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Synthesis, Anticancer and Antimicrobial Evaluation of New (*E*)-*N*′-Benzylidene-2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carbohydrazides

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In search of new anticancer and antimicrobial agents, herein we report the synthesis of new substituted (*E*)-*N*′-benzylidene-2-(2-ethylpyridin-4-yl)-4-methyl thiazole-5-carbohydrazide derivatives (**6a-n**), starting from ethionamide. The newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS analyses. All the synthesized compounds have been evaluated for their anticancer activity. Among fourteen synthesized compounds, five carbohydrazide derivatives have displayed more promising anticancer activity against the lung carcinoma A-549 cells. Also, these compounds were screened for their in vitro antibacterial and antifungal activities. The three carbohydrazide derivatives have exhibited good antibacterial and antifungal activities.

1. Introduction

Cancer is prominent cause of death worldwide.[1] Numerous treatments have been established to cure cancer such as chemotherapy, immunotherapy, radiotherapy and surgery. Chemotherapy is considered as a good choice for anticancer treatment. However, the high toxic effects of chemotherapeutic drugs are major problem in the treatment of cancer,[2] In addition, cancer cells develop resistance to chemotherapeutics, which is a primary reason of failure in chemotherapy.[3]

The emerging newer infectious diseases and increasing number of multidrug resistant microbial pathogens are an important issues of immunosuppressed patients with AIDS and those undergoing anticancer therapy or organ transplants.[4] Therefore, there is a need of innovation and development of newer chemical structures having both anticancer and antimicrobial properties.[5] In recent literature, some carbohydrazides have been reported as anticancer,[6] antimicrobial,[7] antioxidant,[8] antitubercular,[9] anti-inflammatory and analgesic[10] agents. Hydrazonyl pharmacophore is associated with profound biological activities,[11] viz anthelmintic and antimicrobial,[12] cyclooxygenase inhibitor,[13] antioxidant,[14] anti-HIV,[15] and antitubercular.[16] Some of the biologically active hydrazones, relevant to the present work has been shown in Figure 1. Pyridine-thiazole fused heterocyclic systems

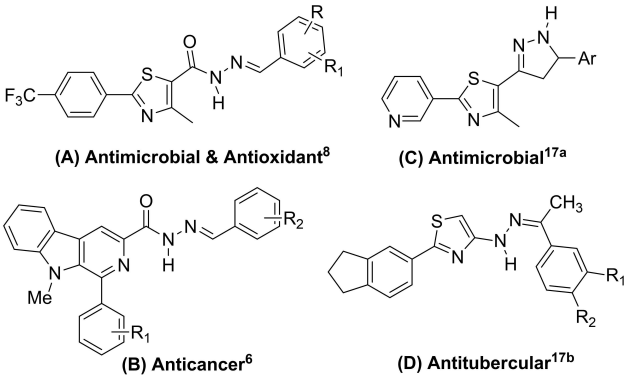

Figure 1. Biologically active hydrazones relevant to the present work

are common structural motifs with significant applications in medicinal chemistry.[17,18] The carbohydrazides clubbed with either pyridyl or thiazolyl moieties have shown significant anticancer and antimicrobial activities. The literature reveals that the carbohydrazides clubbed with both pyridyl and thiazolyl moieties have not been reported. Considering these observations and in continuation of our efforts to identify new bioactive compounds,[19] here it has been thought worthwhile to design and synthesize new hybrid carbohydrazides with thiazolyl and pyridyl scaffolds in a single molecular framework with hope to obtain the new molecules with enhanced anticancer activity. Herein, we reported the multistep synthesis of (*E*)-*N*′-benzylidene-2-(2-ethylpyridin-4-yl)-4-methyl thiazole-5-

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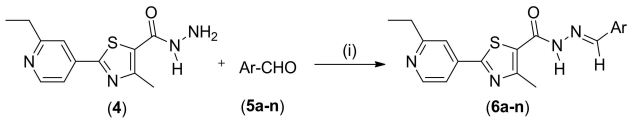
carbohydrazide derivatives (**6a-n**) and their anticancer and antimicrobial evaluation.

