Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

SYNTHESIS, CHARACTERISATION OF PYRIMIDINE DERIVATIVES AND THEIR CYTOTOXIC ACTIVITY

T. Kala Praveen*[1], Boyapati Veeranjaneyulu[1], B. Mamatha[1], K. Komala Devi[1], S. Theo Mercy[1], S. K. Naseema[1], S. Ramya Sri[2]

[1*]Department of Pharmaceutical Chemistry, DCRM Pharmacy College, Inkollu, Prakasam Dist, Andhra Predesh-523 167, India.

[2]Department of Pharmacy, University College of Technology, Osmania University, Hyderabad, Telangana, India.

ABSTRACT

Synthesis of some pyrimidine derivatives which plays an important role in the medicinal chemistry because it possesses promising cytotoxic activity. The synthesized compounds were characterized by ^{13}C, ^{1}H NMR spectral data. Some of the new compounds were evaluated for their potential cytotoxicity against different cancer cell lines on the cells MDAMB (breast cancer) using MTT assays. The pyrimidine derivatives 11a, 11b, 11c and 11e serve as good leads for further studies to develop potent cytotoxic agents.

KEYWORDS

Pyrimidine derivatives, Cytotoxic activity and MTT assay.

Author for Correspondence:

Kala Praveen T,
Department of Pharmaceutical Chemistry,
DCRM Pharmacy College,
Inkollu, Prakasam, Andhra Predesh, India.

Email: rajinisuralabs1@gmail.com

INTRODUCTON

The word cancer came from the father of drugs, Hippocrates, a Greek MD. He used the Greek words, carcinos and malignant neoplastic disease to explain tumors, so job cancer "karkinos". The Greek terms really were words to explain a crab, that Hippocrates thought a growth resembled. Though Hippocrates could have named "Cancer", he was never the primary to find the sickness. At this time one in all the six deaths in us is caused by

cancer. One in four Americans currently living could contract cancer, and common fraction UN agency do therefore can die of it at this time cure rates. In European nation and wales, one fifth of all deaths is thanks to cancer[1].

2d most effective to cardiovascular illnesses in occurrence, most cancers is feared extra than another ailment.

Simplest within the twentieth century, however has there been plenty concern over the sickness. Progress within the remedy of the former most important causes of dying has necessarily brought about a rise within the occurrence of most cancers[2].

What Is Cancer?

Cancer develops when cells in a part of the frame start to grow out of manipulate. Although there are many varieties of most cancers, all of them begin because of "out-of-control" boom of extraordinary cells. Cancer cells regularly journey to different elements of the body where they start to develop and replace everyday tissue. This procedure, called metastasis, occurs as the most cancers cells get into the bloodstream or lymph vessels of our frame. Cancer cells expand because of harm to DNA[3].

Cancer is a general term applied to a series of malignant disease which may affect different parts of the body. Cancer is commonly encountered in all higher animals and plants also develop growth that resembles cancer.

Terminology[2]

The clinical term for "most cancers" or "tumor" is neoplasm, which means that "a highly independent growth of tissue". A cancerous tumor is a malignant neoplasm with ability danger.

The distinction between benign and malignancy is that benign tumors don't distribute, whereas malignant tumors do. A metastasis could be a secondary growth originating from the first neoplasm and growing elsewhere within the body.

There is no system of terminology for a neoplasm is accepted universally. Some tumors square measure named when the individual United Nations agency 1st represented the condition, like Ewing's neoplasm of bone, Paget's illness, and Hodgkin's illness. Some square measure named when the tissue of origin, like papillose, cystic, or vesicle tumors. The suffix - oma virtually means that neoplasm, and also the words with this suffix ask neoplasms.

Cancer Cell Cycle

The cycle is split into 4 primary components, the g 1or gap 1 segment is the period when a newly created cell is born, the time period a cellular stays inside the g1 phase depends on the tissue type and whether it is a regular cellular or a tumor cellular. If the mobile is a proliferating cell, it will speedy move into the s or synthesis section. It's far all through this period the nuclear dna is replicated, and at the end of the s phase copies of dna are present inside the cell. The following section is the g2 or gap2 duration and this section is largely a time in the course of which preparations are made for the final cellular cycle phase, the m section or mitosis. There are predominant manipulate points inside the mobile cycle the sort of is at g1 / s section while cells commit to mirror. The second is at g2 / m section when the cells decide to divide. Of those two essential factors inside the mobile cycle synthesis, the g1 / s is of most important significance in expertise most cancers and cancer remedy. For the duration of the g1 section a cell can take one of the 'three' routes. First the cellular might also input the 's' section. Second the cell in the g1 phase may additionally enter into the fifth segment called g 0 / gap0.1/3 the mobile may additionally terminally differentiate and die[4].

Cancer may be outlined broadly speaking as a sickness during which there's Associate in Nursing uncontrolled / abnormal multiplication of cells and unfold of those abnormal cells at intervals the body. Cancer cells manifest four characteristics that distinguish them from traditional cells.

1. Uncontrolled proliferation
2. Loss of function
3. Metastasis
4. Invasiveness

THE GENESIS OF A CANCER CELL

A normal cell will turn out to be a neoplastic cell attributable to one or a lot of mutations in its polymer, which might be heritable or noninheritable. The event of cancer may be a

advanced period of time method, involving not solely quite one genetic amendment however sometimes additionally different epigenetic factors (hormonal action, co-carcinogen and neoplasm promoter effects, etc.) that don't seem to be themselves cancer manufacturing however that increase the chance of the mutation.

The initiation of the willcer method can occur thanks to

The activation of proto-onocogenes to oncogenes

Proto-oncogenes square measure genes that unremarkably management cellular division, caspase-mediated cell death and differentiation however which might be regenerate to oncogens by microorganism or matter action.

Thanks to the inactivation of tumour suppressor genes

Normal cells contain genes that have ability to suppress malignant changes square measure termed tumour suppressor genes (anti-oncogens). The loss of operate of those cells ends up in cancer[5].

These changes might occur thanks to purpose mutations, factor amplification or body translocation. Normally these changes occur thanks to the action of sure viruses or chemical carcinogens.

The terms cancer, tumour and malignance square measure synonymous; they're distinguished from benign tumors by the properties of adjustment invasiveness and therefore the ability to spread (spread to different elements of the body).

Most of the cancers fall under following classes supported tissue of origin[1].

1. Carcinoma: during this case the tumour originates from animal tissue cells.
2. Sarcoma: If the tumour originates from muscle or animal tissue then it's known as as malignant neoplastic disease.
3. Leukemia's or lymphomas: during this case the tumour originates from humor or haematological origin.
4. Glioma: during this case the tumour originates from the neural origin.

Cancer therapy[11-14]

In general, there are three approaches for treating cancer. They are:

1. Surgical Excision
2. Irradiation
3. Chemotherapy

Role of every these sorts depends on the kind of the tumour and also the stage of its development.

Before the Forties the principal medical procedure treatment of tumour was photograph and radiation therapy, though bound arsenicals and urethanes were conjointly in use. Radioisotopes, element mustards, antifolic acid agents and sex secretions for the treatment of bound varieties of neoplasm's and of adrenal corticoids and Adreno corticotropic hormone (ACTH) for the treatment of leukaemia conjointly developed significantly throughout these years.

Much excitement was generated by these early development in anti-growth medical aid, however it absolutely was later tempered by the conclusion, not solely that the medicine weren't curative however conjointly for the foremost a part of life was a negligibly magnified by the medicine, being principally palliative later there has been an excellent proliferation in each the quantity and also the categories of anti-cancer medicine medical aid of cell kinetic and cell proliferation statistics, in order that with the consequently improved collections and regimens, long run unwellness free remissions ar accomplishable with many neoplasms, and even a number of carcinomas may be cured.

Anyhow, therapy of cancer, as compared thereupon of microorganism illness, presents a tough drawback. In organic chemistry terms, microorganisms ar each quantitatively and qualitatively totally different from human cells. But cancer cells and traditional cells ar therefore similar in several respects that it's harder to search out general exploitable, organic chemistry variations between them. Therefore the majority anti-neoplastic medication have draw backs of severe side-effects.

Common/Toxic side effects associated with antineoplastic drugs[15-19]

- Bone marrow toxicity
- Impaired wound healing
- Loss of hair

- Damage to gastrointestinal epithelium
- Depression of growth in children
- Sterility and teratogenicity.
- They can also be carcinogenic, sometimes with extensive purine catabolism, urates may precipitate in the renal tubules and cause kidney damage.

MATERIAL AND METHODS

Experimental procedure

General procedure for the synthesis of compounds (11a-11f)

A mixture of the appropriate 2-mercapto-dihydroyrimidine derivatives 10aef (1mmol), the propargyl bromide (1mmol), and anhydrous potassium carbonate (1mmol) was refluxed in dry dioxane. Upon completion, as judged by TLC, phosphorous oxychloride was added drop wise with stirring while maintaining the temperature of the reaction mixture. Stirring was continued for additional 1 h. The cooled reaction mixture was poured on crushed ice and the separated solid was filtered off, washed with water, dried and crystallized from aqueous ethanol to yield the pure product.

4-Chloro-6-phenyl-2-(prop-2-yn-1-ylthio) pyrimidine-5- carbonitrile (11a)

Yield 70.5%. White solid. Mp: 131e132 C. 1 H NMR (400 MHz, CDCl3, d, ppm) d 8.18e8.05 (m, 2H, Ar-H), 7.71e7.50 (m, 3H, Ar-H), 4.01 (d, J ¼ 2.6 Hz, 2H, eCH2e), 2.28 (t, J ¼ 2.6 Hz, 1H, ≡CeH). 13C NMR (100 MHz, CDCl3, d, ppm) d 174.02, 168.73, 163.95, 134.07, 132.72, 129.35, 129.02, 114.43, 101.42, 78.17, 71.63, 20.36. FTIR (3328.77, 3202.20, 2920.22, 2851.11, 1659.01, 1611.84, 1517.64, 1416.85, 1346.60, 1168.10, 1082.22, 817.90, 542.97) MASS (91.0541, 134.09, 340.18, 473.2713, 945.53) HR-MS (ESI): Calcd. C14H9ClN3S, [MþH]þm/z: 286.0206, found: 286.0202.

4-Chloro-6-(4-isopropylphenyl)-2-(prop-2-yn-1-ylthio) pyrimidine-5-carbonitrile (11b)

Yield 72.8%. White solid. Mp: 109e110 C. 1 H NMR (400 MHz, CDCl3, d, ppm) d 8.15e8.00 (m, 2H, Ar-H), 7.44 (m, 2H, Ar-H), 4.01 (d, J ¼ 2.6 Hz, 2H, eCH2e), 3.03 (hept, J ¼ 6.9 Hz, 1H, CH), 2.28 (t, J ¼ 2.6 Hz, 1H, ≡CeH), 1.33 (d, J ¼ 6.9 Hz, 6H, eCH3). 13C NMR (100 MHz, CDCl3, d, ppm) d 173.81, 168.55, 163.92, 131.62, 129.53, 127.21, 114.66, 100.97, 84.40, 78.06, 71.57, 34.29, 23.66, 20.31, FTIR (2930.05, 1853.83, 1666.22, 1611.183, 1359.94, 1203.19, 1035.31, 831.77, 742.3, 615.47, 484.58, MASS (311.1550, 415.2176) HRMS (ESI): Calcd. C17H15ClN3S, [MþH]þm/z: 328.0675, found: 328.0677.

