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Synthesis, characterisation and disease oriented preliminary anticancer *in vitro* screening of some novel pyrimidones

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Abstract: *Pyrimidones have been reported to possess significant biological activities, viz., fungicidal, bactericidal, hypnotic and anaesthetic activities. Substituted pyrimidones are also known to exhibit significant anticancer activities.*
The anticancer activities of the newly synthesized compounds were evaluated against human cell lines/panel namely Leukaemia, Non-Small Cell Lungs Cancer, Melanoma, Ovarian Cancer, Renal Cancer, Prostate Cancer, CNS Cancer Melanoma, Breast Cancer and Colon Cancer. Compounds exhibit moderate to high level of activities with cell lines. 1-Acidamide-3-aryl/H-1,3-dihydro-2-thioxo-2H,5H-pyrimidine-4,6-diones substituted compounds are synthesized. Their purity was ascertained by TLC and recrystallization methods and checked with the help of mixed melting points.
These novel thiopyrimidones have been characterized by IR and NMR spectroscopic methods and screening was done for in vitro disease oriented primary anticancer activities. The screening revels good to moderate levels of activities. The anticancer activities were conducted by the Department of Health and Human Services, National Institute of Health, National Cancer Institute, Bethesda, Maryland.
Key word: *Anticancer, Cell lines, in vitro, Sulforbodamine (SBR), Thiopyrimidone,*

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I. Introduction

Thiopyrimidones are widely reported to possess antimicrobial activities[1]. But thiopyrimidine ring and its substituted compounds with antimetabolic[2]activities in cells have also been successfully used in the treatment of various tumours. Thus these are associated with diverse biological activities. Various N-substituted pyrimidones possess hypnotic[3] and anticancer activities[4], e.g., 1,3diaryl-5[arylazo/N-substituted-p-sulphamylbenzeneazo]-1,3-dihydro-2-thioxo-2H,5H-pyrimidine-4,6-diones are reported to exhibit great importance in tumour study. In thiopyrimidones and their substituted analogues gained significant interest due to their increased role in therapeutics and diagnostic applications.

These are reported due to the fact that thiopyrimidones are important structural skeleton in the t-RNA of *E.coli*[5] as pyrimidones are basic to the structure of uracil. Since pyrimidines and purines are the nitrogenous bases present in nuclic acids, they can easily do with the DNA of disease causing bacteria and thus can inhibit them. These speculations are very well observed in their reported antiviral[6], anticancer[7], antibacterial[8], and antifungal agents[9]. In this study we attempt to design, synthesise and investigate the anti-tumour activities of some novel 2-thiopyrimidones derivatives having strong connection that substituted pyrimidones being structural analogues of uracil would surely exhibit some kind of anticancer activities.

Substitution of R^1 and R^2 groups on either side of thiopyrimidones are ingeniously selected with their probable activity enhancer properties based on reports otherwise. Thus emphasis is given on N-substitution of thiopyrimidones synthesizing two series (A and B) compounds with different variables (R^1 and R^2). These two new series of heterocyclic compounds bearing acetamide and aryl groups on N on either sides of thiopyrimidone nucleus are synthesized and their anticancer effects have been studied against Leukemia, Lung Cancer, Melanoma, Ovarian Cancer, Renal Cancer, Prostate Cancer and Breast Cancer.

II. Methodology

All together nine compounds have been prepared under series A and B. Compound A.1, A.2 and A.3 contain substitution only on N-1. All the compounds of series B are also substituted on N-3. The compounds are so engeniously designed as to fit into the DNA array. The starting materials are very preliminary *viz*., substituted phenols and 2-chloropropionic acid. The whole course of reaction, which is evident from the SCHEME, contains methanol, hydrazine hydrate, aryl isothiocynates and malonic acid as reagents[10]. Methanol and acetyl-chloride are used as solvents. Thus the scheme provides a detailed pathway to achieve the goal. All the

compounds synthesized were recrystallized and their melting points were tested in open capillaries. They were characterized by IR, NMR and elemental analyse. The data are given in Table 1.

2.1 Synthesis of compounds of series A: 2-aryloxy propane hydrazides[11]:

Chloropropionic acid was condensed with different phenols in the presence of 40% aqueous sodium hydroxide to yield aryloxy propionic acids[12] which were converted into methyl esters[13].These methyl esters were converted into aryloxypropionyl hydrazines by heating with hydrazine hydrate[14].

2.2 Synthesis of compounds of series B: 2-(aryloxypropanoyl)hydrazinecarbothioamides[10]

These compounds have been prepared by heating aryloxypropionyl hydrazines with aryl isothiocynates in methanol.

