diagram showing the synthesis of 2,6-diaryltetrahydropyran-4-one thiosemicarbazones.

into their corresponding thiosemicarbazones by refluxing with respective thiosemicarbazides in the presence of concentrated hydrochloric acid in methanol medium for 50–72 h. All the synthesized compounds were characterized by analytical and spectral (Mass, IR, ^{1}H and NMR) data. The physical and analytical data of the thiosemicarbazones (**11**–**27**) are presented in Table 1. The stereochemistry of all the synthesized thiosemicarbazones is established using ^{1}H NMR spectral data. The assignment has been made based on characteristic signal positions of functional groups, spin multiplicity, and comparison with those of parent ketones. To determine the structure of the compounds **18**–**27**, the ^{1}H NMR spectrum of compound **18** (for 3-alkyltetrahydropyran-4-one 4′-phenylthiosemicarbazone **19**) and compound **21** (for 3,5-dimethyltetrahydropyran-4-one 4′-phenylthiosemicarbazones **20** and **21**–**27**) were used as examples. The spectral assignment and stereochemistry of compounds **11**–**17** are made by comparing with representative compounds **11** and **14** whose stereochemistry was well established [21]. The ^{1}H NMR and ^{13}C NMR chemical shifts of compounds **11**–**27** along with their parent ketones **1** and **4** are given in Tables 2 and 3, respectively.

2.1. Stereochemistry

The coupling constant values and position of the chemical shifts were used to predict the conformation of the synthesized compounds. The observed vicinal coupling constant values [10.0 ($J^3_{2a,3a}$), 11.5 Hz ($J^3_{5a,5a}$) and 2.0 Hz ($J^3_{6a,5e}$)] of H-6a and H-2a of compound **18** indicate that the six-member heterocyclic ring of compound **18** adopts normal chair conformation with equatorial orientation of phenyl groups at C-2 and C-6, and equatorial

Table 1
Physical data of 2,6-diaryltetrahydropyran-4-one thiosemicarbazones **11**–**27**.

Compound	R	R_1	R_2	R_3	R_4	R_5	Reaction time (h)	Yield (%)	m.p °C	Mass	Elemental analysis[a]			
											C	H	N	S
11	H	CH_3	H	H	H	H	3	90	110–112	340.0281[b]	–	–	–	–
12	H	CH_2CH_3	H	H	H	H	3	90	136–137	354	67.98	6.54	11.92	9.11
13	CH_3	CH_3	H	H	F	H	50	76	140–141	390	61.65	5.40	10.77	8.22
14	CH_3	CH_3	H	H	Cl	H	50	80	212–214	423.3702[b]	–	–	–	–
15	CH_3	CH_3	H	H	Br	H	50	78	184–186	–	46.95	4.18	8.19	6.29
16	CH_3	CH_3	H	H	CH_3	H	50	76	158–161	382	69.24	7.09	11.16	8.39
17	CH_3	CH_3	H	H	OCH_3	H	50	74	172–173	414	63.91	6.47	10.20	7.72
18	H	CH_3	H	H	H	C_6H_5	4	89	122–124	416	72.22	6.12	10.98	7.77
19	H	CH_2CH_3	H	H	H	C_6H_5	4	86	128–130	430	72.61	6.39	9.82	7.49
20	CH_3	CH_3	H	H	F	C_6H_5	72	74	153–154	466	67.12	5.38	9.07	6.91
21	CH_3	CH_3	H	H	Cl	C_6H_5	72	68	202–204	499	53.11	4.25	7.11	5.47
22	CH_3	CH_3	H	H	Br	C_6H_5	72	79	196–198	–	62.61	5.10	8.41	6.45
23	CH_3	CH_3	H	H	CH_3	C_6H_5	72	71	178–180	458	73. 42	6.79	9.14	7.08
24	CH_3	CH_3	H	H	OCH_3	C_6H_5	72	65	188–189	490	68.60	6.32	8.51	6.53
25	CH_3	CH_3	Cl	H	H	C_6H_5	72	68	223–224	499	–	–	–	–
26	CH_3	CH_3	H	Cl	H	C_6H_5	72	65	196–198	499	–	–	–	–
27	CH_3	CH_3	H	OCH_3	H	C_6H_5	72	63	164–165	490	–	–	–	–

[a] The observed elemental analysis values for C, H, N and S are within ±0.4% from their theoretical values.
[b] M + H value obtained from High Resolution Mass Spectrum.