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Iodine catalyzed simple and efficient synthesis of antiproliferative 2-pyridones

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Abstract

A simple and efficient method for the selective synthesis of 2-pyrdones from 4H-pyrans using iodine as catalyst and ethanol as solvent was developed. The present method is equally effective for both aromatic and hetero aromatic ring containing 4H-pyrans. The compatibility with various functional groups, mild reaction conditions, high yields and application of inexpensive, readily and easily available iodine as catalyst and formation of 2-pyridones as major products are the advantages of the present procedure. *In vitro* antiproliferative activity of the final synthesized compounds was evaluated with four different Human cancer cell lines (Lung adenocarcinoma-A549, Hepatocarcinoma-HepG2, Breast carcinoma-MCF-7 and Ovarian carcinoma-SKOV3) and Normal human lung fibroblast cell line (MRC-5). Compounds **2b** showed better inhibition against MCF-7, HepG2 and A549 cell lines (IC_{50} 8.00±0.11, 11.93±0.01 and 15.85±0.04 µM respectively) as compared with doxorubicin and also **2e** showed moderate inhibition against MCF-7, HepG2 (IC_{50} 9.32±0.21 and 20.22±0.01 µM respectively cell lines respectively) as compared with doxorubicin. As many clinically used antiproliferative agents induce apoptosis in cancer cells hence, the 2-pyridone analogues were also tested for their ability to induce apoptosis in MCF-7 cells using the caspases-3 and -9 assays.

2-Pyridone moiety is present in a large number of natural and synthetic bioactive molecules. 2- Pyridones and their analogues have attracted considerable interest recently because of their antiproliferative, antiviral and anti-inflammatory properties.[1-3] The drugs Amrinone[4] (I) and Milrinone (II) [5] used as cardiotonic agents for the treatment of heart failure contains 2-pyridone moiety in their structure. Recently, 2-pyridone derivative (III) has been identified as a specific non nucleoside reverse transcriptase inhibitor of human immuno deficiency virus-1 (HIV-1).[6] 2-Pyrdiones are important intermediates in some synthetic approaches for the synthesis of camptothecin family of antitumor agents. 2-Pyridones and their analogues are targeted compounds in a large number of drug discovery programs related to cancer and inflammatory disorders such as CDK4 and FGFR inhibitors and p38 inhibitors (IV−V) [7-10] respectively (Fig 1). Hence, synthesis of 2-pyridones has gained much chemical and pharmaceutical importance in recent years.

So far, only a few methods have been reported for one-pot synthesis of 2-pyridones by condensation of three components, an aldehyde, a β-ketoester and cyano acetate or cyano acetamide under acidic or basic conditions such as HNO_2, H_2SO_4, Piperidine, NH_4OAc, ZnO, $SOCl_2$ etc,.[11-14] However, these methods suffers from very low yields with a mixture of 2-pyridones as minor and 3,4-dihydro-2-pyridones as major products.

