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Synthesis, anticancer and antimicrobial evaluation of new pyridyl and thiazolyl clubbed hydrazone scaffolds

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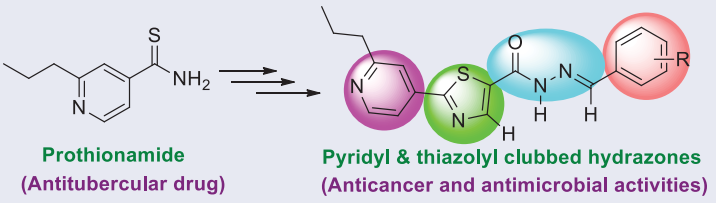
ABSTRACT

A series of new hydrazones bearing pyridyl and thiazolyl scaffolds have been synthesized and evaluated for their *in vitro* anticancer and antimicrobial activities. The anticancer activity was evaluated against the A549 lung cancer cell line. The eight hydrazone derivatives have shown better anticancer activity than positive control doxorubicin against the A549 lung cancer cell line. The antimicrobial activity was evaluated against bacterial and fungal pathogens by using well diffusion method. The four hydrazone derivatives have displayed good antimicrobial activities. Molecular docking studies of the synthesized hydrazone derivatives revealed good binding via hydrogen bond interactions with key residues on active sites as well as neighboring residues with an active site of Focal adhesion kinase (PDB ID 2JKO). A computational study for the prediction of absorption, distribution, metabolism, and excretion (ADME) properties of all compounds has also been performed.

GRAPHICAL ABSTRACT



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KEYWORDS
Anticancer activity; antimicrobial activity; thiazoles; hydrazones; molecular docking study; ADME prediction

Introduction

Cancer has become the most common life-threatening disease representing a major health problem worldwide. In spite of the extensive research in cancer therapy, there is

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still an increasing need for new treatments for cancer.[1] The discovery of new chemotherapeutics is of prime importance due to the essential ability of tumor cells to develop resistance to current agents. The development of multiple drug resistance to antitumor drugs is a major problem in chemotherapy. Hence, research for the invention of novel agents for treating cancer is of prime importance.[2] It has also been reported that lung cancer is the prominent cause of cancer-related deaths.[3] The most common lung cancer i.e. non-small cell lung cancer (NSCLC) poses a continuous and serious threat to public health. In spite of significant improvements in both diagnostic and therapeutic approaches, the overall survival for NSCLC patients remain poor.[4] One main obstacle for the treatment of NSCLC is that most patients are diagnosed at a late stage when the prognosis is poor and therapeutic options are limited.[5]

Diversely substituted thiazole derivatives embedded with a variety of functional groups are found to exist in a large number of well-known naturally occurring compounds such as thiamin and commercial synthetic drugs.[6] A literature survey revealed that thiazole derivatives are found to have many therapeutic activities such as anticancer,[7] antimicrobial,[8] anti-inflammatory,[9] antioxidants,[10] antihypertension[11] and antitubercular.[12] Functionalized pyridines are accompanying many pharmacological activities, such as antioxidant, antimicrobial,[13] β-glucuronidase[14] and cytotoxicity against several human cancer cell lines.[15] Fused heterocyclic compounds with pyridinyl and thiazolyl rings in a molecular frame are common structural designs with substantial applications in medicinal chemistry.[16]

In particular, many studies have pointed out the pivotal role of the hydrazone moiety for anticancer drug development.[17] The synthesis of the hydrazone derivatives have been found to paid more attention due to their antitumor activity against various cancer cell lines such as A549 human lung adenocarcinoma, MCF-7 human breast adenocarcinoma, U-373 MG human glioblastoma, SK-OV-3 human ovary carcinoma, SK-MEL-2 human melanoma, HCT15 human colon carcinoma, MIA PaCa-2 human pancreas carcinoma and HepG2 human hepatocellular carcinoma cell lines.[18] Some of the representative compounds with pyridine, thiazole and hydrazone scaffolds, reported in the literature [19–22] are shown in Figure 1.

Recently, we have reported the synthesis, anticancer and antimicrobial activities of some hydrazone derivatives starting from an antitubercular drug, ethionamide.[23] Considering the biological significance of pyridines, thiazoles and substituted hydrazones and in continuation of our ongoing research on the synthesis of new bioactive molecules,[24] herein we have reported a new series of pyridyl and thiazolyl clubbed hydrazone derivatives (**6a–k**) with anticancer and antimicrobial activities starting from an antitubercular drug, prothionamide.

Results and discussions

Chemistry

The reaction sequence employed for the synthesis of the hydrazone derivatives (**6a–k**) has been shown in Scheme 1. In the first step, 2-propylpyridine-4-carbothioamide (**1**) and ethyl 3-bromo-2-oxopropanoate (**2**) were refluxed in ethanol for 5 h to obtain ethyl 2-(2-propylpyridin-4-yl)thiazole-5-carboxylate (**3**) with 85% yield. The ethyl

