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DESIGN, SYNTHESIS AND EVALUATION OF ANTIMICROBIAL AND ANTICANCER ACTIVITY OF NOVEL 3-AMINOMETHYL PYRIDIN DERIVATIVES

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ABSTRACT

In search of new nitrogen, oxygen and sulphur containing heterocyclic compounds with improved antimicrobial, antifungal and anticancer activities, we report herein the synthesis of amide derivatives **2a-g** and **5a-f** obtained by reaction of 3-aminomethyl pyridine with phenyl bromo acetamide **1a-f** and (N-substituted benz [d]thiazol-2-yl) 2-bromo acetamide **4a-g** derivatives respectively. All the synthesized compounds were evaluated for their antimicrobial and anticancer activities. Compound **2a** and **2b** showed IC_{50} values 0.2129 µM and 1.186 µM respectively against A549 lungs cancer cell line, while compounds **2c**, **2d** and **5a** showed promising anticancer activity with IC_{50} values 0.51µM, 0.14 µM and 0.73 µM respectively against MOLT3 leukaemia cancer cell lines.

KEYWORDS: Aminomethyl pyridine, benzothiazole, antimicrobial activity, anticancer activity.

INTRODUCTION

Heterocyclic compounds containing nitrogen, oxygen and sulphur heteroatom have been used as drugs for various diseases. Since last few decades, bacterial and fungal resistance to known therapies is a growing threat across the world. An increasing proportion of bacterial growth shows reduced susceptibility to our currently available antibacterial agents. *Staphylococcus aureus is* Methicillin resistant.[1] It can also bind proteins in blood to help evade antibody-mediated immune response.[2] Similarly a bacterium like Escherichia coli is a frequent cause of urinary tract infections[3] and also showed high rate of resistance to amoxicillin and tetracycline. '*Pseudomonas aeruginosa'*, a ubiquitous microorganism, is one of the most relevant pathogens affecting the patients admitted to (ICU).[4] Along with the various types of bacteria, different types of fungus also cause healthcare-associated infections.[5] It is well observed from the literature that the fungal activity depends prominently on electron withdrawing groups as well as its positioning on aromatic ring.[6]

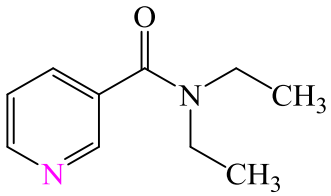
In order to prevent serious medical problems due to drug resistive bacteria the discovery of new types of antibacterial agents is a very important task.[7]

Cancer is considered as fatal disease in terms of morbidity and mortality affecting human health worldwide.[8] It is estimated to further increase of 50% by the end of 2020. The death rates due to lungs cancer and breast cancer in women are very high globally. More than one million cases of lungs cancer are diagnosed every year and is the leading cause of cancer-related death in men and women.[9] Similarly, The incidence of breast cancer has increased intensely in developed countries, however the mortality rate is much higher in developing countries due to lack of early detection of the disease.[10] Despite of substantial research on cancer therapeutics, high toxicity and drug-resistance yet limits the clinical application of some heavy metal containing drugs like Cisplatin which, binds covalently to the N7-guanine of DNA, causing a distortion to the structure of DNA double helix leading to serious side effects, and cell death.[11,13]

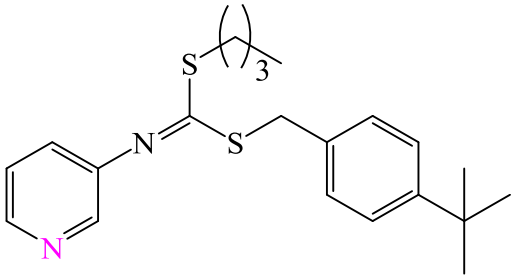
Review of literature indicates that N-containing heterocycles have significant place in the development of pharmacologically important molecules.[14] Likewise Benzothiazole nucleus is also a fertile source of bioactivity in the area of drug discovery because of its varied biological activities viz. Anticancer,[15,16] antimicrobial,[17] and antifungal.[18] Moreover, it has long been known that compounds bearing pyridine ring also occupy a prominent place in medicinal chemistry due to its significant biological activities such as antimicrobial,[19] antiviral,[20] anticancer,[21] and analgesic.[22] Some of the rarely discussed analogue of pyridine like 3-aminomethyl pyridine also showed radical scavenger activity.[23] Several attempts have been made to modify the benzothiazole nucleus to improve their antitumor activities.[24] Various amide derivatives of benzothiazole have potent anticancer property.[25] **Figure-1** and **Figure-2** shows some important Pyridine and benzothiazole containing drugs. Combination of

various amino methyl pyridine and benzothiazole derivatives with acetamide linkage can be a good combination as antimicrobial and anticancer agent.

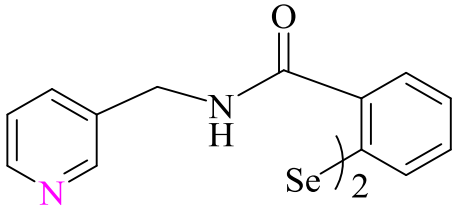
Hence, in continuation of our work on search for potential antimicrobial and anticancer agents,[26,30] we have synthesised compounds **2a-g** and **5a-f** from 3-aminomethyl pyridine which were screened for their antibacterial and antifungal activity using a cup plate method[31] and anticancer activity using MTT assay method.[32]



Nikethamide
1

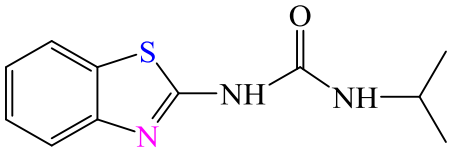


Buthiobate
2

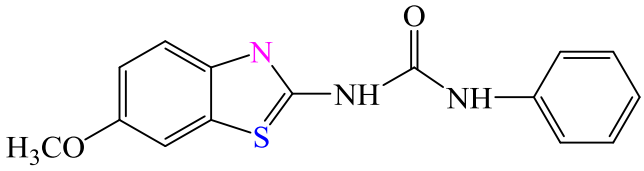


3

Figure-1: Some 3-substituted pyridine derivatives.



Bentarulam
4



Frentizole
5

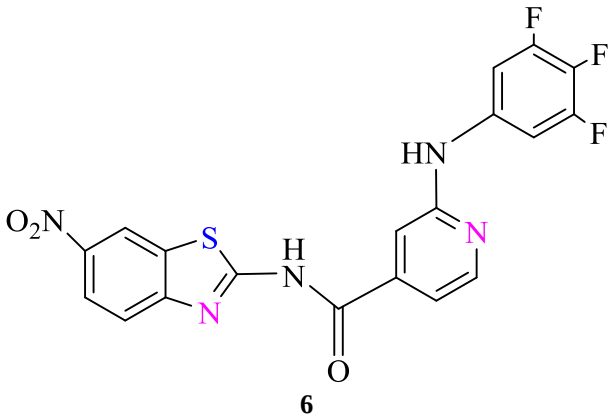


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Figure-2: Some amide derivatives of 2-amino benzothiazole analogues.