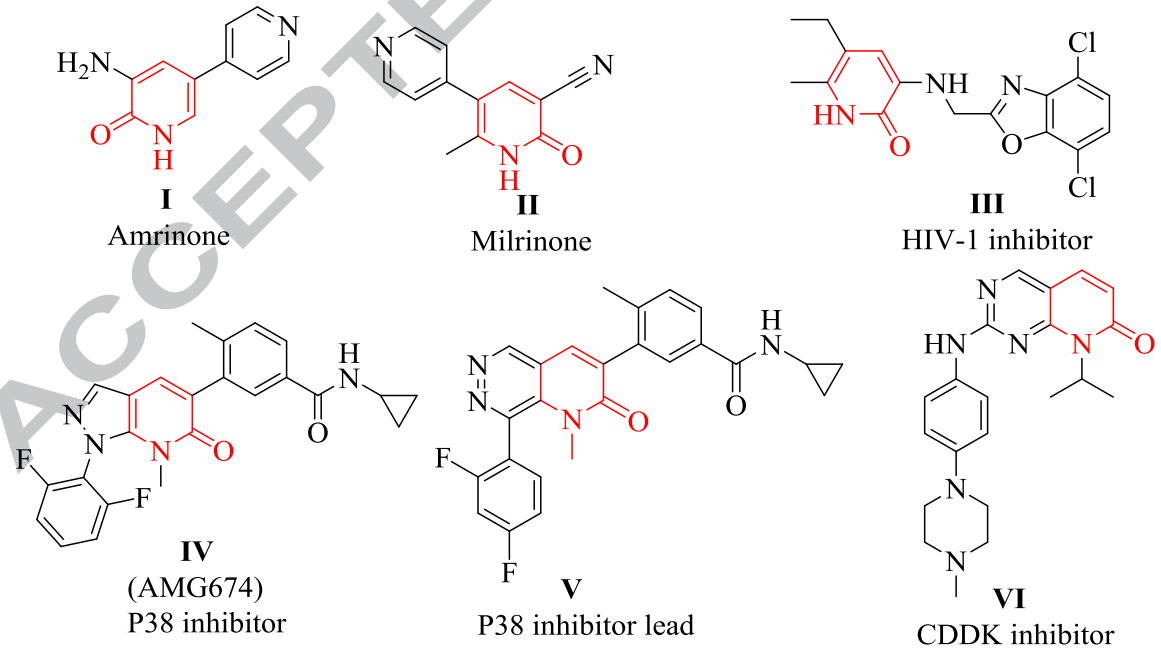


Figure1. Pyridin-2-one containing compounds of medicinal interest.

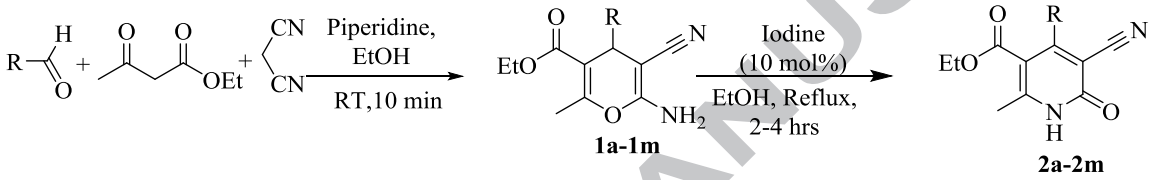
Subsequently, several multistep methods have been reported with somewhat higher yields to synthesize 2-pyridones. In general, these methods involve synthesis of 4H-pyrans by condensation of three components using an aldehyde, a β-ketoester and malononitrile in first step, then conversion of the 4H-pyrans to 2-pyridones in second step. Several reagents have been reported for the synthesis of 4H-pyrans like Al_2O_3/KF, metal oxide nano particles, ionic liquids, solid supported catalysts etc.,[15-20] but for the conversion of 4H-pyrans to 2-pyridones, very few methods were reported under strong acidic conditions like H_2SO_4, HNO_2, and mixture of HNO_2 and H_2SO_4 with very low yields with 2-pyridones as minor and 3,4-dihydro-2-pyridones as major or exclusive products. [21-24] However, many of the reported one-pot as well as multistep methods have significant drawbacks such as expensive and toxic reagents, incompatibility with other functional groups, long reaction times, strong acidic conditions, tedious workup procedures and low yields etc. Thus, there is a need for simple, efficient, economic and eco-friendly procedure to synthesize 2-Pyridones under mild conditions.

As a part of our ongoing work of novel methodologies for the synthesis of bioactive molecules, we were interested to synthesize 2-pyridone derivatives due to their biological importance. Recently, iodine has received considerable attention as an inexpensive, readily available mild and efficient catalyst for various organic reactions such as Suzuki-Miyaura coupling reaction,[25] Michael addition,[26-27] protection[28] and deprotection[29] of acetals, synthesis of bis-indols,[30] β-keto enol ethers,[31] chalcones,[32] and quinolines[33] etc. Here, we report a simple, efficient and mild method for the synthesis of 2-pyridones selectively from 4-H pyrans using iodine as catalyst.

