Synthesis of novel nicotinohydrazide and (1,3,4-oxadiazol-2-yl)-6-(trifluoro methyl)pyridine derivatives as potential anticancer agents

R. Naresh Kumar, Y. Poornachandra, P. Nagender, G. Santhosh Kumar, D. Krishna Swaroop, C. Ganesh Kumar, B. Narsaiah

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Manuscript Draft

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Abstract: A series of novel nicotinohydrazide derivatives 6a-g and 1,3,4-oxadiazole functionalized pyridine derivatives 7a-k and 8a-d were prepared in series of steps. All the compounds were screened for cytotoxicity against HeLa (cervical), DU145 (prostate), HepG2 (liver) and MBA-MB-231 (breast) human cancer cell lines. Compounds 6h, 6i, 7d, 7h, 7i and 8b which showed promising cytotoxicity at <15 µM concentration have been identified. Further optimization of the structure is underway to identify a lead compound.

BN-Sci./2016 May 21, 2016

Editor
Bio-Organic & Medicinal Chemistry Letters

Sub: Submission of revised manuscript as an original article.

Dear Editor,

Thank you very much for considering our manuscript entitled "Synthesis of novel nicotinohydrazide and 1,3,4-oxadiazol-2-yl)-6-(trifluoromethyl)pyridine derivatives as potential anticancer agents" for publication in Bio-Organic & Medicinal Chemistry Letters after revision. The manuscript is revised in line with the suggestions made by reviewers and editor comments and submitting here the revised version of manuscript. The responses to the reviewers comments point wise also submitting here as a separate file. The manuscript has not been previously published, is not currently submitted for review to any other journal, and will not be submitted elsewhere before a decision is made by this journal.

Kindly acknowledge the receipt of revised manuscript.

With best regards

Yours Sincerely,

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Bioorganic Medicinal Chemistry letters

Manuscript Title: Synthesis of novel nicotinohydrazide and 1,3,4-oxadiazol-2-yl) 6(trifluoromethyl) pyridine derivatives as potential anticancer agents

Manuscript Ref. No: BMCL-D-16-00189

Dear editor,

Thank you very much for your valuable comments and suggestions regarding the manuscript. We have modified the manuscript accordingly, and the detailed response to the comments is given point by point in a separate sheet.

The manuscript is being resubmitted to your journal. We look forward to your positive response.

With best regards

Dr. B. Narsaiah
Chief Scientist
Fluoroorganic division
Indian Institute of Chemical Technology
Tarnaka, Hyderabad

Response to the reviewers comments

Editor's Comments:

Comment 1: Address: If there is more than one affiliation, designate authors to institutions by using superscript 'a', 'b', c' etc.

Comment 2: Headings: Please do not use common headings, such as 'Introduction', 'Chemistry', or 'Conclusion', other than 'Acknowledgments' and 'References and Notes'.

Comment 3: R1, R2: Use a superscript numeral for R1, R2, etc. (not a subscript R1, R2) to designate substituents in graphic structures, tables, and text.

Comment 4: Reference Style: For proper reference style, please consult the References and Notes section of the Journal's Guide for Authors found at www.ees.elsevier.com/bmcl. Note that the Journal uses a start page number only for journal articles. For journal title abbreviations, please consult the list provided: Click on Guide for Authors; then click on Journal Title Abbreviation List.

Comment 5: X-ray coordinates: X-ray-coordinates must be deposited with the RCSB Protein Data Bank (PDB) database (or Cambridge Crystallographic Data Centre for small molecules) and the PDB (or CCDC) deposition number mmust be placed in the manuscript.

Comment 6: Experimental Information: All experimental information should be placed in the References and notes section as an endnote or placed in Supporting Information.

Reply: All the editor comments addressed in revised manuscript.

Reviewer #1

Comment 1: The common CF_3 group on all the molecules is however not justified. Did authors tried CH_3 analogs of **6h** and **7i** to find out if the activity is imparted from heterocyclic part of the molecule or from CF_3 group or synergistic effect? The authors need to clarify this in detail and provide the activity data after synthesizing the CH_3 analogs.