4-Chloro-2-(prop-2-yn-1-ylthio)-6-(p-tolyl) pyrimidine-5- carbonitrile (11c)

Yield 65.5%. White solid. Mp: 111e112 C. 1 H NMR (400 MHz, CDCl3, d, ppm) d 8.05 (d, J ¼ 8.2 Hz, 2H, Ar-H), 7.39 (d, J ¼ 8.1 Hz, 2H, Ar-H), 4.01 (d, J ¼ 2.6 Hz, 2H, eCH2e), 2.28 (t, J ¼ 2.6 Hz, 1H, ≡CeH). 13C NMR (100 MHz, CDCl3, d, ppm) d 173.79, 168.53, 163.91, 143.76, 131.30, 129.76, 114.64, 100.96, 84.11, 78.30, 71.57, 21.69, 20.32, FTIR (2920.33, 1737.61, 1632.53, 1441.47, 1374.15, 1161.52, 1093.60, 830.01, 644.29) MASS (340.1819, 473.2713, 945.5341) HRMS (ESI): Calcd. C15H11ClN3S, [MþH]þm/z: 300.0362, found: 300.0363.

4-Chloro-2-(prop-2-yn-1-ylthio)-6-(3, 4, 5-trimethoxyphenyl) pyrimidine-5-carbonitrile (11d)

Yield 68.3%. White solid. Mp: 104e105 C. 1 H NMR (400 MHz, CDCl3, d, ppm) d 7.50 (s, 2H, Ar-H), 3.98 (d, J ¼ 2.7 Hz, 2H, eCH2e), 3.97 (s, 9H, eCH3), 2.26 (t, J ¼ 2.6 Hz, 1H, ≡CeH). 13C NMR (100 MHz, CDCl3, d, ppm) d 173.60, 167.69, 164.07, 153.33, 142.24, 128.70, 114.87, 106.98, 100.65, 78.72, 71.22, 61.08, 56.43, 20.35, FTIR (2920.33, 1737.61, 1632.53, 1441.47, 1161.52, 830.01, 644.29, 527.88) MASS (303.0957, 399.0987, 497.1684) HR-MS (ESI): Calcd. C17H14ClN3NaO3S, [MþH]þm/z: 398.0342, found: 398.0340.

4-Chloro-6-(4-chlorophenyl)-2-(prop-2-yn-1-ylthio) pyrimidine-5-carbonitrile (11e)

Yield 77.2%. White solid. Mp: 121e122 C. 1 H NMR (400 MHz, CDCl3, d, ppm) d 8.17e8.01 (m, 2H, Ar-H), 7.63e7.47 (m, 2H, Ar-H), 4.00 (d, J ¼ 2.6 Hz, 2H, eCH2e), 2.28 (t, J ¼ 2.6 Hz, 1H, ≡CeH). 13C NMR (100 MHz, CDCl3, d, ppm) d

174.20, 167.41, 164.04, 139.39, 132.39, 130.69, 129.40, 114.27, 101.19, 78.07, 71.66, 20.40. FTIR (3455.25, 2918.92, 1735.09, 1629.38, 1436.10, 1301.77, 1198.26, 1017.85, 836.30, 746.78, 532.92) MASS (313.1354, 419.1764) HR-MS (ESI): Calcd. C14H8Cl2N3S, [MþH]þm/z: 319.9816, found: 319.9818.

4-(4-Bromophenyl)-6-chloro-2-(prop-2-yn-1-ylthio) pyrimidine-5-carbonitrile (11f)

Yield 80.5%. White solid. Mp: 137e138 C. 1 H NMR (400 MHz, CDCl3, d, ppm) d 8.08e7.96 (m, 2H, Ar-H), 7.84e7.60 (m, 2H, Ar-H), 4.00 (d, J ¼ 2.6 Hz, 2H, eCH2e), 2.27 (t, J ¼ 2.6 Hz, 1H, ≡ CeH). 13C NMR (100 MHz, CDCl3, d, ppm) d 174.24, 167.54, 164.06, 132.85, 132.39, 130.78, 127.98, 114.24, 101.19, 78.09, 71.65, 20.40, FTIR (3455.25, 2918.92, 1735.09, 1629.38, 1198.26, MASS (313.1354, 335.118, 419.1764) HR-MS (ESI): Calcd. C14H8BrClN3S, [MþH]þm/z: 363.9311, found: 363.9314.

Biological Activity

Anticancer activity has been disbursed for the synthesized compounds mistreatment MDAMB (breast cancer) cell line by MTT Assay. Cell proliferation and viability resolve by 3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide (MTT) assay[48]. The yellow coloured tetrazolium salt (MTT) reduces to a navy water-insoluble formazan by metabolically active cells which is measured quantitatively when soluble in DMSO. The absorbance of the soluble formazan is directly proportional to the quantity of viable cells. Cells were seeded at a density of 1×104 cells in two hundred µL of medium per well of 96-well plate. The 96-well microtiter plates were incubated for twenty-four h before addition of the experimental compounds. Cells were treated with vehicle alone (0.4% DMSO) or compounds (drugs were dissolved in DMSO previously) at totally different concentrations (1, ten and 25µM) of take a look at compounds for forty eight hours. The assay was completed with the addition of MTT (5 nada, 10µL) and incubated for sixty min at 37°C. The supernatant was aspirated and plates were air dried and also the MTT-formazan crystals dissolved in a hundred µL of DMSO. The optical density (O.D.) was measured at 560 nm mistreatment TECAN multimode reader. The expansion share of every treated well of ninety six well plate are calculated supported take a look at wells relative to manage wells.

The cell growth inhibition was calculated by generating dose response curves as a plot of the proportion of living cells versus drug concentration. Anti-proliferative activity of the cancer cells to the take a look at compounds was expressed in terms of IC50value, that defines as a level of compound that created five hundredth absorbance reduction relative to manage.

RESULTS AND DISCUSSION

Results

The compounds 11a, 11b, 11c and 11e showed strong potent activity with IC50 values around 10.6-12.4 µg/ml against MDAMB cell lines where as 11d and 11f were showed poor inhibition activity.

A data of percentage deaths from certified causes in England and Wales

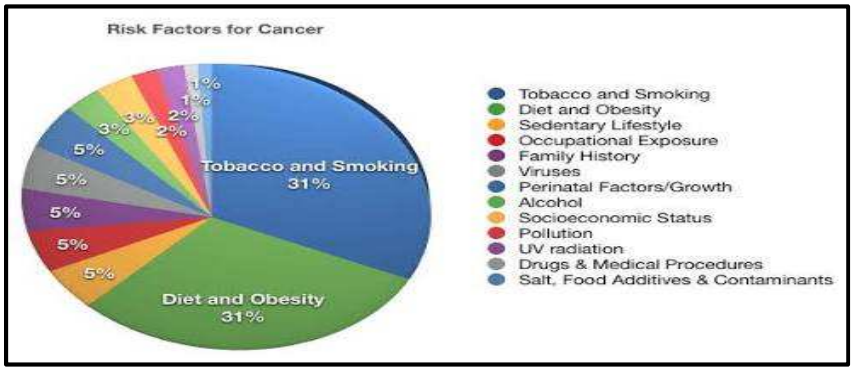
S.No	Cause of death	Percentage of deaths
1	Coronary heart disease	25.9
2	Cancer	20.6
3	Cerebrovascular disease	13.7
4	Pneumonia	8.0
5	Chronic bronchitis	4.1
6	Accidents	8.8

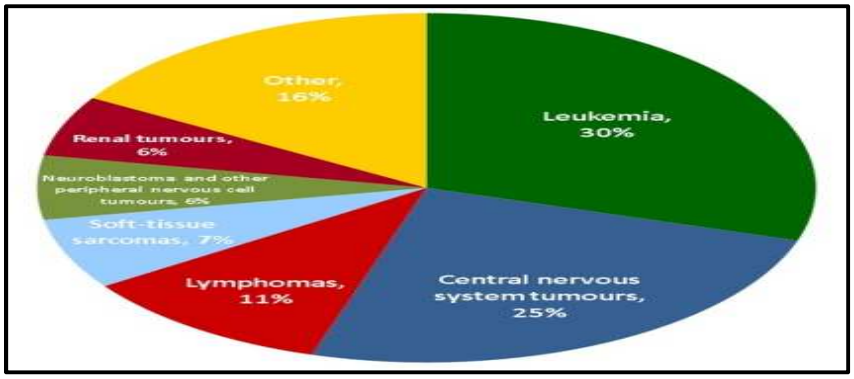
Table No.1: IC_{50} (µM) for the synthesized compounds and (STD) on the cells MDAMB (breast cancer) determined by MTT assay

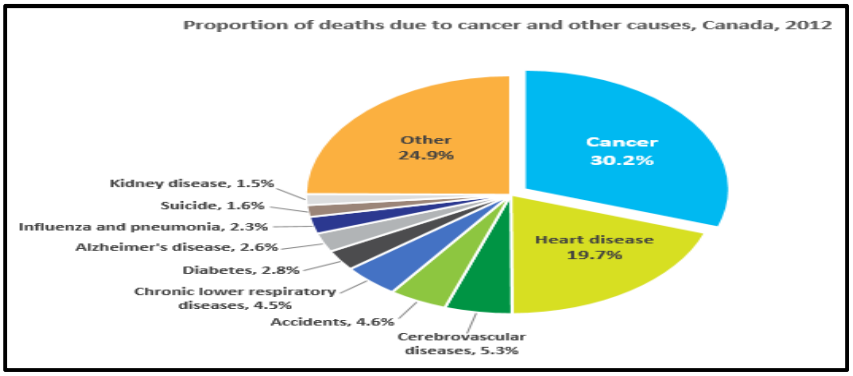
S.No	Compound code	MDAMB (breast cancer)
1	11a	10.6 ± 0.57
2	11b	12.4 ± 0.34
3	11c	11.87 ± 0.54
4	11d	50.06 ± 1.22
5	11e	11.49 ± 0.32
6	11f	44.21 ± 2.03
7	STD	8.9 ± 0.62