It is well known that cancer deaths are more than those caused by AIDS, malaria, and tuberculosis combined. The drugs like Indomethacin, doxorubicin has created some hope for the life of cancer patients. However, the chemotherapeutic agents under present use suffer from various drawbacks. This undoubtedly underscores the need of developing new chemotherapeutic agents for more effective and economical treatment of cancer.

In this paper, we report a novel methodology for the synthesis of various 2-pyridones and the resulting analogues were also screened for *in vitro* antiproliferative activity using four different human cancer cell lines and Normal human cell line. Because of many clinically used antiproliferative agents induce apoptosis in cancer cells[34], we tested the 2-pyridone analogues for their ability to induce apoptosis in MCF-7 cells using the caspases-3 and 9 assays.

Initial attempt of one pot synthesis of 2-pyridones by condensation of an aldehyde, a β-keto ester and malononitrile with either molecular Iodine (I_2) or metal iodides like HgI, NaI, CuI and KI was not successful. Then two step method was devised in which first 4H-pyrans were prepared by condensation of an aldehyde, malononitrile and ethylacetoacetate as per the reported methods [35-36] but with slight modifications. In the second step, different 2-pyridones were synthesized selectively from the 4H-pyrans under reflux conditions in the presence of iodine as catalyst and ethanol as a solvent (Scheme).



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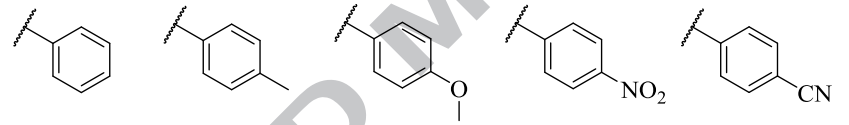
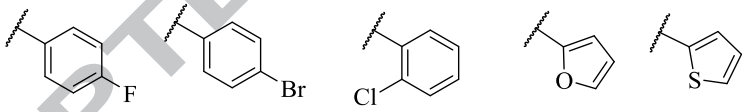
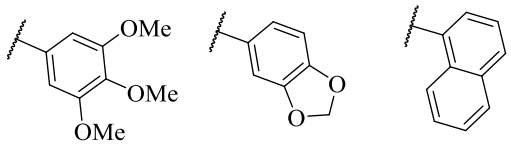


(**2a**, 90%, 3.5 h) (**2b**, 85%, 2.5 h) (**2c**, 75%, 6 h) (**2d**, 87%, 2.5 h) (**2e,** 89%, 2 h)



(**2f**, 91%, 4 h) (**2g**, 93%, 3 h) (**2h**, 73%, 3.5 h) (**2i**, 68%, 2 h) (**2j,** 70%, 2 h)



(**2k**, 95%, 2 h) (**2l,** 74%, 3 h) (**2m**, 72%, 2.5 h)

Scheme: Iodine catalyzed simple and efficient synthesis of 2-pyridones.

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The reaction proceeded *via* iodination at benzylic positon of 4H-pyran in the presence of iodine at 80 ^{o}C to form intermediate **I,** which further underwent formation of oxonium ion **II** by leaving iodide ion and shifting of the double bond. Further rearrangement took place by

instantaneous opening of pyran to give pyridonium ion **III** and finally removal of hydrogen iodide (HI) resulted 2-pyridone (Fig. 2).

