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SYNTHESIS AND ANTICANCER ACTIVITY OF SOME NOVEL 2-AMINO THIAZOLE DERIVATIVES

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ABSTRACT

A series of 2-aminothiazoles derivatives have been synthesized and tested for their anticancer activity. All the synthesized novel compounds were screened for anticancer activity. It was also found that compounds NS1 , NS2, NS6 and NS8 showed very good anticancer activity whereas all the other compound have showed mild to moderate anticancer activity as compared to standard drug. Syntheses have been carried out following simple methodology in excellent isolated yields. The structure and purity of the original compounds were confirmed by IR, NMR, and elemental analysis. These preliminary results indicate that some of compounds are exhibiting good activity.

KEYWORDS: Thiazole, 2-Chloro-N-(thiazol-2-yl) acetamide, Synthesis, anticancer activity, Chemotherapeutic Science International.

INTRODUCTION

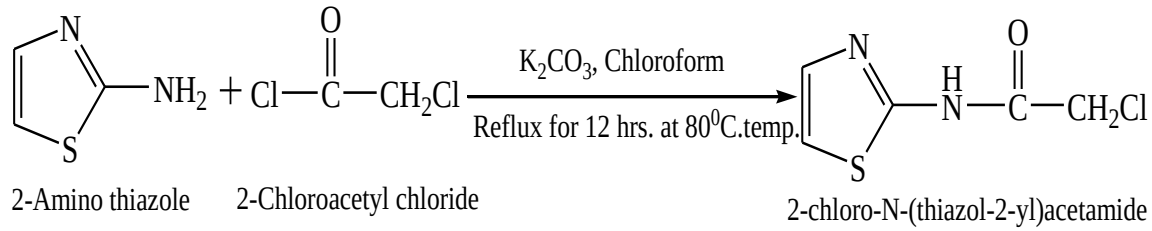
Cancer is currently second leading cause of death after cardiovascular disease. Consequently, there is great unmet medical need for new anticancer small molecule therapeutics. A tumour is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissue and continues in the same manner after cessation of the stimuli which have initiated it. The past two decades have witnessed a remarkable revolution in the field of tumour chemotherapy. Wealth of basic knowledge with regard to molecular and cellular biology, better understanding of mechanism of cellular division, tumour immunology and detailed information of fundamental factors involved in both viral and chemical carcinogenesis and the improved investigative techniques have ultimately led to the introduction of a substantial number of newer antineoplastic agents. On the basis of exhaustive literature review, it has been found that 2-aminothiazole have good potential to exhibit anticancer activity. So, it was decided to synthesize some novel 2-aminothiazole derivative to evaluate their anticancer activity.[1]

Thiazole derivatives are an important class of heterocyclic compounds. They occupy an important position in medicinal chemistry, presenting a wide range of bioactivities. As medicines, many of them display including antibacterial & antifungal.[1,2] anti-HIV,[3] hypertension,[4] anti-inflammatory,[5] anticancer,[6] anti-convulsant,[7] antidepressant and tubercular activities.[8] Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities. Thiazole, particularly the 2-amino thiazole nucleus have been incorporated into a wide variety of therapeutically interesting candidates.

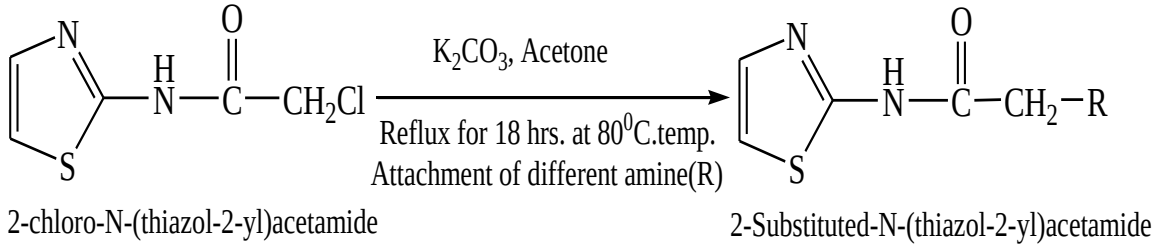
Recent studies have shown the synthesis of some new thiazole candidates as adenosine receptor antagonists and more recently 2-aminothiazole analogues reported as potential neuroprotective agents for the treatment of neurological diseases and modulators of transcriptional repression for treatment of Huntington's disease.

Prompted by the observed biological activities of the above mentioned derivatives and in continuation of our ongoing studies on novel biologically active molecules, we have designed and synthesized some novel 2-aminothiazoles derivatives as potential anticancer agents.

Experimental Section
1. Synthetic Scheme
Synthetic Scheme
STEP-1



STEP-2



Procedure for synthesis[8-10]

(A). Procedure for the synthesis of intermediate Compound 2-Chloro-N-(thiazol-2yl) acetamide (NS)

Accurately weighed, 10.0gm (0.1mole) 2-Amino thiazole was dissolved in 75 ml of chloroform in a 500 ml two neck round bottom flask. To this solution 13.82 gm (0.1mol) of anhydrous potassium carbonate was added and placed on water bath for reflux. A dropping funnel was fitted to the RBF and in the dropping funnel a solution of 8.06ml (0.1mol) of chloroacetylchloride in chloroform was taken. A very slow drop wise addition of chloroacetylchloride solution was done. The reaction mixture was refluxed in a water bath at 80^0C for 12 hours. After 12 hours, Excess of solvent and chloroacetyl chlorides was removed by distillation under residue pressure and the residue was washed with aqueous sodium bicarbonate (5% w/v, 30 ml) and subsequently with cold water (50 ml). The crude product was dried and on recrystallisation from ethanol afforded white crystalline solid 2-Chloro-N-(thiazol-2yl) acetamide.

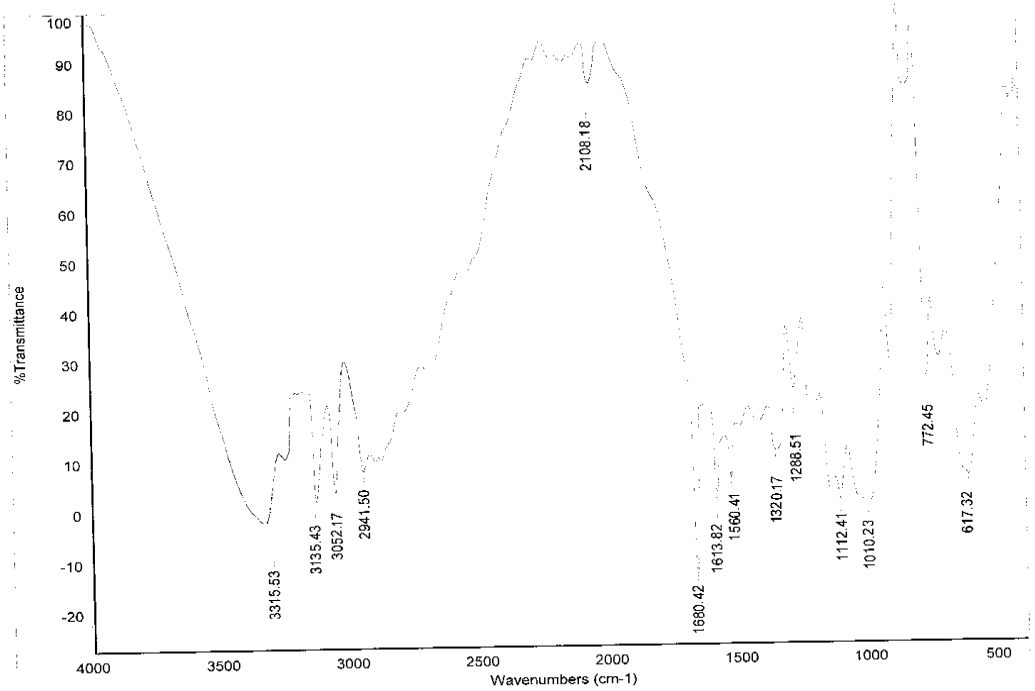
Table 2: Physical Constant of Different Synthesized Compounds.