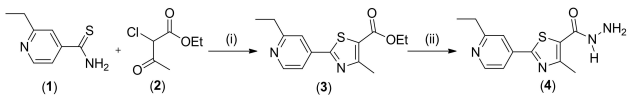
2. Results and Discussion

2.1. Chemistry

The synthetic routes employed for the synthesis of the target compounds are shown in Schemes 1 and 2. In the first step, 2-



Scheme 1. *Reaction Conditions*: (i) EtOH, reflux, 5 h; (ii) $H_2N\text{-}NH_2.H_2O$, EtOH, reflux, 4 h.



Scheme 2. *Reaction Conditions*: (i) DIPEAc, rt, 30 min.

ethylpyridine-4-carbothioamide (**1**) and ethyl 2-chloro-3-oxobutanoate (**2**) were refluxed in ethanol for 5 h and obtained 2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxylate (**3**) with 90% yield. When 2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxylate (**3**) and excess of hydrazine hydrate were refluxed in ethanol for 4 h gave 2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carbohydrazide (**4**) with 75% yield. The condensation of aromatic aldehydes (**5a-n**) and 2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carbohydrazide (**4**) were carried in diisopropylethylammonium acetate (DIPEAc) to obtain the respective substituted (*E*)-*N*′-benzylidene-2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carbohydrazides (**6a-n**) with better to excellent yields. The DIPEAc is displaying dual role as a medium and catalyst in acceleration of the condensation of the acid hydrazide and aldehydes to furnish the corresponding substituted carbohydrazides (**6a-n**) rapidly.[20] The products obtained were purified by crystallization and their structures have been elucidated by spectral analyses (Incorporated in supporting information file) and the physical data is presented in Table 1.

2.2. Biological Evaluation

2.2.1. Anticancer activity

The anticancer potential of the synthesized compounds (**6a-n**) was evaluated in vitro against three types of cancer cells (Breast cancer cells T47 D, Lung cancer cells A549 cells and Skin cancer cells SKMEL2), the effect of the compounds on the A549 cells growth was observed (Figure 2). The A549 cells were exposed to the compounds for 24 h with concentration, ranges from 0

Table 1. Physical data of substituted carbohydrazides (**6a-n**)

Entry	Ar	M. P. [°C]	Yield [%][a]
6a	4-(Br)C_6H_4	295-297	90
6b	4-(CH_3)C_6H_4	241-243	80
6c	4-(Cl)C_6H_4	275-277	87
6d	3-(NO_2)C_6H_4	277-279	92
6e	2-(Br)C_6H_4	310-312	89
6f	2-(OCH_3)C_6H_4	256-258	82
6g	4-(F)C_6H_4	234-236	87
6h	4-(OCH_3)C_6H_4	241-243	82
6i	1-Furyl	214-216	85
6j	4-(NO_2)C_6H_4	255-257	91
6k	3-(Br)C_6H_4	281-283	90
6l	3-(Cl)C_6H_4	265-267	86
6m	C_6H_5	283-285	85
6n	2-(NO_2)C_6H_4	226-228	92

[a] Isolated yields.

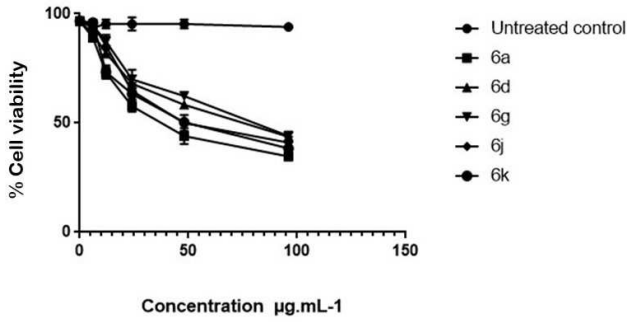


Figure 2. Antiproliferative action of substituted carbohydrazides (**6a-n**) on human lung cancer A549 cells.

$\mu g.mL^{-1}$ to 100 $\mu g.mL^{-1}$. The dilutions of these compounds were prepared in DMSO. The compounds were added to the 24 h grown A549 cells in RPMI 1640 with FBS (10% v/v). The seeding density for the cell line was $>5\times10^3$ cell per well/200 mL of medium. The IC_{50} was determined by using EIA scan at 570 nm. The inhibitory concentration (IC_{50}) was determined by addition of the compound in 24 h grown cells. The MIC of compounds were determined by using the MTT formation of compounds.