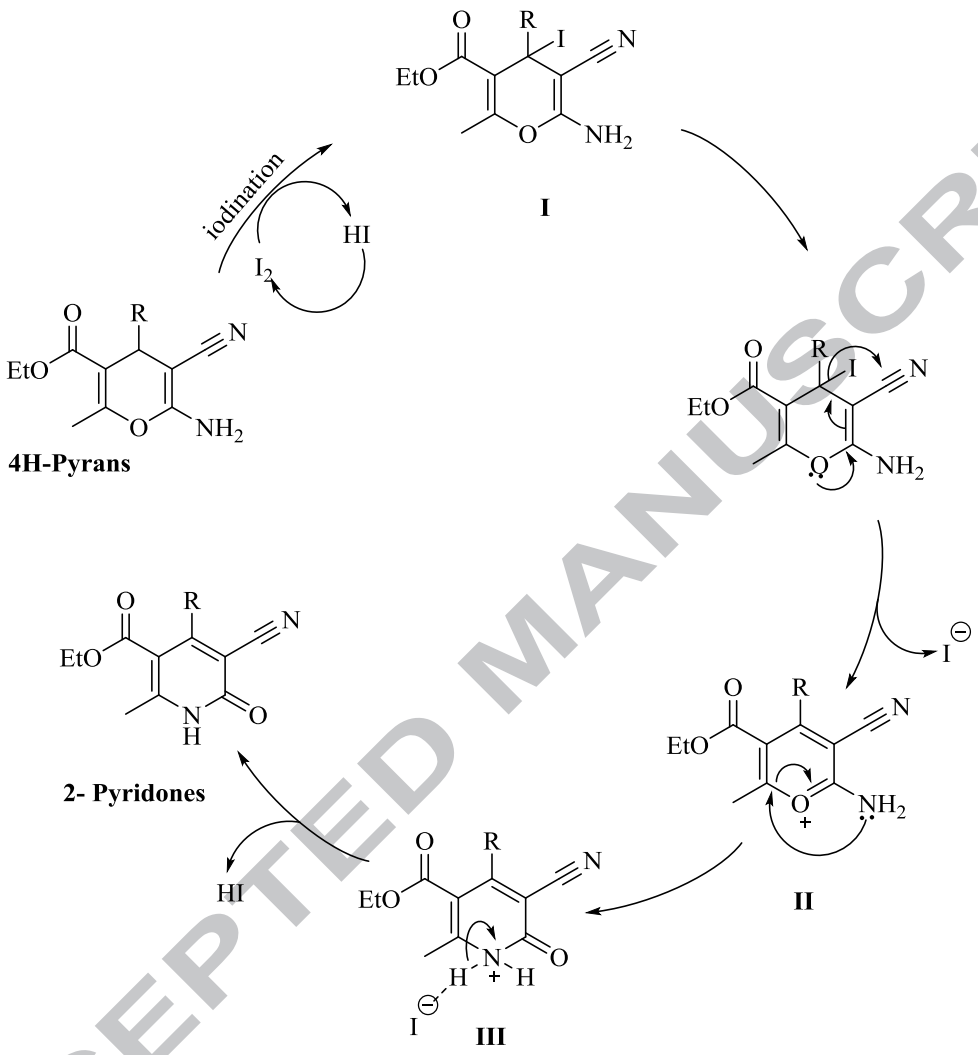


Figure 2: Plausible mechanism for 2-pyridines formation.

The method was also optimized with respect to different catalysts, solvents and catalyst load etc. It was observed that molecular iodine and ethanol are the most effective catalyst and solvent in terms of yields and reaction times than other catalyst sources such as HgI, NaI, CuI and KI (Table 1) and solvents such as toluene, DCM, dichloroethane, $CHCl_3$, acetone, methanol, ethanol, CH_3CN, THF, propane-2-ol, ethanol+water, etc (Table 2, entry 4). When catalyst load increased from 2.5 to 10 mol %, yields were steadily increased and thereafter no significant change was observed from 10 to 20 mol %. But, further increase in catalyst load,

led to significant decrease in the yields of the final product. This may be due to the coagulation of I_2.