S.NO.	Code	R	Molecular Formula	Melting point* (±2ºC)	% Yield	●Rf Value
1.	NS-1	Pyrrolidine	$C_9H_{13}N_3OS$	125	65	0.64
2.	NS-2	Morpholine	$C_9H_{13}N_3O_2S$	105	50	0.52
3.	NS-3	Piperazine	$C_9H_{14}N_4OS$	118	47	0.60
4.	NS-4	Imidazole	$C_8H_8N_4OS$	155	52	0.57
5.	NS-5	N-Methylpiprazine	$C_{10}H_{16}N_4OS$	180	48	0.51
6.	NS-6	N-Ethylpiperazine	$C_{11}H_{18}N_4OS$	200	50	0.59
7.	NS-7	N-Phenylpiperazine	$C_{15}H_{18}N_4OS$	170	52	0.55
8.	NS-8	2-Methylimidazole	$C_9H_{10}N_4OS$	130	42	0.53

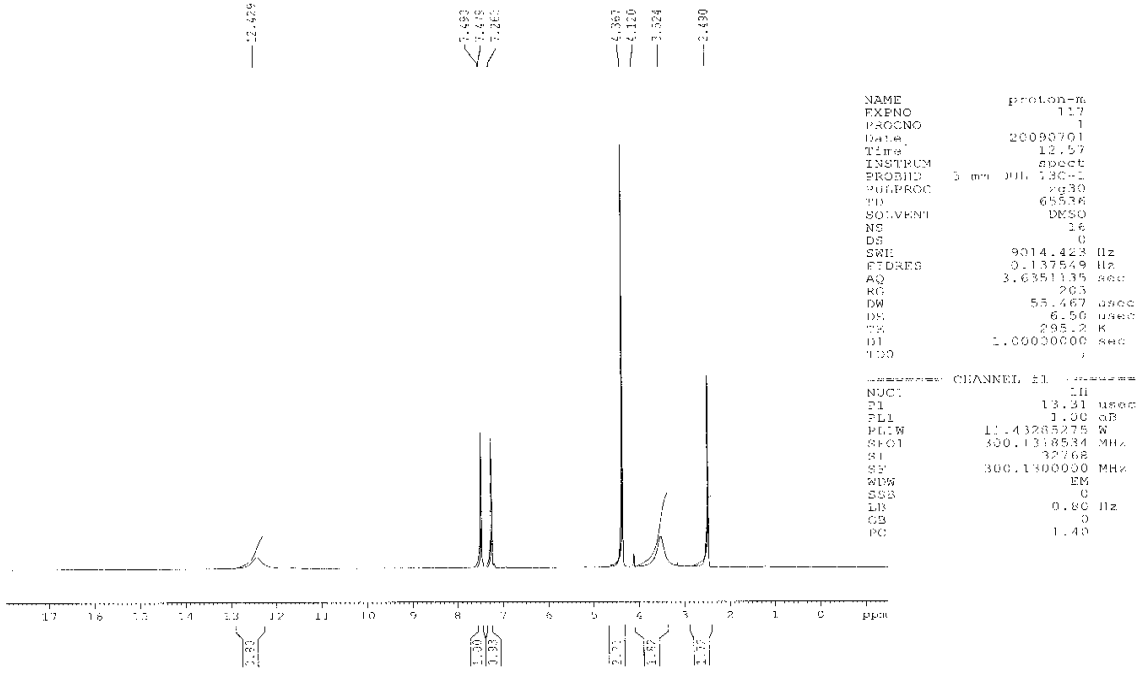
Spectral data of intermediate Compound

Obtained as white crystals, Yield 85.0%; mp 172ºC, IR (KBr, cm-1) : 3315(N-H str.), 2900- 3052(Aliphatic &ArC-H str.), 1680(C=O str), 1560(C=C str.), 745(N-Cl str.), 617(ArC-S str.); The 1HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 12.42 (1H,Ar-NH), 4.36(2H,C=O-CH_2),

IR Spectral Data



NMR Spectral Data



General procedure for the synthesis of 2-Substituted-N-(thiazol-2-yl)acetamide derivatives (NS 1-8)

A mixture of 2-Chloro-N-(thiazol-2yl) acetamide (NS) (0.006mol) with different amines and K_2CO_3 (0.012mol) in acetone (100 mL) was refluxed for 15-20 hrs. After 16 Hrs, The solvent was removed by vacuum distillation and the residue was treated with sodium bicarbonate (5%w/v) to remove acid impurities. The residue was washed with water, dried and on recrystallisation from ethanol afforded 2- Substituted - N- (thiazol-2-yl) acetamide derivatives (NS1-8).

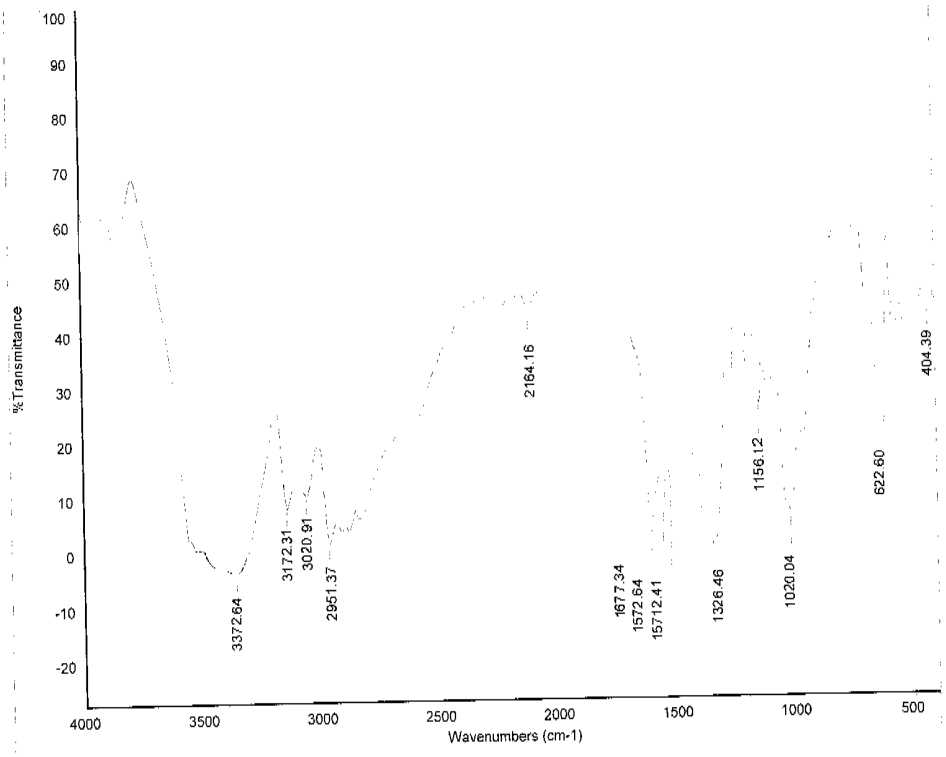
Spectral Data of Different Derivatives

Synthesis of 2-(Pyrrolidin-1-yl)-N-(thiazol-2-yl) acetamide (NS-1)

Yield 65.0%; mp 125ºC, IR (KBr, cm-1) : 3372(N-H str.), 2951-3020(Aliphatic &ArC-H str.), 1677 (C=O str), 1572(C=C str.), 1326.46(C-N str.),622(ArC-S str.);The 1HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-

CH), 6-7 (1H,ArS-CH), 8.47 (1H,Ar-NH), 3.27(2H,C=OCH_2), 2.32(4H, -CH_2).