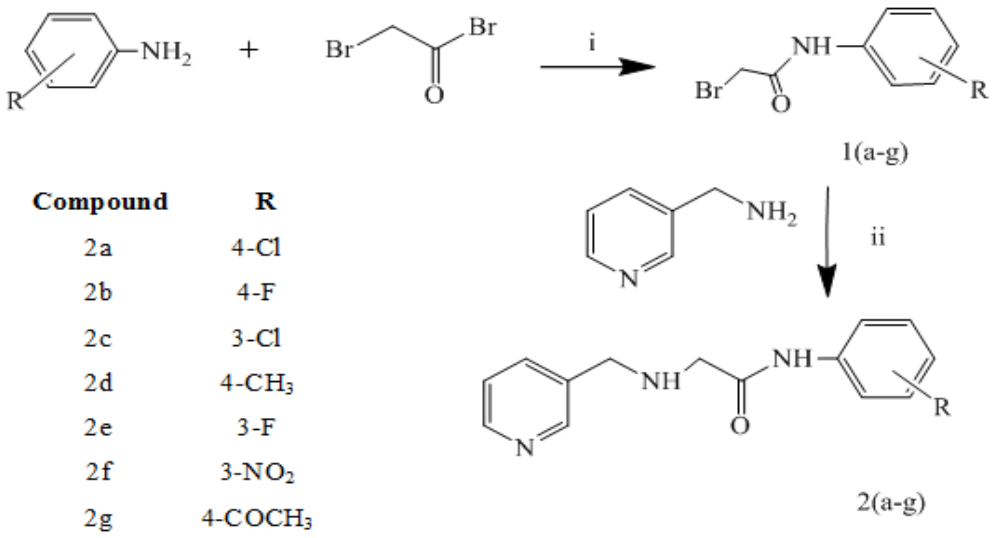
RESULTS AND DISCUSSION

Chemistry

The synthetic routes are depicted in scheme 1 and 2 for the desired target compounds. Compounds **2a-g** as shown in **(scheme-1)** and **5a-f (scheme-2)** were synthesized by reaction of 3-amino methyl pyridine with seven different phenylbromoacetamide of substituted anilines **1a-g** and with six different N-(substituted benzo [d] thiazol-2-yl)-2-bromo acetamide **4a-f** respectively. Compounds 2-bromo-N-substituted phenyl acetamide 1a-g were prepared by reaction of various substituted anilines with bromo acetyl bromide in presence of

catalytic amount of base triethylamine in dichloromethane. Compounds N-(substituted benzo [d] thiazol) **3a-f** were synthesized by the reaction of various substituted anilines with potassium thiocyanate (KSCN) in presence of bromine in acetic acid[33][a,b] further stirring of **3a-f** with bromo acetyl bromide gave N-(substituted benzo [d] thiazol-2-yl)-2-bromo acetamide 4(a-f).[34][a,b] Thus compounds **1a-g** and **4a-f** on substitution reaction with 3-aminomethyl pyridine in dimethylformamide (DMF) in presence of triethylamine (TEA) gave the desired compounds **2a-g** and **5a-f** in good yields respectively. The Structures of all the synthesized compounds were confirmed by its ^{1}H NMR, ^{13}C NMR, IR, Mass Spectra and CHNS analysis. The IR spectrum of compound **2a** exhibited strong band at 3383 cm^{-1} for the characteristic –NH stretching vibrations. Another strong band at 1691 cm^{-1} for the –CO group of amide and another strong band exhibited at 2710 cm^{-1} for –CH stretching vibration, The band at 1612 cm^{-1} indicated C=N stretching vibration. In ^{1}H NMR spectrum of **2a** the two –CH_2 groups were observed as singlet for the two protons each at δ 4.0 and 4.4 for –$COCH_2$ and -CH_2NH respectively. All aromatic protons observed between δ7.20 – 8.40. The amide proton was observed as a singlet at downfield to the aromatic protons i.e at δ 10.5 to 11. In the ^{13}C NMR spectrum of compound **2a** showed two carbons for methylene groups observed at δ 47 and 48.The characteristic –CO carbon was observed at δ 164. All aromatic carbons observed at δ120 to 150. The ESI mass spectrum of compound **2a** showed M^{+} peak at 291.

Scheme-1

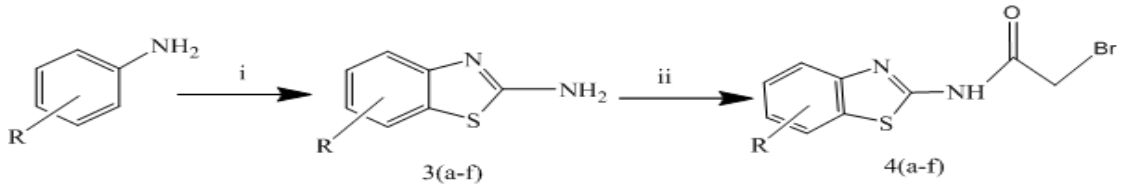


Compound	R
2a	4-Cl
2b	4-F
2c	3-Cl
2d	4-CH_3
2e	3-F
2f	3-NO_2
2g	4-$COCH_3$

Figure-3(Scheme-1): Synthesis of *N*-substituted phenyl-2-[(pyridin-3-ylmethyl) amino] acetamide.

Reagents & conditions: (i) TEA, Stirring at 0- 5°C 30 min, RT, 2 h, DCM, (ii)TEA, RT Stirring 8h, DMF.

Scheme-2



Compound	R
5a	H
5b	4-CH_3
5c	6-Cl
5d	4-Cl
5e	6-Br
5f	4-CH_3-6-NO_2

Figure-4(Scheme-2): Synthesis of 3-amino methyl pyridine based acetamide derivatives of substituted 2-amino benzothiazole.

Reagents and Conditions: (i) KSCN, Br_2 in Acetic acid, 0-5°C, room temperature (RT) string 8-10 hrs. Liq. NH_3 (25%). (ii) $BrCOCH_2Br$, TEA, DCM, string at 0-5°C; 30min, room temperature string 10 hrs. (iii) TEA, DMF, 3-aminomethyl pyridine, room temperature String 12 hrs.

