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Synthesis of Newer Substituted of Thiazoles Analogues and Study for Anticancer Activity

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Abstract— *A novel series of thiazole were designed and prepared via the reaction of the 4-(naphthalene-5-yl) semicarbazide of appropriate different aldehydes groups (ArCHO) was added and contained in a round bottom flask. Thiazole compounds are selected for 3 Compound (**3a, 3c & 3f**) were evaluated for their anticancer activity in one dose assay and showed moderate activity on various cell lines. Compound **5-(4-nitroyphenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3c)** showed maximum activity with growth percent (GP) of 58.13 on SR (Leukemia), 75.57 on NCI-H522 (Non-Small Cell Lung Cancer A549/ATCC) and mean growth percent (GP) of 94.11. And Compound **5-(3,4,5-trimethoxyphenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3f)** showed maximum activity with growth percent (GP) of 68.75 on T-47D (Breast Cancer), 64.16 on NCI-H522 (Non-Small Cell Lung Cancer A549/ATCC), 85.74 on SNB-75 (CNS Cancer) and mean growth percent (GP) of 91.22.*

Keywords— thiazole; structure activity relationship anticancer activity;.

I. Introduction

Cancer is a serious and life-threatening disease and has been a major health problem for decades. The administration of chemotherapy is still considered an important part of cancer treatment, but is often limited by the severity of the disease and the growth of tumor cell resistance to cytotoxic drugs. Using high doses of immunosuppressive drugs to overcome resistance can lead to serious diseases (11). Therefore, there is an urgent need to develop new vaccines and strategies.

It is reported that liver cancer is among the top 10 cancers in the world and its mortality rate is among the top 5 cancers (2, 4). Research reports have shown interest in the synthesis of functional thiazole derivatives due to their high antibacterial properties [6], antibacterial properties [7], antibacterial properties [6,] and anti-inflammatory drugs [9], among others.], antioxidants [8], antituberculosis agents [10] and anticancer agents [11-14]. The thiazole derivatives have attracted widespread attention due to their wide range of activities such as antibacterial, antifungal, antiviral, anti-hepatitis B, anti-inflammatory, anti-inflammatory, antibacterial and antiviral, CNS depressant, antioxidant, anti-

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inflammatory, and anti-inflammatory. Antidiabetic, mollusk, antihypertensive. It has diuretic, analgesic, antibacterial, ant tuberculosis, anticonvulsant and anticancer activity [17-24].

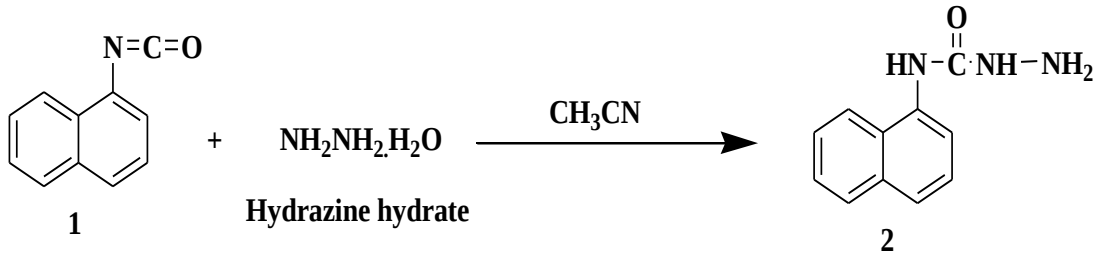
II. Experimental

GENERAL METHOD OF SYNTHESIS OF THIAZOLE

Step-I General method for the synthesis of 4-(naphthalene-5-yl) semicarbazide:-

To a solution of hydrazine hydrate (0.2mol, 10ml) in Acetonitrile (0.76mol, 40ml) were contained in a round bottom flask for 15min. with stirring and added in drop wise 1-naphthylisocyanate (0.6mol, 10gm) in cold condition for 40min. on a sand bath with vigorous stirring. The reaction was monitored by TLC using chloroform: methanol (9:1) as mobile phase. The reaction mixture was filtered under vacuum to remove solid 4-(naphthalene-5-yl) semicarbazide (2). The solid thus obtained was washed with methanol, dried and used for next step.