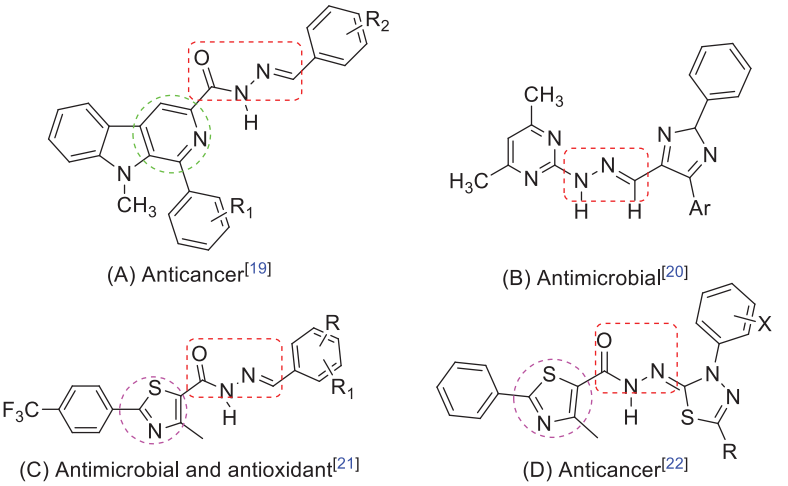
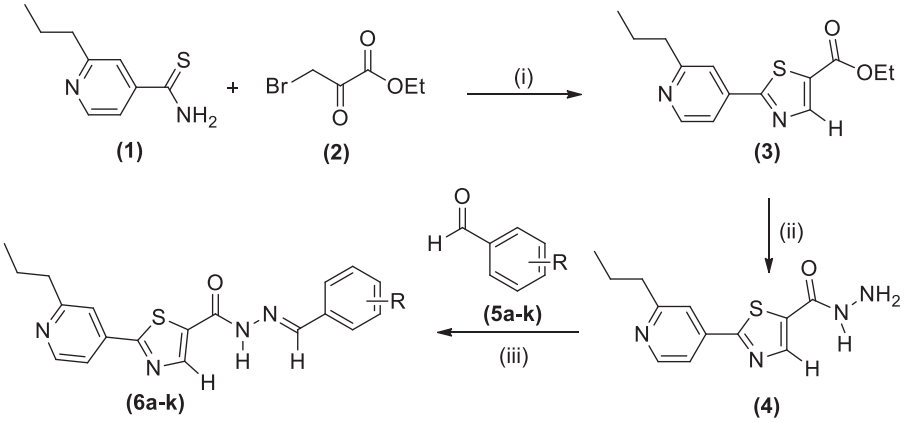


Figure 1. Pyridine, thiazole, and hydrazone containing bioactive molecules.



Scheme 1. Reaction conditions: (i) EtOH, reflux, 5 h; (ii) $H_2N–NH_2.H_2O$, EtOH, reflux, 4 h; (iii) DIPEAc, rt, 30 min.

2-(2-propylpyridin-4-yl)thiazole-5-carboxylate (**3**) was condensed with hydrazine hydrate in refluxed ethanol to furnish a key intermediate, 2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (**4**) with 76% yield. The condensations of aromatic aldehydes (**5a–k**) and 2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (**4**) was carried out in diisopropylethylammonium acetate (DIPEAc) to obtain the corresponding substituted (*E*)-*N*'-benzylidene-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazides (**6a–k**) with 80-90% yields. The obtained products were purified by crystallization using ethanol.

The structures of synthesized (*E*)-*N*'-benzylidene-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazides (**6a–k**) were established based on their ^{1}H and ^{13}C NMR spectral data and satisfactory HRMS analysis. The IR spectrum of hydrazone **6b** shows characteristic peaks at 3273 and 1663 cm^{-1} indicate the presence of amide N–H and amido carbonyl groups, respectively. The ^{1}H NMR spectrum of **6b** displays two singlet peaks at δ 8.40 and 10.52 ppm indicates the presence of thiazolyl-H and amide N–H, respectively. According to the literature, the singlet at deshielded region, δ = 8.27–8.87 ppm indicates

the presence of -CH = N signal, exclusively accounts for the formation of *E*-isomers.[25] In ^{13}C NMR spectrum of **6b**, the peaks at δ 14.04, 23.24, and 40.58 ppm are due to the carbons of the *n*-propyl group attached to a pyridine ring. The peak at δ 166.69 ppm indicates the presence of the amide carbonyl group. The HRMS analysis of compound **6b**, displays $(M + H)^+$ peak at 419.0501 for its molecular formula $C_{19}H_{16}Cl_2N_4OS$. The spectral data of the remaining compounds are consistent with the assigned structures.

Anticancer activity

All the synthesized hydrazones (**6a–k**) were screened for their in vitro anticancer activity against A549 lung cancer cell line by using MTT assay.[26] The compounds dilutions (μM) 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 $>5 \times 10^3$ cells per well/200 mL of medium. The cells were incubated for 24 h. The IC_{50} was determined by using an EIA scan at 570 nm (Figure 2). Inhibition of cell proliferation by these active compounds at various concentrations was measured and their IC_{50} (the concentration that causes a 50% cell proliferation inhibition) values were calculated and summarized in Table 1. The doxorubicin was used as a positive control. The compounds with IC_{50} lower than 20 μM are found to be active against the cells.

In the present study, we have prepared hydrazones having electron-withdrawing substituents. The nitro substituent at *ortho* position displayed better anticancer activity as compared to *meta* and *para* position. The hydrazones with halogen substituents at all positions (*ortho*, *meta* and *para*) have shown good anticancer activity. Exceptionally, the compound **6i** with *ortho*-chloro substituent on the aryl ring showed a very week activity. In fact, out of eleven hydrazone derivatives, seven derivatives having one or more either chloro or bromo showed better effects than the positive control, doxorubicin against A549 lung cancer cells.