Reply1: The comments expressed by the reviewer are quite interesting and encouraging. Nevertheless, in the present study, attempts were made to synthesize the CH_3 analogs as suggested, and it was observed that it follows a different strategy unlike the one mentioned in the present study that results in a large set of different heterocyclic compounds for anticancer evaluation, which itself is an independent detailed study to execute. Therefore, the synthesis

of the CH_3 analogs and its cytotoxicity evaluation for comparison purpose at present is not feasible.

Comment 2: Authors need to provide the scanned copies of ^{1}H, ^{13}C and ^{19}F NMR of all the compounds synthesized. This information should be included in the supporting information.

Reply 2: The ^{1}H, ^{13}C and ^{19}F NMR spectral data for all the new compounds have been included in the supporting information.

Reviewer #2

Comment 1: Although the authors reported the synthetic routes, corresponding yields were not included in the paper. A clear table about reaction yields in each step should be included in the paper. Results of melting point can be moved to supporting information.

Reply 1: The corresponding reaction yields are included in Table 1 of the revised manuscript, and melting points have been shifted to supporting information.

Comment 2: Do these oxadiazole derivatives still proceed the same mechanism with 5-fluorouracil to inhibit cancer cell line? Also, what is the role of these compounds? The discussion about the inhibitory mechanism will enhance the importance of this paper.

Reply 2: Based on the literature survey, 5-fluorouracil is known to exhibit several mechanisms responsible for the inhibition of cancer cell proliferation. And one among them is the induction of apoptosis of cancer cells through the activation of caspase cascade. Based on this evidence, we presume that the synthesized oxadiazole derivatives may also be exhibiting a similar cell death mechanism as that of 5-fluorouracil. The required information along with the references has been included in the revised manuscript as suggested by the reviewer.

Comment 3: Since 5-fluorouracil exhibits serious adverse effects, does these nicotinopyridine derivatives also have the same issue or not?

Reply 3: Published literature claims that 5-fluorouracil may be exhibiting serious adverse effects; however, the nicotinopyridine derivatives examined in the present study have not been evaluated for any of the toxicological studies. So it is difficult to comment at this juncture as to whether these nicotinopyridine derivatives exhibit the same adverse effects or not.

Graphical Abstract

Synthesis of novel nicotinohydrazide and (1,3,4-oxadiazol-2-yl)-6-(trifluoromethyl) pyridine derivatives as potential anticancer agents

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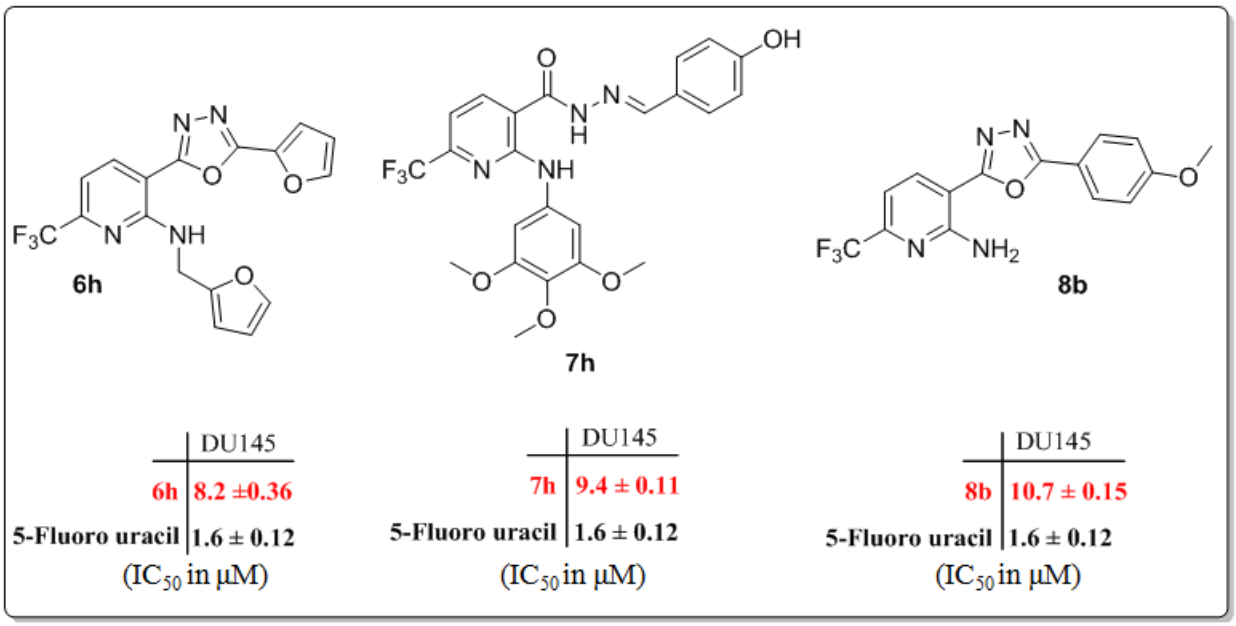