IR Spectral Data



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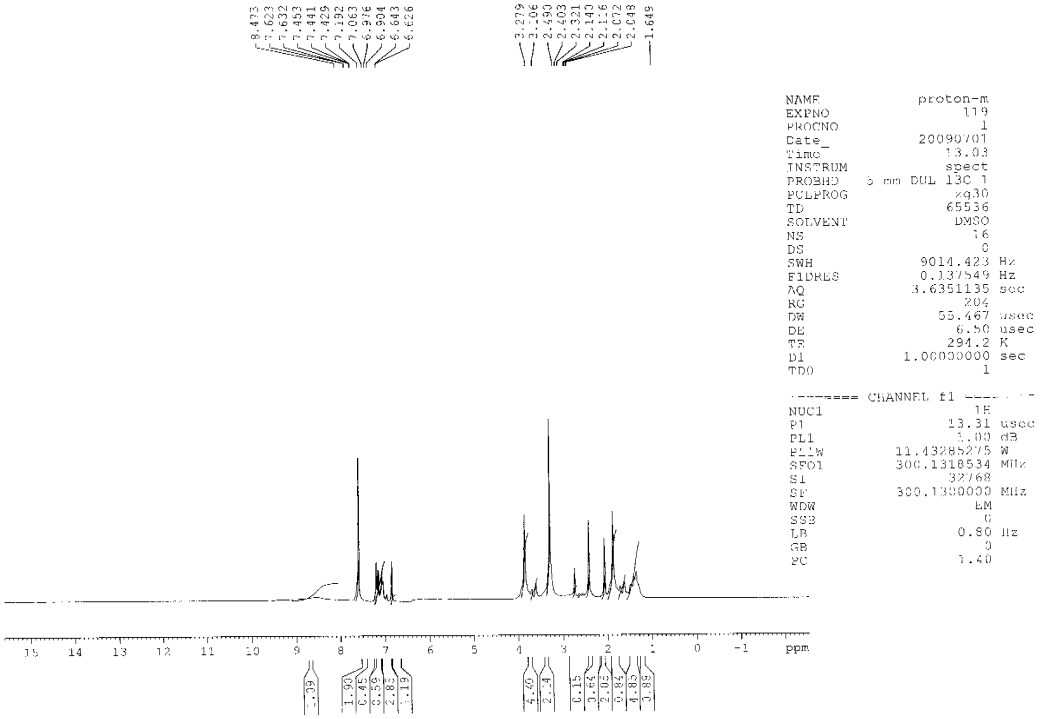
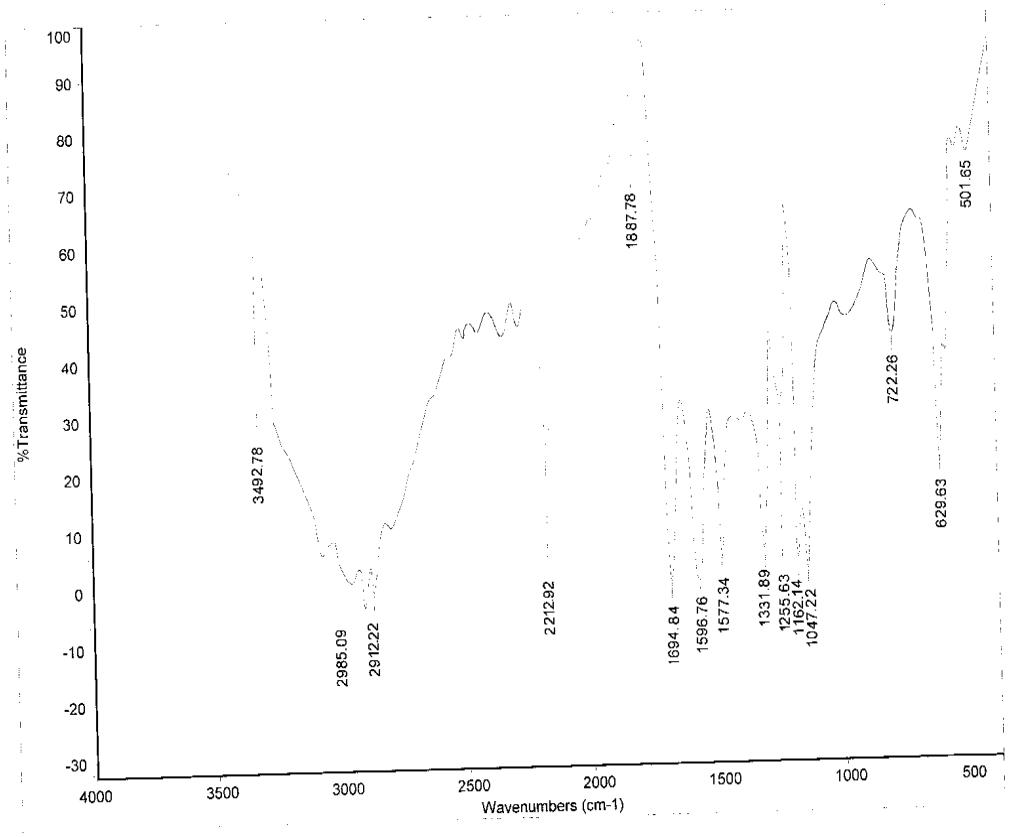


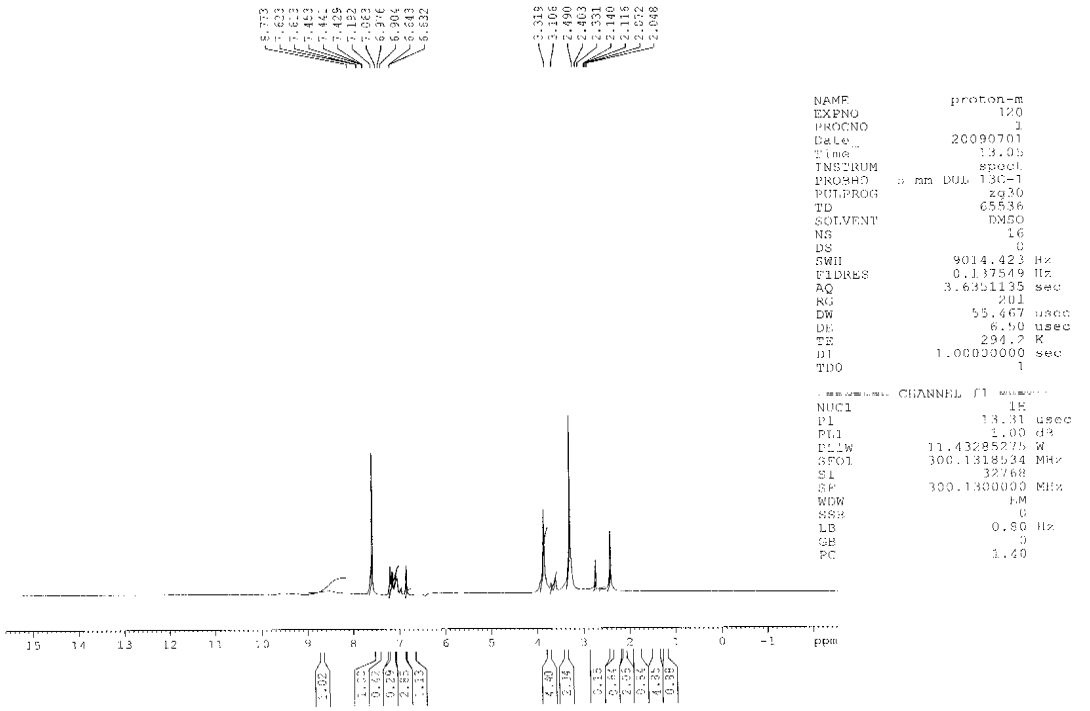
Synthesis of 2-Morpholino-N-(thiazol-2-yl) acetamide (NS-2)