General reaction



Step-II General method for the synthesis of 5-(substituted phenyl)-N-(naphthalen-5-yl)-1, 3-thiazol-2-amine analogues (3a-3f):

To a mixture solid of 4-(naphthalene-5-yl) semicarbazide (0.02mol, 410mg) in 15-25ml of Dimethyl sulphoxide (DMSO), equimolar quantity of appropriate aldehydes (ArCHO) was added and 1-2ml of Sodium bisulphate, contained in a round bottom flask. The solution was refluxed for 28-30 hr on sand bath with vigorous stirring. The reaction solution when cooled and then poured into cursed ice. The resultant precipitate was filtered, solid thus obtained then washed and crystallized with cold water.

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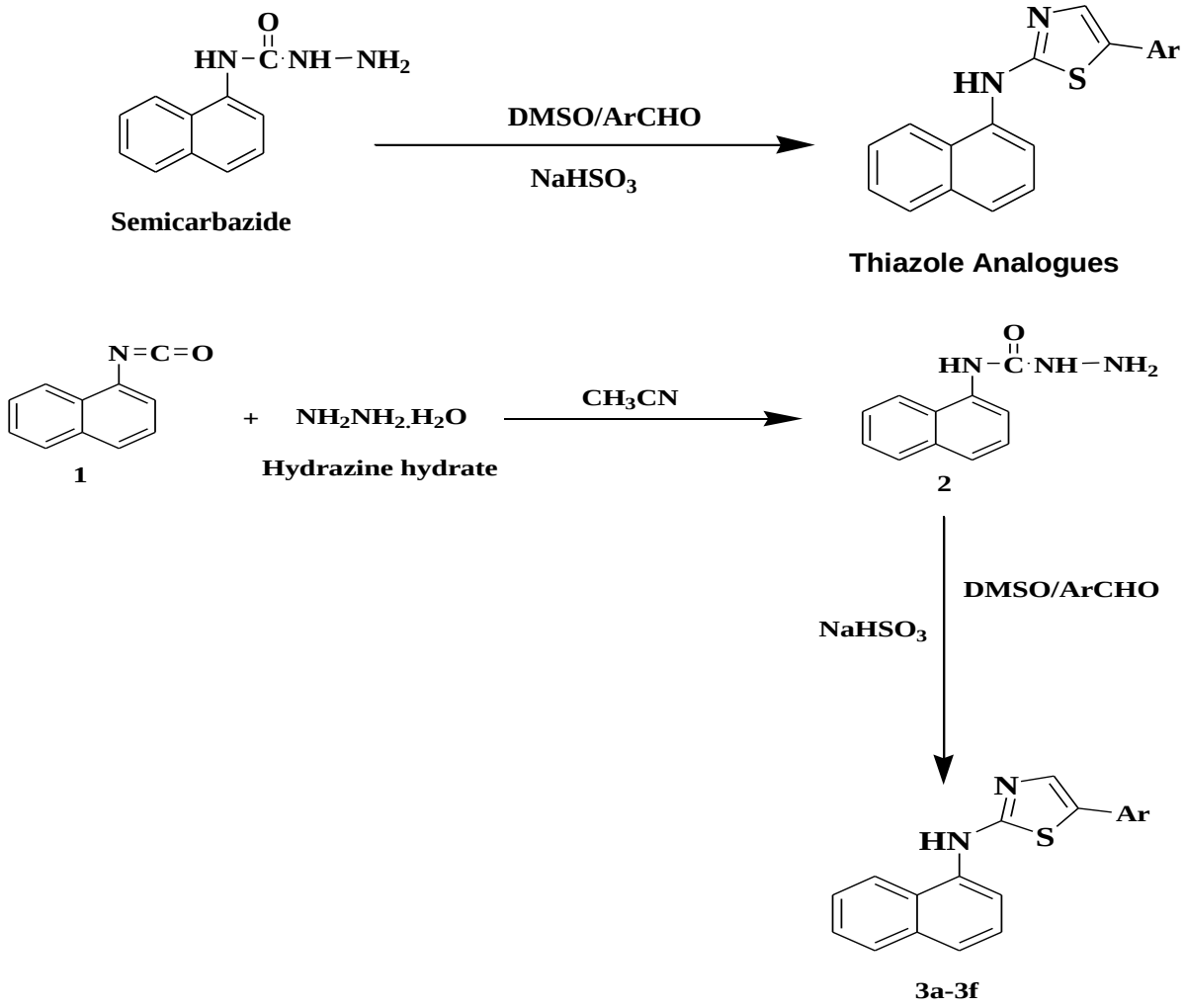
General reaction



