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SYNTHESIS AND DOCKING STUDIES OF 2-AMINOTHIAZOLE-5-AROMATIC CARBOXAMIDE DERIVATIVES

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Keywords:

2-amino-thiazole-5-carboxamide derivatives, Piperazine derivatives, Docking and 2GQG, anti-cancer activity

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ABSTRACT

A novel N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-pipearazinyl]-2-methyl-4-pyrimidinyl] amino]-5-thiazolecarboxamide derivatives (6a-6d) and (8a-8b) were synthesized by coupling 2-[(6-chloro-2-methylpyrimidin-4ylamino]-N-(2-chloro-6-methylphenyl) thiazole-5-Carboxamide(3) with Piperazine derivatives(4,7) in butanol and DIPEA (Diisopropylethylamine) at 120ºC for 4-5hrs. All the synthesized compounds were characterized physically and elucidated by Infrared spectroscopy, Mass spectroscopy, ^{1}H-NMR spectroscopic techniques. All the synthesized compounds were subjected to Molecular docking studies by using 2GQG as its PDB ID. Among all the compounds, 6a, 6b, 6d, 8c and 8b exhibit anticancer activity.

INTRODUCTION: Molecules containing a thiazole amine-moiety exhibit interesting biological activities depending on the substitution pattern at the thiazole ring [1]. 2-Aminothiazole nucleus is a potential pharmacophore for a broad spectrum of activities, comprising of antibacterial [2], anti-fungal [3], antitubercular [4], anti-HIV [5], pesticidal [6], anti-inflammatory [7], antiprotozoal [8], hypertension, [9] schizophrenia [10] *etc.*

Aminothiazoles are known to be ligands of estrogen receptors [11] as well as a novel class of adenosine receptor antagonists [12] whereas other analogues are used as fungicides, inhibiting in vivo growth of *Xanthomonas* and as an ingredient of herbicides or as schistosomicidal and anthelmintic drugs [13]. It is reported that 2-aminothiazole-5-aromatic carboxamides are useful as kinase inhibitors of protein tyrosine kinase and p38 kinase, intermediates and crystalline forms thereof [14].

Docking is a method which predicts the preferred orientation of one molecule to a second whenbound to each other to form a stable complex [15].

Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions.

By considering the above kinase inhibitor activities of 2-aminothiazole-5-aromatic caroboxamides, we have synthesized some new 2-aminothiazole-5-aromatic carboxamide derivatives containing pyrimidine, piperazine ring extensions and check their anti-cancer activity through Molecular docking studies by using 2GQG as their PDB ID and Dasatinib as a reference.