Graphical Abstract

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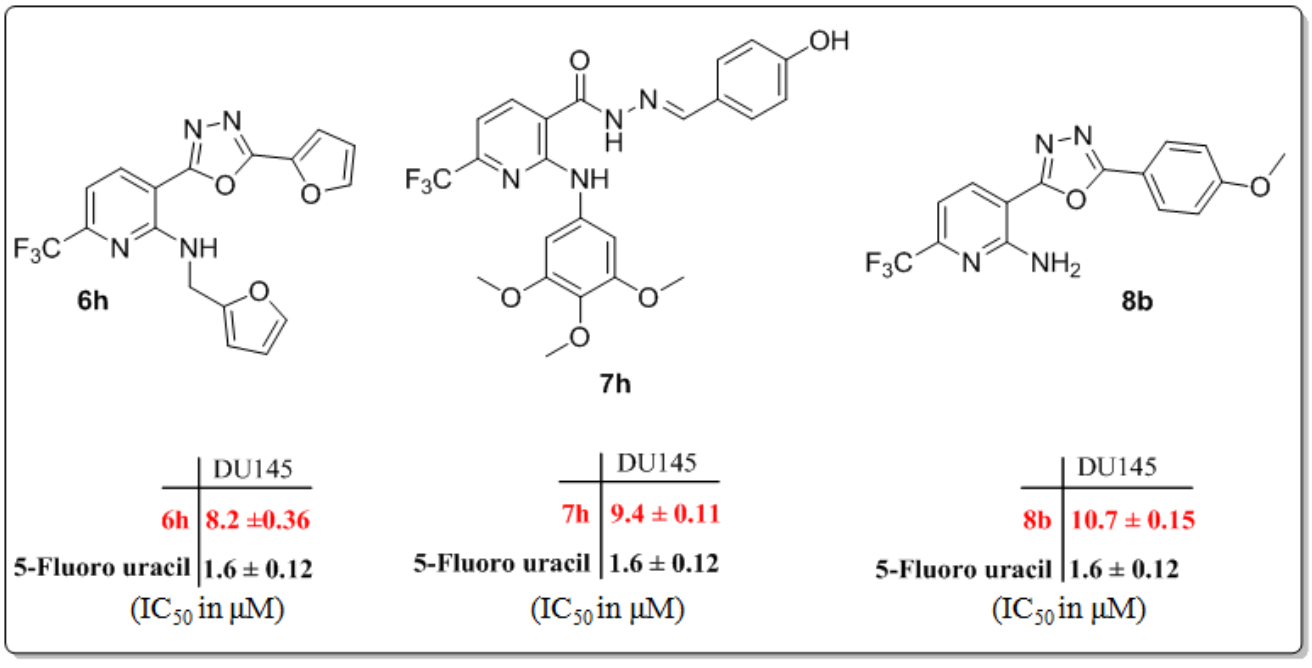

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Synthesis of novel nicotinohydrazide and (1,3,4-oxadiazol-2-yl)-6-(trifluoro methyl)pyridine derivatives as potential anticancer agents

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ABSTRACT

A series of novel nicotinohydrazide derivatives **6a-g** and 1,3,4-oxadiazole functionalized pyridine derivatives **7a-k** and **8a-d** were prepared in series of steps. All the compounds were screened for cytotoxicity against HeLa (cervical), DU145 (prostate), HepG2 (liver) and MBA-MB-231 (breast) human cancer cell lines. Compounds **6h**, **6i**, **7d**, **7h**, **7i** and **8b** which showed promising cytotoxicity at <15 µM concentration have been identified. Further optimization of the structure is underway to identify a lead compound.