Similarly in the IR spectrum of compound **2b** exhibited strong band at 3398 cm^{-1} for the characteristic -NH stretching vibrations. Another strong band at 1689 cm^{-1} for the –CO stretching of amide and another strong band exhibited at 2710 cm^{-1} for –CH stretching and 1620 cm^{-1} for >C=N stretching. In ^{1}H NMR spectrum of **2b** the two $–CH_2$ groups were observed as singlet for the two protons each at δ 4.03 and 4.46 for $-COCH_2$ and $-CH_2NH$ respectively. All aromatic protons observed between δ7.12 to 9.07. The amide protons were observed as two singlets at downfield to the aromatic protons i.e at δ 10.08 and 11.08. In general for all **2a-g**, the IR spectra showed one characteristic band at δ 3380 cm^{-1} for the NH stretching, Strong band at 1690 cm^{-1} for Carbonyl and band at 1612 cm^{-1} for >C=N stretching. In ^{1}H NMR of all **2a-g**, two methylene protons observed around δ 4.0-4.5 as two singlets. All aromatic protons were observed at δ 7.16 -8.82. The –NH protons observed downfield to the all other aromatic protons at δ 10 and 11. In the ^{13}C NMR spectrum of compounds **2a–g** showed two carbons for methylene groups at around δ 47 and 48. The characteristic –CO (Carbonyl) carbon was observed at δ 164. All the other aromatic carbons observed between δ120 to 150. Similarly, for the synthesised compounds **3a-f**, In the IR spectrum of compound **3b** showed two bands at 3433 cm^{-1} and 3285 cm^{-1} indicated free NH_2 group. ^{1}H NMR of compound **3b** showed singlet at δ 2.42 for three protons indicates $–CH_3$ group. Multiplates at 6.88, 7.01 and 7.40 for three protons indicated all three aromatic protons. Downfield Singlet at δ 7.45 for two protons indicated $–NH_2$ protons thus confirmed the structure of compound **3b.** The reaction of **3b** with bromo acetyl bromide at room temperature gave compound **4b.** In the IR spectrum of compound **4b**, showed one band at 3187 cm^{-1} indicated –NH stretching frequency. A sharp band at 1661cm^{-1} indicated –CO stretching frequency of amide. The C=O absorption of amide occurs at lower frequency than the normal carbonyl absorption due to the resonance effect. In ^{1}H NMR of compound **4b,** showed singlet at δ 2.53 for three protons indicated $–CH_3$ group. Another singlet at δ 4.19 for two protons indicated $–CH_2$ group. The multiplet for two protons at δ 7.16 and δ 7.23 indicated two aromatic protons and another doublet at δ 7.74 for one proton indicated third aromatic proton. Broad singlet at δ 12.83 indicated –NH proton. Further ^{13}C NMR of compound **4b,** showed two carbons at δ 17.86 and 28.36 indicated two aliphatic carbons of $–CH_3$ and $–CH_2$ groups respectively. In aromatic region presence of seven carbons between δ 118.96 to δ 156.63 and one carbonyl carbon at δ 165.80 confirmed the structure of compound **4b.** The reaction of compound **4b** with 3-amino methyl pyridine in DMF at room temperature gave compound **5b.** The IR spectrum of compound **5b** showed sharp band at 3320 cm^{-1} indicated –NH stretching vibration. A sharp stretching band at 1691cm^{-1} indicated carbonyl stretching frequency of amide group. The ^{1}H NMR spectrum of compound **5b,** showed singlet at δ 2.36 for three proton of –CH3 group. Two singlets at δ 4.16 and δ 4.48 for two protons each indicated $-CH_2N-$ and $–CH_2-CO-N-$ protons respectively. Six signals in aromatic region for one proton each indicated six aromatic protons. One broad singlet and one sharp singlet at δ 10.15 and 10.98 for one proton each indicated two,-NH protons. In ^{13}C NMR spectrum of compound **5b** showed three aliphatic carbons at δ 19.42, 46.92 and 47.79 for one $–CH_3$ and two $–CH_2$ carbons. The remaining eleven carbons in aromatic region between δ 123.13 to δ 146.66 and one carbonyl carbon at δ 164.26 confirmed the formation of compound **5b.** Further mass spectrum of compound **5b** showed M^+ peak at 312 confirmed the structure of compound**5b.**

In general, the IR spectra of compounds **5a-f** exhibited one strong band in range of 1690-1710 $cm^{-1}$for the carbonyl stretching frequency of amide group and another broad band observed approximately at 3275cm^{-1} to 3300cm^{-1} indicates the –NH stretching vibrations. In the ^{1}H-NMR spectra of **5a–f**, two separate singlet peaks for the two methylene protons observed in range of approximately δ 3.95 to 4.65 and the aromatic protons in the range of δ 6.99 to 8.93. In the ^{13}C NMR spectrum of **5a-f** all the aromatic carbons exhibited in the range of approximately δ 122 to δ 147, Carbon atom at position 5 of the thiazole ring showed signal around δ 110 to δ 112. One carbonyl carbon observed in the range of approximately δ 160 to δ 165 confirms the general structure of the synthesized compounds **5a-f**. Mass spectra showing specific molecular ion peak further confirmed the synthesis of desired products. All these new chemical entities were subjected to *in vitro* studies.

Biological Evaluation

Antimicrobial and antifungal activity

The antibacterial activity of compounds **2a-g** and compounds **5a-f** was evaluated and compared with standard drugs. All the synthesized compounds were screened for their antibacterial activity against two *Gram positive* bacterial strains (*Staphylococcus aureus*, *Bacillus Subtilis*) and two *Gram negative* bacterial strains (*Escherichia coli*, and *Pseudomonas aeruginosa*) and all the compounds were also tested for their antifungal activity against one fungal strain (*C. albicans)* by cup plate method at 0-250 µg concentration in DMF as a solvent. Ciprofloxacin and Flucanazole were used as standard drugs for determining the antimicrobial and antifungal activity respectively. **Table-1** shows antimicrobial activity of all the newly synthesized compounds **2a-g** and **5a-f**.

Table 1: *In Vitro* antibacterial and antifungal activity of compounds 2a-g and 5a-f.

MIC of antibacterial and antifungal agent (µM)							
Sr. No	**Compound**	**-R**	**S. aureus**	**B. Subtilis**	**E. Coli**	**P. aeruginosa**	**C. albicans**
01	2a	4-Cl	100	100	100	200	100
02	2b	4-F	200	250	100	150	100
03	2c	3-Cl	50	50	200	250	100
04	2d	4-CH_3	200	150	150	200	100
05	2e	3-F	50	50	200	>250	50
06	2f	3-NO_2	>250	150	150	150	150
07	2g	4-$COCH_3$	200	250	150	250	100
08	5a	-H	150	300	>300	>300	>300
09	5b	-CH_3	80	>300	>300	>300	>300
10	5c	6-Cl	80	150	>300	>300	>300
11	5d	4-Cl	>300	>300	>300	>300	>300
12	5e	6-Br	80	300	>300	>300	>300
13	5f	4-CH_3-6-NO_2	300	>300	>300	>300	>300
14	Ciprofloxacin		15	05	20	10	-
15	Flucanazole		-	-	-	-	10

Table 1: Antimicrobial and antifungal activity of compound 2(a-g) and 5(a-g).
S. aureus *= Staphylococcus aureus,* ***B. Subtilis*** *=Bacillus Subtilis,* ***E. coli*** *=Escherichia coli,* ***P. aeruginosa*** *= pseudomonas aeruginosa,* ***C. albicans*** *=Candida albicans.*

Compounds **2(a-g) and 5(a-f)** were screened for their antimicrobial and antifungal activities. Both of the Compounds **2c** and **2e** showed promising antibacterial activity at 50 µM concentrations against tested bacteria (*S. aureus and B. Subtilis)* and Compound **2e** showed promising antifungal activity at 50 µM against fungi *C. albicans.* Compound **2a** showed moderate activity at 100 µM against all the four pathogenic bacterial strains. Compound **2b** remained moderate active against *E. coli* and *P. aaeruginosa.* Both the compounds **2a** and **2b** showed moderate activity against fungi *C. albicans.* Compound **2f** and **2g** showed some activity against fungi *C. albicans.* Among the synthesized compounds **5a-f** Compound **5b**, **5c**, and **5e** remained moderately active at 80 µg concentrations against tested bacteria (*S. aureus*) while compounds **5a**, **5d** and **5f** remained inactive against all the bacterial strains and fungi C. *albicans.* In general it is also concluded that when phenyl ring of amine is substituted at 3rd position plays important role in showing antibacterial as well as antifungal activity. The structure variations such as methyl and halo groups at *meta* and *para* positions of phenyl ring bearing amide linkage resulted in promising antibacterial and antifungal activity.