SCHEME FOR PREPARATION OF 6a-6d AND 8a-8b

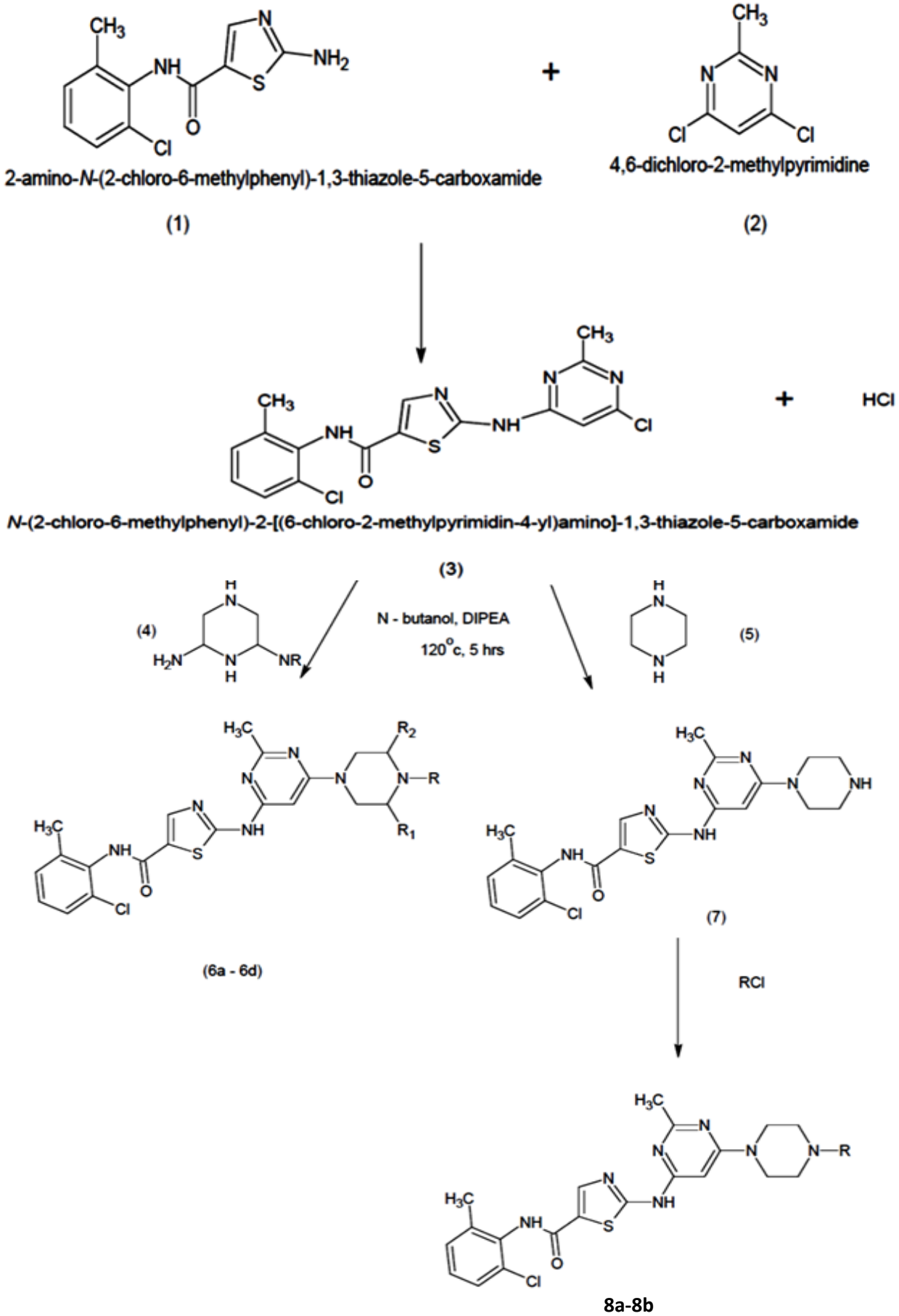


TABLE 1: LIST OF SUBSTITUTED GROUPS IN PLACE OF R_1, R, R_2

Compound	R1	R	R2
6a	H	CH_3	H
6b	H	CH_2CH_3	H
6c	H	C_6H_5	H
6d	CH_3	H	CH_3
8a		CH_2-C_6H_5	
8b		CH_3-CH-CH_3	

EXPERIMENTAL:

Chemistry: Melting points were determined on open capillaries using a cintex melting point apparatus. T.L.C analyses were performed on pre-coated silicagel (E-Merck Kieselgel 60F254) plates and visualization was done by exposing to iodine vapour. Solvents were purified by standard procedures before use. IR Spectra were recorded in KBr on Perkin-Elmer Spectrum. 1H-NMR spectrum was recorded in DMSO-d_6 with TMS as internal standard on a Bruker spectrometer at 400 MHz.(chemical shifts in δ ppm). Mass spectra were scanned on a Varian MATCH-7 and Jeol JMSD-300 mass spectrometer at 70ev. All the chemicals used in this work were purchased from Aldrich chemicals. Docking studies were performed at NATCO Research Centre, Hyderabad.

General procedure for the preparation of compounds:

1. **Synthesis of N-(2-chloro-6-methyl phenyl)(6-chloro-2-methylpyrimidine-4-ylamino)- 1,3-thiazole carboxamide(3):** To a stirring solution of 2-Amino-N-(2-chloro-6-methylphenyl)-1,3-thiazole- 5-carboxamide (1) (5gr, 18.67mmol) and 4,6-dichloro-2 methylpyrimidine (2) (3.65gr, 22.4mmol) was added in Tetrahydrofuran (65ml) and stirred for 15min.