Cancer is a collection of different life-threatening diseases, in which a group of cells display uncontrolled growth in a body. According to the statistics, cancer is the second most common cause of death worldwide after cardiovascular diseases. About 200 types of cancers affecting major organs like lungs, brain, kidneys, colon, breasts and stomach have been identified. Various synthetic approaches based on chemical modification have been undertaken with an aim to improve the safety profile of NSAIDs. Five-membered heterocycles containing two nitrogen and one oxygen or sulfur atoms have been reported to exhibit a broad spectrum of biological activities.[1] Much attention has been paid to the chemistry and biological activities of 1,3,4-oxadiazole nucleus. Among them, 2,5-disubstituted 1,3,4-oxadiazole scaffolds are known to exhibit a significant role in various pharmaceutical applications.[2-4] A stable and neutral hetero aromatic nucleus that is associated with potent pharmacological activity, can be attributed due to the presence of toxophoric –N=C–O– linkage.[5] Further, 1,3,4-oxadiazole heterocycles are very good bioisosteres of amides and esters, which can contribute substantially in increasing pharmacological activity by participating in hydrogen bonding interactions with the receptors.[6] In particular, among these, a few differently substituted 1,3,4-oxadiazoles have exhibited potent antitumor activities.[7,8] Apart from, other biological activities have also been reported for 1,3,4-oxadiazole derivatives such as potential antimicrobial,[9] anticancer[10] antitubercular,[11] vasodialatory,[12] cytotoxic,[13] anti-inflammatory,[14] analgesic,[15] antidiabetic,[16] hypolipidemic[17] and ulcerogenic[18] activity. The development of an efficient, and selective anticancer agents represents a major interest and challenge to the contemporary medicinal chemistry.

Drug resistance constitutes lack of response to many chemically and mechanically unrelated anticancer agents by cancer cells. It is one of the main causes for failure of chemotherapy and can lead to re-occurrence of disease or even death.[19] The 5-chloro-3-methyl-indole-2-carboxylic acid benzylidene hydrazides are identified as potent apoptosis inducers by inhibiting tubulin polymerization in G2/M phase against breast cancer cell lines T47D (IC_{50} = 0.2l M). Literature survey revealed that the hydrazide-hydrazone (-CO-NH-N=CH-) moiety has shown significant role as various antitumor agents. Based on the above findings, the search is on for more effective and less toxic potent anticancer drugs. Moreover, the diverse biological activity of pyridines and 1,3,4-oxadiazoles/hydrazide-hydrazones encouraged us to predict the combination of both pharmacophores in a compact system. In continuation to our efforts,[20-22] we focused to construct a new molecular framework. Thus, a series of novel 2-substituted 3-(1,3,4–oxadiazole) functionalized derivatives having 6-trifluoromethyl group on pyridine and other hydrazide-hydrazone

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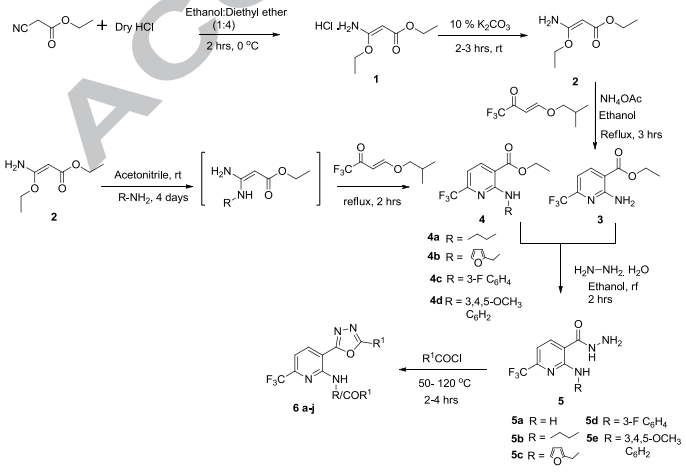
derivatives were synthesized and evaluated for their *in vitro* anticancer activity against four human cancer cell lines such as HeLa (cervical), HepG2 (liver), MDA-MB-231 (breast) and DU145 (prostate).