Yield 50.0%; mp 105ºC, IR (KBr, cm-1) : 3492(N-H str.), 2912-2955(Aliphatic &ArC-H str.), 1694 (C=O str), 1577(C=C str.), 1331(C-N str.),629(ArC-S str.); The 1HNMR(δ, ppm): (DMSO*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 8.77 (1H,Ar-NH), 3.37(2H,C=O-CH_2), 3.84(4H, -CH_2).

IR Spectral Data



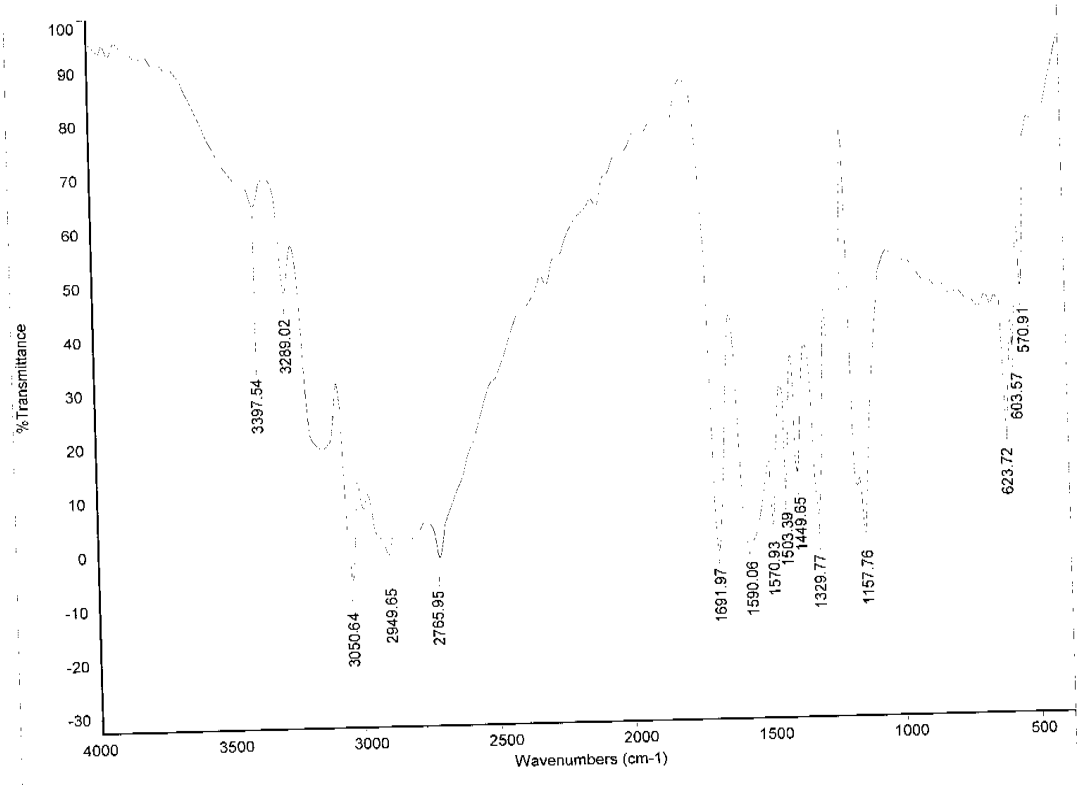
NMR Spectral Data



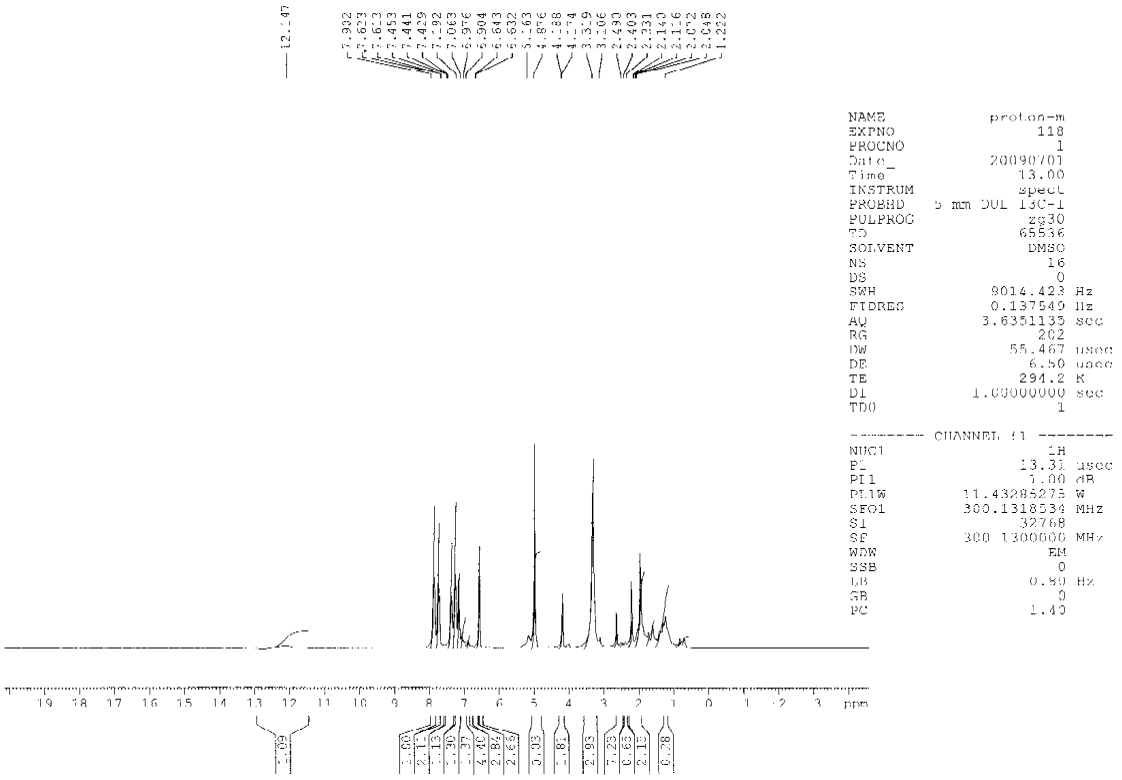
Synthesis of 2-(Piperazin-1-yl)-N-(thiazol-2-yl) acetamide (NS-3)

Yield 47.0%; mp 118ºC, IR (KBr, cm-1) : 3397(N-H str.), 2949-3050(Aliphatic &ArC-H str.), 1691 (C=O str), 1570(C=C str.), 1329(C-N str.),623(ArC-S str.); The 1HNMR(δ, ppm): (DMSO*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 12.14 (1H,Ar-NH), 4.18 (-NH in piperazine), 3.30(2H,C=O-CH_2), 2-3(4H, -CH_2).