Anticancer Activity

The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to screen only five test compounds **2a**, **2b**, **2c**, **2d** and **2f** from seven synthesized compounds **2a-g** for their cytotoxic potential against lung cancer cell line A549. Among the tested five compounds of **2a-g**; only three Compounds 2a, 2b and 2f showed promising anticancer activity against A549 cell line with IC_{50} 0.2129 µM, 1.863 µM and 32.63 µM while compounds **2c** and **2d** remained inactive. Three compounds namely compounds 2a, 2e and **2f** were tested against breast cancer cell line MCF7 from all the synthesized compounds **2a-g** as presented in **Table-2** among which only two compounds **2a** and **2f** showed cytotoxic potential with IC_{50} 950.1µM and 90.78 µM while compound **2e** remained inactive against MCF7 cancer cell line. For various amide derivatives of various substituted anilines with amino methyl pyridine it has been observed that 3rd position Cl substitution showed very good anticancer activity against all the three leukaemia cancer cell lines. Similarly a bar chart representation for the anticancer activity of four compounds **5a**, **5c**, **5d** and **5f** from the synthesized benzothiazole derivatives against A549 (lung cancer cell line) showed % inhibition at 5 different concentrations ranging from 0-200µM **Figure-5.** All the synthesized compounds **2a-g** and **5a**,**5c**,**5d** and **5f** were screened for their efficacy as anticancer agent against three leukaemia cancer cell lines namely K562 (Human Chronic Myelogenous leukaemia cell line), KG1 (Human acute Myeloid Leukaemia cells) and MOLT-3 (Human Acute Lymphoblastic Leukaemia cell line). IC_{50}µM values for compounds **2a-g** and **5a**, **5c**, **5d** and **5f** are summarized in **Table-3**. Compound **2c** showed very good cytotoxic potential with IC_{50} 2.351 µM against K562 cell line compared to all other compounds. Likewise, compound **2c** and **2d** also showed very good anticancer activity with IC_{50} 0.51 µM and 0.14 µM against MOLT3 cell line compared to other Compounds. Similarly, Compound **2c** showed better cytotoxic potential with IC_{50} 0.374 µM against KG1 cell line. All the compounds showed good anticancer activity against two leukemia cancer cell line (MOLT3 and KG1) with IC_{50} potential ranging from 1.0 µM to 50 µM except **5c** and **5f**. The bar chart presentation for compounds **2a-g** on K562, KG 1 and MOLT 3 cell growth and determining their % cell viability are shown in **Figure-5**.Similarly bar chart presentation for compounds **5a**, **5c**, **5d** and **5f** on K562,

KG 1 and MOLT 3 cell growth and determining their % cell viability are shown in Figure-**6**. In benzothiazole derivatives it has been observed that without any substitution on benzene ring of benzothiazole showed good activity and 6-chloro substitution showed better activity.

Inhibition (%) = (Absorbance of blank-Absorbance of test/Absorbance of blank) X 100

Table 2: IC_{50} (µ/mL) values for Lung and Brest cancer cell lines for compounds 2(a-g).

No.	Compounds Code	-R	A549	MCF7
			IC_{50} (µM)	IC_{50} (µM)
01	2a	4-Cl	0.2129	950.1
02	2b	4-F	1.186	ND
03	2c	3-Cl	NA	ND
04	2d	4-CH_3	NA	ND
05	2e	3-F	ND	NA
06	2f	3-NO_2	32.63	90.78
07	2g	4-$COCH_3$	ND	ND

ND=**Not Done,** NA=**Not Active.**

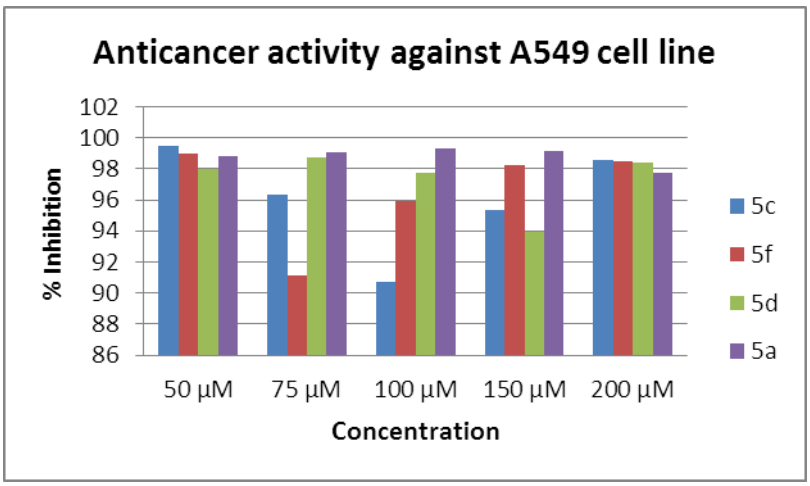


Figure 5: Bar chart representation for the anticancer activity of four compounds from 5(a-f) against A549 (lung cancer cell line) showing % inhibition at 5 different concentrations ranging from 0-200µM.

Table 3: IC_{50} (µM) values for three different Leukaemia cancer cell lines.

No.	Compounds	-R	K 562	Cancer cell lines MOLT 3	KG 1
			IC_{50}(µM)	IC_{50}(µM)	IC_{50}(µM)
01	2a	4-Cl	50.19	3.881	6.228
02	2b	4-F	16.32	1.25	9.73
03	2c	3-Cl	2.35	0.51	0.374
04	2d	4-CH_3	20.47	0.14	4.968
05	2e	3-F	55.94	14.73	3.437
06	2f	3-NO_2	8.304	3.094	3.883
07	2g	4-$COCH_3$	13.57	3.64	4.499
08	5a	-H	284.3	0.73	53.67
09	5c	6-Cl	244.2	67.68	2.34
10	5d	4-Cl	225.2	8.82	0.50
11	5f	4-CH_3-6-NO_2	225.0	96.35	20.36

Table-3: Anticancer activity of compounds **2a-g** and compounds **5a**, **5c**, **5d** and **5f** against three different Leukemia cell lines. Data are reported as IC_{50} values (concentrations of complexes required to inhibit cell viability by 50%) determined by MTT assay after 48h of continuous exposure to each compound. The data represent the mean values ± SEM (standard error of mean) of at least three independent experiments.