Antimicrobial activity

The newly synthesized hydrazone derivatives (**6a-k**) were screened for *in vitro* antibacterial activity against bacterial strains *Staphylococcus aureus* ATCC 6538, *Bacillus megaterium* ATCC 2326, *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC8739, *Salmonella typhi* ATCC9207, *Shigella boydii* ATCC 12034, *Enterobacter aerogenes* ATCC13048, *Pseudomonas aeruginosa* ATCC9027, *Salmonella abony* NCTC6017 and antifungal activity against fungal strains *Aspergillus niger* ATCC 16404, *Saccharomyces cereviseae* ATCC 9763, *Candida albicans* ATCC10231. Antimicrobial activity was performed by using a well diffusion method.[27] Streptomycin and fluconazole were used as antibacterial and antifungal standard reference compounds, respectively. The results of antibacterial and antifungal activities in the zone of inhibition (mm) are presented in Table 2.

The structure-activity relationship analysis revealed that among the hydrazone derivatives (**6a–k**), compound **6b** (R = 3, 5-Dichloro) and **6c** (R = 4-Chloro) showed moderate activity against almost all the pathogens. The compounds **6e** (R = 3-Nitro), **6f** (R = 2-Nitro) and **6g** (R = 3-Chloro) have shown moderate activity against pathogens *S. typhi*, *E. aerogenes*, *B. subtilis*, *S. aureus*, *A. niger,* and *C. albicans*. The convincing

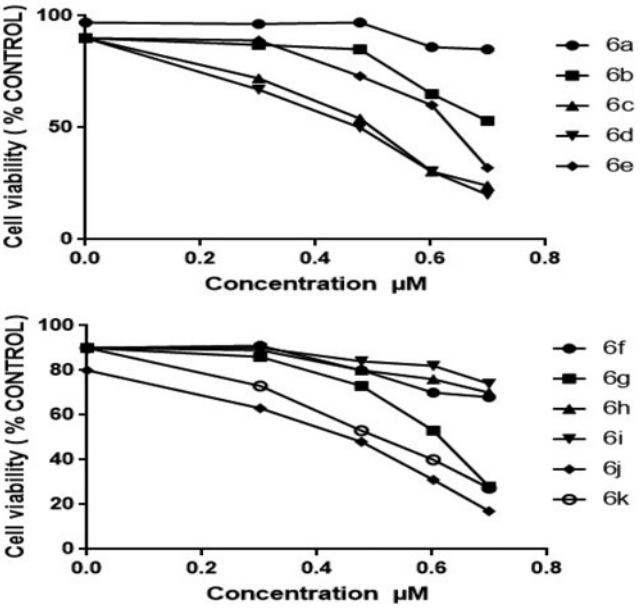


Figure 2. Antiproliferative action of hydrazone derivatives (**6a–k**).

antimicrobial activity of synthesized hydrazones (**6a–k**) in our preliminary screening (Table 2) leads us to determine the minimum inhibitory concentration. The MIC was deduced by following the method and guidelines of the Clinical and Laboratory Standard Institute (CLSI) (Table 3). In this study, the MIC was determined for the most potent selected antimicrobial compounds **6b**, **6e**, **6f,** and **6g**.

Molecular docking study

Docking analysis was utilized to establish the mode of action of synthesized hydrazones (**6a-k**) for their anticancer potential. Grip based docking analysis was performed keeping protein structure in rigid conformation and ligand structures in flexible conformation with cocrystallized bis-anilino pyrimidine inhibitor as a reference molecule.[28] Molecular docking was performed using the crystal structure of the Focal adhesion kinase (PDB ID 2JKO). Focal adhesion kinase is a key regulator of cell division and proliferation and it also possesses all the critical attributes to act as a promising anticancer target. The compound **6c** was found to be interacting with the formation of two hydrogen bond interactions with ILE428, GLU430 and hydrophobic interactions with ASN551, GLY563, ASP564, LEU567 (Figure 3). The compound **6f** showed hydrogen bond interaction with GLU430 and hydrophobic interactions with GLY429 and GLU430 (Figure 4). The bonding interactions of the remaining compounds are given in supplementary material.

ADME predictions

ADME predictions of all the synthesized hydrazone derivatives (**6a–k**) were predicted using Swiss ADME portal (Table 4).[29] All the molecules have shown excellent

Table 1. Antiproliferative activity of hydrazone derivatives (**6a–k**).