IR Spectral Data



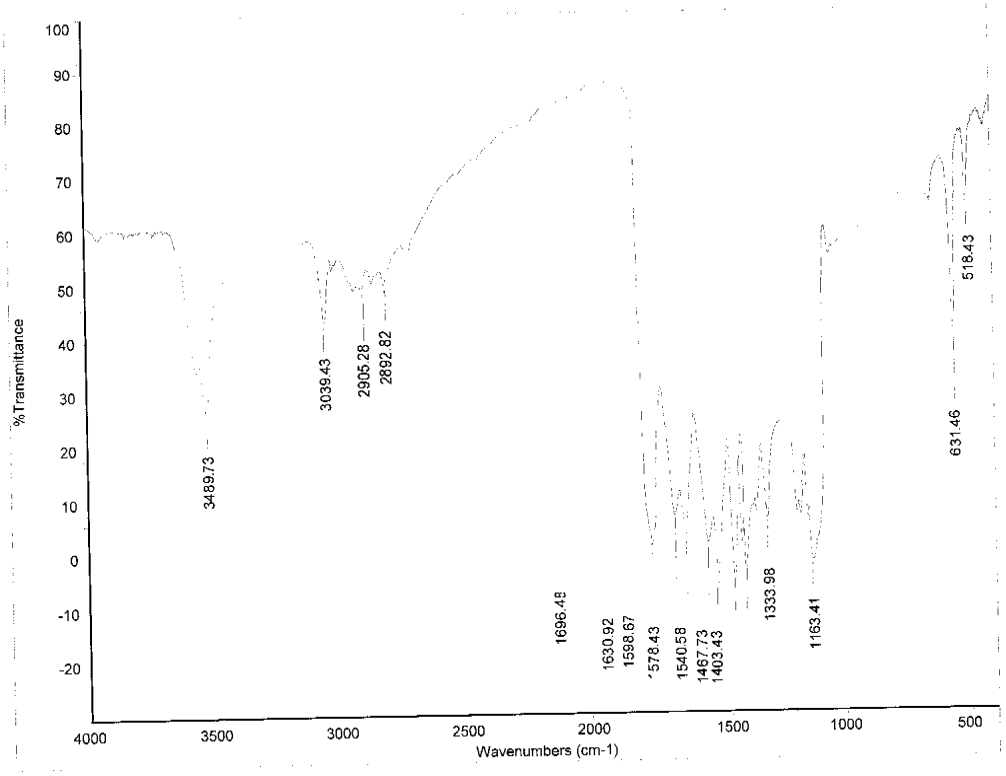
NMR Spectral Data



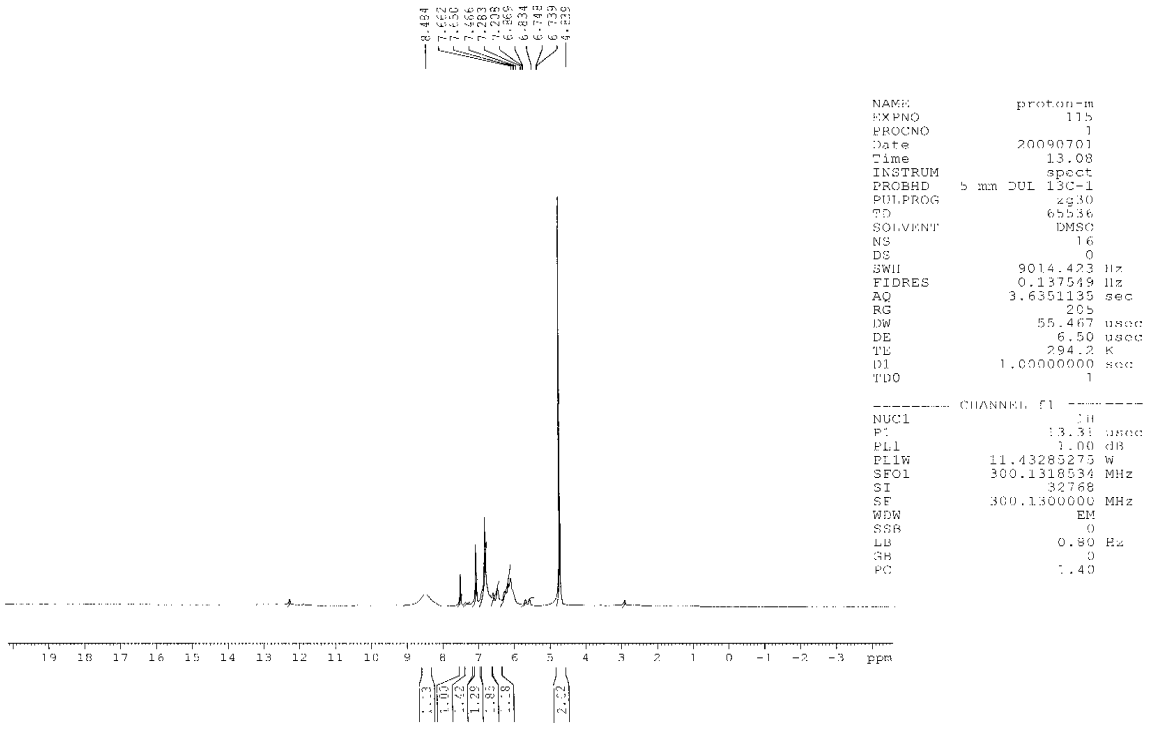
Synthesis of 2-(1H-Imidazol-1-yl)-N-(thiazol-2-yl) acetamide (NS-4)

Yield 52.0%; mp 155ºC, IR (KBr, cm-1) : 3489(N-H str.), 2905-3039(Aliphatic &ArC-H str.), 1696 (C=O str), 1578(C=C str.), 1333(C-N str.),631(ArC-S str.); The 1HNMR(δ, ppm): (DMSO*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 8.48 (1H,Ar-NH), 6-8 (imidazole ring), 4.83(2H,C=O-CH_2), 2-3(4H, -CH_2).