STD= Fluorouracil

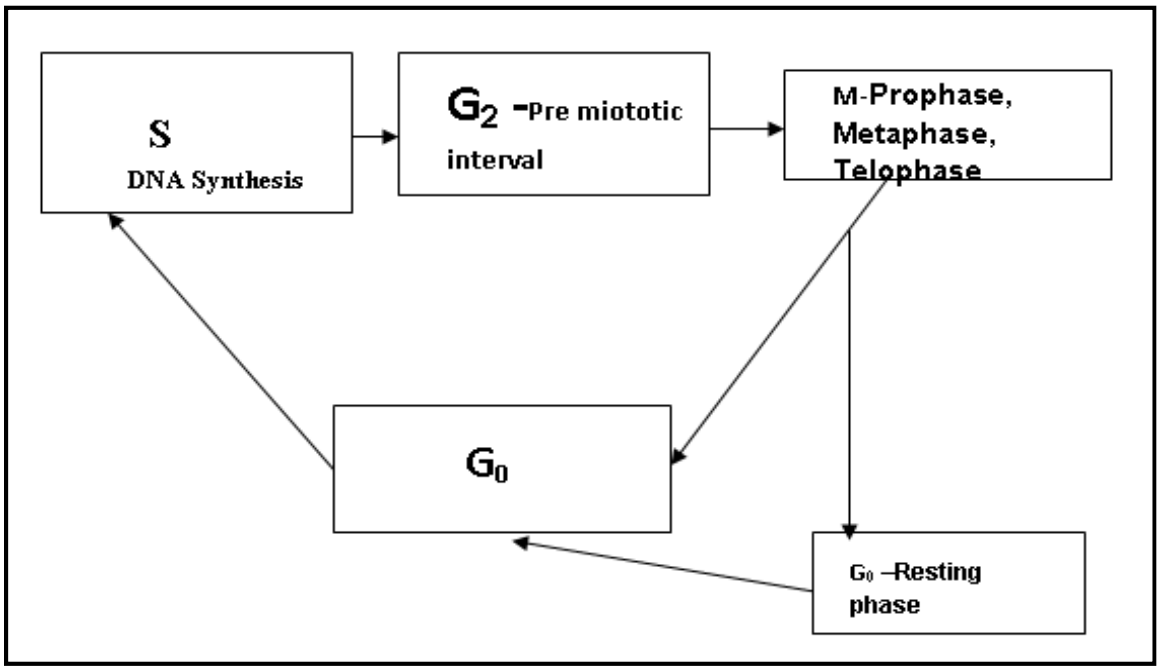
Data represented as mean ± standard deviation

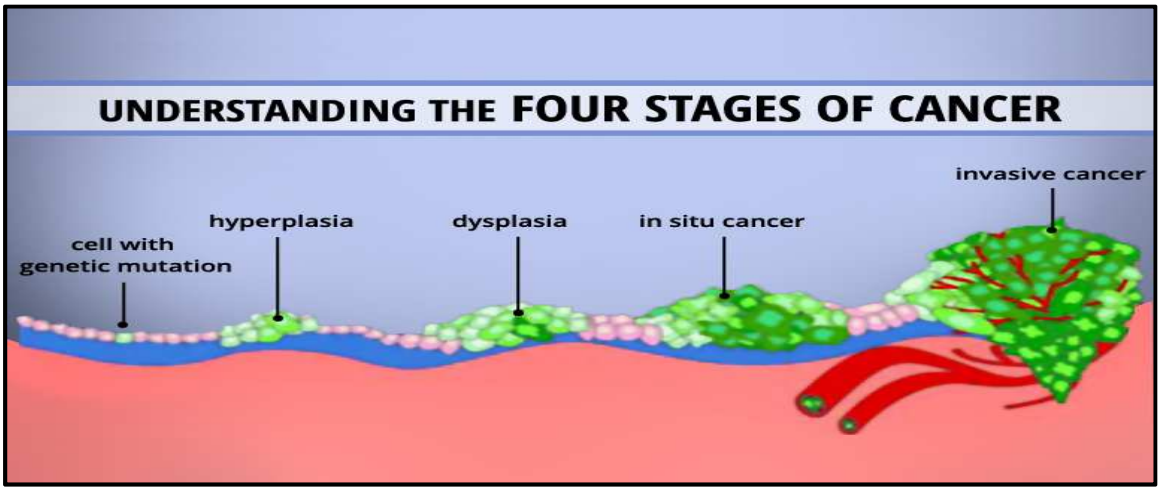


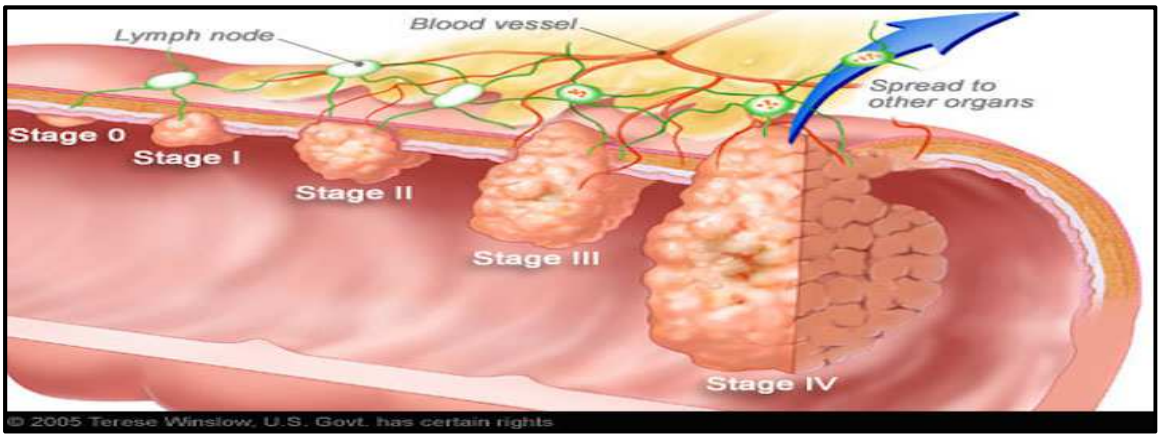




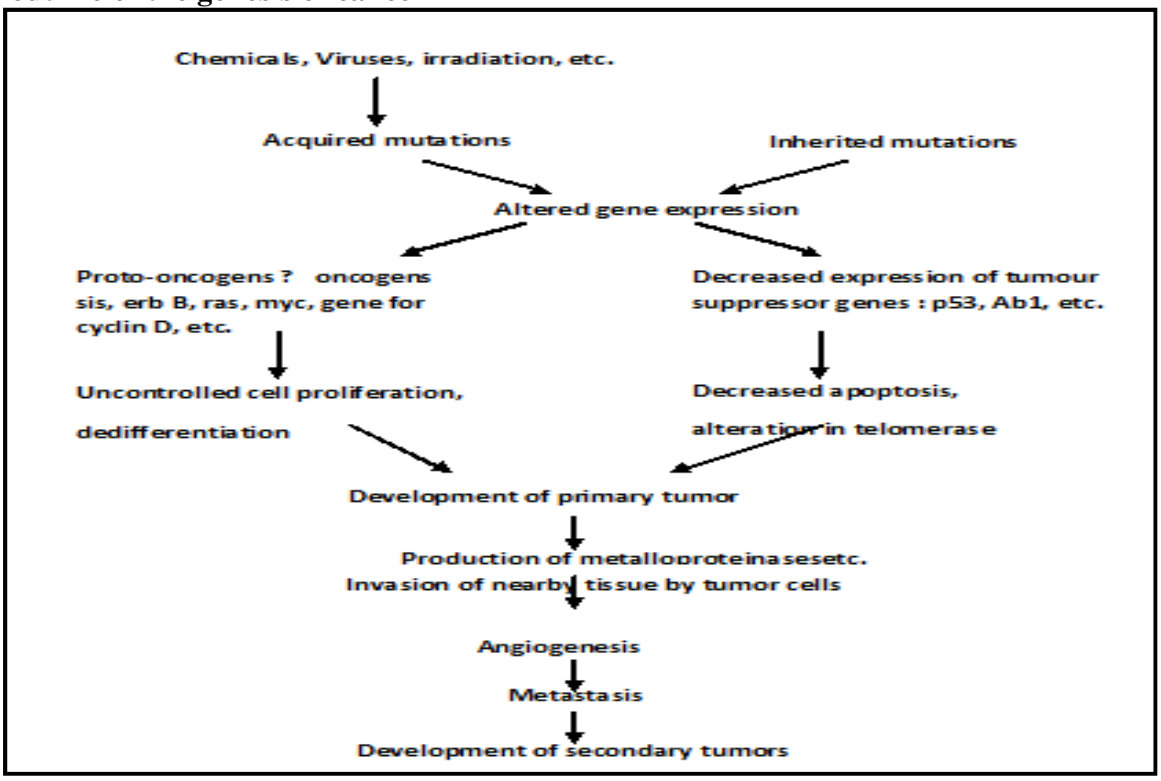
CELL CYCLE

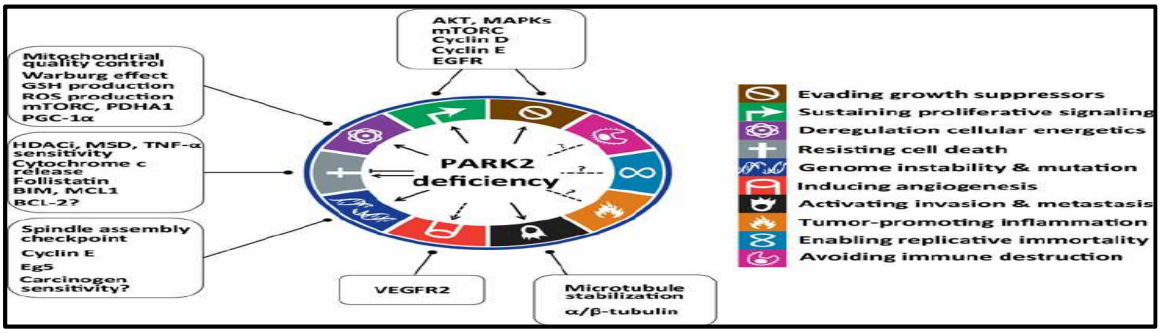

S
DNA Synthesis
G2 -Pre miototic interval
M-Prophase, Metaphase, Telophase
G0
G0 –Resting phase


UNDERSTANDING THE FOUR STAGES OF CANCER
cell with genetic mutation
hyperplasia
dysplasia
in situ cancer
invasive cancer

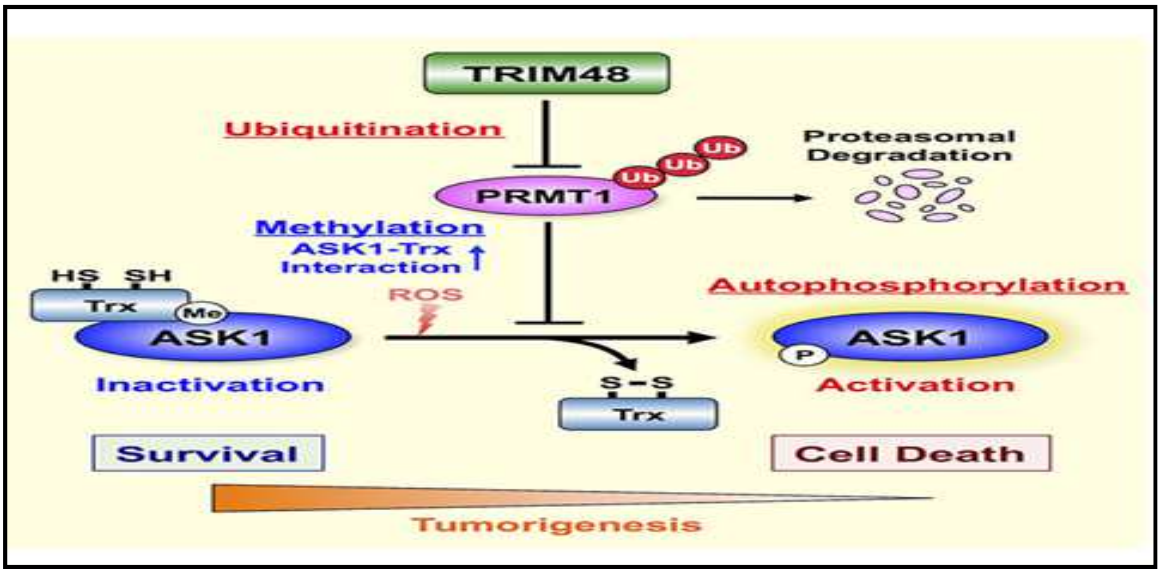

Lymph node
Blood vessel
Spread to other organs
Stage 0
Stage I
Stage II
Stage III
Stage IV
© 2005 Terese Winslow, U.S. Govt. has certain rights