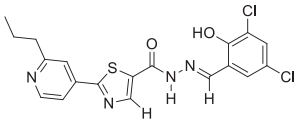
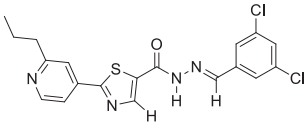
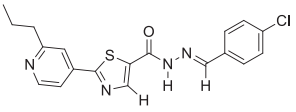
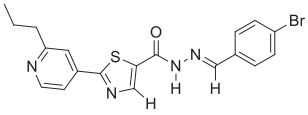
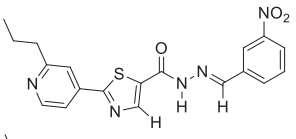
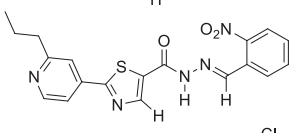
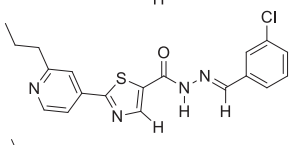
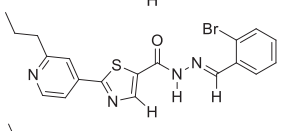
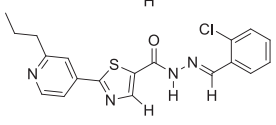
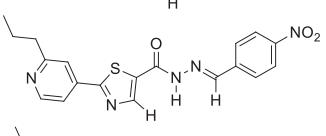
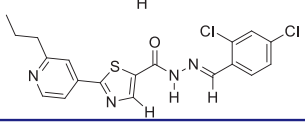
Entry	Compounds (6a-k)	IC_{50} (μM)
6a		3.83 ± 0.23
6b		3.81 ± 0.20
6c		3.11 ± 0.10
6d		4.27 ± 0.15
6e		50.92 ± 0.55
6f		3.04 ± 0.10
6g		5.84±0.20
6h		3.46 ± 0.40
6i		79.83 ± 0.37
6j		20.92 ± 0.18
6k		3.61 ± 0.15

Table 2. Antimicrobial activity of hydrazone derivatives (**6a–k**).

Entry	*S. typhi*	*E. aerogenes*	*B. subtilis*	*P. aeruginosa*	*S. abony*	*E. coli*	*S. aureus*	*S. boydii*	*B. cerus*	*A. niger*	*S. cerevisiae*	*C. albicans*
6a	–	–	30	–	–	–	15	–	–	–	–	–
6b	12	14	20	11	16	14	5	14	13	12	18	13
6c	12	16	10	9	16	14	5	14	12	12	–	–
6d	–	20	9	–	–	–	13	–	–	7	16	–
6e	9	19	10	–	14	–	16	–	–	9	–	6
6f	13	12	12	–	14	–	8	–	12	9	–	7
6g	18	16	14	–	13	–	6	–	7	6	10	7
6h	13	–	–	–	–	–	15	–	–	–	15	–
6i	15	20	–	–	–	–	7	–	–	–	–	–
6j	–	–	6	–	–	–	5	–	–	–	–	–
6k	11	–	–	–	–	–	8	–	–	–	–	–
Streptomycin	33	33	32	32	32	29	29	34	33	NA	NA	NA
Fluconazole	NA	NA	NA	NA	NA	NA	NA	NA	NA	30	30	30

NA: not applicable; (–): inactive.

Table 3. MIC values of most potent antimicrobial hydrazone derivatives (μg/mL).

Entry	*B. subtilis*	*E. aerogenes*	*C. albicans*
6b	90 ± 0.47	170 ± 0.83	150 ± 0.78
6c	260 ± 1.67	120 ± 0.54	280 ± 2.19
6f	75 ± 1.12	85 ± 0.76	210 ± 1.57
6g	120 ± 2.37	150 ± 1.43	250 ± 0.75
Streptomycin	25 ± 0.34	30 ± 0.59	NA
Fluconazole	NA	NA	30 ± 0.17

NA: not applicable.

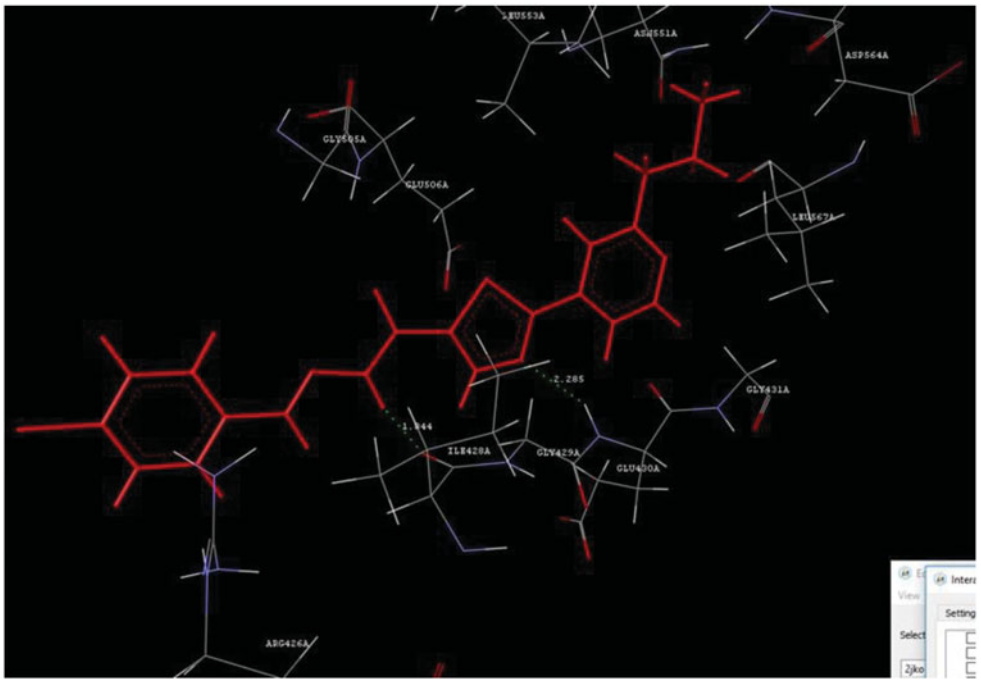


Figure 3. Docking interactions of **6c**.

physicochemical parameters with low Lipinski violation, which is desirable for the oral absorption of drug candidates.