IR Spectral Data



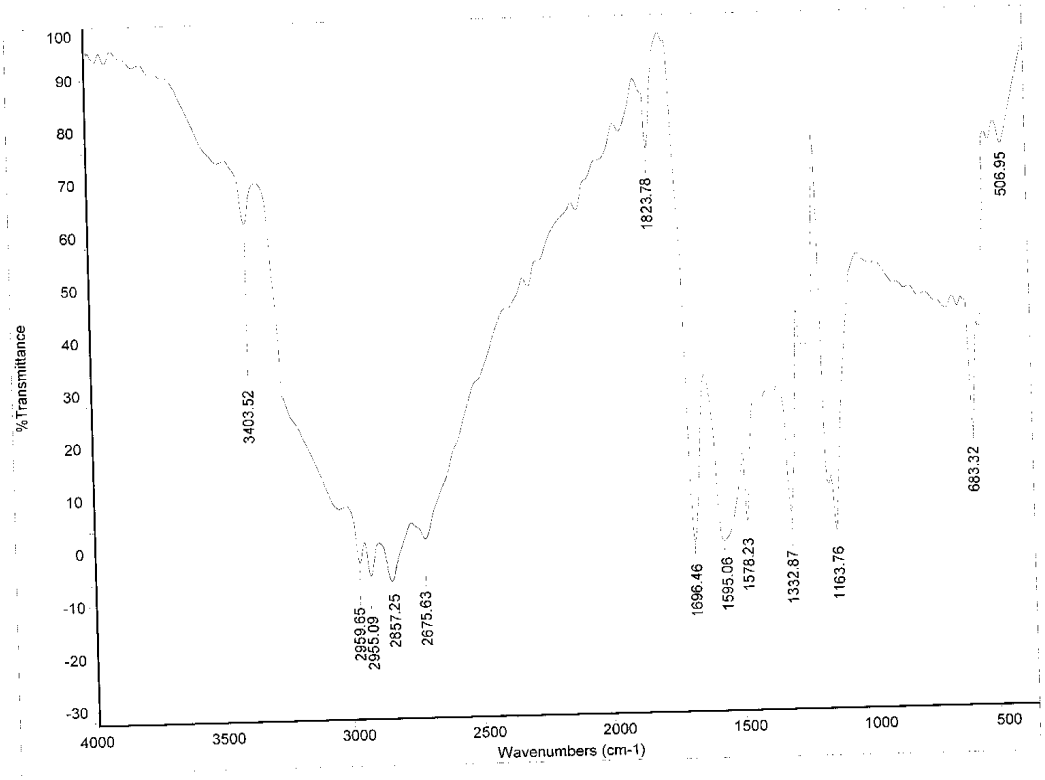
NMR Spectral Data



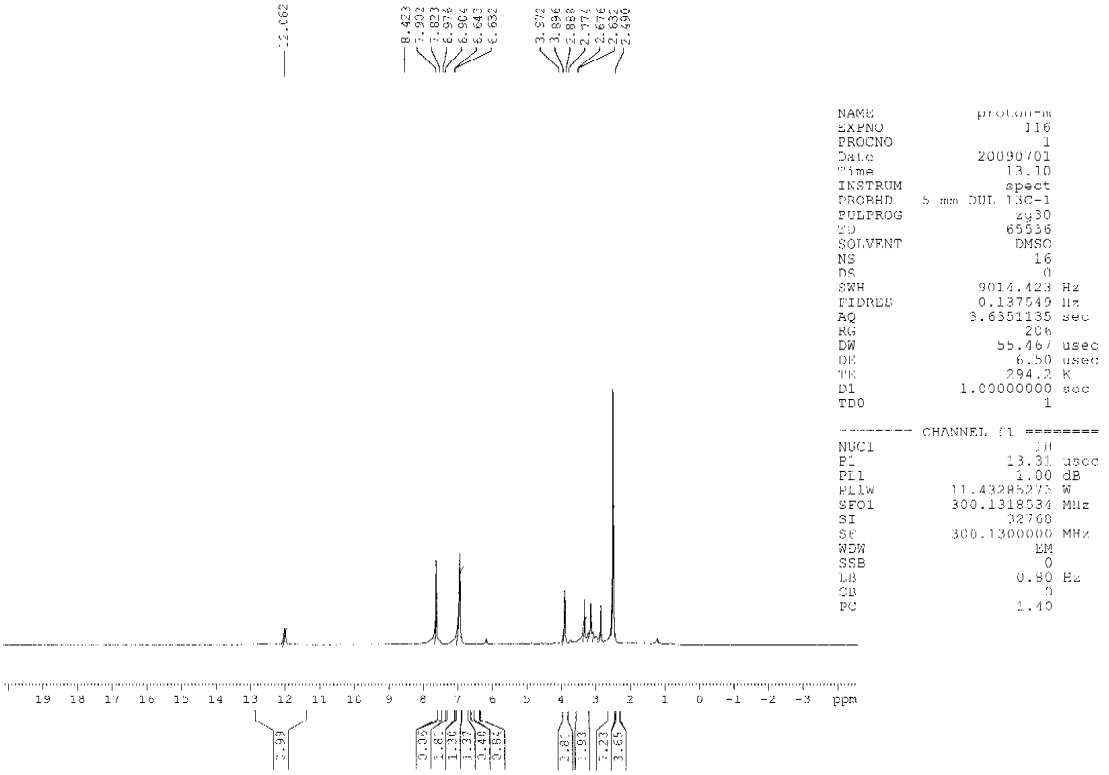
Synthesis of 2-(4-Methylpiperazin-1-yl)-N-(thiazol-2-yl) acetamide (NS-5)

Yield 42.0%; mp 130ºC, IR (KBr, cm-1) : 3403(N-H str.), 2955-2959(Aliphatic &ArC-H str.), 1696 (C=O str), 1578(C=C str.), 1332(C-N str.),683(ArC-S str.); The 1HNMR(δ, ppm): (DMSO*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 12.06 (1H,Ar-NH), 3.97(2H,C=O-CH_2), 2- 3(8H, -CH_2), 2.49 (-CH_3 attached to piperazine ring).

IR Spectral Data



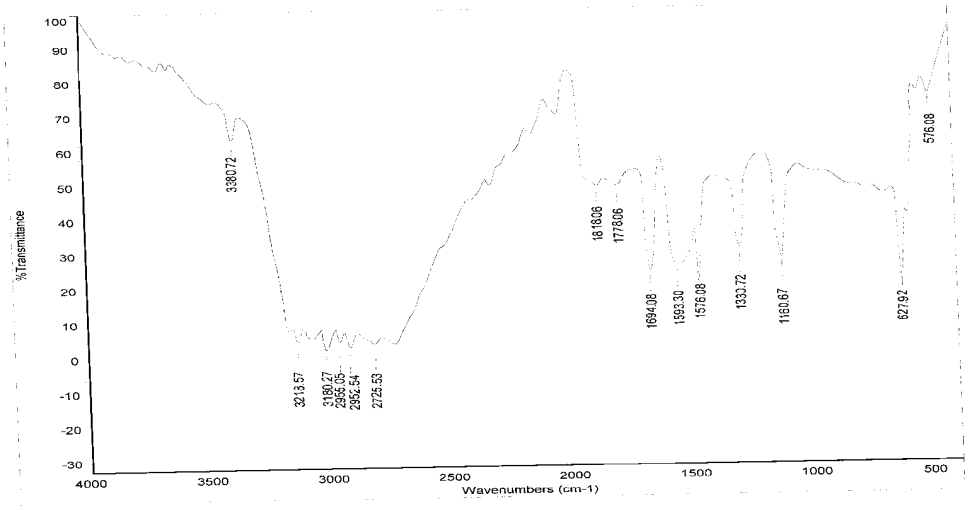
NMR Spectral Data



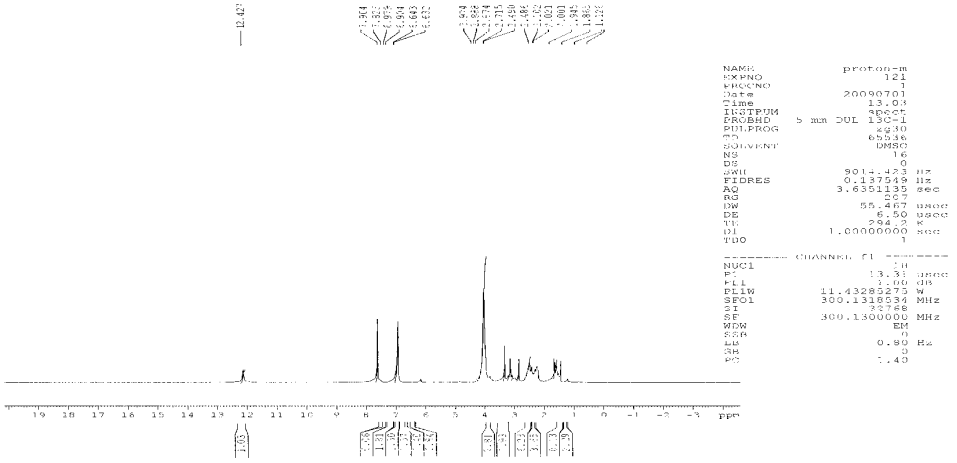
Synthesis of 2-(4-Ethylpiperazin-1-yl)-N-(thiazol-2-yl) acetamide (NS-6)