   To this a 30% wt solution of sodium-t-butoxide in Tetrahydrofuran (21gr,65.36mmol) was added slowly with cooling to keep the temperature at 10-20ºC. The mixture was stirred for 1.5hr and cooled to 0-5^{o}C. Then 21.5ml of 2N HCl was added slowly and the mixture was collected by vacuum filtration. Then the compound was washed with water (15ml) and dried to give 6.63g (86.4%) of cream coloured solid, M.P 282-286.5^{o}C.

2. **Synthesis of N-(2-chloro-6-methylphenyl)-2-{[6-(piperazin-1-yl)-2-methylpyrimidin-4-yl] amino} - 1, 3 -thiazole- 5 - carboxamide (7):** To N-(2-chloro-6-methylphenyl)(6-chloro-2-methyl pyrimidine-4-ylamino)-1,3- thiazole carboxamide (3) (5gr, 0.01mol) in n-butanol (40ml), piperazine (5) (5.45gr, 0.06mol) was added. Slowly followed by addition of Diisopropylethylamine (4.42ml, 0.02 mol). The reaction mixture was heated at 120^{o}C for 4-5hr. Then, the mixture was cooled slowly to room temperature. The obtained solid was collected by vacuum filtration, washed with n-butanol and dried to give 8.1gr (81.2%) of cream coloured solid, M.P 256-260^{o}C.

3. **General procedure for synthesis of compounds (6a-6d):** To a mixture of N-(2-chloro-6-methyl phenyl)(6-chloro-2-methylpyrimidine-4-ylamino)-1,3- thiazole carboxamide (3) (2gr, 0.005mol) in 40ml of n-Butanol, 1.766ml (0.01mol) of DIPEA (Diisopyopylethyl amine) was added. To this, reaction mixture piperazine derivative (4) (4gr, 0.025mol) was added. Slowly the slurry was heated at 120^{o}C for 4-5hr then cooled slowly to room temperature. The obtained solid was collected by vacuum filtration, washed with 2ml of n-Butanol and dried. The product obtained was dissolved in hot 40ml of ethanol: water mixture (80:20) , and the solution was clarified by filtration. The hot solution was slowly diluted with 7ml of water and cooled slowly to room temperature. The solid was collected by vacuum filtrattion and washed with 2ml of 50% ethanol- water and dried.

4. **Synthesis of N-(2-chloro-methyl-phenyl)-2-(6-(4-methyl) piperazin-1-yl)-2-methylpyrimidin-4-ylamino) thiazole-5-carboxamide (6a):** Compound 6a was synthesized by reacting N-(2-chloro-6-methyl phenyl)(6-chloro-2-methylpyrimidine-4-ylamino)- 1,3- thiazole carboxamide(3) with N-methyl piperazine. The compound 6a obtained as white solid with 74.5% yield. **IR** ((KBr cm^{-1}): 3193.7cm^{-1} (NH-streching), 3059.1cm^{-1}(Ar- CH), 1622cm^{-1}(C=O,amide streching), 1579cm^{-1}(Ar- C=C streching), 1292cm^{-1}(Ar-C-Nstreching,2^o Amine), 765cm^{-1}(C-Cl streching). **Mass Spectra** (*m/z*) M+, found 458.3, Calculated 458**. ^{1}H-NMR** (400MHz, DMSO-d_6): 11.479(1H,s)(CONH), 9.879 (1H,s)(NH),

8.220(1H,s)(ArH), 7.2377(3H,m)(ArH), 6.051(1H,s)(ArH), 3.513(4H,t)($2CH_2$), 2.407 (3H,s) (CH_3), 2.356-2.368(4H,t)($2CH_2$), 2.212-2.239 (6H,s) ($2CH_3$).