The synthesis of 6-(trifluoromethyl) nicotinohydrazide and 1,3,4-(oxadiazol-2-yl)-6-(trifluoromethyl) pyridine derivatives involves series of steps. Ethyl 2-cyanoacetate was taken in mixture of ethanol and diethyl ether (1: 4) ratio and dry hydrochloric acid (HCl) gas was continuously passed through the mixture upto 2 hours afforded hydrochloride salt of ethyl 3-amino-3-ethoxyacrylate **1.** Compound **1** was neutralized with 10% potassium carbonate and extracted with diethyl ether to obtain ethyl 3-amino-3-ethoxyacrylate **2**. Compound **2** on reaction with 4-isobutoxy-1,1,1-trifluorobut-3-en-2-one in ethanol in the presence of ammonium acetate resulted in ethyl 2-amino-6-(trifluoromethyl) nicotinate **3**. The sequence of reaction is mainly an attack of ammonia on β-carbon of compound **2** from ammonium acetate in situ followed by reaction with isobutyl vinyl trifluoro acetyl ether to form product **3.** The 3,3-diamino ethyl acrylate amine nucleophile selectively attack on vinyl carbon of isobutyl vinyl trifluoro acetyl ether followed by elimination of isobutanol and cyclization to form product **3.** An alternate strategy has been adopted to have substituted amine at second position of compound **3** and accomplished the compound **4**. Thus, ethyl 3-amino-3-ethoxyacrylate **2** was reacted with alkyl or aryl amines in acetonitrile for 4 days at room temperature, followed by addition of 4-isobutoxy-1,1,1-trifluorobut-3-en-2-one and refluxed for 2 hours, as a result ethyl 2-(alkyl/substituted arylamino)-6-(trifluoromethyl)nicotinate **4a-d** formed. Ethyl 2-amino-6-(trifluoromethyl) nicotinate **3** or ethyl 2-(alkyl/substituted arylamino)-6-(trifluoromethyl) nicotinate **4a-d** and hydrazine hydrate were refluxed in ethanol resulted 2-amino/substituted amino-6-(trifluoromethyl) nicotinohydrazide **5a-e**. Compound **5a-e** on reaction with alkyl/aryl acid chlorides obtained (1,3,4-oxadiazol-2-yl)-6-(trifluoromethyl) pyridin-2-yl)alkyl/arylamide or pyridin-2-amine **6a-j**. In addition, compound **5a-e** were reacted with substituted benzaldehydes in the presence of catalytic amount of piperidine at 70 ^{o}C afforded 2-amino or substituted amino-*N*'-substituted benzylidene-6-(trifluoromethyl) nicotino hydrazide **7a-k.** Compounds **7a-k** were in presence of iodine and potassium carbonate in dimethyl sulphoxide at 100 ^{o}C, resulted 3-(5-(4-substituted phenyl)-1,3,4-oxadiazol-2-yl)-6-(trifluoromethyl) pyridin-2-amine **8a-d**. Synthetic pathways of all the derivatives were represented in Scheme 1 and 2. The physical properties of products are shown in Tables 1 and 2.