Yield 50.0%; mp 200ºC, IR (KBr, cm-1) : 3380(N-H str.), 2952-3180(Aliphatic &ArC-H str.), 1694(C=O str), 1576(C=C str.), 1330(C-N str.),627(ArC-S str.); The 1HNMR(δ, ppm): (DMSO*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 12.47 (1H,Ar-NH), 3.97(2H,C=O-CH_2), 2- 3(8H, -CH_2), 2-3 (2H,-CH_2 attached to piperazine ring).

IR Spectral Data



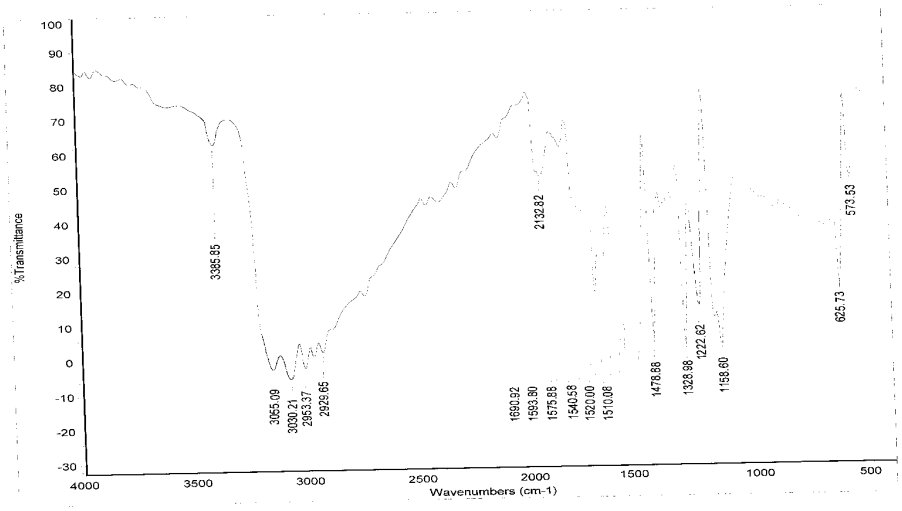
NMR Spectral Data



Synthesis of 2-(4-Phenylpiperazin-1-yl)-N-(thiazol-2-yl) acetamide (NS-7)

Yield 52.0%; mp 170ºC, IR (KBr, cm-1) : 3385(N-H str.), 2953-3065(Aliphatic &ArC-H str.), 1690(C=O str), 1575(C=C str.), 1328(C-N str.),625(ArC-S str.); The 1HNMR(δ, ppm): (DMSO*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 12.14 (1H,Ar-NH), 3.31(2H,C=O-CH_2), 2- 3(8H, -CH_2), 6-8 (5H, phenyl ring attached to piperazine ring).

IR Spectral Data



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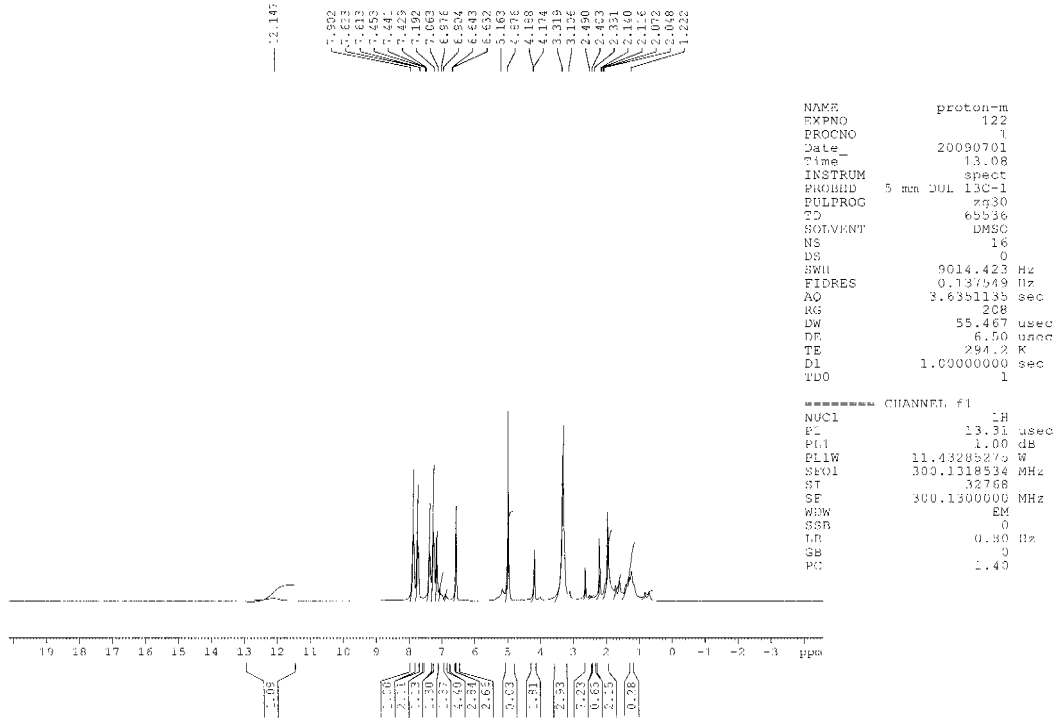
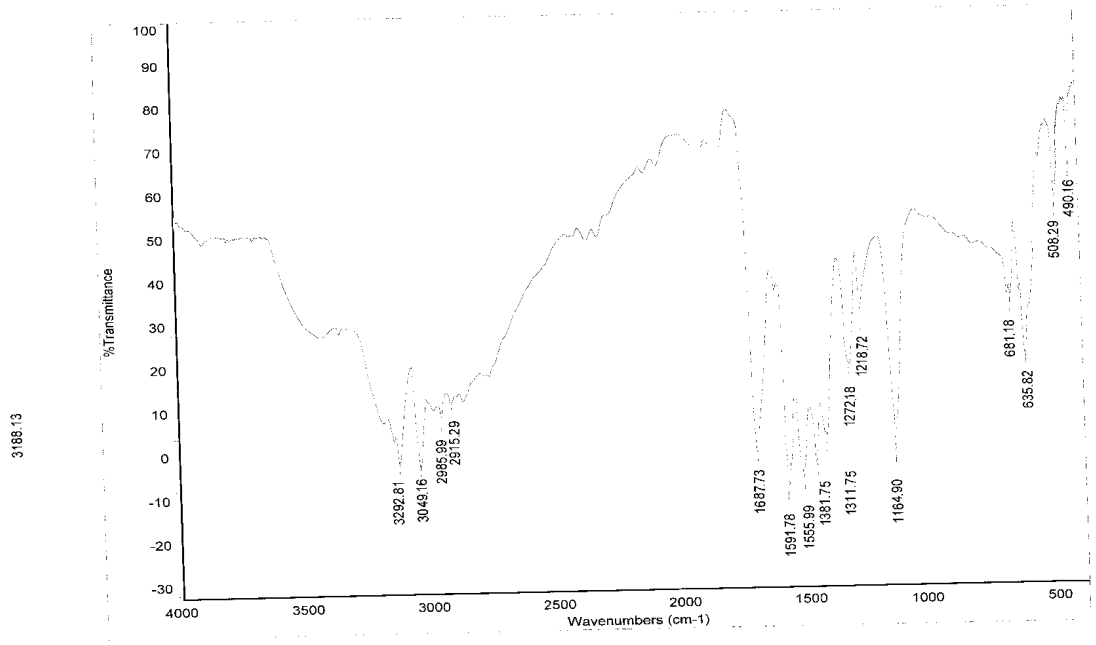