Paclitaxel was used as a standard reference anticancer drug. It is observed that most of the synthesized compounds of the series were found to be active against A549 lung cancer cells. Among them, compounds **6a**, **6d**, **6g**, **6j** and **6k** have shown effective inhibition for the growth of A549 lung cancer cells. The compound **6a** with 4-bromo substituent on benzene ring has displayed promising anticancer action on A549 lung cancer cells with IC_{50} value 4.49 $\mu g.mL^{-1}$ better than standard Paclitaxel drug (IC_{50} value 6.40 $\mu g.mL^{-1}$). Compounds **6d** and **6k** having a 3-nitro and 3-bromo substituent on benzene ring were found to be active against A549 lung cancer cells with IC_{50} 7.86 and 8.86 $\mu g.mL^{-1}$ respectively. In addition to this, compounds **6j** ($IC_{50}=12.30$ $\mu g.mL^{-1}$) and **6g** ($IC_{50}=20.54$ $\mu g.mL^{-1}$) showed significant anticancer activity. However, **6b**,

6c, **6e**, **6f**, **6h**, **6i**, **6l**, **6m** and **6n** did not show any activity up to 50 μg.mL^{-1} concentration (Table 2).

Table 2. IC_{50} values of substituted carbohydrazides (**6a-n**)

Entry	IC_{50} [μg.mL^{-1}]
6a	4.49 ± 0.23
6b	> 50
6c	> 50
6d	7.86 ± 0.44
6e	> 50
6f	> 50
6g	20.54 ± 1.00
6h	> 50
6i	> 50
6j	12.30 ± 0.56
6k	8.86 ± 0.49
6l	> 50
6m	> 50
6n	> 50
Paclitaxel	6.40 ± 0.35

IC_{50} = Concentration of drug that decrease the viability of the cells by 50% compared to the untreated control cells. The values are the mean of the IC_{50} of triplicate experiments.

2.2.2. Antibacterial and antifungal activities

Antibacterial and antifungal activities were evaluated against pathogen bacteria and fungi by agar well diffusion method.[21] The pathogens were selected in accordance to their resistance to clinically used drugs and severity of infections caused by them. For antibacterial activity, Gram positive pathogens; *Staphylococcus aureus, Bacillus cereus, Bacillus megaterium, Micrococcus glutamicum, Bacillus subtilis;* and Gram negative pathogens *Escherichia coli, Salmonella typhi, Shigella boydii, Enterobacter aerogenes, Pseudomonas aerogenosa*, *Salmonella abony* were used (Table 3). Antifungal activity was determined against *Aspergillus niger, Saccharomyces cereviseae*, *Candida albicans* (Table 4). Tetracycline and Nystatin were used as standard antibacterial and antifungal drugs, respectively.

For antimicrobial activity determination, Mueller Hinton agar was prepared. The 20 mL of the medium was poured in each sterile Petri plate. After solidification, the medium was seeded with 24 h old culture of bacterial and fungal pathogens. Wells were cut in the medium. The 100μL of the test compounds with 2 mg/mL concentration and standards were added in to each well. The 100μL of the solution was placed in a well. The compounds were considered positive for the antimicrobial activity, if the zone of inhibition is observed around the well of the respective compounds on petri plate containing growth of the pathogen. The results were measured and recorded in millimetre (mm). The compounds **6c**, **6k** and **6l** showed very good antibacterial and antifungal activities among all the synthesized compounds. Compound **6c** gave maximum zone of inhibition against *S. aureus* and *B. subtilus.* Compound **6k** showed very effective and maximum zone of inhibition against *S. boydii* and *S. aureus.* Compound **6l** has shown effective antifungal activity among the synthesized compounds.

2.2.3. Minimum inhibitory concentration (MIC)

Minimum inhibitory concentration (MIC) is the lowest concentration of compounds that will inhibit the visible growth of a microorganism after overnight incubation. The MIC was determined for most potent selected antimicrobial compounds

Table 3. Antibacterial activity of substituted carbohydrazides (**6a-n**).[a]