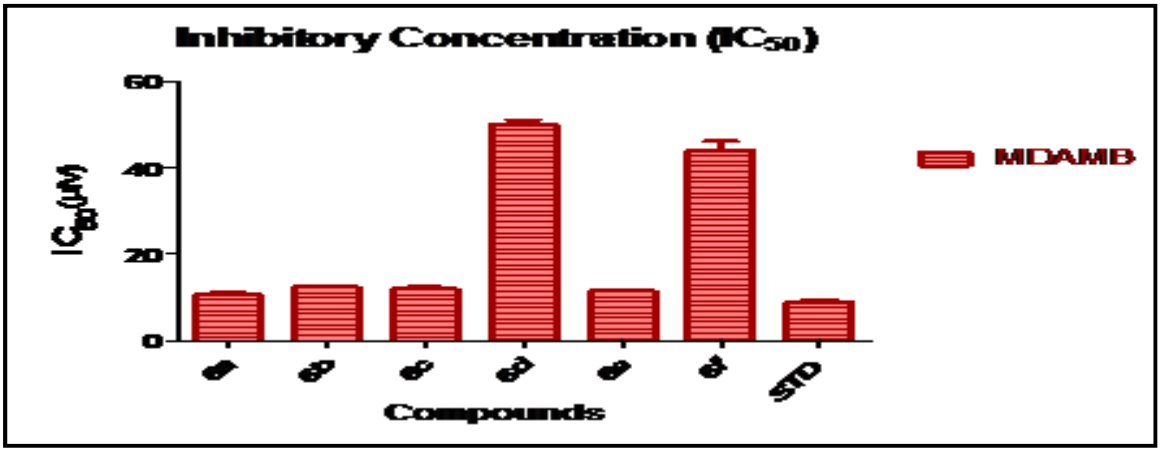
Simplified outline of the genesis of cancer[8-10]





Interacting Drug	Common Use	Effect of Interaction
Plant Alkaloids digoxin	Cardiac problems	Decrease serum level of digoxin
phenytoin	Seizure disorders	Increased risk of seizures
oral anticoagulants	Blood thinners	Prolonged bleeding
Antimetabolites digoxin	Cardiac problems	Decrease serum level of digoxin
phenytoin	Seizure disorders	Decreased need for antiseizure medication
nonsteroidal anti-inflammatory drugs (NSAIDs)	Pain relief	Methotrexate toxicity
Alkylating Drugs aminoglycosides	Anti-infective agents	Increased risk of nephrotoxicity and ototoxicity
loop diuretics	Heart problems and edema	Increased risk of ototoxicity
phenytoin	Seizure disorder	Increased risk of seizure
Antineoplastic Antibiotics digoxin	Cardiac problems	Decrease serum level of digoxin





Graph No.1: Comparison of IC_{50} (µM) for the synthesized compounds and (STD) on the MDAMB cells

Supporting Information

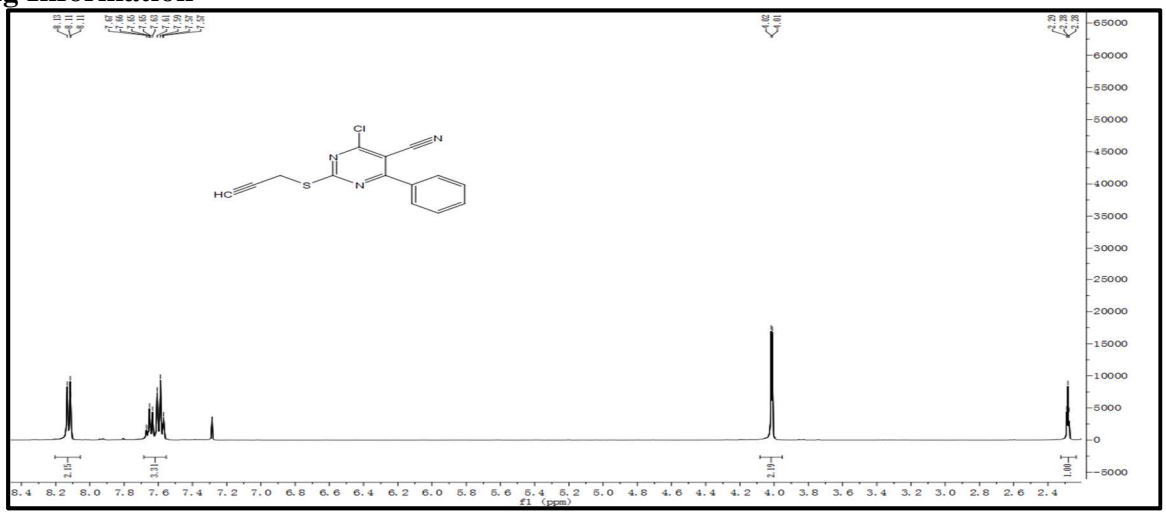


Figure No.1: ^1H NMR spectrum of compound 11a

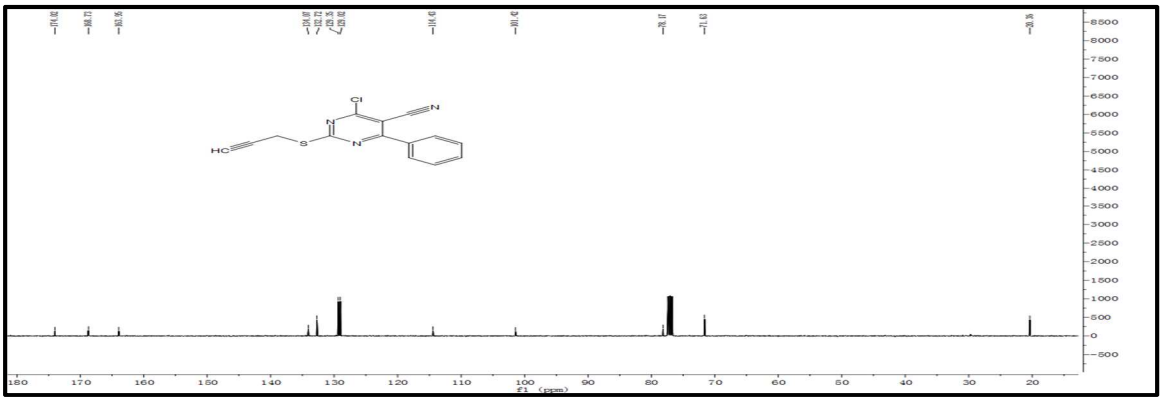
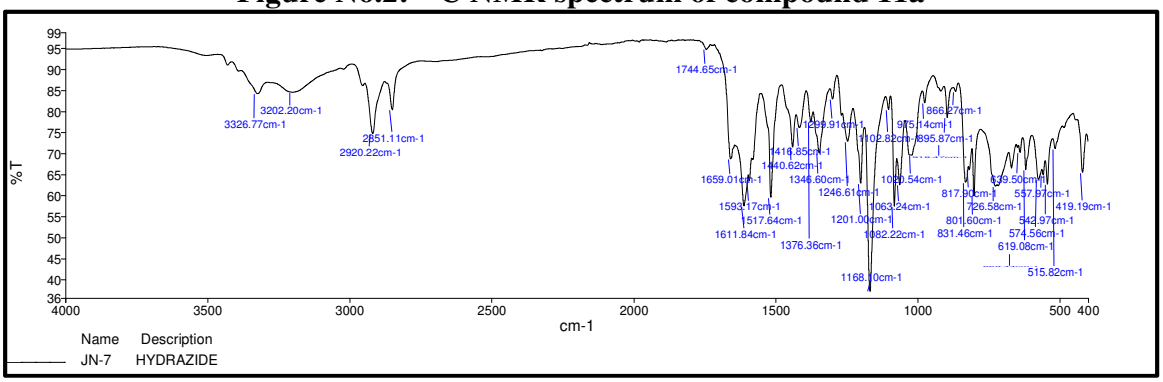
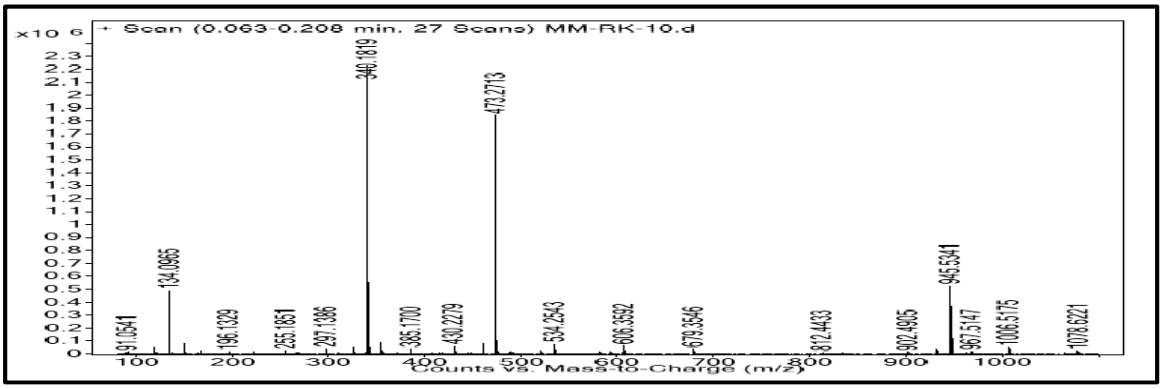