Table 1: Catalysts screened for the synthesis of pyridin-2-one[a]

Entry	Lewis acid	Solvent	Time	Yield[b] (%)
1	KI 10 mol%	EtOH	10 hrs	30
2	NaI 10 mol%	EtOH	12 hrs	20
3	HgI 10 mol%	EtOH	24 hrs	15
4	CuI 10 mol%	EtOH	8 hrs	35
5	I_2 2.5 mol%	EtOH	5 hrs	40
6	I_2 5 mol%	EtOH	5 hrs	60
7	**I_2 10 mol%**	**EtOH**	**5 hrs**	**95**
8	I_2 15 mol%	EtOH	5 hrs	95
9	I_2 20 mol%	EtOH	5 hrs	95
10	I_2 25 mol%	EtOH	5 hrs	70
11	I_2 30 mol%	EtOH	5 hrs	50
12	I_2 40 mol%	EtOH	5 hrs	40

[a]ethyl-6-amino-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl)-4H-pyran-3-carboxylate (1k) (3.521 mmol), was refluxed at 80^0C in 5 ml EtOH for stipulated time in the presence of specific amount of catalyst.
[b]Isolated yield of pure product.

The above methodology was tolerant to a wide variety of electron releasing as well as electron withdrawing 4H-pyrans to give the corresponding products (**2a-m**) in excellent yields selectively. The reaction with ethyl-6-amino-5-cyano-4-(4-fluorophenyl)-2-methyl-4H-pyran-3-carboxylate, ethyl-6-amino-5-cyano-4-(4-bromophenyl)-2-methyl-4H-pyran-3-carboxylate and ethyl-6-amino-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl)-4H-pyran-3-carboxylate maintained high yield and gave the corresponding products **2f, 2g** and **2k** in 91, 93 and 95 % yields respectively. Also, the reaction with other 4H-pyrans viz., **1a, 1b, 1c, 1d, 1e, 1h, 1i, 1j, 1l** and **1m** with iodine gave corresponding products **2a, 2b, 2c, 2d, 2e, 2h, 2i, 2j, 2l** and **2m** in 90, 85, 75, 87, 89, 73, 68, 70, 74 and 72 % yields respectively (Scheme).

Table 2. Solvent screened with 10 mol% of catalyst[a]

Entry	Solvent	Substrate	Product	Time	Yield[b] (%)
1	$CHCl_3$	1i	2i	4hrs	65
2	Toluene	1i	2i	4 hrs	60
3	MeOH	1i	2i	4 hrs	85
4	**EtOH**	**1i**	**2i**	**2 hrs**	**95**
5	THF	1i	2i	5 hrs	75
6	Acetonitrile	1i	2i	5 hrs	45
7	Propane-2-ol	1i	2i	5 hrs	50
8	DCM	1i	2i	4 hrs	50
9	EtOH+Water	1i	2i	6 hrs	80
10	Acetone	1i	2i	4 hrs	75
11	Dichloroethane	1i	2i	6 hrs	40

[a]ethyl-6-amino-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl)-4H-pyran-3-carbox- ylate (1k) (3.521 mmol), was heated at 80 ^{0}C in 5 mL solvent for stipulated time in the presence of 10 mol % I_2.
[b]Isolated yield of the pure product.

Antiproliferative activity of the synthesized 2-Pyridones were evaluated in *in vitro* mode using 3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay[37] on the human cancer cell lines and as well as normal cell line i.e., Human lung adenocarcinoma cell line (A549), Human hematoma (HepG2), Human breast adenocarcinoma (MCF-7), Human Ovarian carcinoma cell line (SKOV3) and Normal human lung fibroblast cell line (MRC-5). The assay is based on the reduction of MTT by the mitochondrial dehydrogenase of viable cells into purple formazan crystals which gets dissolved in DMSO and read at 570 nm. The results of *in vitro* cytotoxic activity were expressed as the IC_{50} (µM) and doxorubicin was used as positive control. As shown in Table 3, most of the compounds were moderately active but, compound **2b** showed better inhibition against MCF-7, HepG2 and A549 cell lines (IC_{50} 8.00±0.11, 11.93±0.01 and 15.85±0.04 µM respectively) as compared with doxorubicin and also **2e** showed better inhibition against MCF-7, HepG2 cell lines (IC_{50} 9.32±0.21 and 20.22±0.01 µM respectively) as compared with doxorubicin. Compounds **2b, 2f, 2e** and **2k** showed better inhibition against HepG2 cell line (IC_{50} **2b**: 11.93±0.01; **2f**: 18.55±0.01; **2e**: 20.22±0.01 and **2k**: 20.92±0.02 µM) as compared with doxorubicin. Keeping in view the above fact, the cell viability of these test compounds was also determined in normal human lung cell line (MRC-5). All the tested compounds were considered non-cytotoxic since the IC_{50} values were >100 µM against the normal cell line.