5. **Synthesis of N-(2-chloro-methyl-phenyl)-2-(6-(4-ethyl) piperazin-1-yl)-2-methylpyrimidin-4-ylamino) thiazole-5-carboxamide (6b):** Compound 6b was synthesized by reacting N-(2-chloro-6-methyl phenyl)(6-chloro-2-methylpyrimidine-4-ylamino)- 1,3- thiazole carboxamide(3) with N-ethyl piperazine. **IR** ((KBr cm^{-1}): 3215.7cm^{-1} (NH-streching), 2947.1cm^{-1}(Ar- CH), 1628.8cm^{-1}(C=O,amide streching), 1577cm^{-1}(Ar- C=C streching), 1289.3cm^{-1}(Ar-C-Nstreching,2^o Amine), 766cm^{-1}(C-Cl streching). **Mass Spectra**(*m/z*) M+1, found 473.3 , Calculated 472: **^{1}H NMR** (400MHz, DMSO-d_6): 11.465(1H,s)(CONH), 9.873(1H,s) (NH), 8.215(1H,s)(Ar-H), 7.236-7.407(3H,m) (ArH), 6.052 (1H,s)(ArH), 3.512(4H,t) ($2CH_2$), 2.406 (7H,m) (CH_3,$2CH_2$), 2.3332.369 (2H,q) (CH_2), 2.237 (3H,s)(CH_3), 1.013-1.048(3H,t) (CH_3).

6. **Synthesis of N-(2-chloro-methyl-phenyl) - 2 -(6-(4-phenyl) piperazin-1-yl)-2-methylpyrimidin-4-ylamino) thiazole – 5 -carboxamide (6c):** Compound 6c was synthesized by reacting N-(2-chloro-6-methyl phenyl)(6-chloro-2-methyl pyrimidine-4-ylamino)- 1,3- thiazole carboxamide(3) with N-phenyl piperazine.The compound obtained as cream colour solid with 75.31% yield. **IR** ((KBr $cm^{-1)}$: 3188cm^{-1} (NH-streching), 2846cm^{-1}(Ar- CH), 1620.2cm^{-1}(C=O,amide streching),1578.5cm^{-1}(Ar- C=C streching), 1293.7cm^{-1}(Ar-C-Nstreching,2^o Amine), 766.7cm^{-1}(C-Cl streching). **Mass Spectra**(*m/z*) M+1, found 520.1, Calculated 519. **^{1}H NMR** (400MHz, DMSO-d_6): 11.525(1H,s)(CONH), 9.889(1H,s)(NH), 8.234(1H,s)(Ar-H), 6.798-7.412(8H,m)(ArH), 6.121 (1H,s)(ArH), 3.688(4H,t) ($2CH_2$), 3.240(4H,t)($2CH_2$), 2.439(3H,s)(CH_3), 2.246 (3H,s)(CH_3).

7. **Synthesis of N-(2-chloro-methyl-phenyl)-2-(6-(3,5-dimethyl) piperazin-1-yl)-2-methylpyrimidin-4-ylamino) thiazole-5-carboxamide (6d):** Compound 6d was synthesized by reacting N-(2-chloro-6-methyl phenyl)(6-chloro-2-methylpyrimidine-4-ylamino)- 1,3- thiazole carboxamide(3) with 2,6-dimethyl piperazine.The compound obtained as cream coloured solid with 95% yield. **IR** ((KBr cm^{-1}): 3227cm^{-1} (NH-streching), 2862 cm^{-1}, 2959cm^{-1}(Ar- CH), 1620.2cm^{-1}(C=O,amide streching), 1578.5cm^{-1}(Ar- C=C streching), 1293.7cm^{-1}(Ar-C-Nstreching, 2^o Amine), 766.7cm^{-1}(C-Cl streching). **Mass Spectra** (*m/z*) M+1, found 473.1, Calculated 472. **^{1}H NMR** (400MHz,DMSO-d_6): 11.369 (1H,s)(CONH), 9.866(1H,s)(NH), 8.212(1H,s) (Ar-H), 7.235-7.407(3H,m)(ArH), 6.047(2H,s)(Ar-H), 4.078 (2H,s)(2CH), 2.29-2.319,2.69(4H,t)($2CH_2$), 2.40 (3H,s)(CH_3), 2.237(3H,s)(CH_3), 1.015-1.03 (6H,d) ($2CH_3$).

8. **General procedure for Synthesis of compounds (8a-8b):** To mixture of compound *N*-(2-chloro-6-methylphenyl)-2-{[6-(piperazin-1-yl)-2-methyl pyrimidin-4-yl] amino}-1, 3-thiazole-5-carboxamide (7) (2gr, 0.005mol) in 40ml of n-butanol, DIPEA (0.52ml, 0.0045mol) was added. To this reaction mixture (0.52ml, 0.0045mol) of alkyl or aryl chloride was added. Slowly the slurry was heated at 120^{o}C for 4-5hr then cooled slowly to room temperature. The obtained solid was collected by vacuum filtration, washed with 2ml of n-Butanol and dried. The product obtained was dissolved in hot 40ml of ethanol: water mixture (80:20) , and the solution was clarified by filtration. The hot solution was slowly diluted with 7ml of water and cooled slowly to room temperature. The solid was colected by vacuum filtrattion and washed with 2ml of 50% ethanol- water and dried.