Figure No.2: ^{13}C NMR spectrum of compound 11a





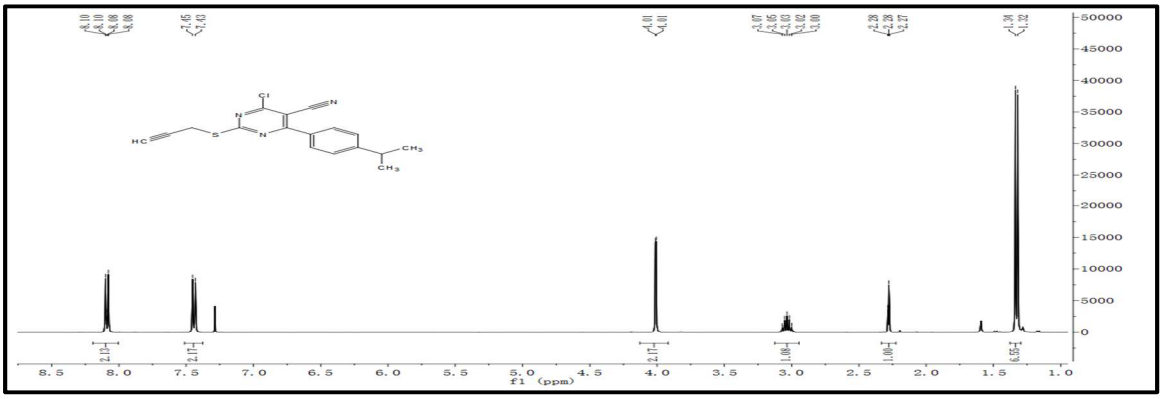


Figure No.3: ^{1}H NMR spectrum of compound 11b

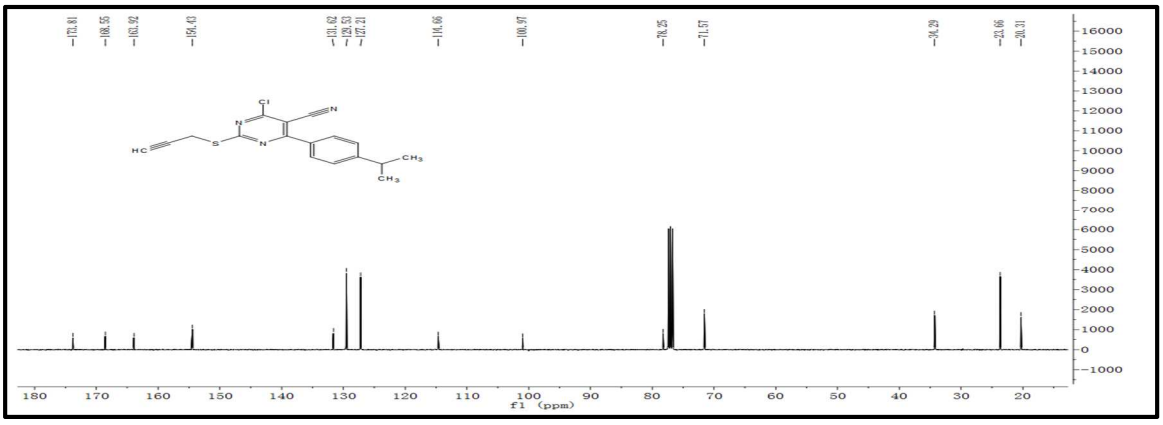
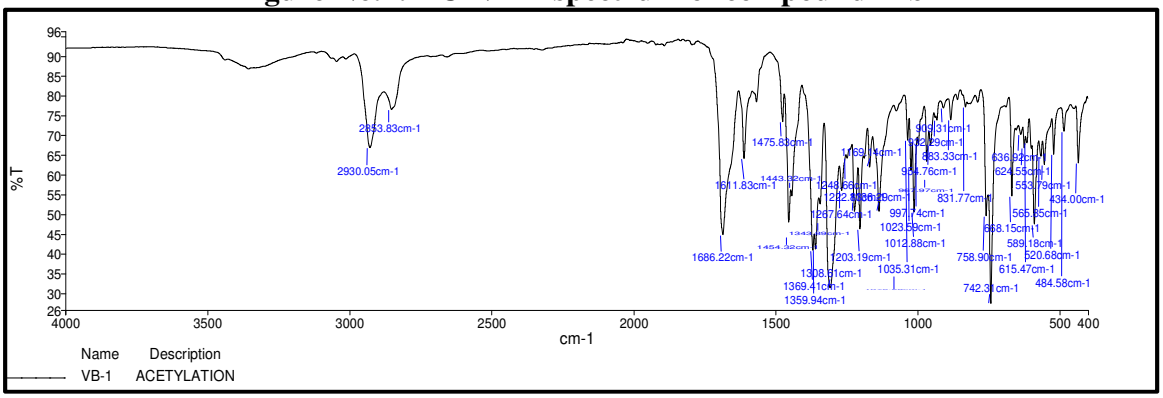
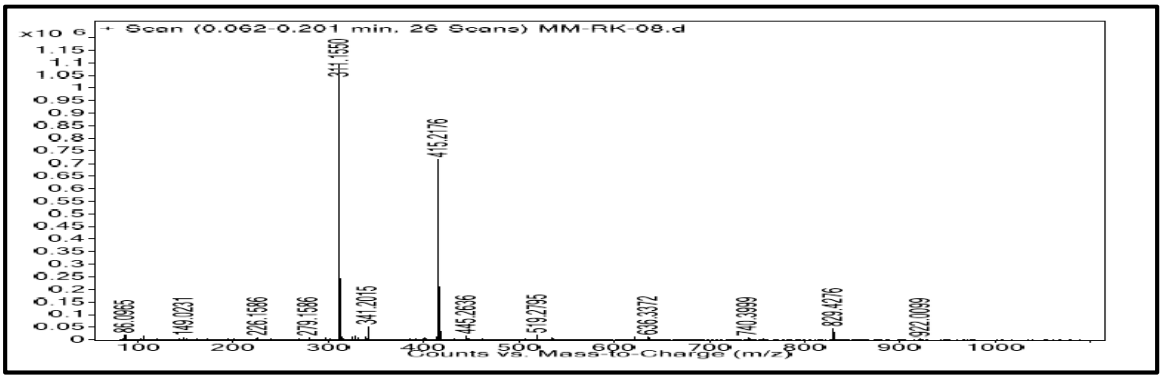


Figure No.4: ^{13}C NMR spectrum of compound 11b





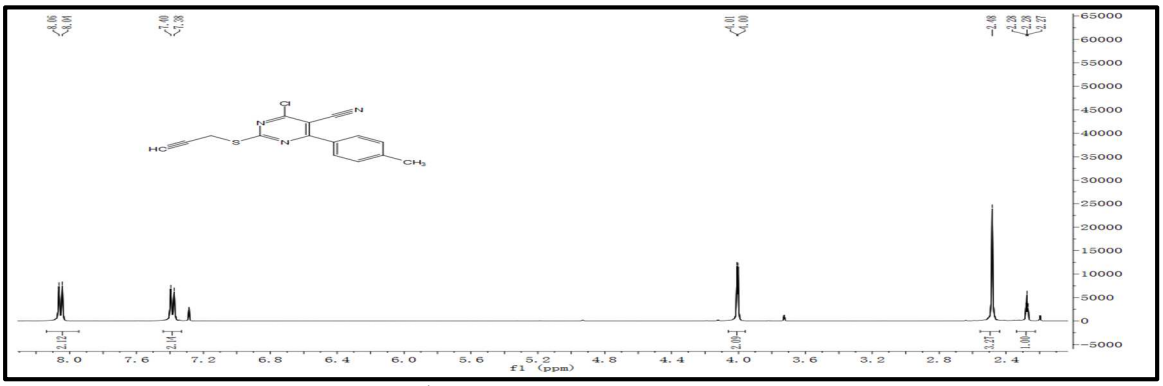


Figure No.5: ^{1}H NMR spectrum of compound 11c

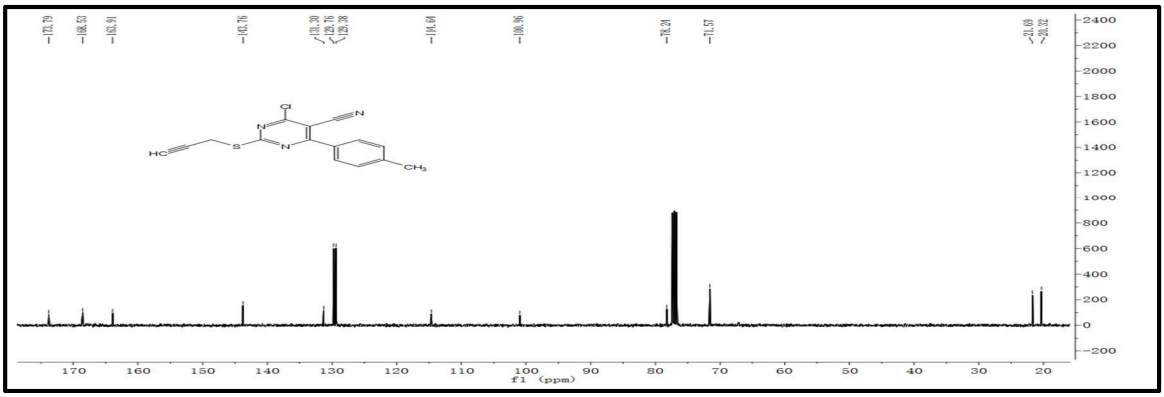
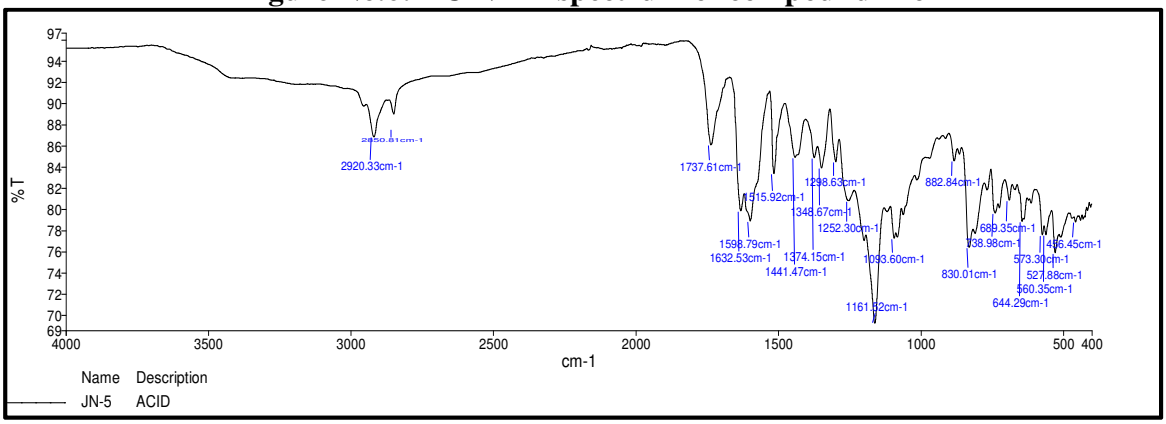