Experimental

The commercially available laboratory grade chemicals were used. The IR spectra were recorded on Brucker FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on Brucker DRX-400 NMR spectrometer. The trimethylsilane (TMS) was used as an internal standard. The coupling constants (*J*) are reported in hertz (Hz).

Synthesis of substituted (E)-N′-benzylidene-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazides (6a–k)

The substituted aromatic aldehydes (**5a–k**) (1.0 mmol) and 2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (**4**) (1.0 mmol) was dissolved in diisopropylethylammonium

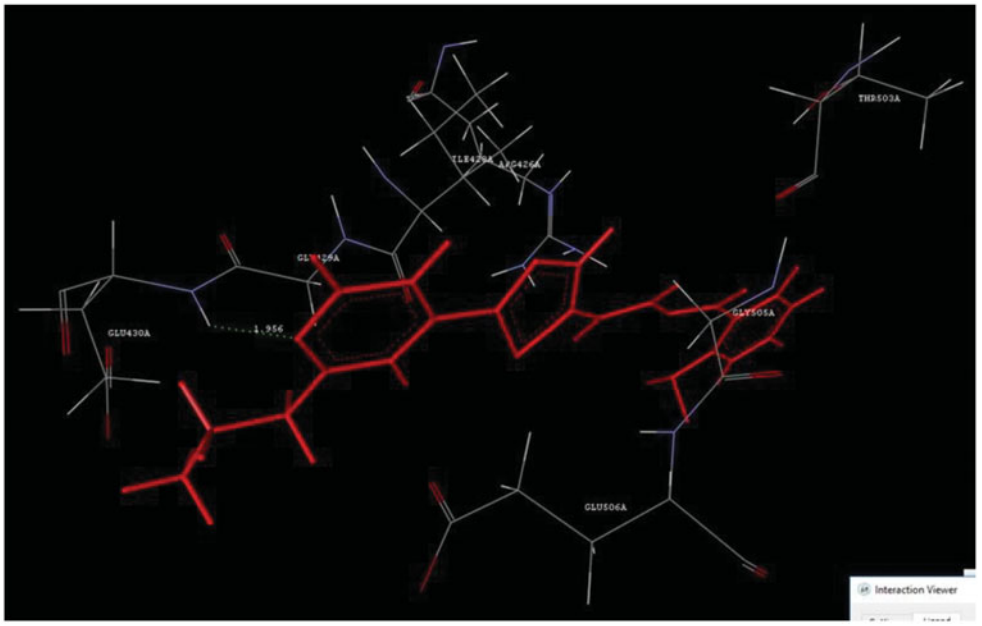


Figure 4. Docking interactions of **6f**.

Table 4. Pharmacokinetic parameters of hydrazone derivatives (**6a–k**).

Entry	H-bond acceptors	H-bond donors	MR	TPSA	XLOGP3	Bioavailability score
6a	5	2	113.14	115.71	4.88	0.55
6b	4	1	111.11	95.48	5.23	0.55
6c	4	1	106.1	95.48	4.61	0.55
6d	4	1	108.79	95.48	4.67	0.55
6e	6	1	109.92	141.3	3.81	0.55
6f	6	1	109.92	141.3	3.81	0.55
6g	4	1	106.1	95.48	4.61	0.55
6h	4	1	108.79	95.48	4.67	0.55
6i	4	1	106.1	95.48	4.61	0.55
6j	6	1	109.92	141.3	3.81	0.55
6k	4	1	111.11	95.48	5.23	0.55

acetate (DIPEAc) (5 ml) and stirred at room temperature for 30 min. After completion of reaction, the reaction mixture was poured on cold water. The solid obtained was filtered and washed with cold water. The products obtained were crystallized from ethanol to furnish corresponding substituted (*E*)-*N*′-benzylidene-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazides (**6a–k**)with 80–90% yields

(E)-N′-(3,5-Dichloro-2-hydroxybenzylidene)-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6a)

Yield: 85%; M. P.: 220–222 °C; IR (Neat) ν cm^{-1}: 3424, 3116, 2907, 2840, 1682, 1600, 1534, 1444, 1347, 1285, 1222, 1177, 994, 849, 796, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.08 (t, *J* = 6.7 Hz, 3H, CH_3), 1.90 (m, 2H, CH_2), 2.93 (t, *J* = 6.7 Hz, 2H, CH_2), 7.39–7.38 (m, 1H, Ar–H), 7.44 (s, 1H, Ar–H), 7.77 (d, *J* = 12.9 Hz, 2H, Ar–H), 8.45 (s, 1H, thiazolyl–H), 8.69 (s, 2H, Ar–H), 11.23 (s, 1H, Ar–OH), 12.00 (s, 1H, amido–NH);

^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ = 13.87, 23.06, 29.62, 119.55, 122.62, 123.73, 126.69, 128.43, 131.28, 139.33, 148.88, 149.31, 150.17, 152.94, 156.59, 166.33; HRMS $(ESI)^+$ calcd. for $C_{19}H_{16}Cl_2N_4O_2S$ $[M+H]^+$: 435.0371 and found 435.0443.