Scheme: Protocol for synthesis of thiazole analogues (3a- 3f):-

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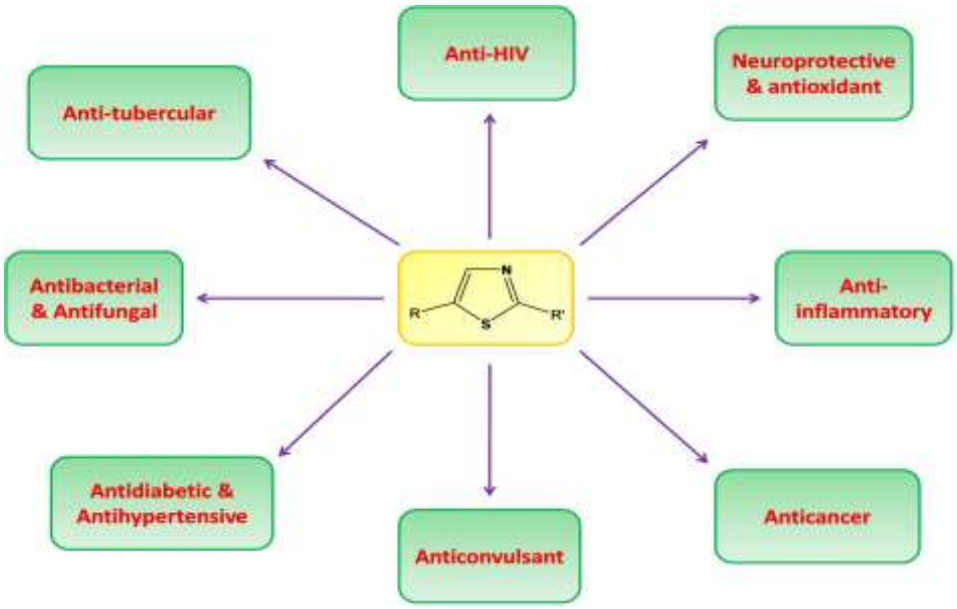

Fig. Biological activity of Thiazole Moiety.

III. Chemistry of Thiazole

5-(4-chlorophenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3a) Compound:

To a mixture solid of 5-(4-chlorophenyl)-N-(naphthalen-5-yl) semicarbazide (0.03mol, 430mg) in 15-25ml of Dimethyl sulphoxide (DMSO), equimolar quantity of appropriate aldehydes (ArCHO) was added and 1-2ml of Sodium bisulphate, contained in a round bottom flask. The solution was refluxed for 38-40 hr on sand bath with vigorous stirring. The reaction solution when cooled and then poured into cursed ice. The resultant precipitate was filtered, solid thus obtained then washed and crystallized with cold water.

Spectral data ^{1}H NMR (400 MHz, DMSO-d6): δ 12.16 (S, NH), 7.61 (S, CH), δ 6.9 (d, 2H, Ar-H, C4, C5-thiazole), δ 7.57 (m, Ar-H, C2, C6) δ 7.58 (m, Ar-H, C3, C5) δ 3.7(S, OCH3) IR (KBr, cm^{-1}): 3278 (OH, Stretch), 3078 (CH, Stretch, Aromatic), 2919 (CH, Stretch, Asymmetric, Aliphatic), 2718 (CH, Stretch, Symmetric, Aliphatic), 1751 (C=O, Stretch), 1603 (C=C, Stretch, Aromatic), 1541, 1454 (C=C, Stretch, Aromatic), 1443, 1382, 1224 (C-O, Stretch), 849. MS (*m/z*): 205 (100, M^{+}), 175 (22), 144 (30), 159 (95), 135(75), 95 (40), 48 (38).

5-(4-methoxyphenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3b) Compound:

To a mixture solid of 5-(4-methoxyphenyl)-N-(naphthalen-5-yl) semicarbazide (0.02mol, 400mg) in 15-25ml of Dimethyl sulphoxide (DMSO), equimolar quantity of appropriate aldehydes (ArCHO) was added and 2-4ml of Sodium bisulphate, contained in a round bottom flask. The solution was refluxed for 22-30 hr on sand bath with vigorous stirring. The reaction solution when cooled and then poured into cursed ice. The resultant precipitate was filtered, solid thus obtained then washed and crystallized with cold water.