Synthesis of 2-(2-Methyl-1H-imidazol-1-yl)-N-(thiazol-2-yl) acetamide (NS-8)

Yield 52.0%; mp 170ºC, IR (KBr, cm-1) : 3292(N-H str.), 2915-3049(Aliphatic &Ar C-H str.), 1687(C=O str), 1592(C=C str.), 1331(C-N str.),635(ArC-S str.); The 1HNMR(δ, ppm): (DMSO*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 8.13 (1H,Ar-NH), 4.61 (2H,C=O-CH_2), 6-7 (2H, imidazole ring), 2.48 (3H, -CH_3 attached to imidazole ring).

IR Spectral Data



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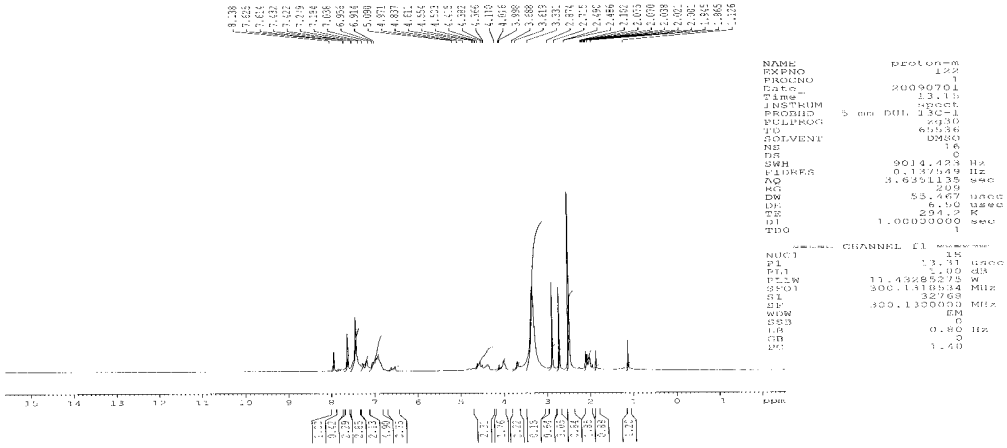

2. Anticancer Activities [1, 2].

Method

Three different human cancer cell lines, A-549, Bel7402 and HCT-8, were obtained from the Amala Cancer Research Centre, Trissur, Kerala, India and cultured on RPMI1640 medium at 37^0C in a humidified atmosphere with 5% CO_2 for 24 h. All cells to be tested in the following assays had a passage number of 3–6. For the drug treatment experiments, the cancer cells were treated with the compounds (predissolved in DMSO) at 5μg/mL for a period of three days. At the end of the drug treatment period, MTT (2-(4-Ethylpiperazin-1-yl)-N-(thiazol-2-yl) acetamide) solution (150μL, 0.5 mg/mL) in PBS (PBS without MTT as the blank) was fed to each well of the culture plate. After 4 h incubation, the formazan crystal formed in the well was dissolved with 150μL of DMSO for optical density reading at 544 nm.

Table 1: The anticancer activity of title compounds at 5 μg/mL (%, inhibitory).

S.NO.	Compound Code	A-549	Bel7402	HCT-8
1.	NS-1	35	18	6
2.	NS-2	34	16	13
3.	NS-3	-4	12	-7
4.	NS-4	-17	14	44
5.	NS-5	25	20	4
6.	NS-6	50	7	24
7.	NS-7	23	10	6
8.	NS-8	45	18	4
9.	5-Fluorouracil	**55**	**75**	**80**

RESULT

The anticancer results of title compounds are listed in Table 1, 5-fluorouracil was used as controls. As shown in Table 1, some of the title compounds showed good inhibitory against A-549 at a concentration of 5μg/mL, such as compound NS-1 (35%), NS-2 (34%), NS-6 (50%) and NS-8 (45%), which is a little lower than that of control, while some of them exhibited low activity against A-549. Furthermore, compound NS-3 and NS-4 can increase the A-549 cell growth. All the title compounds exhibited no inhibition or low inhibitor effect against Bel7402 and HCT-8. Only compound NS-4 **(**44%) displayed moderate inhibitory against HCT-8.

Melting Points were determined in open capillary method and are corrected. IR spectra were recorded on Perkinelmer FTIR-spectrophotometer using KBr disc method. The 1H-NMR spectra were recorded on sophisticated multinuclear FT-NMR spectrometer model Avance-II (Bruker) using dimethylsulphoxide-d6 as solvent and tetramethylsilane as internal standard.

RESULTS AND DISCUSSION

Literature review reveal that thiazole derivatives could be used as a template for the development and designing of more potent therapeutic agents through modification or derivatization. These finding suggested that derivatives of thiazole possess different type of biological activities including antibacterial, antifungal, anticancer, anti-inflammatory, antidepressant, antipsychotics and antipyretic activity.[11-14]

Thus eight different derivatives of 2-aminothiazole were synthesized. The synthesis of 2-chloro- N-(thiazol-2-yl) acetamide (NS) was accomplished by reacting 2-amino thiazole and Chloro acetyl chloride in the presence of potassium carbonate in chloroform. The 2-chloro-N-(thiazol-2-yl) acetamide (NS) was reacted with various substituted amines in the presence of K_2CO_3 in acetone

afforded various derivatives viz, NS-1, NS-2, NS-3, NS-4, NS-5, NS-6, NS- 7& NS-8.Yields obtained from 42% to 65%. The structures of these compounds were established on the basis of IR spectral analysis and 1H-NMR spectral studies.

The purity and homogeneity of all compounds were confirmed by their sharp melting point and TLC. All the above result positively confirmed the formation of the synthesized compounds and hence correctness of the anticipated structures drawn for synthesized compounds. All the synthesized compounds have been tested for anticancer. The compounds showed mild to good anticancer activity.

CONCLUSION

Present study reports synthesis of novel 2-aminothiazole derivatives viz, NS-1, NS-2, NS-3, NS- 4, NS-5, NS-6, NS-7 and NS-8 which are synthesized according to scheme and the identity of the compounds were confirmed on the basis of their sharp melting point, TLC, IR and 1H-NMR data.

All the synthesized compounds have been tested for anticancer activity. These compounds showed mild to good anticancer activity. The compound NS-1 (35%), NS-2 (34%), NS-6 (50%) and NS-8 (45%) showed potent anticancer activity.

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