Conclusions

In summary, we have reported new pyridyl and thiazolyl clubbed hydrazone scaffolds starting from an antitubercular drug, prothionamide. The synthesized hydrazone derivatives were evaluated for their *in vitro* antitumor activity against the A549 lung cancer cells. As compared to the standard drug, doxorubicin, the hydrazones **6a**, **6b**, **6c**, **6d**, **6f**, **6g**, **6h,** and **6k** were shown better inhibitory activity with MIC values 3.83, 3.81, 3.11, 3.04, 4.27, 5.84, 3.46, and 3.61 μM, respectively. The synthesized hydrazone derivatives have also been evaluated for their antimicrobial activity against gram-positive and gram-negative pathogens. Among them, hydrazone derivatives **6b**, **6c**, **6f,** and **6g** have displayed good antimicrobial activities. Besides, the molecular docking study was performed using the crystal structure of the Focal adhesion kinase (PDB ID 2JKO). We believe these results laid a foundation for further improving the potency and the selectivity of this series of compounds as anticancer and antimicrobial agents.

Full experimental detail, ^{1}H and ^{13}C NMR spectra, HRMS spectra and docking images, these materials can be found via the "Supplementary Content" section of this article's webpage.

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References

[1] Gabr, M. T.; El-Gohary, N. S.; El-Bendary, E. R.; El-Kerdawy, M. M. Synthesis and *in Vitro* Antitumor Activity of New Series of Benzothiazole and Pyrimido[2,1-*b*]Benzothiazole Derivatives. *Eur. J. Med. Chem.* **2014**, *85*, 576–592. doi:10.1016/j.ejmech.2014.07.097.

[2] (a) Farkona, S.; Diamandis, E. P.; Blasutig, I. M. Cancer Immunotherapy: The Beginning of the End of Cancer? *BMC Med.* **2016**, *14*, 73. doi:10.1186/s12916-016-0623-5. (b) Bhatt, P.; Kumar, M.; Jha, A. Design, Synthesis and Anticancer Evaluation of Oxa/Thiadiazolylhydrazones of Barbituric and Thiobarbituric Acid: A Collective *in Vitro* and *in Silico* Approach. *ChemistrySelect.* **2018**, *3*, 7060–7065. doi:10.1002/slct.201800832.

[3] Xue, Y.; Hou, S.; Ji, H.; Han, X. Evolution from Genetics to Phenotype: Reinterpretation of NSCLC Plasticity, Heterogeneity, and Drug Resistance. *Protein Cell.* **2017**, *8*, 178–190. doi:10.1007/s13238-016-0330-1.

[4] Li, L.; Zhu, T.; Gao, Y.-F.; Zheng, W.; Wang, C.-J.; Xiao, L.; Huang, M.-S.; Yin, J.-Y.; Zhou, H.-H.; Liu, Z.-Q. Targeting DNA Damage Response in the Radio(Chemo)Therapy of Non-Small Cell Lung Cancer. *IJMS.* **2016**, *17*, 839. doi:10.3390/ijms17060839.

[5] Ansari, J.; Shackelford, R. E.; El-Osta, H. Epigenetics in Non-Small Cell Lung Cancer: From Basics to Therapeutics. *Transl. Lung Cancer Res.* **2016**, *5*, 155–171. doi:10.21037/tlcr.2016.02.02.

[6] (a) Ayati, A.; Emami, S.; Asadipour, A.; Shafiee, A.; Foroumadi, A. Recent Applications of 1,3-Thiazole Core Structure in the Identification of New Lead Compounds and Drug Discovery. *Eur. J. Med. Chem.* **2015**, *97*, 699–718. doi:10.1016/j.ejmech.2015.04.015. (b) Das, D.; Sikdar, P.; Bairagi, M. Recent Developments of 2-Aminothiazoles in Medicinal Chemistry. *Eur. J. Med. Chem* **2016**, *109*, 89–98. doi:10.1016/j.ejmech.2015.12.022.

[7] (a) Gomha, S. M.; Khalil, K. D. A Convenient Ultrasound-Promoted Synthesis and Cytotoxic Activity of Some New Thiazole Derivatives Bearing a Coumarin Nucleus. *Molecules.* **2012**, *17*, 9335–9347. doi:10.3390/molecules17089335. (b) Gomha, S. M.; Salah, T. A.; Abdelhamid, A. O. Synthesis, Characterization and Pharmacological Evaluation of Some Novel Thiadiazoles and Thiazoles Incorporating Pyrazole Moiety as Potent Anticancer Agents. *Monatsh Chem.* **2015**, *146*, 149–158. doi:10.1007/s00706-014-1303-9.

[8] Karegoudar, P.; Karthikeyan, M. S.; Prasad, D. J.; Mahalinga, M.; Holla, B. S.; Kumari, N. S. Synthesis of Some Novel 2,4-Disubstituted Thiazoles as Possible Antimicrobial Agents. *Eur. J. Med. Chem.* **2008**, *43*, 261–267. doi:10.1016/j.ejmech.2007.03.014.

[9] Roy, N. K.; Bordoloi, D.; Monisha, J.; Padmavathi, G.; Kotoky, J.; Golla, R.; Kunnumakkara, A. B. Specific Targeting of Akt Kinase Isoforms: Taking the Precise Path for Prevention and Treatment of Cancer. *CDT.* **2017**, *18*, 421–435. doi:10.2174/1389450117666160307145236.

[10] Cassinelli, G.; Zuco, V.; Gatti, L.; Lanzi, C.; Zaffaroni, N.; Colombo, D.; Perego, P. Targeting the Akt Kinase to Modulate Survival, Invasiveness and Drug Resistance of Cancer Cells. *CMC.* **2013**, *20*, 1923–1945. doi:10.2174/09298673113209990106.