9. **Synthesis of N-(2-chloro-methyl-phenyl)-2-(6-(4-benzyl) piperazin-1-yl)-2-methylpyrimidin-4-ylamino) thiazole-5-carboxamide (8a):** Compound 8a was synthesized by reacting N-(2-chloro-6-methylphenyl)-2-{[6-(piperazin-1-yl)-2-methylpyrimidin-4-yl] amino}-1,3-thiazole-5-carboxamide (7) with benzyl chloride. The compound obtained as cream coloured solid with 83.3% yield. **IR** ((KBr cm^{-1}): 3189cm^{-1} (NH-streching), 2813 cm^{-1}, 2937.8cm^{-1}(Ar- CH), 1624cm^{-1}(C=O,amide streching), 1577cm^{-1}(Ar- C=C streching), 1293.4cm^{-1}(Ar-C-Nstreching, 2^o Amine), 764.6cm^{-1}(C-Cl streching). **Mass Spectra** (*m/z*) M+, found 534.2, Calculated 534. **^{1}H-NMR** (400MHz,DMSO-d_6): 11.447(1H,s)(CONH), 9.873 (1H,s)(NH), 8.216(1H,s)(ArH), 7.2547.408 (8H,m)

(ArH), 6.028(1H,s)(Ar-H), 3.453-3.516(6H,m) (3CH_2), 2.402-2.766(7H, m)(CH_3), 2.238(3H,s) (CH_3).

10. **Synthesis of N-(2-chloro-methyl-phenyl)-2-(6-(4-propane-2-yl) piperazin-1-yl)-2-methylpyrimidin-4-ylamino) thiazole-5-carboxamide (8b):** Compound 8b was synthesized by reacting N-(2-chloro-6-methylphenyl)-2-{[6-(piperazin-1-yl)-2-methylpyrimidin-4-yl] amino}-1, 3-thiazole-5-carboxamide (7) with isopropyl chloride. The compound obtained as brick colour solid with 54.65 yield. **IR** ((KBr $cm^{-1)}$: 3208.7cm^{-1} (NH-streching), 2813 cm^{-1}, 2937.8cm^{-1}(Ar- CH), 1624.2cm^{-1}(C=O,amide streching), 1580.1cm^{-1}(Ar-C=C streching), 1291.8cm^{-1}(Ar-C-Nstreching,2º Amine), 761.8cm^{-1}(C-Cl streching). **Mass Spectra** (*m/z*) M+1, found 486.2, Calculated 485: **^{1}H-NMR** (400MHz,DMSO-d_6): 11.503(1H,s)(CONH), 9.905 (1H,s)(NH), 8.249(1H,s)(ArH), 7.2587.410 (3H,m) (ArH), 6.117(1H,s)(ArH), 3.685(2H,t)(CH2), 3.5313.567(2H,t)(CH_2), 3.663.398(1H,m)(CH), 3.099(4H,m)(2CH_2), 2.434(3H,s)(CH_3), 2.242 (3H,s)(CH_3), 1.234-1.251(6H,d)(2C?CCH_3).

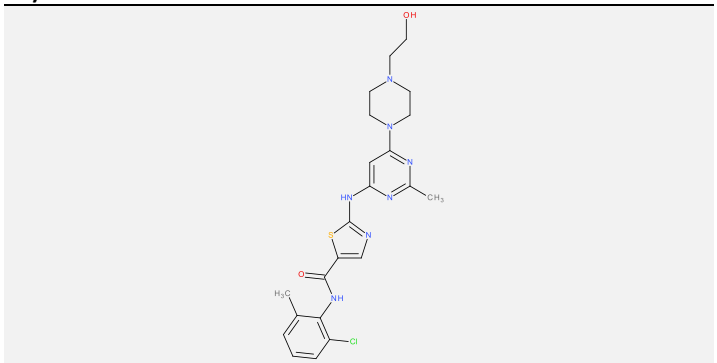
Table-2 physical characterization of synthesized compounds (6a-6d) & (8a-8b)