Figure No.6: ^{13}C NMR spectrum of compound 11c



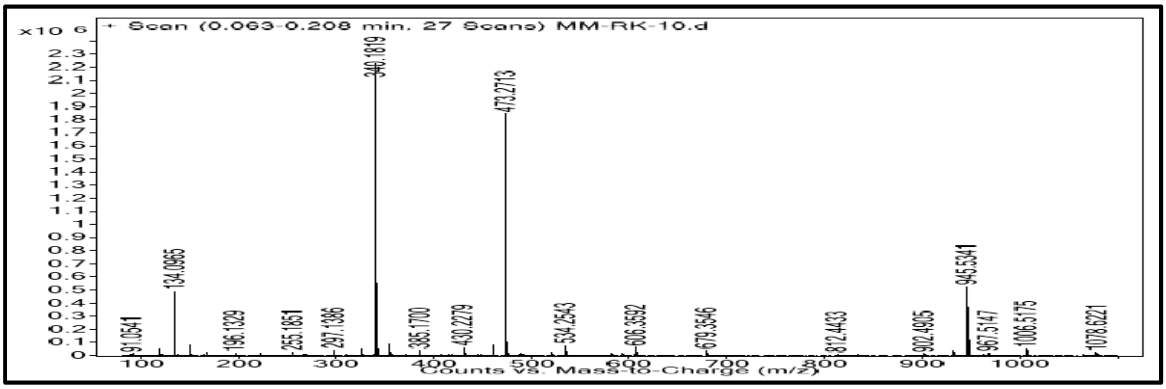


Figure No.7: ^{1}H NMR spectrum of compound 11d

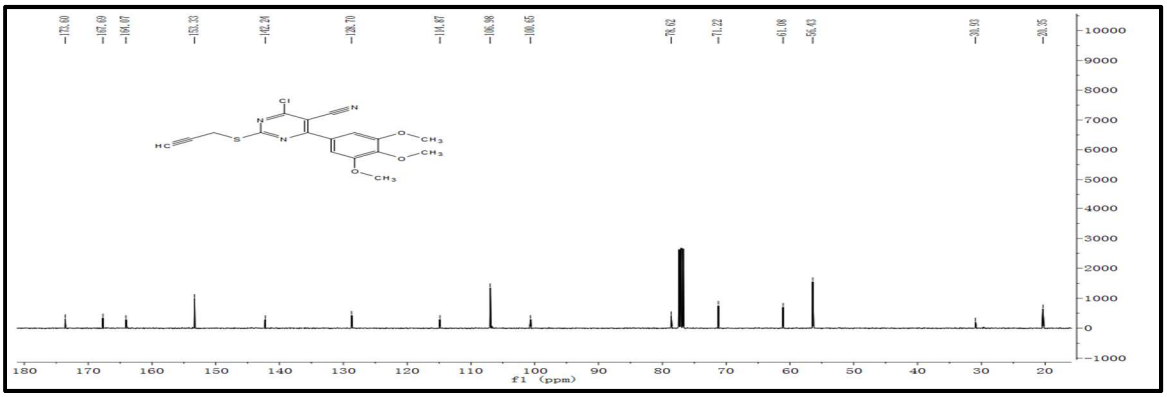
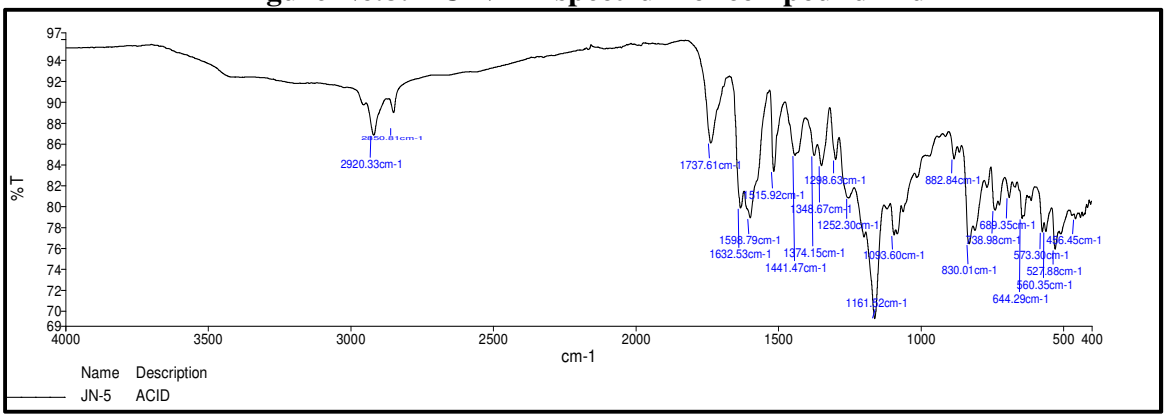
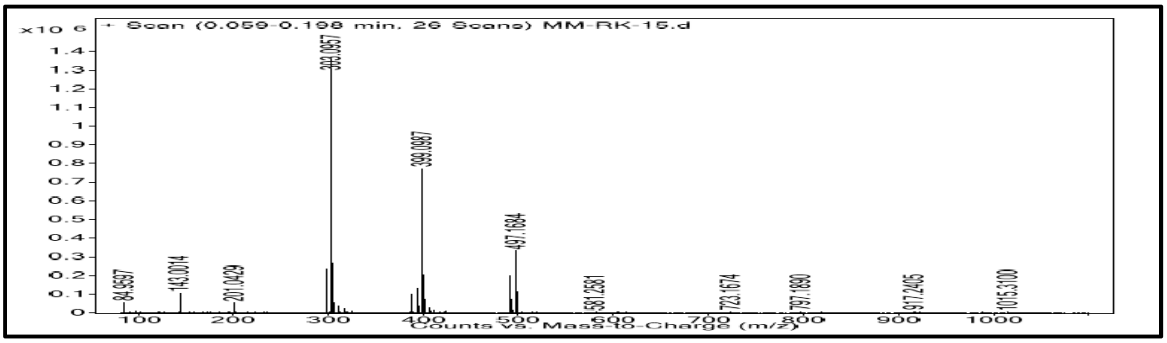


Figure No.8: ^{13}C NMR spectrum of compound 11d





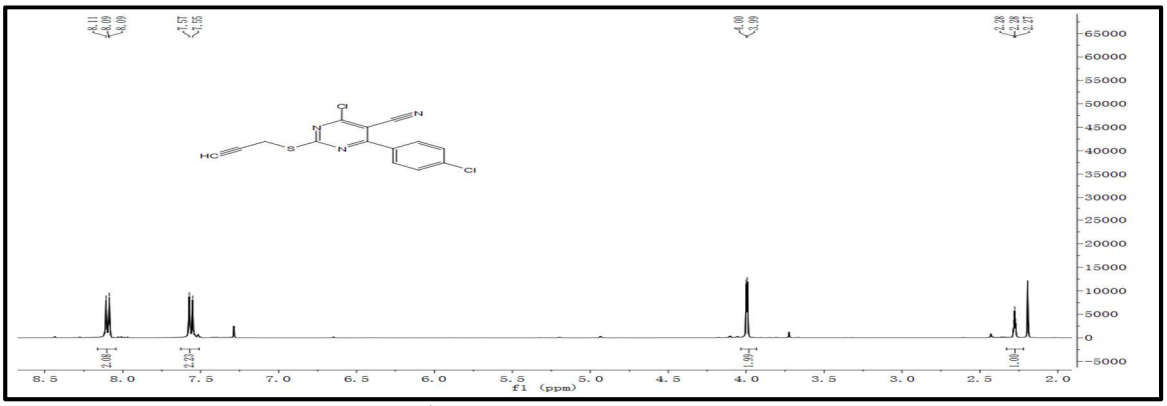


Figure No.9: ^{1}H NMR spectrum of compound 11e

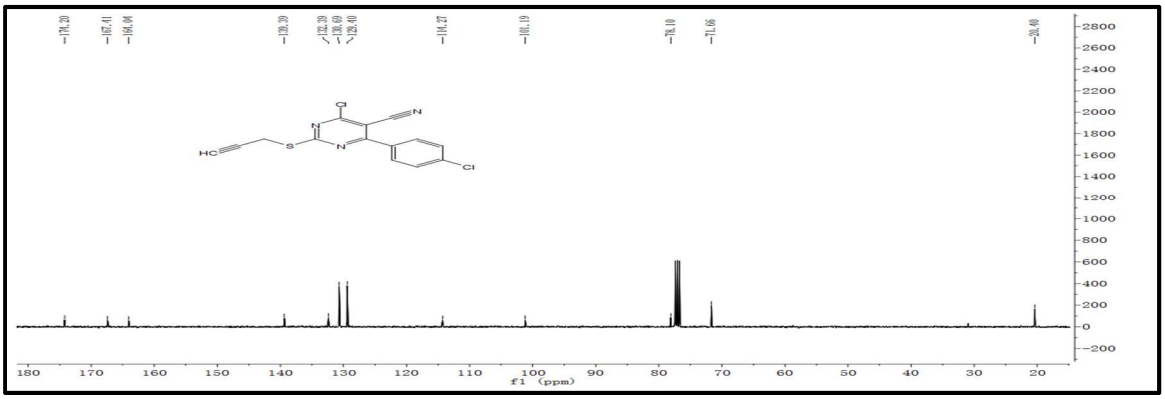
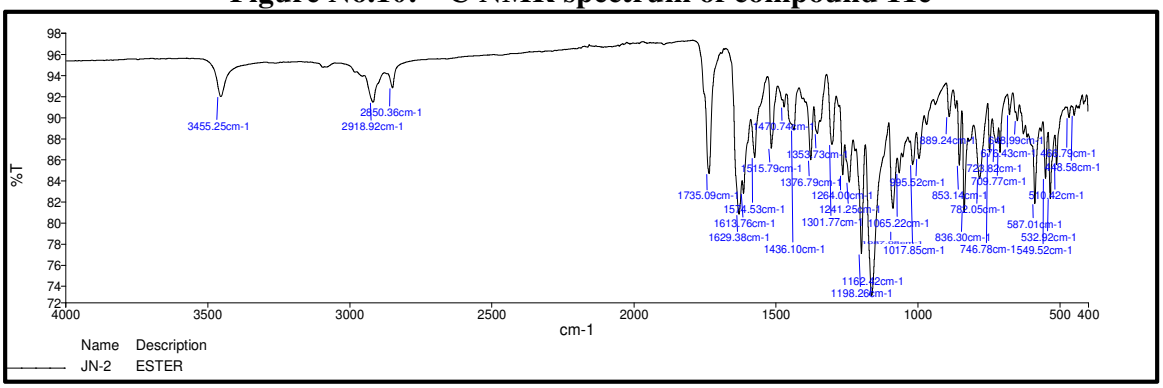
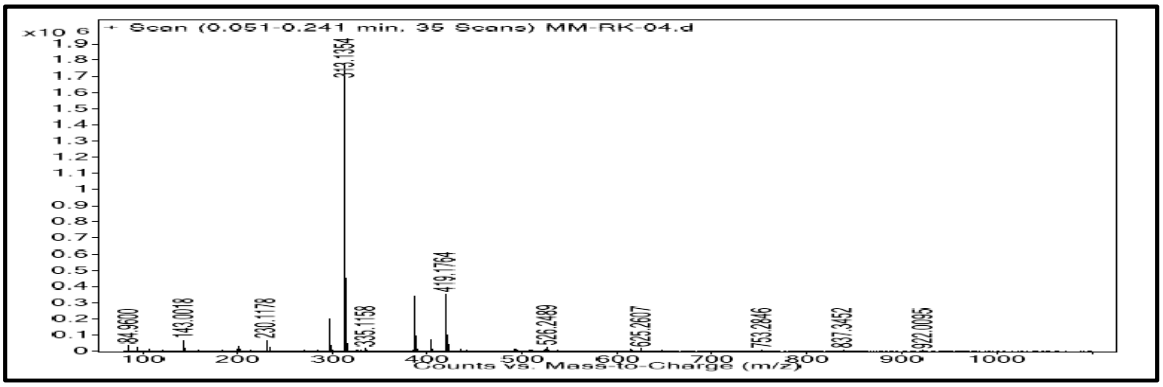