[11] Gyoba, J.; Shan, S.; Roa, W.; Bedard, E. L. R. Diagnosing Lung Cancers through Examination of Micro-RNA Biomarkers in Blood, Plasma, Serum and Sputum: A Review and Summary of Current Literature. *IJMS.* **2016**, *17*, 494. doi:10.3390/ijms17040494.

[12] Abhale, Y. K.; Shinde, A. D.; Deshmukh, K. K.; Nawale, L.; Sarkar, D.; Choudhari, P. B.; Kumbhar, S. S.; Mhaske, P. C. Synthesis, Antimycobacterial Screening and Molecular Docking Studies of 4-Aryl-4′-Methyl-2′-Aryl-2,5′-Bisthiazole Derivatives. *Med. Chem. Res.* **2017**, *26*, 2889–2899. doi:10.1007/s00044-017-1988-5.

[13] (a) Vicini, P.; Incerti, M.; La Colla, P.; Loddo, R. Anti-HIV Evaluation of Benzo[*d*]Isothiazole Hydrazones. *Eur. J. Med. Chem.* **2009**, *44*, 1801–1807. doi:10.1016/j.ejmech.2008.05.030. (b) Jin, Y.; Tan, Z.; He, M.; Tian, B.; Tang, S.; Hewlett, I.; Yang, M. SAR and Molecular Mechanism Study of Novel Acylhydrazone Compounds Targeting HIV-1 CA. *Bioorg. Med. Chem.* **2010**, *18*, 2135–2140. doi:10.1016/j.bmc.2010.02.003.

[14] (a) Bedia, K. K.; Elcin, O.; Seda, U.; Fatma, K.; Nathaly, S.; Sevim, R.; Dimoglo, A. Synthesis and Characterization of Novel Hydrazide-Hydrazones and the Study of Their Structure-Antituberculosis Activity. *Eur. J. Med. Chem.* **2006**, *41*, 1253–1261. doi:10.1016/j.ejmech.2006.06.009. (b) Eswaran, S.; Adhikari, A. V.; Chowdhury, I. H.; Pal, N. K.; Thomas, K. D. New Quinoline Derivatives: synthesis and Investigation of Antibacterial and Antituberculosis Properties. *Eur. J. Med. Chem.* **2010**, *45*, 3374–3383. doi:10.1016/j.ejmech.2010.04.022.

[15] (a) Bondock, S.; Naser, T.; Ammar, Y. A. Synthesis of Some New 2-(3-Pyridyl)-4,5-Disubstituted Thiazoles as Potent Antimicrobial Agents. *Eur. J. Med. Chem.* **2013**, *62*, 270–279. doi:10.1016/j.ejmech.2012.12.050. (b) Dhumal, S. T.; Deshmukh, A. R.; Bhosle, M. R.; Khedkar, V. M.; Nawale, L. U.; Sarkar, D.; Mane, R. A. Synthesis and Antitubercular Activity of New 1,3,4-Oxadiazoles Bearing Pyridyl and Thiazolyl Scaffolds. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3646–3651. doi:10.1016/j.bmcl.2016.05.093.

[16] Dhumal, S. T.; Deshmukh, A. R.; Khillare, L. D.; Arkile, M.; Sarkar, D.; Mane, R. A. Synthesis and Antitubercular Activity of New Thiazolidinones with Pyrazinyl and Thiazolyl Scaffolds. *J. Heterocyclic Chem.* **2017**, *54*, 125–130. doi:10.1002/jhet.2552.

[17] (a) Kumar, P.; Narasimhan, B. Hydrazides/Hydrazones as Antimicrobial and Anticancer Agents in the New Millennium. *Mini-Rev. Med. Chem.* **2013**, *13*, 971–987. doi:10.2174/1389557511313070003. (b) Xia, Y.; Fan, C.-D.; Zhao, B.-X.; Zhao, J.; Shin, D.-S.; Miao, J.-Y. Synthesis and Structure-Activity Relationships of Novel 1-Arylmethyl-3-Aryl-1H-Pyrazole-5-Carbohydrazide Hydrazone Derivatives as Potential Agents against A549 Lung Cancer Cells. *Eur. J. Med. Chem.* **2008**, *43*, 2347–2353. doi:10.1016/j.ejmech.2008.01.021.

[18] (a) Narang, R.; Narasimhan, B.; Sharma, S. A. A Review on Biological Activities and Chemical Synthesis of Hydrazide Derivatives. *CMC.* **2012**, *19*, 569–612. doi:10.2174/092986712798918789. (b) Vogel, S.; Kaufmann, D.; Pojarová, M.; Müller, C.; Pfaller, T.; Kühne, S.; Bednarski, P. J.; Angerer, E. V. Hydrazones of 2-Phenylindole-3-Carbaldehydes as Novel Antimitotic Agents. *Bioorg. Med. Chem.* **2008**, *16*, 6436–6447. doi:10.1016/j.bmc.2008.04.071. (c) Alam, M. S.; Choi, S.-U.; Lee, D.-U. Synthesis, Anticancer, and Docking Studies of Salicyl-Hydrazone Analogues: A Novel Series of Small Potent Tropomyosin Receptor Kinase a Inhibitors. *Bioorg. Med. Chem.* **2017**, *25*, 389–396. doi:10.1016/j.bmc.2016.11.005.