Figure-6

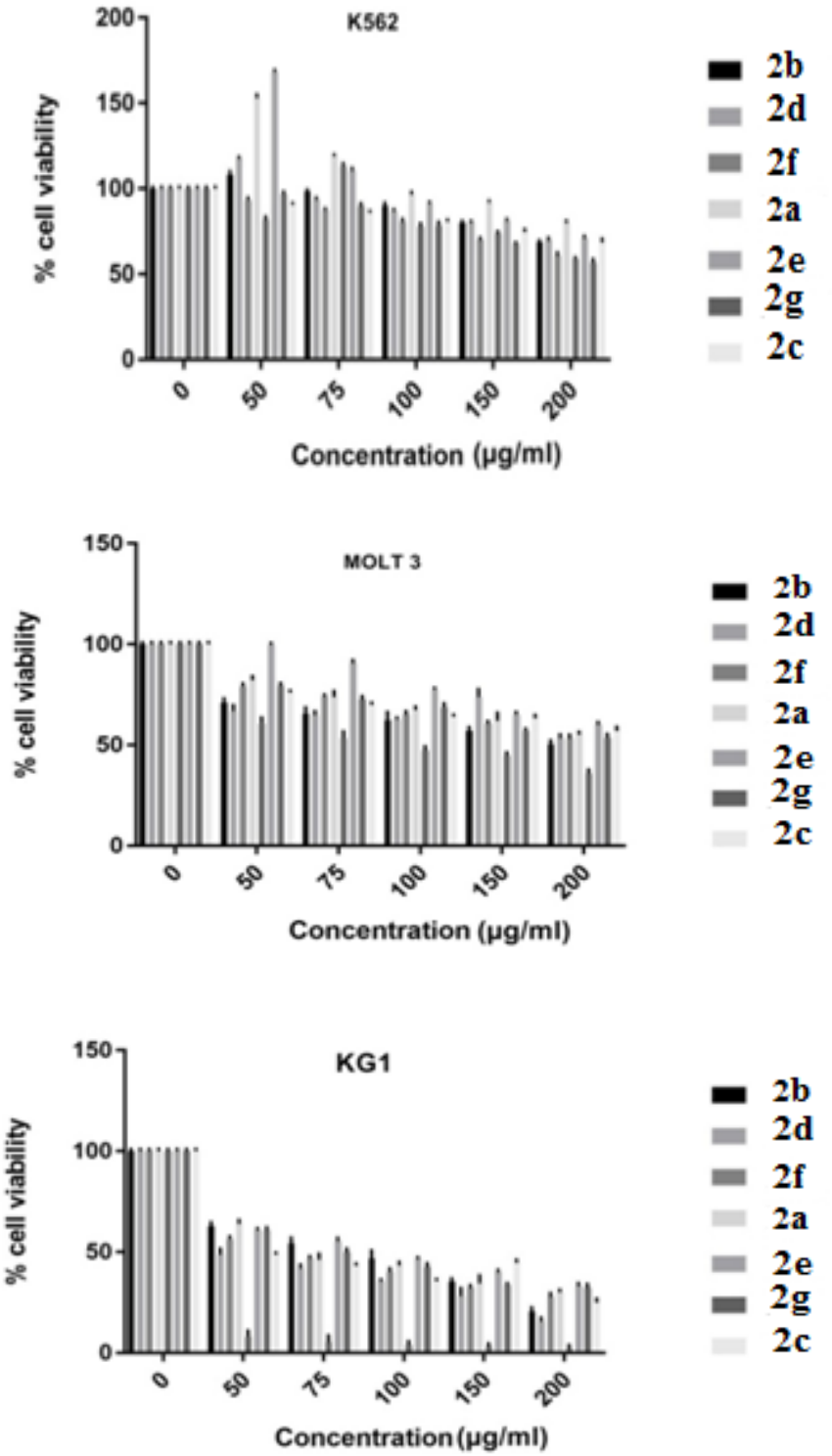


Figure 6: Bar chart representation for the effect of compounds 2a-g on K562, KG 1 and MOLT 3 cell growth and determining % cell viability.

Figure-7

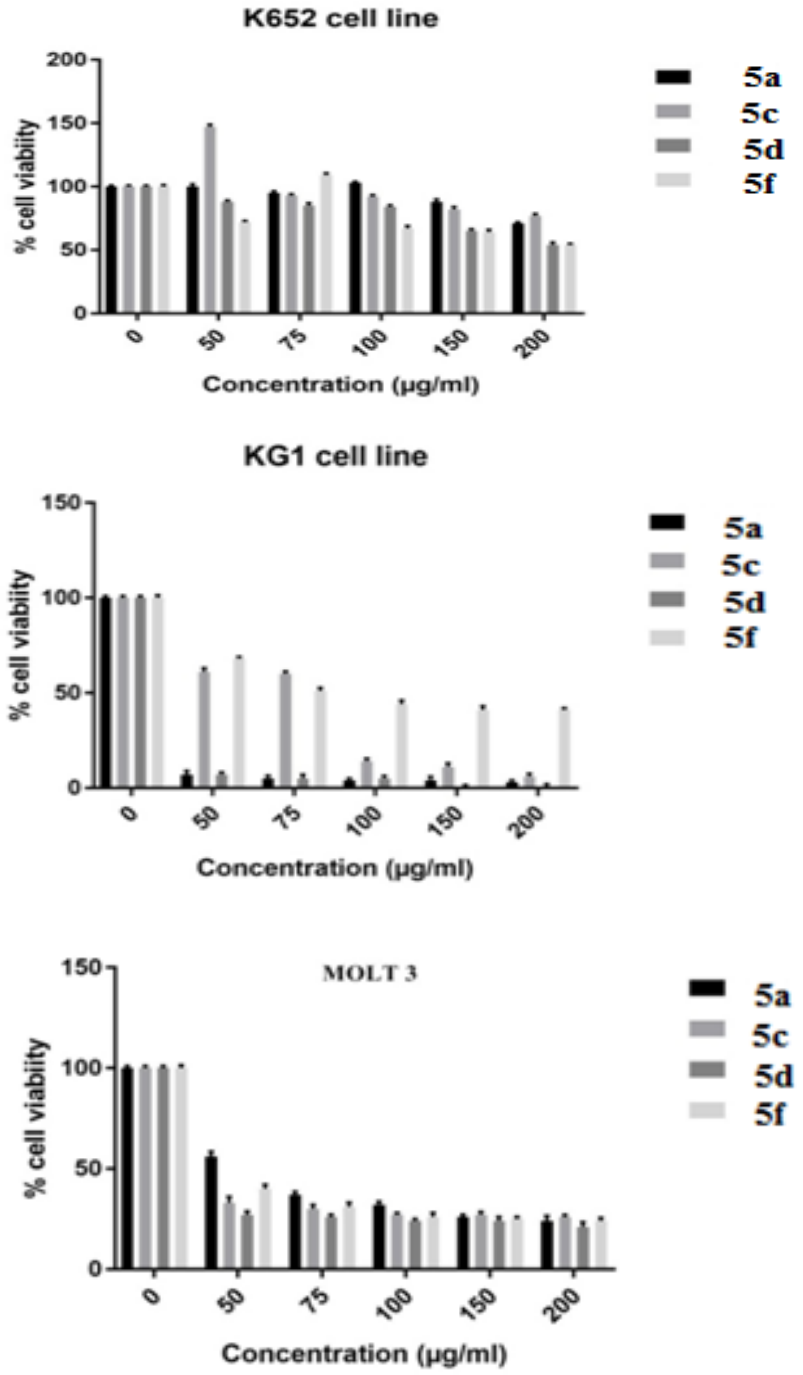


Figure-7: Effect of compounds 5a, 5c, 5d and 5f on K562, KG 1 and MOLT 3 cell growth and determining % cell viability. Cells were cultured and treated with DMSO and 5-Flouro Uracil and % viability was determined by MTT assay test, Experiments were conducted in triplicate and repeated thrice. The value represents the mean ±SD.

MATERIALS AND METHOD

EXPERIMENTAL

Melting points are uncorrected and measured in open capillary using a Rolex melting point apparatus. Reagent grade chemicals and solvents were purchased from commercial supplier and used after purification. 3-amino methyl pyridine was purchased from M/s TCI chemicals; Japan. TLC was performed on silica gel F254 plates (Merck). Acme's silica gel (60-120 mesh) was used for column chromatographic purification. All reactions were carried out in nitrogen atmosphere. IR spectra were recorded as KBr pellets on Perkin Elmer RX-1 spectrometer. ^{1}H NMR and ^{13}C NMR spectral data were recorded on Advance Bruker 400 spectrometer (400

MHz) with $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. *J* values are in Hz. Mass spectra were determined by ESI-MS, using a Shimadzu LCMS 2020 apparatus. Elemental analyses were recorded on Eager Xperience Element Analyser.

Chemistry

General procedure for Synthesis of 2-amino substituted benzothiazole 3(a-f) by reported method[33a,b]

The appropriate various substituted aniline derivatives (0.1mol) and equimolecular amount of potassium thiocyanate (KSCN) were added to 100 mL glacial acetic acid with cooling of the reaction mixture in ice bath. The temperature of the ice bath is maintained at 0-5°C. The mixture was left at this temperature up to 20 minute. Then bromine (0.1mol) in glacial acetic acid was added very slowly so that the temperature of the reaction mixture maintained below 10°C, then the mixture was stirred at room temperature for 4-6 h to furnish the hydro bromide (HBr) salt. The salt was then isolated by filtration, washed with acetic acid, dried in vacuum oven and then dissolved in sufficient aqueous ammonia solution to ensure the PH was 11.0. The solid precipitate thus formed was filtered, washed with water and dried in vacuum oven to yield the intermediates **3(a-g).** The progress of the reaction was monitored by TLC with Ethyl acetate-Petroleum ether(3:7) as mobile phase.