Spectral data ^{1}H NMR (400 MHz, DMSO-d6): δ 11.18 (S, NH), 6.81 (S, CH), δ 5.9 (d, 2H, Ar-H, C_4, C_5-thiazole), δ 7.70 (m, Ar-H, C_2, C_6) δ 7.88 (m, Ar-H, C_3, C_5) δ 4.7(S, OCH_3) IR (KBr, cm^{-1}): 3278 (OH, Stretch), 3078 (CH, Stretch, Aromatic), 2919 (CH, Stretch, Asymmetric, Aliphatic), 2818 (CH, Stretch, Symmetric, Aliphatic), 1741 (C=O, Stretch), 1603 (C=C, Stretch, Aromatic), 1541, 1454 (C=C, Stretch, Aromatic), 1413, 1342, 1274 (C-O, Stretch), 819. MS (*m/z*): 205 (100, M^+), 185 (22), 124 (30), 129 (95), 125(75), 91 (40), 58 (38)..

5-(4-nitroyphenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3c) Compound:

To a mixture solid of 5-(4-nitrophenyl)-N-(naphthalen-5-yl) semicarbazide (0.03mol, 420mg) in 25-30ml of Dimethyl sulphoxide (DMSO), equimolar quantity of appropriate aldehydes (ArCHO) was added and 2-4ml of Sodium bisulphate, contained in a round bottom flask. The solution was refluxed for 32-35 hr on sand bath with vigorous stirring. The reaction solution when cooled and then poured into cursed ice. The resultant precipitate was filtered, solid thus obtained then washed and crystallized with cold water.

Spectral data ^{1}H NMR (400 MHz, DMSO-d6): δ 11.18 (S, NH), 6.81 (S, CH), δ 5.9 (d, 2H, Ar-H, C_4, C_5-thiazole), δ 7.70 (m, Ar-H, C_2, C_6) δ 7.88 (m, Ar-H, C_3, C_5) δ 4.7(S, OCH_3) IR (KBr, cm^{-1}): 3778 (OH, Stretch), 3178 (CH, Stretch, Aromatic), 2949 (CH, Stretch, Asymmetric, Aliphatic), 2848 (CH, Stretch, Symmetric, Aliphatic), 1742 (C=O, Stretch), 1623 (C=C, Stretch, Aromatic), 1551, 1458 (C=C, Stretch, Aromatic), 1473, 1342, 1254 (C-O, Stretch), 849. MS (*m/z*): 205 (100, M^+), 185 (22), 124 (30), 149 (95), 125(75), 91 (40), 58 (38)..

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5-(2-hydroxyphenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3d) Compound:

To a mixture solid of 5-(2-hydroxyphenyl)-N-(naphthalen-5-yl) semicarbazide (0.03mol, 430mg) in 25-30ml of Dimethyl sulphoxide (DMSO), equimolar quantity of appropriate aldehydes (ArCHO) was added and 2-4ml of Sodium bisulphate, contained in a round bottom flask. The solution was refluxed for 30-35 hr on sand bath with vigorous stirring. The reaction solution when cooled and then poured into cursed ice. The resultant precipitate was filtered, solid thus obtained then washed and crystallized with cold water.

Spectral data ^{1}H NMR (400 MHz, DMSO-d6): δ 11.78 (S, NH), 6.81 (S, CH), δ 5.9 (d, 2H, Ar-H, C_4, C_5-thiazole), δ 7.80 (m, Ar-H, C_2, C_6) δ 7.78 (m, Ar-H, C_3, C_5) δ 4.75(S, OCH_3) IR (KBr, cm^{-1}): 3788 (OH, Stretch), 3148 (CH, Stretch, Aromatic), 2929 (CH, Stretch, Asymmetric, Aliphatic), 2878 (CH, Stretch, Symmetric, Aliphatic), 1752 (C=O, Stretch), 1643 (C=C, Stretch, Aromatic), 1571, 1488 (C=C, Stretch, Aromatic), 1475, 1372, 1274 (C-O, Stretch), 889. MS (*m/z*): 245 (100, M^+), 187 (22), 185 (30), 145 (95), 128(75), 96 (40), 58 (37).

5-(3,4-dimethoxyphenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3e) Compound:

To a mixture solid of 5-(3,4-dimethoxyphenyl)-N-(naphthalen-5-yl) semicarbazide (0.03mol, 430mg) in 15-20ml of Dimethyl sulphoxide (DMSO), equimolar quantity of appropriate aldehydes (ArCHO) was added and 2-4ml of Sodium bisulphate, contained in a round bottom flask. The solution was refluxed for 20-25 hr on sand bath with vigorous stirring. The reaction solution when cooled and then poured into cursed ice. The resultant precipitate was filtered, solid thus obtained then washed and crystallized with cold water.