[19] Barbosa, V. A.; Formagio, A. S. N.; Savariz, F. C.; Foglio, M. A.; Spindola, H. M.; de Carvalho, J. E.; Meyer, E.; Sarragiotto, M. H. Synthesis and Antitumor Activity of β-Carboline 3-(Substituted-Carbohydrazide) Derivatives. *Bioorg. Med. Chem.* **2011**, *19*, 6400–6408. doi:10.1016/j.bmc.2011.08.059.

[20] Kamal, R.; Kumar, R.; Kumar, V.; Kumar, V.; Bansal, K. K.; Sharma, P. C. Synthesis, Anthelmintic and Antimicrobial Evaluation of New 2-Arylidene-1-(4-Methyl-6-Phenylpyrimidin-2-yl)Hydrazines. *ChemistrySelect*. **2019**, *4*, 713–717. doi:10.1002/slct.201802822.

[21] Nastasa, C.; Tiperciuc, B.; Duma, M.; Benedec, D.; Oniga, O. New Hydrazones Bearing Thiazole Scaffold: synthesis, Characterization, Antimicrobial and Antioxidant Investigation. *Molecules.* **2015**, *20*, 17325–17338. doi:10.3390/molecules2009917325.

[22] Gomha, S. M.; Kheder, N. A.; Abdelaziz, M. R.; Mabkhot, Y. N.; Alhajoj, A. M. A Facile Synthesis and Anticancer Activity of Some Novel Thiazoles Carrying 1,3,4-Thiadiazole Moiety. *Chem. Cent. J.* **2017**, *11*, 25. doi:10.1186/s13065-017-0255-7.

[23] Muluk, M. B.; Dhumal, S. T.; Rehman, N. N. M. A.; Dixit, P. P.; Kharat, K. R.; Haval, K. P. Synthesis, Anticancer and Antimicrobial Evaluation of New (*E*)-*N*′-Benzylidene-2-(2-Ethylpyridin-4-yl)-4-Methylthiazole-5-Carbohydrazides. *ChemistrySelect.* **2019**, *4*, 8993–8997. doi:10.1002/slct.201902030.

[24] (a) Phatak, P. S.; Bakale, R. D.; Dhumal, S. T.; Dahiwade, L. K.; Choudhari, P. B.; Siva Krishna, V.; Sriram, D.; Haval, K. P. Synthesis, Antitubercular Evaluation and Molecular Docking Studies of Phthalimide Bearing 1,2,3-Triazoles. *Synth. Commun.* **2019**, *49*, 2017–2028. doi:10.1080/00397911.2019.1614630. (b) Muluk, M. B.; Dhumal, S. T.; Phatak, P. S.; Rehman, N. N. M. A.; Dixit, P. P.; Choudhari, P. B.; Mane, R. A.; Haval, K. P. Synthesis, in Vitro Evaluation and Molecular Docking Study of Formylnaphthalenyloxy Methyl-triazolyl-N-Phenylacetamides. *J. Heterocyclic Chem.* **2019**, *56*, 2411–2418. doi:10.1002/jhet.3628. (c) Kulkarni, R. S.; Haval, N. B.; Kulkarni, J. A.; Dixit, P. P.; Haval, K. P. Synthesis, Characterization and Biological Evaluation of Substituted 2-Phenoxynicotinaldehydes as α-Amylase Inhibitors. *ECB.* **2019**, *8*, 26–30. doi:10.17628/ecb.2019.8.26-30.

[25] Baldisserotto, A.; Demurtas, M.; Lampronti, L.; Moi, D.; Balboni, G.; Vertuani, S.; Manfredini, S.; Onnis, V. Benzfuran Hydrazones as Potential Scaffolds in the Development of Multifunctional Drugs: Synthesis and Evaluation of Antioxidant, Photoprotective and Antiproliferative Activity. *Eur. J. Med. Chem.* **2018**, *156*, 118–125. doi:10.1016/j.ejmech.2018.07.001.

[26] Dhumal, S. T.; Deshmukh, A. R.; Kharat, K. R.; Sathe, B. R.; Chavan, S. S.; Mane, R. A. Copper Fluorapatite Assisted Synthesis of New 1,2,3-Triazoles Bearing a Benzothiazolyl

Moiety and Their Antibacterial and Anticancer Activities. *New J. Chem.* **2019**, *43*, 7663–7673. doi:10.1039/c(nj00377k.

[27] Phatak, P. S.; Sathe, B. P.; Dhumal, S. T.; Rehman, N. N. M. A.; Dixit, P. P.; Khedkar, V. M.; Haval, K. P. Synthesis, Antimicrobial Evaluation and Docking Studies of Substituted Acetylphenoxymethyl-triazolyl-*N*-Phenylacetamides. *J. Heterocyclic Chem.* **2019**, *56*, 1928–1938. DOI doi:10.1002/jhet.3568.

[28] Kondhare, D. D.; Gyananath, G.; Tamboli, Y.; Kumbhar, S. S.; Choudhari, P. B.; Bhatia, M. S.; Zubaidha, P. K. An Efficient Synthesis of Flavanones and Their Docking Studies with Aldose Reductase. *Med. Chem. Res.* **2017**, *26*, 987–998. doi:10.1007/s00044-017-1813-1.

[29] Daina, A.; Michielin, O.; Zoete, V. A Boiled-Egg to Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *Chem Med Chem*. **2016**, *11*, 1117–1121. doi:10.1002/cmdc.201600182.