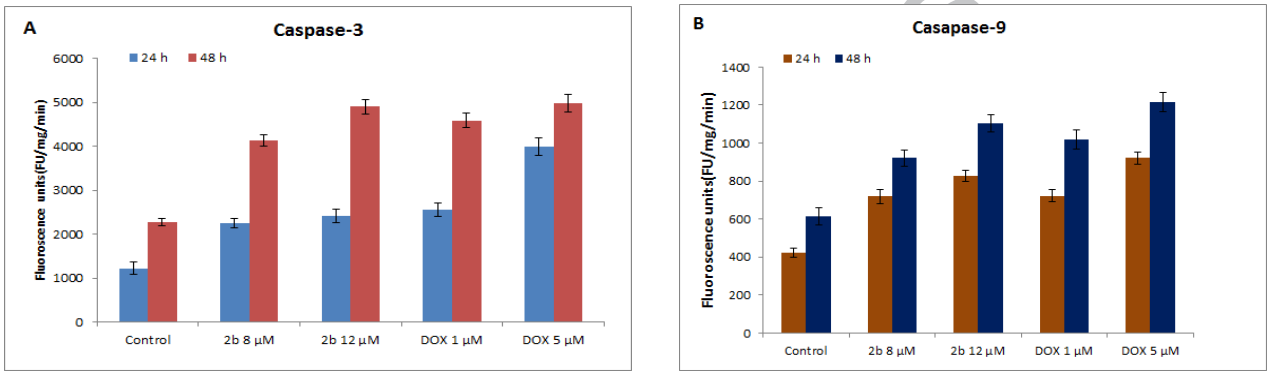
Table 3: Antiproliferative activity of compound **2a-2m**.

Compound	Antiproliferative activity (IC_{50} in µM)				
	A549	**HepG2**	**MCF-7**	**SKOV3**	**MRC-5**
2a	>100	38.45±0.10	21.96±0.01	>100	220.37±0.09
2b	**15.85±0.04**	**11.93±0.01**	**8.00±0.11**	>100	438.36±0.034
2c	25.12±0.04	51.51±0.01	36.07±0.04	>100	192.14±0.144
2d	>100	21.72±0.11	81.95±0.04	>100	2228.21±0.025
2e	>100	**20.22±0.01**	**9.32±0.21**	>100	1220.37±0.09
2f	**15.40±0.05**	**18.55±0.01**	22.94±0.01	>100	148.931±0.085
2g	>100	65.50±0.03	31.75±0.01	>100	309.68±0.064
2h	25.00±0.11	34.07±0.01	25.38±0.04	>100	228.68±0.206
2i	>100	57.35±0.01	**17.52±0.04**	76.01±0.21	406.86±0.106
2j	**20.10±0.06**	74.05±0.05	33.44±0.11	97.31±0.11	205.28±0.035
2k	23.37±0.02	**20.92±0.02**	**18.12±0.04**	>100	252.81±0.112
2l	27.33±0.04	>100	33.98±0.24	>100	191.96±0.068
2m	24.03±0.01	32.32±0.01	31.38±0.04	>100	195.67±0.075
Doxo	0.23±0.01	3.39±0.11	1.94±0.01	25.04±0.01	89.68±0.064