General procedure for the Synthesis of Compounds 1(a-g) and 4(a-f) by reported method[34a,b]

To a well stirred solution of substituted aniline 1.0eq. or substituted 2-amino benzothiazole 3(a-f) derivatives in dichloromethane, tri ethyl amine (2.09 mmol,1.01eq.) was added slowly and allowed to stir at 0-5°C for 30 minute. To this bromo acetyl bromide (1.0eq.) added slowly and the reaction mixture was stirred at room temperature for 6-8 hrs. The completion of the reaction monitored on TLC and then the reaction mixture was extracted with ethyl acetate. The extract was washed with water, dilute HCl and again washed with water and dried over anhydrous sodium sulphate and concentrated under vacuum. The yellow precipitates obtained were crystallized from ethanol to give **1(a-g)** and **4(a-f)** as off-white solid.

General Procedure for the Synthesis of final Compounds 2 a-g and 5a-f

To a well stirred solution of **1(a-g)** and **4(a-f)** 1.0eq. in dimethylformamide 15 mL, tri ethyl amine (2.09 mmol,1.01eq.) was added slowly and allowed to stir at 0-5°C for 30 minute. To this 3-amino methyl pyridine (1.0eq.) was added slowly and the reaction mixture was stirred at room temperature for 10-12 hrs. The completion of the reaction monitored on TLC and then the reaction mixture was poured on crushed ice. The solid thus obtained was filtered and washed with excess of water and extracted with ethyl acetate. The extract was washed with excess of water, and dried over anhydrous sodium sulphate and concentrated under vacuum. The precipitates obtained were crystallized from ethanol to give **2(a-g)** and **5(a-f)** as off-white solid.

***N-(4-chlorophenyl)-2-[(pyridin-3-ylmethyl) amino] acetamide* 2a.**

Yield 75%; m.p: 210-212°C; IR(KBr): 3383, 3063, 2968, 2710, 1691, 1612, 1550, 1492, 1400, 1313, 1292, 1251, 1087, 939, 827, 794, 688.cm^{-1};^{1}H-NMR (DMSOd_6, 400MHz) δ 4.026 (S, 2H), 4.405 (S, 2H), 7.39 (d, *J* = 8.0Hz, 2H), 7.66 (d, *J*=8.0Hz,2H), 7.83 (S,1H), 8.46 (S,1H), 8.81(S,1H), 8.97(S,1H), 10.04(S,1H) 11.21 (s ,1H) (amidic proton)^{13}C NMR: δ 47.26, 48.29, 121.25, 125.78, 127.94, 129.28, 130.23, 137.63, 143.81, 146.16, 147.63, 164.24 Molecular weight:275.73g/mol; Mol. Formula: $C_{14}H_{14}ClN_3O$; Elemental analysis; (C,H,N), (Cal: found.), (60.98, 5.12, 15.24: 61.00, 5.14, 15.25). EI MS: 276(m+1).

N-(4-flouro phenyl)-2-[(pyridin-3-ylmethyl) amino acetamide 2b

Yield 75%; m.p: 222-224°C;IR(KBr): 3383, 3063, 2968, 1689, 1564, 1510, 1502, 1410, 1377, 1315, 1259, 1220, 1192, 1116, 1014, 912, 827, 793, 685.cm^{-1};^{1}H-NMR (DMSOd_6,400MHz) δ 4.026 (S,2H), 4.462 (S,2H),7.12-7.21 (m, *J*=16Hz,2H),7.64-7.66(m, *J*=7.6.Hz,2H), 7.83(S,1H), 8.024 (d, *J* = 6.8Hz, 1H) 8.67(S, *J*=6.8.Hz,1H), 8.92 (S,1H), 9.07 (s,1H), 10.09(s,1H) 11.082 (s,1H) (amidic proton).^{13}CNMR:46.96, 48.27, 115.89, 116.11, 121.68, 126.66, 131.68, 135.02, 144.08, 146.28, 157.57, 159.96, 163.94., Molecular weight: 259.23 g/mol; Molecular Formula:$C_{14}H_{14}FN_3O$; Elemental analysis; (C,H,N), (Cal:Obs.), (64.85,5.44,16.21: 64.87,5.42,16.23). EI MS(m/z): 260(m+1).

N-(3-chlorophenyl)-2-[(pyridin-3-yl methyl) amino] acetamide 2c.

Yield 64%; m.p : 204 -206°C; IR (KBr) :3392, 3246, 3065, 2928, 2812, 1691, 1608, 1597, 1546, 1477, 1414, 1375, 1286, 1246, 1192, 1166, 1076, 918, 869, 788, 756, 711, 682cm^{-1}; ^{1}H-NMR(DMSO d_6, 400MHz) δ 3.99 (S, 2H), 4.33(S,2H), 7.17 (d, *J* = 8.0 Hz, 1H) 7.37 (d, *J* = 8.0Hz,1H), 7.49(d, *J* = 8.0 Hz, 1H),7.64(t, *J*=13 Hz,3H),7.80 (S,1H), 8.21(d, *J*=8.0Hz,1H) 8.70 (d, *J*=4Hz,1H), 8.83(S,1H), 9.86(S,1H), 11.14(S,1H) ^{13}C NMR δ:47.60, 48.23, 118.15, 119.17, 124.17, 124.83, 128.97, 131.17, 133.62, 140.03,140.93,148.65,149.91,164.54. Molecular weight: 259.23g/mol; Mol. Formula: $C_{14}H_{14}ClN_3O$; Elemental analysis; (C, H, N), (Cal: Obs.), (60.98, 5.12, 15. 24:60.96, 5.32, 15.26),. EI mass (m/z): 275(m+1).

2-[(pyridin-3-yl methyl) amino] –N-P-tolyl acetamide 2d.

Yield 71%; m.p:208-210°C; IR (KBr): 3412, 3213, 3176, 3055, 2991, 2781, 1690, 1577, 1510, 1483, 1427, 1410, 1388, 1334, 1307, 1292, 1255, 952, 918, 821, 802, 769, 729.cm^{-1};^{1}H-NMR (DMSO d_6, 400MHz) δ2.25(S,3H), 3.94(S, 2H), 4.29 (S,2H), 7.14 (d, *J* = 8.0 Hz, 2H) 7.48-7.54(m,3H), 8.09 (d, *J*=8.0Hz,1H), 8.63 (d, *J*=8.0Hz,

2H), 8.76 (S,1H), 10.75(S,1H).^{13}C NMR δ:20.93,45.72, 48.10, 119.68, 124.25, 129.75, 133.38, 139.27, 149.96, 151.60, 163.80.Molecular weight; 255.14g/mol, Molecular formula;$C_{15}H_{17}N_3O$ Elemental analysis (C,H,N) (Cal: Obs.), (70.56,6.71,16.41:70.73,6.69,16.43) .EI MS(m/z):256(m+1).

N-(3-flouro phenyl)-2-[(pyridin-3-ylmethyl) amino] acetamide 2e.