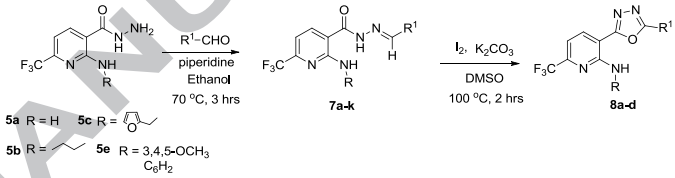
Compounds **6a-j**, **7a-k** and **8a-d** were subjected to cytotoxicity evaluation against four human cancer cell lines such as HeLa (cervical), DU145 (prostate), HepG2 (liver) and MBA-MB-231 (breast) using 5-fluorouracil as standard. Compounds **6h**, **6i**, **7d**, **7h**, **7i** and **8b** showed promising cytotoxicity against all the cell lines at <15 μM concentration. All the remaining compounds except **7b** showed moderate activity against all the tested cell lines.



Scheme 1. Synthetic pathways of **6a-j** derivatives

Table 1. Physical properties of 1,3,4-oxadiazol-2-yl)-6-(trifluoromethyl) pyridin-2-yl)alkyl/aryl amide or pyridin-2-amine (**6a-j**) derivatives

S. No.	Compd No.	R	R^1	Yield (%)
1	**6a**	-	$CH_2CH_2CH_3$	88
2	**6b**	-	C_6H_5	92
3	**6c**	-	4-$OCH_3C_6H_4$	94
4	**6d**	-	C_2H_5	84
5	**6e**	3-FC_6H_4	C_2H_5	64
6	**6f**	3-FC_6H_4	$CH_2CH_2CH_3$	74
7	**6g**	3,4,5-$(OCH_3)_3C_6H_2$	C_2H_5	62
8	**6h**	2-methylfuryl	2-furyl	65
9	**6i**	C_3H_7	2-furyl	68
10	**6j**	C_3H_7	4$OCH_3C_6H_4$	90



Scheme 2. Synthetic pathways of **7a-k** and **8a-d** derivatives

Table 2. Physical properties of **7a-k** and **8a-d** derivatives

S .No.	Compd No.	R	R^1	Yield (%)
1	**7a**	H	4-$CF_3C_6H_4$	92
2	**7b**	H	4-$OCH_3C_6H_4$	82
3	**7c**	H	4-ClC_6H_4	78
4	**7d**	H	4-BrC_6H_4	74
5	**7e**	3,4,5-$(OCH_3)_3C_6H_2$	4-$NO_2C_6H_4$	76
6	**7f**	C_3H_7	2-furyl	74
7	**7g**	C_3H_7	4-$OCH_3C_6H_4$	78
8	**7h**	3,4,5-$(OCH_3)_3C_6H_2$	4-OHC_6H_4	81
9	**7i**	3,4,5-$(OCH_3)_3C_6H_2$	C_6H_5	67
10	**7j**	H	C_6H_5	76
11	**7k**	C_5H_5O	C_6H_5	81
12	**8a**	H	4-$CF_3C_6H_4$	84
13	**8b**	H	4-$OCH_3C_6H_4$	78
14	**8c**	H	4-ClC_6H_4	85
15	**8d**	H	4-BrC_6H_4	72

The structure- activity relationship (SAR) study revealed that the promising activity exhibited by the identified compounds was attributed due to the presence of 2-furyl substituent in compounds **6h** and **6i**. While, the compound **7d** has 4-bromophenyl substituent, the compounds **7h** and **7i** has 3,4,5-trimethoxy phenyl substituent and the presence of 4-OCH_3 phenyl substituent in **8b** which promoted this activity. Based on the cytotoxicity data in the present study, further optimization of the structure is underway to identify a lead compound. Based on the literature survey, 5-fluorouracil is known to exhibit several mechanisms responsible for the inhibition of cancer cell proliferation. And one among them is the induction of apoptosis of cancer cells through the activation of caspase cascade.[23,24] Based on this evidence,

we presume that the synthesized derivatives may also be exhibiting a similar cell death mechanism as that shown by 5-fluorouracil. All the results to this regard are included in Tables 3 and 4.