Compounds→ Pathogens ↓	6a	6b	6c	6d	6e	6j	6k	6 l	6 m	Tetracycline
S.typhi	–	–	13 ± 0.33	–	–	–	12 ± 1.15	10 ± 0.25	–	28 ± 0.33
E.aerogenes	–	–	12 ± 0.03	–	–	–	11 ± 0.33	19 ± 1.33	11 ± 1.25	29 ± 0.27
B.subtilis	–	–	15 ± 0.25	–	13 ± 0.33	18 ± 0.04	16 ± 1.55	20 ± 0.09	–	34 ± 0.13
P.aerogenosa	–	–	13 ± 0.25	–	–	10 ± 0.33	12 ± 0.33	8 ± 0.66	12 ± 0.13	30 ± 0.19
S.abony	12 ± 0.33	14 ± 0.25	10 ± 0.33	14 ± 0.61	12 ± 0.20	–	5 ± 0.25	13 ± 0.33	–	35 ± 0.22
B.megaterium	–	–	9 ± 0.33	–	12 ± 0.55	–	15 ± 0.40	12 ± 0.21	–	28 ± 0.41
E.coli	–	11 ± 0.35	12 ± 0.66	–	–	16 ± 0.26	14 ± 0.25	19 ± 0.40	13 ± 1.15	30 ± 0.12
S.aureus	–	–	16 ± 0.33	–	–	6 ± 1.13	14 ± 0.19	14 ± 0.27	–	27 ± 0.17
S.boydii	–	–	13 ± 0.57	–	12 ± 0.33	–	16 ± 1.33	14 ± 1.21	12 ± 0.19	31 ± 0.23
B.cereus	–	–	14 ± 0.30	–	13 ± 0.57	14 ± 1.15	13 ± 0.17	13 ± 0.73	–	36 ± 0.67
M.glutamicus	–	–	14 ± 0.25	–	–	–	10 ± 1.33	14 ± 0.22	10 ± 0.62	33 ± 0.54

[a] The carbohydrazides **6f**, **6g**, **6h**, **6i** and **6n** not shown any significant microbial activities. All the results were expressed as mean ± standard deviation (SD).

Table 4. Antifungal activity of substituted carbohydrazides (**6a-n**).[a]

Compounds→ Pathogens ↓	6a	6b	6c	6d	6e	6j	6k	6 l	6 m	Nystatin
C.albicans	–	–	8 ± 1.33	–	–	–	13 ± 0.12	18 ± 1.23	–	32 ± 0.56
S.cerevisiae	–	–	6 ± 0.56	–	–	–	11 ± 1.22	16 ± 0.45	–	31 ± 0.13
A.niger	12 ± 0.34	–	5 ± 0.21	12 ± 0.40	–	10 ± 0.21	15 ± 0.72	12 ± 0.81	–	35 ± 1.33

6c, **6k** and **6l**. The MIC was determined against *S.aureus*, *E.coli* and *B.cereus* by following the method and guidelines of Clinical and Laboratory Standard Institute (CLSI). All experiments were performed in triplicates and results are expressed as mean ± SD in μg.mL^{-1} (Table 5).

Table 5. MIC values of most potent antimicrobial compounds [μg.mL^{-1}]

Compounds→ Pathogens ↓	6c	6k	6 l	Tetracycline
S.aureus	50.0 ± 0.188	60 ± 0.227	30 ± 0.288	6.5 ± 0.455
E.coli	40.5 ± 0.120	30 ± 0.565	25 ± 0.288	4.5 ± 0.657
B.cereus	35 ± 0.217	55 ± 0.270	70 ± 0.288	5 ± 0.230

All the results were expressed as mean ± standard deviation (SD).

Conclusions

In summary, the molecular diversity of (*E*)-*N*′-benzylidene-2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carbohydrazides as potential antiproliferative agents was explored. Among them, the carbohydrazide derivatives **6a**, **6d** and **6k** exhibited more potent anticancer activity against A549 lung cancer cells with IC_{50} values 4.49, 7.85 and 8.86 μg.mL^{-1}, respectively. Compound **6a** was found to be more active than the standard drug paclitaxel. The compounds **6c**, **6k** and **6l** have shown good antibacterial and antifungal activities. The obtained results suggest that these pyridyl-thiazole-carbohydrazide hybrids may serve as lead chemical entities for further modification in the search of new classes of potential anticancer and antimicrobial agents.

Supporting Information Summary

The supporting information contains anticancer activity data (**Table S1**), detailed experimental procedures and spectral data (^{1}H NMR, ^{13}C NMR and HRMS) interpretation.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Anticancer · Antimicrobial · Carbohydrazides · Hydrazones · Thiazoles

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