Yield 62%; m.p:199-201°C; IR (KBr):3421, 3255, 3200, 3124, 3084, 2972, 2858, 2723, 1691, 1610, 1493, 1481, 1317, 1274, 1257, 1244, 1234, 1190, 1142, 1141, 1074, 1030, 916, 866, 806, 775, 709, 677cm^{-1}; ^{1}H-NMR (DMSOd_6, 400 MHz) δ 3.95 (S,2H) ,4.27 (S,2H),6.94 (t, *J* = 16Hz , 1H) 7.46 (S,1H) , 7.33-7.41(m, J=16Hz,8Hz, 2H) 7.46-7.49 (m,1H) ,7.57-7.60 (d,1H) 8.01 (d, *J* =8Hz,1H), 8.60(d, *J*=8Hz,1H).8.72(S,1H),10.05(S,1H), 11.06(S,1H),^{13}C NMR (DMSOd_6 :100MHz) δ47.95, 48.32, 106.67, 111.02, 115.52, 124.05, 128.30, 131.18, 138.56, 140.23, 140.34, 150.47, 151.64, 164.77. Molecular weight 259.27g/mol, Molecular Formula: $C_{14}H_{14}FN_3O$; Elemental analysis: (C, H, N) (Cal: Obs.), (64.85, 5.44, 16.21:64.87, 5.45, 16.23).EI Ms(m/z) : 260(M+1).

N-(3-Nitro phenyl)-2-[(pyridin-3-ylmethyl) amino] acetamide 2f

Yield 59%; m.p:208-210°C; IR (KBr) : 3435, 3244, 3178, 3057, 3012, 2929, 2872, 1693, 1670, 1600, 1545, 1535, 1481, 1365, 1357, 1321, 1271,1257, 1201, 1174, 1030, 962, 937, 908, 840, 802, 707, 609 cm^{-1}; ^{1}H-NMR (DMSOd_6, 400MHz) δ 4.02 (S, 2H), 4.29 (S, 2H),7.49 (m,1H), 7.76 (d, *J* = 8.4Hz, 2H),7.95(d, J=8.4 Hz, 2H), 8.05 (d, *J* = 7.6Hz,1H), 8.61 (d, 1H), 8.74 (s, 1H), 9.84 (s,1H) 11.30 (s,1H).^{13}C NMR (DMSOd_6,100MHz) δ:45.73, 47.92, 119.03, 124.04, 128.20, 130.04, 132.70, 138.66, 142.92, 150.45, 151.67, 164.90, 197.04. Molecular weight: 286.28g/mol, Molecular formula: $C_{14}H_{14}N_4O_3$ Elemental analysis (C, H, N) (Cal: Obs.), (58.73, 4.93, 19.57:58.76, 4.91, 19.57). ESI MS (m/z): 287(m+1).

N-(4-acetyl phenyl)-2-[(pyridin-3-ylmethyl) amino] acetamide 2g.

Yield 68 %; m.p:216-218°C; IR (KBr) : 3412, 3213, 3176, 3055, 2991, 2781, 1690, 1577, 1510, 1483, 1427, 1410, 1388, 1334, 1307, 1292, 952, 918, 821, 802, 769, 729.cm^{-1};^{1}H-NMR (DMSOd_6, 400MHz) δ 2.50(S,3H), 3.82 (S,2H), 4.15 (S,2H), 7.42-7.61(m, J=8.0Hz,2Hz,1H),7.62-7.66 (m, J=8.0 Hz, 2Hz 1H) 7.87-7.90 (m, 3H),7.93-7.99 (m,1H), 82.41-8.42 (d, J=2Hz, 1H) 8.56-8.67(m, J=16Hz, 2Hz,2H),11.29 (S,1H).^{13} C NMR (DMSO d_6,100 MHz)δ: 8.9, 48.62, 49.52, 113.84, 118.74, 123.99, 125.73, 130.49, 130.81, 137.92, 139.91, 148.41, 149.93, 151.18, 166.99. Molecular weight: 283g/mol, Molecular formula: $C_{16}H_{17}N_3O_2$, Elemental analysis :(C, H, N) (Cal: Obs.),(67.83, 6.05, 14.83:67.86, 6.03, 14.85).ESI Ms(m/z):284(M+1).

N – (Benzo [*d*]thiazol-2-yl)-2-((pyridine-3-yl methyl) amino) acetamide. 5a

Yield 42%, Light yellow coloured solid , mp: 95-97 °C: IR (KBr, cm- 1):3318, 3167, 3048, 2898, 1917, 1702, 1402, 1251,1144, 958, 863, 762, 747, 712, 665; 1H NMR (400 MHz, DMSO-d6) δ : 4.20(s,2H), 4.42(s, 2H), 6.99-7.18(m, 2H), 7.29-7.45(m, 2H), 7.70-7.76(m, 1H), 7.89-7.95(m, 1H), 8.38-8.50(dd, *J*=8.8Hz 1H), 8.74-8.97(d, *J*=8.8 Hz 1H).13C NMR (75 MHz, DMSO-d6) δ : 45.39, 47.08, 121.61, 123.82, 124.80, 126.17, 129.04, 130.85, 131.34, 135.60, 142.11, 143.14, 148.17, 165.22, 172.48.Elemental analysis For C15H14N4OS: (Anal: Cal), (C, H, N) C 60.40; H 4.69; N 18.79, C 60.42; H 4.73: N 18.74.M.W=298 g/mol.

N – (4-Methyl benzo [*d*]thiazol-2-yl)-2-((pyridine-3-yl methyl) amino) acetamide. 5b

Yield 55 %, Light yellow coloured solid , mp: 146-148 °C: IR (KBr, cm-1):3320, 3172, 3051, 2896, 2855, 2724, 1691, 1598, 1564, 1479, 1408, 1286, 1262, 1146, 960, 865, 767, 749, 713, 666; 1H NMR (400 MHz, DMSO-d6) δ : 2.40(s, 3H), 4.23(s, 2H), 4.55(s, 2H), 8.09(s,2H),8.18(s, 1H),8.31(s, 1H), 8.79(s, 1H), 8.97(s, 1H), 9.17(s, 1H), 10.18(s, 1H), 10.96(s, 1H).13C NMR (75 MHz, DMSO-d6) δ : 19.06, 46.49, 47.50, 123.13, 124.94, 125.57, 126.74, 131.26, 140.26, 140.93, 143.96, 145.56, 146.54, 146.66, 164.26.Elemental analysis For C16H16N4OS: (Anal: Cal), (C, H, N) C 61.54; H 5.13; N 17.95, C 61.58; H 5.09: N 17.99M.W=312 g/mol.

N-(6-Chloro benzo [*d*]thiazol-2-yl)-2-((pyridine-3-yl methyl) amino) acetamide. 5c

Yield 45%, Light yellow coloured solid, mp: 176-178°C:IR (KBr, cm-1):3171, 3066, 2978, 1702, 1664, 1698, 1560, 1441, 1267, 1107, 812, 760; 1H NMR (400 MHz, DMSO-d6) δ:3.50(s,2H), 3.81(s, 2H), 7.32-7.40(m, 2H), 7.41-7.44(m, 1H), 7.68-7.78(m, 1H), 8.05(s,1H), 8.45(d, *J* =3.2 Hz, 1H), 8.55(s, 1H). 13C NMR (75 MHz, DMSO-d6) δ 49.69, 51.02, 121.18, 121.54, 123.21, 126.26, 127.62, 133.14, 135.35, 135.64, 147.34, 147.97, 149.36, 158.35, 171.35.Elemental analysis For C15H13N4OClS: (Anal: Cal), (C, H, N) C 61.54; H 5.13; N 17.95, C 61.58; H 5.09: N 17.99 .M.W=332 .81g/mol.