Table 3. Anticancer activity of 1,3,4-oxadiazol-2-yl)-6-(trifluoro methyl)pyridin-2-yl)alkyl /arylamide or pyridin-2-amine (**6a-j**) derivatives

S.No	Test compound	IC_{50} values (μM)			
		HeLa	DU145	HepG2	MDA-MB-231
1	**6a**	24.9 ± 0.26	23.1 ± 0.44	19.8 ± 0.26	18.2 ± 0.12
2	**6b**	29.2 ± 0.19	30.3 ± 0.38	31.6 ± 0.44	28.4 ± 0.38
3	**6c**	18.5 ± 0.25	17.7 ± 0.16	13.4 ± 0.18	20.2 ± 0.36
4	**6d**	26.2 ± 0.32	24.8 ± 0.18	31.1 ± 0.36	28.7 ± 0.21
5	**6e**	20.9 ± 0.31	22.2 ± 0.11	26.4 ± 0.34	18.7 ± 0.21
6	**6f**	19.6 ± 0.23	18.9 ± 0.52	17.7 ± 0.18	13.5 ± 0.16
7	**6g**	23.3 ± 0.37	22.1 ± 0.25	19.9 ± 0.16	20.5 ± 0.32
8	**6h**	9.8 ± 0.11	8.2 ±0.36	9.5 ± 0.19	8.7 ± 0.22
9	**6i**	12.8 ± 0.22	10.1 ± 0.24	11.6 ± 0.36	9.9 ± 0.17
10	**6j**	20.8 ± 0.15	18.2 ± 0.18	17.6 ± 0.17	18.8 ± 0.16
5-Fluoro uracil[a]		1.9 ± 0.11	1.6 ± 0.12	1.3 ± 0.09	1.8 ± 0.11

[a] = standard

Table 4. Anticancer activity of **7a-k** and **8a-d** derivatives

S.No	Compd	IC_{50} values (μM)			
		HeLa	DU145	HepG2	MDA MB-231
1	**7a**	40.9 ± 0.52	50.2 ± 0.54	53.4 ± 0.46	39.8 ± 0.41
2	**7b**	-	-	-	-
3	**7c**	36.6 ± 0.28	40.2 ± 0.32	35.4 ± 0.24	29.8 ± 0.36
4	**7d**	14.6 ± 0.18	13.2 ± 0.28	15.1 ± 0.33	12.8 ± 0.45
5	**7e**	23.1 ± 0.26	20.2 ± 0.11	22.4 ± 0.28	23.9 ± 0.34
6	**7f**	22.6 ± 0.22	21.8 ± 0.18	19.8 ± 0.27	20.4 ± 0.32
7	**7g**	21.9 ± 0.44	15.6 ± 0.16	14.5 ± 0.21	20.1 ± 0.18
8	**7h**	11.8 ± 0.23	9.4 ± 0.11	10.6 ± 0.32	12.3 ± 0.17
9	**7i**	13.9 ± 0.41	14.2 ± 0.24	12.1 ± 0.36	11.8 ± 0.21
10	**7j**	20.7 ± 0.15	18.8 ± 0.48	19.2 ± 0.22	21.0 ± 0.38
11	**7k**	31.4 ± 0.52	30.5 ± 0.44	32.2 ± 0.18	26.6 ± 0.23
12	**8a**	20.4 ± 0.34	15.4 ± 0.48	19.2 ± 0.22	20.3 ± 0.45
13	**8b**	14.8 ± 0.28	10.7 ± 0.15	11.2 ± 0.22	13.5 ± 0.19
14	**8c**	15.9 ± 0.24	14.1 ± 0.32	13.8 ± 0.23	12.2 ± 0.33
15	**8d**	17.0 ± 0.26	15.5 ± 0.16	14.1 ± 0.22	18.2 ± 0.35
5-Fluorouracil[a]		1.9 ± 0.11	1.6 ± 0.12	1.3 ± 0.09	1.8 ± 0.11

A series of novel nicotinohydrazide and 1,3,4-oxadiazol-2-yl)-6-(trifluoromethyl)pyridine derivatives synthesized, screened for anticancer activity. Compounds **6h**, **6i**, **7d**, **7h, 7i** and **8b** which showed highest activity against DU145 (prostate), HepG2 (liver) cell lines have been identified.

Acknowledgements

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