S. No.	Compound Name	Molecular Formula	Molecular Weight	Melting Point (°C)	% Yield	R_f value
1	6a	$C_{21}H_{24}N_7SOCl$	458.3	345.9-350.9	74.5%	0.6
2	6b	$C_{22}H_{26}N_7SOCl$	472.3	295-299	75.31%	0.57
3	6c	$C_{26}H_{26}N_7SOCl$	520.1	334.5-340.7	83.6%	0.72
4	6d	$C_{22}H_{26}N_7SOCl$	472.3	319.9-324.08	95%	0.5
5	8a	$C_{27}H_{28}N_7SOCl$	486.2	318.3-324.9	83.3%	0.27
6	8b	$C_{23}H_{28}N_7SOCl$	485	263-278	54.6%	0.32

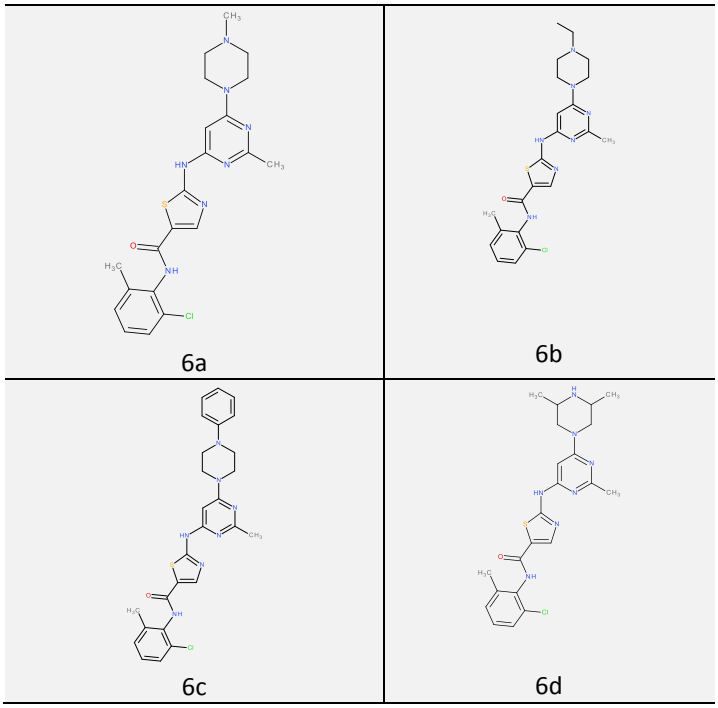
Docking Studies: The docking studies were carried out for the synthesized compounds to know the activity of the compounds for its anti-cancer effects. The various steps for the docking process is as follows:

Library of Compounds: A chemical library or compound library is a collection of stored chemicals usually used ultimately in high throughput screening. The chemical library can consist in simple terms of a series of stored chemicals. Once the target is identified, it is then is docked with the designed library of compounds the library prepared was

TABLE- 3 DESIGNS AND DOCKING STUDIES OF 2-AMINOTHIAZOLE-5-AROMATIC CARBOXAMIDE DERIVATIVES (6a-6b)



DASATINIB

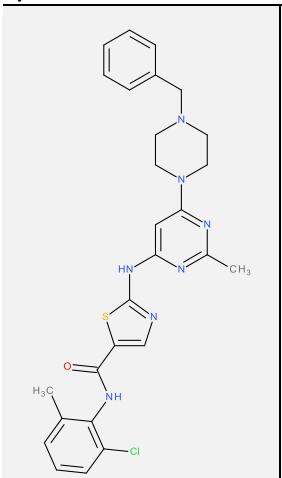


6a 6b 6c 6d

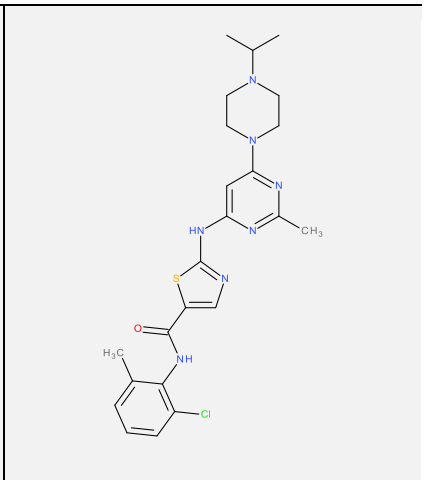
DOCKING: Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. Given the biological and pharmaceutical significance of molecular docking, considerable efforts have been directed towards improving the methods used to predict docking.