N-(4-Chloro benzo [*d*]thiazol-2-yl)-2-((pyridine-3-yl methyl) amino) acetamide. 5d

Yield 45%, Light yellow coloured solid, mp: 176-178°C: IR (KBr, cm-1):3171, 3066, 2978, 1702, 1664, 1698, 1560, 1441, 1267, 1107, 812, 760; 1H NMR (400 MHz, DMSO-d6) δ : 3.98(s, 2H), 4.04(s, 2H), 6.91-6.95(m, 1H), 7.21-7.32(m, 1H), 7.44-7.46(d, *J=8.*4 Hz, 1H),7.52-7.54(d, *J=8.4* Hz, 1H), 7.86-7.88(d, *J* = 8.0 Hz 1H) 8.41-8.42(d, *J* =4Hz, 1H), 8.51(s,1H)^{13}C NMR (75 MHz, DMSO-d6) δ: 49.64, 51.01, 119.51, 121.28, 123.22, 124.48, 125.40,126.03, 132.12, 133.06, 145.41, 149.41, 158.64, 167.27, 171.44. Elemental analysis ForC15H13N4OClS: (Anal: Cal), (C, H, N) C 61.54; H 5.13; N 17.95, C 61.51; H 5.10: N 17.92. M.W=332 .81g/mol.

N-(6-bromo benzo [*d*]thiazol-2-yl)-2-((pyridine-3-yl methyl) amino) acetamide. 5e

Yield 39 %, light brown coloured solid, mp: 185-187°C: IR (KBr,cm1): 3325, 3164, 3066, 2908, 2837, 1703, 1668, 1597, 1557, 1478, 1439, 1391, 1330, 1266, 1197,1140, 1085, 1048, 957, 896, 810, 751, 710, 639; 1H NMR (400 MHz, DMSO-d6) δ : 3.95(s, 2H), 4.73(s, 2H), 7.23-7.39(m, 2H), 7.45-7.55(m, 1H) 7.64-7.78(m, 1H), 8.15(s, 1H),8.45- 8.50(m, 1H), 8.50-8.66(m, 1H).^{13}C NMR (75 MHz, DMSO-d6) δ: 47.02, 48.19, 121.94, 123.47, 123.97, 128.93, 132.49, 133.65, 135.65, 147.64, 147.94, 148.48, 149.33, 158.31,171.34 Elemental analysis For C15H13BrN4OS: (Anal: Cal), (C, H, N) C 47.71; H 3.44; N 14.84, C 47.69; H 3.42: N 14.81.M.W=377.26 g/mol.

N-(4-methyl-6-Nitro benzo [*d*]thiazol-2-yl)-2-((pyridine-3-yl methyl) amino) acetamide 5f

Yield 59%, light brown coloured solid, mp: 195-197°C: IR (KBr, cm1):3539, 3473, 3224, 3073, 2959, 2935, 2726, 2601, 1689, 1636, 1609, 1550, 1518, 1468, 1448, 1349, 1267,1230, 1120, 1097, 1064, 980, 879, 804, 744, 680.; 1H NMR (400 MHz, DMSO-d6) δ :2.36(s,3H), 4.16(s,2H), 4.47(s,2H), 8.03(s,1H), 8.21(d, *J*= 1.6Hz, 1H),8.33(d, *J*=1.6Hz,1H), 8.67(d, *J* =6.0Hz, 1H) 8.93(s,1H), 9.07(s,1H), 10.15(s,1H), 10.99(s,1H).^{13}*C* NMR 75 MHz, DMSO-d6) δ: 19.06, 46.49, 47.50, 122.66, 124.28, 124.94, 126.50, 131.03, 139.74, 140.41, 142.83, 144.53, 146.04, 146.86, 163.68. EI MS (m/z):356.49 (m-1). Elemental analysis For C16H15N5O3S: (Anal: Cal), (C, H, N) C 47.71; H 3.44; N 14.84, C47.69; H 3.42: N 14.81. M.W=357 g/mol.

Biological Activity Screening

Antimicrobial Activity

Method: Cup-plate agar diffusion using nutrient agar.[31] Antibacterial activity of all the synthesized compounds was tested in vitro by (cup plate method) serial agar dilution in which bacterial strains of Gram negative (*Escherichia coli*, *Pseudomonas aeruginosa*) and Gram positive (*Staphylococcus aureus*, *Bacillus Subtilis*) were used, using serial agar dilution (cup plate method). The two microorganisms were cultured in petri dishes containing agar medium, (four bacterial species and one fungi) cups (8 mm) were put onto the dishes and each synthesized compound dissolved in DMF (0.1 ml of 10 mg/ml) was added into the cups under aseptic condition. Then, the petri dishes were incubated at 37^{o}C for 24 h. The zone of inhibition of the growth of the bacteria, which were produced by diffusion of the compounds from the cup into the surrounding medium, was measured to evaluate the antibacterial activity. Each experiment was repeated twice. DMF was used as a positive control for the experiments. The antimicrobial activity of tested compounds is shown in **Table-1.**

Anticancer activity

Method: MTT Assay for Anticancer activity.[32]

A549, MCF7, K562, MOLT3 and KG1 cell line cultures were purchased from National Centre for Cell Science, Pune, India. All growth media, supplements and reagents were purchased from HiMedia Labs, Mumbai, India. For the assay, cells were seeded at 10^5 cells/ml in a 96-well plate in dulbecco's modified minimum essential medium (DMEM) supplemented with 10% fetal bovine serum (FBS). To each well, test compounds were added at six different concentrations of 100µM, 50µM, 10µM, 5µM, 1µM and 0.5µM particularly for A549 and MCF7 cell line and other concentrations ranging from 50µM, 100µM, 150µM, 200µM and 250µM particularly for K562, KG1 and MOLT3 cell lines. Each concentration was tested in triplicates. The cells were incubated with these compounds at 37^{o}C under 5% CO_2 for 48 hours. Following this, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) was added to each well at a final concentration of 0.5mg/ml. Cells were incubated with this tetrazolium dye for 4 hours. Subsequently, purple crystals of formazan were observed in each well, formed as a metabolic product of MTT. These crystals were dissolved in Isopropanol and the absorbance in each well was recorded at 570nm in a microplate reader (MicrotekSigma360). Absorbance at 570nm directly correlates with cell viability. Cells were cultured and treated with DMSO and 5-Flouro Uracil and % viability was determined. Experiments were conducted in triplicate. The values represent the mean ±SD. Data are reported as IC_{50} values i.e. (concentrations of complexes required to inhibit cell viability by 50%) The IC_{50} (µM) values were determined using Graph Pad prism software. The data represent the mean values ± SEM (standard error of mean) of at least three independent experiments.

Statistical analysis

All determinations were performed at least in triplicate, means and standard deviations were determined. Discovery determined using the Two-stage linear step up procedure of Benjamin, Krieger and Yekutieli[35], with Q=1%. Each raw was analysed individually, without assuming a consistent Standard deviation (SD). The Multiple t-test statistical analysis was performed using Graph Pad PRISM® (biostatistics software version 7.0.)

CONCLUSION

In conclusion, we have reported synthesis of compounds **2a-g** and **5a-f** with good yields and screened for their antimicrobial, antifungal and anticancer activities. The compounds of series **2a-g**, two compounds namely **2c** and **2e** showed good antimicrobial activity against *S. aureus and B. Subtilis* and fungi *C. albicans* at 50µg concentration respectively. The screening of compounds **2a-g** and **5a-f** gave very promising results with IC_{50} values 0.51µM, 0.14 µM and 0.73 µM for compounds **2c**, **2d** and **5a** respectively against MOLT3 leukemia cancer cell line. In general it is also concluded that when phenyl ring of amine is substituted at 3rd position plays important role in showing antibacterial as well as antifungal activity. The structure variations such as methyl and halo groups at *meta* and *para* positions of phenyl ring bearing amide linkage resulted in promising

antibacterial and antifungal activity. Furthermore it can be concluded that the designing of amide derivatives of various aromatic amines and 2-amino benzothiazoles with 3-amino methyl pyridine gave the biologically active molecules that can lead to discovery of potential drug candidate.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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