2.3 Synthesis of compounds of series C: 2-(2-aryloxypropanoyl)-*N*-arylhydrazinecarbothioamide[10]:

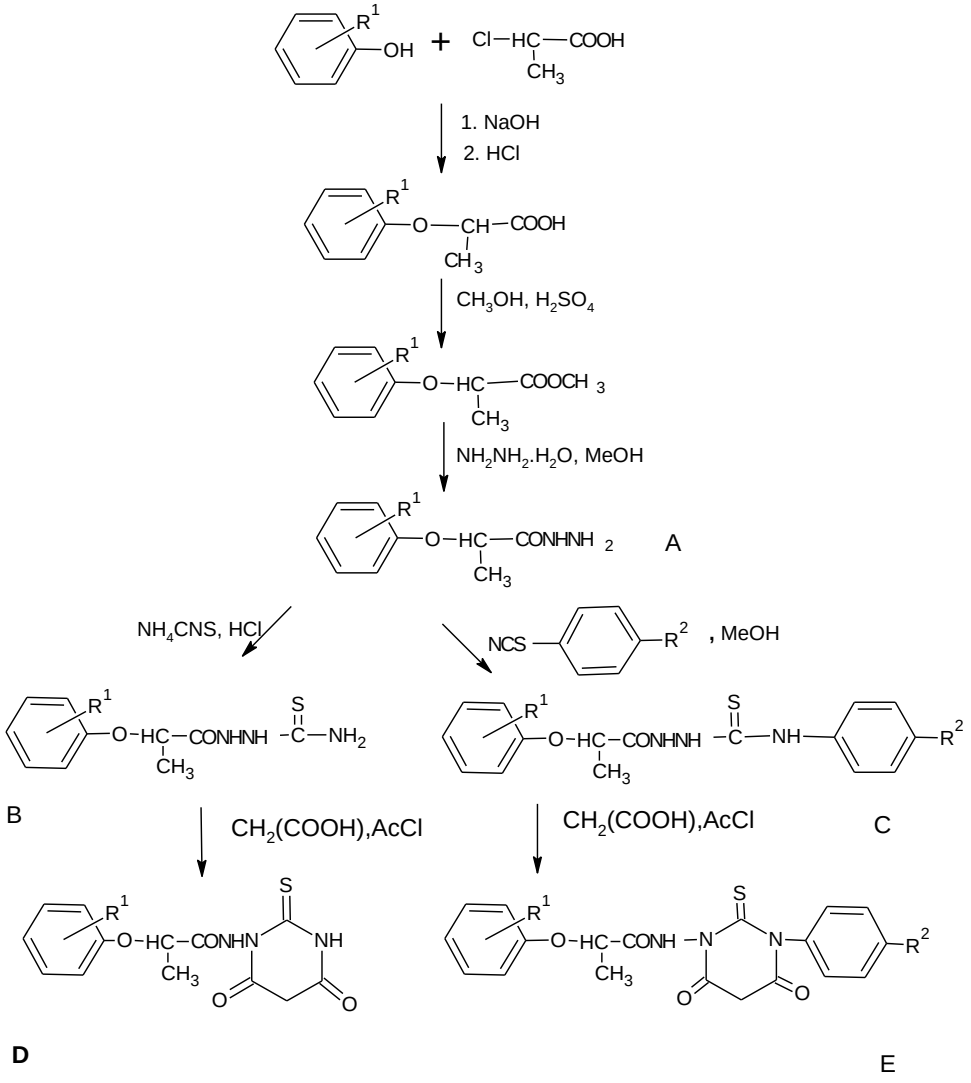
These compounds have been synthesized by heating aryloxypropionyl hydrazines with ammonium thiocynates in the presence of HCl.

2.4 Synthesis of Compounds of Series D and E:

N-(4,6-thioxo-tetrahydropyrimidin-1(2H)-yl)-2-(aryloxy)propanamide

2-(2-Aryloxypropanoyl)-*N*-arylhydrazinecarbothioamide[6] (0.005M), malonic acid (0.73g; 0.007M) and 5.0 ml of acetyl chloride[15] were gently heated for four hours on water bath and cooled. The resulting mass was poured

SCHEME



R^1= 2-CH_3, 2-Cl, 2-4-dichloro

R^2= H, CH_3, Cl, OCH_3

into cold water, stirred well, kept overnight and filtered. The residue was washed with water, dried and recrystallized from aqueous ethanol.