Here, the docking is carried out between the designed set of molecules and the protein 2GQG by using the auto dock software; the various interactions are shown in the results.

TABLE 4: DESIGNS AND DOCKING STUDIES OF 2-AMINOTHIAZOLE-5-AROMATIC CARBOXAMIDE DERIVATIVES (8a-8b)



8a



8b

Docking Report:

- Title: X-ray crystal structure of dasatinib (BMS-354825) bound to activated ABL kinase Domain.
- PDB id: 2GQG.
- Chain : B
- Classification: Transferases.
- Software: AUTODOCK VINA.
- Binding Site Prediction: Grid based approach.

Parameter;

1. Center_X = 45.092
2. Center_Y = 21.198
3. Center_Z = -44.022
4. Size_X = 18
5. Size_Y = 20
6. Size_Z= 18.

The docking was carried out by grid based approach for the 2GQG molecule and the interaction sites and the binding distances from the molecule was found to be at a distance of 45.092 from x-axis, 21.918 from Y-axis and -44.022 from z-axis from the center and at a distance of 18, 20, 18 from the x, y, z axis respectively from the sides.

TABLE 5: THE INTERACTIONS OF THE VARIOUS MOLECULES WITH THE RECEPTOR AND ITS INTERACTION RESIDUES ALONG WITH THE DISTANCES

Sl. No	Molecule	H-bond residue and distances	Binding Affinity
1	DASATINIB (REFERENCE)	THR 315 (2.24) MET 318 (1.83) MET 318 (2.22) HOH 623 (2.41) TYR 323 (2.88)	-9.6
2	DSN-VI-NMP 6a	THR 315 (2.28) MET 318 (1.883) MET 318 (2.16) HOH 623 (2.62)	-10
3	DSN-VI-NEP 6b	THR 315 (2.23) MET 318 (1.81) MET 318 (2.17) HOH 623 (2.47)	-9.9
4	DSN-VI-NPP 6c	THR 315 (2.03) MET 318 (1.93) HOH 623 (2.59)	-9.0
5	DS-VI-DMP 6d	THR 315 (2.28) MET 318 (1.85) MET 318 (2.06) HOH 623 (2.59)	-10.3

6	DSN-P-BZCL 8a	THR 315 (2.25) MET 318 (1.83) MET 318 (2.19) HOH 623 (2.57)	-10.2
7	DSN-P-IPB 8b	THR 315 (2.25) MET 318 (1.82) MET 318 (2.18) HOH 623 (2.45)	-10.0

Therefore, from the above docking studies the interaction with the various residues and the binding of the molecule with its active pharmacological sites can depict a valid action and thus the synthesized molecules can show a good pharmacological action than the reference (Dasatinib).

RESULT & DISCUSSION: The compounds were synthesized by coupling N-(2-chloro-6-methyl phenyl)(6-chloro-2-methylpyrimidine-4-ylamino)- 1,3-thiazole carboxamide with various piperazine derivatives. All the synthesized compounds were physically characterized by determining their physical state, M.P, solubility and it is tabulated (**table 1**) . The structures of the compounds were established by means of IR, MASS, ^{1}H-NMR spectra. The compounds (6a-6d) & (8a-8b) were evaluated for anti-cancer activity by docking studies using Dasatinib as a reference compound, and the results were tabulated (**table 5**). Among all the compounds 6a, 6b, 6d, 8a and 8b can show a good pharmacological action i.e., anti-cancer activity more than the reference drug.

CONCLUSION: The results shows (table 5) that compounds 6a, 6b, 6d, 8a and 8b is having considerable anti-cancer activity than reference compound (Dasatinib).

Thus. the present investigation offers the synthesis of newer compounds with anti-cancer activity having 2-aminothiazole as a basic nucleus

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