The activity of caspases- 3 and 9 was determined according to reported method[38] in the active compound **2b** to confirm its antiproliferative active before generating more toxicological data in animals and also we need to carry out mechanistic studies to detect the main target of these 2-pyridones. Caspases (cysteine aspartase enzyme), a group of intracellular proteases, are responsible for the induction of apoptosis. Among all the caspases, caspase-3 is one of the effective caspases that is activated by initiator caspases (caspase-8 and 9) by proteolytic cleavage[39]. Synthesis of a large number of analogues and their evaluation in different type of cell lines is required to understand these intriguing observations, which may pave the way to compounds with highly selective toxicity profiles. The induction of apoptosis by the potent compound **2b** was investigated using the MCF-7 cell line in both time-dependent and dose-dependent manner in the proportion of cells undergoing apoptosis by activation of caspases-3 and 9 with the maximum occurring after 48 h of treatment. Considering this fact, it was interesting to understand the association of cytotoxicity with that of apoptosis by the compound **2b**. In the present study, the MCF-7 cells were treated with **2b** compound (8 and 12 µM) along with the positive control doxorubicin at different concentrations and observed for the activation of caspase-3, and 9. The results showed 2 to 3 fold increase in both caspase-3 and 9 activities when compared to untreated control cells indicating that they have the capacity to induce

apoptosis by the activation of caspases in MCF-7 cells (figure 3). Nevertheless, it is contemplated that a slight structural modification of these active derivatives may yield prospective anti-proliferative agents.

The main molecular target of these 2-pyridones are inhibitors of DNA gyrase, a type II DNA topoisomerases. DNA topoisomerases are a class of enzymes that regulate the topological structure of DNA in living organisms. In eukaryotes type II DNA topoisomerases are essential for chromosome segregation at the final stage of DNA replication[40].



The results were expressed as means of fluorescence intensity ± standard deviation (SD) of two independent experiments performed in triplicates.

Figure 3: The effect of 2b (A) caspase-3 and (B) caspase-9 activity was tested in the MCF-7 cell line.

In conclusion we have developed an efficient method for the selective synthesis of 2-pyrdones from 4H-pyrans using iodine as catalyst and ethanol as solvent. The present procedure is equally effective for both hetero aromatic and aromatic ring contained pyrans and electron donating as well as electron withdrawing substituents. The compatibility with various functional groups, mild reaction conditions, high yields and application of inexpensive, readily available iodine as catalyst and formation of 2-pyridones as major products are the advantages of the present procedure. All the synthesized compounds were screened for antiproliferative activity using four different Human cancer cell lines and Normal cell line (human lung fibroblast -MRC-5). Introducing methyl, cyano and fluoro groups at fourth position on benzene ring induced antiproliferative activity of 2-pyridones (**2b:** IC_{50} 8.00±0.11 µM against MCF-7

cell line; **2b:** IC_{50} 11.93±0.01 µM against HepG2 cell line; **2b:** 15.85±0.04 µM against A549 cell line.; **2e:** IC_{50} 9.32±0.21 µM against MCF-7 cell line; IC_{50} 20.22±0.01 µM against HepG2 cell; **2f:** IC_{50} 15.40±0.05 µM against A549 cell line IC_{50} 18.55±0.01 µM against HepG2 cell line) when compared with the unsubstituted 2-pyridone (**2a**). Similarly, substitution of three methoxy groups at 3,4,5 positions exhibited enhanced activity (**2k:** IC_{50} 18.12±0.04 µM against MCF-7 cell line; IC_{50} 20.92±0.02 µM against HepG2 cell) when compared to the mono methoxy substituted 2-pyridone at fourth position (**2c**). In the case of introduction of hetero aromatic ring in place of phenyl ring, it was observed that 2-pyridones with furan ring was active against MCF-7 cell line (**2i:** IC_{50} 17.52±0.04 µM) and thiophene ring was active against A549 cell lines (**2j:** IC_{50} 20.10±0.06 µM). As the antiproliferative effect results from the apoptosis inducing ability of these 2-pyridones, as confirmed by the caspases-3 and 9 assays with the **2b** compound. The potent apoptosis inducing power of the selected **2b** compound is pronounced at concentrations as low as 8 µM.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.10.15. These data include NMR, MASS spectral data, materials and methods.

Acknowledgements

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