III. Anticancer Activity Tests On Human Cancer Cell Lines

The anticancer *in vitro* activities were done at National Cancer Institute, Florida. All the compounds were tested against most common nine types of cancer cells *viz.*, Leukaemia, Non-Small Cell Lung Cancer, Colon Cancer, CNS Cancer, Melanoma, Ovarian Cancer, Renal Cancer, Prostate Cancer, and Breast Cancer.
In each type of cancers, different cell lines were used to test the compounds in order to get broad spectrum of their anticancer activities. Two anticancer drug MG- MID delta range were used as reference. The reference is evident from the value of IC_{50} (concentration causing inhibition by 50% or more and GI_{50} bar diagram.

IV. Result And Discussion

The structures of all the compounds prepared were ascertained by their melting points, IR, NMR, data and elemental analyses, Which give proof to the molecular formula and molecular weight. Investigation of IR data gives a strong peak at ~1570 $cm^{-1}(\nu_{max})$. It gives a strong evidence of β-diketone in a cyclic structure. Presence of thioxo group is also evidenced by a peak at ~1050 $cm^{-1}((\nu_{max})$. The NMR data also stands in full support of total proton count and of different kind of –H present on different carbon *viz.*, NMR spectrum of δ ($CDCl_3$) * CONH signal overlapped with aromatic region. 6.7- 7.6 (1H, m, Ar-H), 5.0- 5.3 (1H, q, -CH-), 2.6-2.8 (2H, S, $-CH_{2-}$),1.7-1.9(3H, d, $-CH_3$).

Regarding anticancer activities a closer look at GI_{50} bar diagram gives very encouraging results. Compounds A1 is found equally active against Leukemia (CCRF-CEM cell line) and Melanoma (UACC-62 cell line), as compare to references MG-MID delta range. This compound also shows moderate activity against lung cancer (NCI-H226 cell line). Compound A2 is found remarkably active against breast cancer (T-47D, MCF7 cell lines), compound A3 is found very active on two cell lines of Leukemia *viz*., MG-MID delta range. It is also moderately active against breast cancer (BT-549 cell lines). Compound B1 is found precisely active against Leukemia (CCRF-CEM), K-562, RPMI-8226 cell lines). It is also active against CNS Cancer (SNB-19 cell lines), compound B2 was found only moderately active against Leukemia (HL-60TB cell lines), Lung Cancer (HOP-92 cell lines) and Renal Cancer (786-0, RXF-393 cell lines), compound B3 is very active against Leukemia on HL-60(TB), cell lines and moderately active on SR cell lines, compound B4 was found active only against Leukemia (CCRF-CHEM, MOLT-4 cell lines), compound B5 is moderately active against Leukemia (CCRF-CHEM, HL-60(TB) cell lines). Compound B6 was found most promising anticancer compound. It shows profound level of anticancer activity against Leukemia on (CCRF-CHEM cell lines) and moderalty active on (HL-60(TB) cell lines).

Thus most of the compounds are found active against leukemia and their activities are at par with the used references MG-MID delta range. It is evident that the thiopyrimidone ring finds itself to compete with hydrogen bonding may disrupt DNA array, thus causing cytotoxic activity.

The activities are found increasing when similar groups are substituted on the aryl and aryloxy groups on both sides of thiopyrimidones e.g., The activity is highest with compound B6 when the substituents are –Cl. Again the activity is profoundly high when the two groups are –Me (in compound B4).

V. Table

S.No.	Compound No.	R^1	R^2	m.p.(^{0}C)	Elemental analysis			
					N%		S%	
					Calc.	Found	Calc.	Found
1	A.1	$-CH_3$	-	108	13.06	13.04	9.95	9.91
2	A.2	-2-Cl	-	110	12.28	12.24	9.38	9.34
3	A.3	-2,4-Cl	-	113	11.26	11.22	8.50	8.51
4	B1	$-CH_3$	-H	115	10.05	10.01	7.97	7.93
5	B2	-Cl	-H	120	9.96	9.92	7.01	7.00
6	B3	-2,4-Cl	-H	125	8.99	8.94	7.00	6.99
7	B4	$-CH_3$	$-CH_3$	130	10.00	9.99	7.70	7.68
8	B5	$-CH_3$	-Cl	120	9.12	9.11	7.02	7.00
9	B6	-Cl	-Cl	100	9.08	9.04	6.97	6.94

VI. Conclusion

The synthetic procedure very well fit in the present work as well as the compounds synthesized are proved to have native structures. The structure activity relationship of the compounds shows that derivatives of thiopyrimidones can be used as potential anticancer drugs. -Cl substituted aryl and aryloxy groups increase the activity to a much higher level which may be due to their powerful electronegative behaviour. At the same time

$-CH_3$ substitutions are also found to increase activity, which may be done to its resemblance to thymine (nitrogenous base present in DNA).

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