Spectral data ^{1}H NMR (400 MHz, DMSO-d6): δ 10.88 (S, NH), 7.81 (S, CH), δ 5.4 (d, 2H, Ar-H, C_4, C_5-thiazole), δ 7.85 (m, Ar-H, C_2, C_6) δ 7.52 (m, Ar-H, C_3, C_5) δ 4.55(S, OCH_3) IR (KBr, cm^{-1}): 3748 (OH, Stretch), 3145 (CH, Stretch, Aromatic), 2949 (CH, Stretch, Asymmetric, Aliphatic), 2828 (CH, Stretch, Symmetric, Aliphatic), 1755 (C=O, Stretch), 1645 (C=C, Stretch, Aromatic), 1541, 1428 (C=C, Stretch, Aromatic), 1476, 1372, 1274 (C-O, Stretch), 829. MS (*m/z*): 275 (100, M^+), 1827 (22), 155 (30), 185 (95), 148(75), 98 (40), 48 (37).

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5-(3,4,5-trimethoxyphenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3f) Compound:

To a mixture solid of 5-(3,4-dimethoxyphenyl)-N-(naphthalen-5-yl) semicarbazide (0.03mol, 430mg) in 15-20ml of Dimethyl sulphoxide (DMSO), equimolar quantity of appropriate aldehydes (ArCHO) was added and 2-4ml of Sodium bisulphate, contained in a round bottom flask. The solution was refluxed for 20-25 hr on sand bath with vigorous stirring. The reaction solution when cooled and then poured into cursed ice. The resultant precipitate was filtered, solid thus obtained then washed and crystallized with cold water.

Spectral data ^{1}H NMR (400 MHz, DMSO-d6): δ 11.78 (S, NH), 7.21 (S, CH), δ 5.7 (d, 2H, Ar-H, C_4, C_5-thiazole), δ 7.82 (m, Ar-H, C_2, C_6) δ 7.42 (m, Ar-H, C_3, C_5) δ 4.57(S, OCH_3) IR (KBr, cm^{-1}): 3148 (OH, Stretch), 3185 (CH, Stretch, Aromatic), 2449 (CH, Stretch, Asymmetric, Aliphatic), 2848 (CH, Stretch, Symmetric, Aliphatic), 1775 (C=O, Stretch), 1640 (C=C, Stretch, Aromatic), 1571, 1428 (C=C, Stretch, Aromatic), 1446, 1272, 1254 (C-O, Stretch), 819. MS (*m/z*): 245 (100, M^+), 1727 (22), 155 (30), 145 (95), 158(75), 95 (40), 44 (37).

Table 1 Physical Data of Synthesized compound (3a- 3f):-

Compounds	Ar	Mol. Wt g/mol	% Yield	Mp(°C)	R_f Value
3 a	4-Chlorophenyl	321.77	75.20	102-104	0.70
3 b	4-Methoxyphenyl	317.35	90.12	130-132	0.48
3 c	4-Nitrophenyl	332.32	89.75	118-120	0.72
3 d	2-Hydroxyphenyl	303.32	61.38	125-127	0.59
3 e	3,4-Dimethoxyphenyl	347.37	62.82	95-97	0.58
3 f	3,4,5-Trimethoxyphenyl	377.40	68.96	108-110	0.71

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IV. Results & Discussions

Molecular docking

Thiazole derivatives are a class of anti-proliferative agents, privileged scaffold and have been reported as newer tubulin inhibitors [5]. In the present studies, the oxadiazole analogues were designed, based on the core skeleton of anti-tubulin agent, IMC038525, hence we selected the tubulin as a potential target of the oxadiazole analogues (**3a-g**). Tubulin active site consists of large hydrophobic cavity which can accommodate a range of smaller to larger scaffolds. Thiazole derivatives comprising of different substitutions like phenyl on one side ring comprising of chloro, hydroxyl, methoxy, dimethoxy, trimethoxy and nitro on the other side were tested for anticancer studies. The binding mode analyses of these compounds were studied using Glide. According to the docking simulation frame work, compounds **3a-g** were well accommodated in the colchicine binding site, while remaining compounds **3a-g** were differed in their binding modes with respect to the compounds **3a-g**. Binding site of colchicine in tubulin enzyme consists of hydrophic cavity, lined with a few active residues like Lys254, Cys241, Lys352, THR179, Ala250 and Ala317. For the compound **3f**, the presence 3,4,5-trimethoxy seems to be unfavorable for its potency despite of exhibiting H-bond (Cys241) binding with O-atom in phenyl ring; H-bond (Thr179) binding with NH group; and π-Cationic (Lys254) binding with naphthalene ring. In case of the compounds **3d** they exhibited the H-bond with crucial residue Ala250 binding to N-atom oxadiazole ring, The compounds **3a, 3b** and **3c** are similar binding modes for π-Cationic (Lys352) binding with naphthalene ring, in case the compound **3g** they exhibited of with crucial residue π-Cationic (Lys254) binding with phenyl ring.