Figure No.10: ^{13}C NMR spectrum of compound 11e





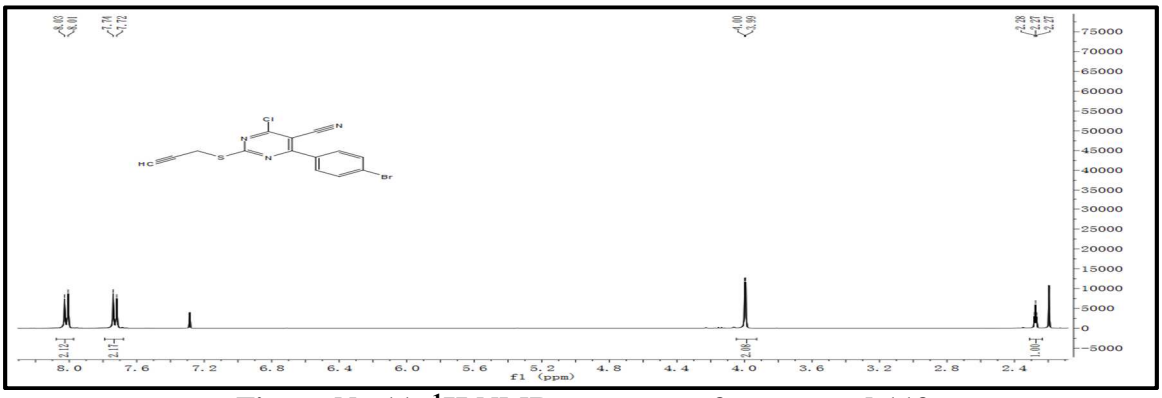


Figure No.11: ^{1}H NMR spectrum of compound 11f

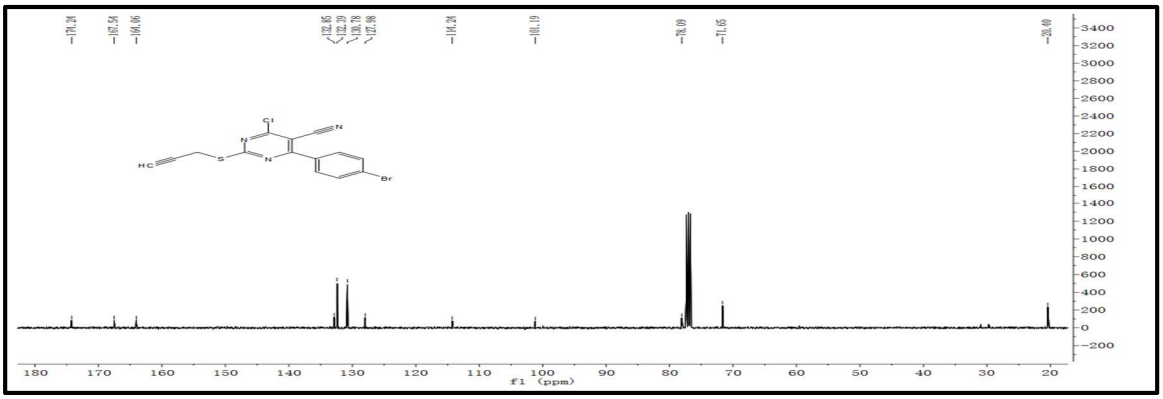
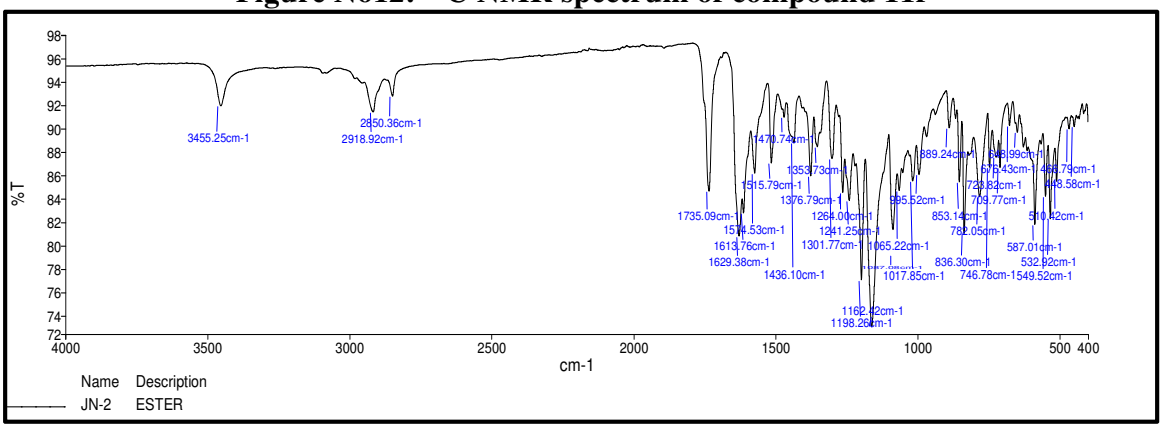
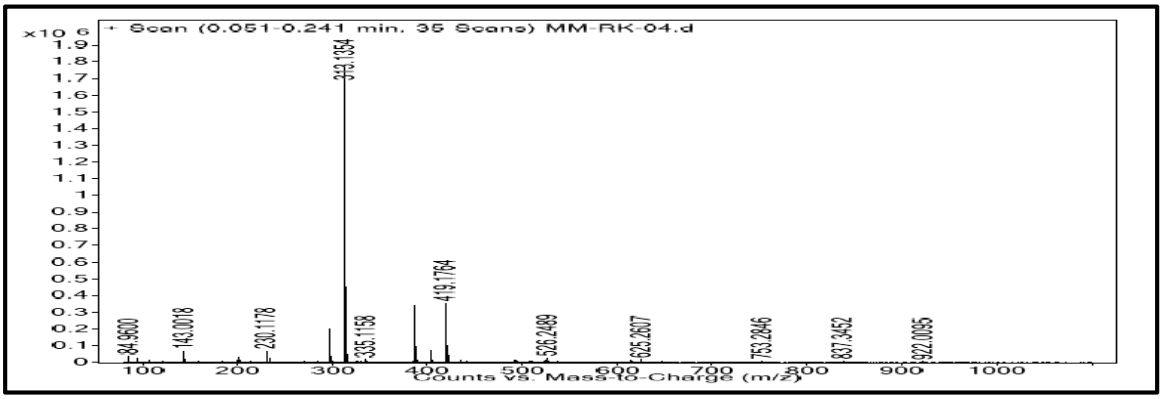


Figure No12: ^{13}C NMR spectrum of compound 11f





CONCLUSION

Thus the pyrimidine derivatives 11a, 11b, 11c and 11e serve as good leads for further studies to develop potent cytotoxic agents.

ACKNOWLEDGEMENT

The authors are thankful to DCRM Pharmacy College, Inkollu and Sura Labs, Dilshukhnagar, Hyderabad for providing necessary facilities for the research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Jin C, Liang Y J, He H, Fu L. Synthesis and antitumor activity of ureas containing pyrimidinyl group, *Eur. J. Med. Chem,* 46(1), 2011, 429e-432.
2. Zhu S L, Wu Y, Liu C J, Wei C Y, Tao J C, Liu H M. Design and stereoselective

synthesis of novel isosteviol-fused pyrazolines and pyrazoles as potential anticancer agents, *Eur. J. Med. Chem,* 65, 2013, 70e-82.

3. Claudio V J, Amanda D, Vanderlan Da Silva B, Eliezer J B, Carlos Alberto Manssour F. Molecular hybridization: a useful tool in the design of new drug prototypes, *Curr. Med. Chem,* 14(17), 2007, 1829e-1852.
4. Gediya L K, Njar V C. Promise and challenges in drug discovery and development of hybrid anticancer drugs, *Expert Opin. Drug Discov,* 4(11), 2009, 1099e-1111.
5. Sharma N, Mohanakrishnan D, Shard A, Sharma A, Saima, Sinha A K, Sahal D. Stilbeneechalcone hybrids: design, synthesis, and evaluation as a new class of antimalarial scaffolds that trigger cell death through stage specific apoptosis, *J. Med. Chem,* 55(1), 2011, 297e-311.
6. McGuigan C, Barucki H, Blewett S, Carangio A, Erichsen J T, Andrei G, Snoeck R, De Clercq E, Balzarini J. Highly potent and selective inhibition of Varicella-Zoster Virus by bicyclic furopyrimidine nucleosides bearing an aryl side chain, *J. Med. Chem,* 43(26), 2000, 4993e-4997.
7. Hopkins A L, Ren J, Tanaka H, Baba M, Okamato M, Stuart D I, Stammers D K. Design of MKC-442 (Emivirine) analogues with Improved activity against drugresistant HIV Mutants, *J. Med. Chem,* 42(22), 1999, 4500e-4505.
8. Pontikis R, Dolle V, Guillaumel J, Dechaux E, Note R, Nguyen C H, Legraverend M, Bisagni E, Aubertin A M, Grierson D S, Monneret C. Synthesis and evaluation of "AZT-HEPT", "AZT-pyridinone", and "ddC-HEPT" conjugates as inhibitors of HIV reverse transcriptase1, *J. Med. Chem,* 43(10), 2000, 1927e-1939.
9. Palanki M S S, Erdman P E, Gayo-Fung L M, Shevlin G I, Sullivan R W, Goldman M E, Ransone L J, Bennett B L, Manning A M, Suto M J. Inhibitors of NF-kB and AP-1 gene expression: SAR studies on the pyrimidine portion of 2- chloro-4-trifluoromethylpyrimidine-5-[N-(3050 - bis(trifluoromethyl)phenyl) carboxamide], *J. Med. Chem,* 43(21), 2000, 3995e-4004.
10. Esteban-Gamboa A, Balzarini J, Esnouf R, De Clercq E, Camarasa M J, Perez-P Erez M J. Design, synthesis, and enzymatic evaluation of multisubstrate analogue inhibitors of Escherichia coli thymidine phosphorylase, *J. Med. Chem,* 43(5), 2000, 971e-983.
11. Rostom S A F, Ashour H M A, Abd El Razik H A. Synthesis and biological evaluation of some novel polysubstituted pyrimidine derivatives as potential antimicrobial and anticancer agents, *Arch. Pharm,* 342(5), 2009, 299e-310.
12. Curtin N J, Barlow H C, Bowman K J, Calvert A H, Davison R, Golding B T, Huang B, Loughlin P J, Newell D R, Smith P G, Griffin R J. Resistance-modifying agents. 11.1 pyrimido [5, 4-d] pyrimidine modulators of antitumor drug activity, Synthesis and structureeactivity relationships for nucleoside transport inhibition and binding to a1-acid glycoprotein, *J. Med. Chem,* 47(20), 2004, 4905e-4922.
13. Conejo-García A, García-Rubino M E, Marchal J A, Nú - Nez M C, Ramírez A, Cimino S, García M A, Ar Anega A, Gallo M A, Campos J M. Synthesis and anticancer activity of (RS)-9-(2, 3-dihydro-1,4-benzoxaheteroin-2-ylmethyl)- 9H-purines, *Eur. J. Med. Chem,* 46(9), 2011, 3795e-3801.
14. Lopez-Cara L C, Conejo-García A, Marchal J A, Macchione G, Cruz-L Opez O, Boulaiz H, García M A, Rodríguez-Serrano F, Ramírez A, Cativiela C, Jimenez A I, García-Ruiz J M, Choquesillo-Lazarte D, Ar Anega A, Campos J M. New (RS)-benzoxazepin-purines with antitumour activity: the chiral switch from (RS)-2, 6-

dichloro-9-[1-(p-nitrobenzenesulfonyl)-1, 2, 3, 5-tetrahydro4, 1-benzoxazepin-3-yl]-9H-purine, *Eur. J. Med. Chem,* 46(1), 2011, 249e-258.