Table 2 The docking score and E model of synthesized compounds against the colchicine binding site of tubulin.

Sr. No.	Compounds	Interaction with Amino Acid	Docking Score	Glide E Model Score
1.	**3a**	π-Cationic (Lys352)	-6.344	-58.333
2.	**3b**	π-Cationic (Lys352)	-6.501	-60.206
3.	**3c**	π-Cationic (Lys352)	-6.572	-60.678

4.	**3d**	H-bond (Ala250)	-6.117	-60.725
5.	**3f**	H-bond (Cys241); H-bond (Thr179); π-Cationic (Lys254)	-6.549	-65.921
6.	**3g**	π-Cationic (Lys254)	-7.167	-69.033

Anticancer Screening of synthesized compounds

The anticancer screening was carried out as per the NCI US protocol. All compounds submitted to the NCI 60 Cell screen were tested initially at a single high dose (10^{-5} M) on leukemia, Melanoma, Lung, Colon, CNS, Ovarian, renal, prostate, and Breast Cancer cell Lines, nearly 60 in number. Compound *5-(3,4,5-Trimethoxyphenyl)-N-(naphthalene-5-yl)-thiazol-2-amine* **(3f)** showed maximum activity with mean growth percent (GP) of 92.62 followed by 5-*(4-Chlorophenyl)-N-(naphthalene-5-yl)- thiazol-2-amine* **(3a)** with mean GP of 96.25 while *5-(4-Nitrophenyl)-N-(naphthalene-5-yl)- thiazol-2-amine* **(3c)** showed mean GP of more than 96.31. The compound **3f** was highly active on T-47D (Breast Cancer) [GP=66.70], NCI-H522 (Non-Small Cell Lung Cancer A549/ATCC) [GP=68.96], SNB-75 (CNS Cancer) [GP=75.64]. The compound **3a** showed maximum activity on A498 (Renal Cancer) [GP=78.31], SF-268 (CNS Cancer) [GP=83.14], TK-10 (Renal Cancer) [GP=84.77]. The compound **3c** showed maximum activity on SR (Leukemia) [GP=59.73], NCI-H522 (Non-Small Cell Lung Cancer A549/ATCC) [GP=72.77], LOX IMVI (Melanoma) [GP=76.63], MCF7 (Breast Cancer) [GP=81.32]. The maximum activity was observed with **3c** on SR (Leukemia) with GP=59.73. The anticancer activity of the compounds is given in Table 5.2 in biological screening section.

V. Summary

A Series of newer ***5-(Substituted Phenyl)-N-(Naphthalen-5-Yl)- Thiazol-2-Amine*** Analogues was subjected to molecular properties prediction by mol soft and Molinspiration software and was synthesized in satisfactory yields. All the compounds followed the Lipinski "rule of five "which makes them potentially active agents. 3 Compound (**3a, 3c & 3f**) were evaluated for their anticancer activity in one dose assay and showed moderate activity on various cell lines. Compound ***5-(4-nitroyphenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3c)*** showed maximum activity with growth percent (GP) of 58.13 on SR (Leukemia), 75.57 on NCI-H522 (Non-Small

Cell Lung Cancer A549/ATCC) and mean growth percent (GP) of 94.11. and Compound ***5-(3,4,5-trimethoxyphenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3f)*** showed maximum activity with growth percent (GP) of 68.75 on T-47D (Breast Cancer), 64.16 on NCI-H522 (Non-Small Cell Lung Cancer A549/ATCC), 85.74 on SNB-75 (CNS Cancer) and mean growth percent (GP) of 91.22. Compound ***5-(4-chlorophenyl)-N-(naphthalen-5-yl) thiazol-2-amine (3a)*** could be considered as lead further discovery and could be modified to potentiate the anticancer activity.

VI. Reference

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