15. Martin D S, Bertino J R, Koutcher J A. ATP depletion þ pyrimidine depletion can markedly enhance cancer therapy: fresh insight for a new approach, *Cancer Res,* 60(24), 2000, 6776e-6783.
16. Morales F, Ramírez A, Conejo-García A, Morata C, Marchal J A, Campos J M. Anti-proliferative activity of 2, 6-dichloro-9- or 7-(ethoxycarbonylmethyl)- 9H- or 7H-purines against several human solid tumour cell lines, *Eur. J. Med. Chem,* 76, 2014, 118e-124.
17. Abdel-Mohsen H T, Ragab F A F, RamLa M M, El Diwani H I. Novel benzimidazoleepyrimidine conjugates as potent antitumor agents, *Eur. J. Med.Chem,* 45(6), 2010, 2336e-2344.
18. Peng-Cheng L V, Zhu Hai-L, Li Huan-Qiu, Sun J, Zhou Y. Synthesis and biological evaluation of pyrazole derivatives containing thiourea skeleton as anticancer agents, *Bioorganic. Med. Chem,* 18(13), 2010, 4606-4614.
19. Parveen H, Hayat F, Salahuddin A, Azam A. Synthesis, characterization and biological evaluation of novel 6-ferrocenyl-4-aryl-2-substituted pyrimidine derivatives, *Eur. J. Med. Chem,* 45(8), 2010, 3497e-3503.
20. Choi Y, Li L, Grill S, Gullen E, Lee C S, Gumina G, Tsujii E, Cheng Y C, Chu C K. Structureeactivity relationships of (E)-5-(2-bromovinyl) uracil and related pyrimidine nucleosides as antiviral agents for Herpes viruses, *J. Med. Chem,* 43(13), 2000, 2538e-2546.
21. Gao Y, Dickerson J B, Guo F, Zheng J, Zheng Y. Rational design and characterization of a Rac GTPase-specific small molecule inhibitor, *Proc. Natl. Acad. Sci. U. S. A,* 101(20), 2004, 7618e-7623.
22. Bugge S, Kaspersen S J, Larsen S, Nonstad U, Bjørkøy G, Sundby E, Hoff B H. Structureeactivity study leading to identification of a highly active thienopyrimidine based EGFR inhibitor, *Eur. J. Med. Chem,* 75, 2014, 354e-374.
23. Aher N G, Pore V S, Mishra N N, Kumar A, Shukla P K, Sharma A, Bhat M K. Synthesis and antifungal activity of 1, 2, 3-triazole containing fluconazole analogues, *Bioorg. Med. Chem. Lett,* 19(3), 2009, 759e-763.
24. Yu S, Wang N, Chai X, Wang B, Cui H, Zhao Q, Zou Y, Sun Q, Meng Q, Wu Q. Synthesis and antifungal activity of the novel triazole derivatives containing 1, 2, 3-triazole fragment, *Arch. Pharmacal Res,* 36(10), 2013, 1215e-1222.
25. Demaray J A, Thuener J E, Dawson M N, Sucheck S J. Synthesis of triazoleoxazolidinones via a one-pot reaction and evaluation of their antimicrobial activity, *Bioorg. Med. Chem. Lett,* 18(17), 2008, 4868e-4871.
26. Wang X L, Wan K, Zhou C H. Synthesis of novel sulfanilamide-derived 1, 2, 3-triazoles and their evaluation for antibacterial and antifungal activities, *Eur. J. Med. Chem,* 45(10), 2010, 4631e-4639.
27. Buckle D R, Outred D J, Rockell C J M, Smith H, Spicer B A. Studies on vtriazoles. 7. Antiallergic 9-oxo-1H, 9H-benzopyrano [2, 3-d]-v-triazoles, *J. Med. Chem,* 26(2), 1983, 251e-254.
28. Giffin M J, Heaslet H, Brik A, Lin Y C, Cauvi G, Wong C H, McRee D E, Elder J H, Stout C D, Torbett B E. A copper (I)-catalyzed 1, 2, 3-triazole azideealkyne click compound is a potent inhibitor of a multidrug-resistant HIV-1 protease variant, *J. Med. Chem,* 51(20), 2008, 6263e-6270.
29. Patpi S R, Pulipati L, Yogeeswari P, Sriram D, Jain N, Sridhar B, Murthy R, Anjana Devi T, Kalivendi S V, Kantevari S. Design, synthesis, and structureeactivity correlations of novel dibenzo [b, d] furan, dibenzo [b, d] thiophene, and N-methylcarbazole clubbed 1, 2, 3-triazoles as potent inhibitors of

mycobacterium tuberculosis, *J. Med. Chem,* 55(8), 2012, 3911e-3922.

30. De Simone R, Chini M G, Bruno I, Riccio R, Mueller D, Werz O, Bifulco G. Structure-based discovery of inhibitors of microsomal prostaglandin E2 synthase-1, 5-lipoxygenase and 5-lipoxygenase-activating protein: promising hits for the development of new anti-inflammatory agents, *J. Med. Chem,* 54(6), 2011, 1565e-1575.
31. Ohmoto K, Yamamoto T, Horiuchi T, Imanishi H, Odagaki Y, Kawabata K, Sekioka T, Hirota Y, Matsuoka S, Nakai H, Toda M, Cheronis J C, Spruce L W, Gyorkos A, Wieczorek M. Design and synthesis of new orally active nonpeptidic inhibitors of human neutrophil elastase, *J. Med. Chem,* 43(26), 2000, 4927e-4929.
32. Duan Y C, Zheng Y C, Li X C, Wang M M, Ye X W, Guan Y Y, Liu G Z, Zheng J X, Liu H M. Design, synthesis and antiproliferative activity studies of novel 1, 2, 3-triazoleedithiocarbamateeurea hybrids, *Eur. J. Med. Chem,* 64, 2013, 99e-110.
33. Fargualy A M, Habib N S, Ismail K A, Hassan A M M, Sarg M T M. Synthesis, biological evaluation and molecular docking studies of some pyrimidine derivatives, *Eur. J. Med. Chem,* 66, 2013, 276e-295.
34. Duan Y C, Ma Y C, Zhang E, Shi X J, Wang M M, Ye X W, Liu H M. Design and synthesis of novel 1, 2, 3-triazole-dithiocarbamate hybrids as potential anticancer agents, *Eur. J. Med. Chem,* 62, 2013, 11e-19.
35. Ram V J, Prabhakar Y S. A QSAR Study on the Antileishmanial Activity of Some Substituted Pyrimidines and Pyrazolo [1, 5-a] Pyrimidines, *Indian Journal of Pharmaceutical Sciences,* 59(6), 1997, 286-291.
36. Gangjee A, Jain H D, Phan J, Lin X, Song X, McGuire J J, Kisliuk R L. Dual inhibitors of thymidylate synthase and dihydrofolate reductase as antitumor agents: design, synthesis, and biological evaluation of classical and nonclassical pyrrolo [2, 3-d] pyrimidine antifolates, *Journal of medicinal chemistry,* 49(3), 2006, 1055-1065.
37. Hu M, Li J, Yao S Q. In situ "click" assembly of small molecule matrix metalloprotease inhibitors containing zinc-chelating groups, *Org. Lett,* 10(24), 2008, 5529e-5531.
38. Wilkening I, Signore G D, Hackenberger C P R. Synthesis of phosphonamidate peptides by Staudinger reactions of silylated phosphinic acids and esters, *Chem. Commun,* 47, 2011, 349e-351.
39. Zheng Y C, Duan Y C, Ma J L, Xu R M, Zi X, Lv W L, Wang M M, Ye X W, Zhu S, Mobley D, Zhu Y Y, Wang J W, Li J F, Wang Z R, Zhao W, Liu H M. Triazoleedithiocarbamate based selective Lysine Specific Demethylase (LSD1) inactivators inhibit gastric cancer cell growth, invasion, and migration, *J. Med. Chem,* 56(21), 2013, 8543e-8560.
40. Kamal A, Mallareddy A, Suresh P, Lakshma Nayak V, Shetti R V C R N, Sankara Rao N, Tamboli J R, Shaik T B, Vishnuvardhan M V P S, Ramakrishna S. Synthesis and anticancer activity of 4b-alkylamidochalcone and 4b-cinnamido linked podophyllotoxins as apoptotic inducing agents, *Eur. J. Med. Chem,* 47(1), 2012, 530e-545.
41. Danenberg P V, Malli H, Swenson S. Thymidylate synthase inhibitors, *In Seminars in oncology,* 26(6), 1999, 621-631.
42. Harapanhalli R S, Howell R W, Rao D V. Bis-benzimidazole dyes, Hoechst 33258 and Hoechst 33342: radioiodination, facile purification and subcellular distribution, *Nucl, Med. Biol,* 21(4), 1994, 641e-647.
43. Chen Z, Liang X, Zhang H, Xie H, Liu J, Xu Y, Zhu W, Wang Y, Wang X, Tan S, Kuang D, Qian X, A new class of naphthalimide-based antitumor agents that inhibit topoisomerase II and induce lysosomal membrane permeabilization and apoptosis, *J. Med. Chem,* 53(6), 2010, 2589e-2600.

44. Vermes I, Haanen C, Reutelingsperger C. Flow cytometry of apoptotic cell death, *J. Immunol. Methods,* 243(1-2), 2000, 167e-190.
45. Filippova M, Evans W, Aragon R, Filippov V, Williams V M, Hong L, Reeves M E, Hughes P D. The small splice variant of HPV16 E6, E6⋆, reduces tumor formation in cervical carcinoma xenografts, *Virology,* 450-451, 2014, 153-164.
46. Ali, Fergus K, Wright F C, Pritchard K I, Kiss A, Warner E. The impact of a breast cancer diagnosis in young women on their relationship with their mothers, *The Breast,* 23(1), 2014, 50-55.
47. Lam S W, Jimenez C R, Boven E. Breast cancer classification by proteomic technologies: Current state of knowledge, *Cancer,* 40(1), 2014, 129-138.
48. Deutsch E, Maggiorella L, Eschwege P, Bourhis J, Soria J C, Abdulkarim B. Environmental, genetic, and molecular features of prostate cancer, *The Lancet Oncology,* 5(5), 2004, 303-313.
49. Cubero M. J, Saiz M, Gonzalez L J, Alvarez J C, Lorente J A, Cozar J M. Genetic analysis of the principal genes related to prostate cancer: A review, *Urologic Oncology,* 31(8), 2013, 1419-1429.
50. Alessia Catalano, Alessia Carocci, Ivana Defrenza, Marilena Muraglia, Antonio Carrieri, Françoise Van Bambeke, Antonio Rosato, Filomena Corbo, Carlo Franchini. 2-Aminobenzothiazole derivatives: Search for new antifungal agents, *A European Journal of Medicinal Chemistry,* 64, 2013, 357-364.
51. Aliabadi A, Eghbalian E, Kiani A. Synthesis and evaluation of the cytotoxicity of a series of 1, 3, 4-thiadiazole based compounds as anticancer agents, *Iranian journal of basic medical sciences,* 16(11), 2013, 1133.

Please cite this article in press as: Kala Praveen T *et al.* Synthesis, characterisation of pyrimidine derivatives and their cytotoxic activity, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences,* 7(2), 2019, 596-614.