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International Journal of Pharmaceutical Sciences and Drug Research
2017; 9(3): 139-144

Research Article

ISSN: 0975-248X
CODEN (USA): IJPSPP



# Substituted Thiazole Linked Murrayanine-Schiff's Base Derivatives as Potential Anti-Breast Cancer Candidates: Future EGFR Kinase Inhibitors

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## ABSTRACT

Cancer is the second leading causes of mortality across the planet which has had affected millions. In spite of massive efforts in producing new molecules and chemotherapeutic approaches for managing cancer, it continued to be the global threat. Small hybrid molecules have gained popularity in chemotherapy due to their potential and smart characteristics in modulating biological targets. The present research attempts in developing few novel hybridized derivatives of murrayanine (an active carbazole derivative) by the semi-synthetic approach to form substituted thiazole linked murrayanine-Schiff's base derivatives. The protocol involved murrayanine 1 as the template material for constructing a hybridized Schiff's base intermediate 3, which further by Hantzch's cyclization was subsequently converted to various hybridized thiazoles analogs 5a-5f. The purity of the synthesized compounds was ascertained by sophisticated analytical techniques. The anti-cancer potential was screened against breast cancer cell lines; MCF-7 and MDA-MB-231 by Sulforhodamine B (SRB) assay. The compound 5b displayed most potent anti-proliferative activity with $IC_{50}$ values of 23.41µM against MCF-7 cell line and 32.15µM against MDA-MB-231 cell line. It has been observed that analogs having electron withdrawing substituents exhibited pronounced anticancer activity. The docking study was performed by Autodock Vina where the results were found to be in full agreement with the cytotoxic study, depicting that the probable cytotoxic outcome by EGFR inhibitory mechanism. The study revealed the potential of novel hybridized derivatives as active anti-breast cancer candidates. The research will encourage (medicinal) chemists in rationally designing of semi-synthetic analogs of a heterocyclic prototype having pronounced anti-cancer activity.

**Keywords:** Murrayanine, Thiazole, Schiff's base, Carbazole, Cancer, EGFR.

**DOI: 10.25004/IJPSDR.2017.090307** **Int. J. Pharm. Sci. Drug Res. 2017; 9(3): 139-144**

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**Relevant conflicts of interest/financial disclosures:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
**Received:** 14 April, 2017; **Revised:** 25 April, 2017; **Accepted**: 30 April 2017; **Published:** 29 May 2017

## INTRODUCTION

Cancer is the second leading causes of mortility across the planet which has had affected millions. [1] In spite of massive efforts in producing new molecules and chemotherapeutic approaches for managing cancer, it continued to be the global threat. Cancer is swiftly moving ahead in recent era and is forecasted to affect 25 million people in next 20 years. [2] The search for unexplored classes of the molecule against deadly cancer cells remained the chief attraction among the scientific community. Small molecular weight ligands of natural origin have a very high reputation of delivering promising anti-cancer activity. [3]

*Murraya koenigii* L. or Curry tree (Rutaceae) is an important traditional herb of Indian origin that has been in practice for centuries. [4] It is well known for its ethno pharmacological importance for treating various ailments including free radical induced cancer, various cancer forms, prevention of metastasis, apoptosis, etc. [5] Water, alcohol, hydroalcoholic, petroleum ether, and chloroform extract of *M. koenigii* L. leaves and stem bark [6], have demonstrated potent anti-cancer activity owing to the presence of carbazole components. The phytochemical studies have revealed the presence of several carbazole alkaloids like murrayanine [7], mahanine [8], mahanimbine, mahanimbicine [9], murrayacine [10], koenoline [11], girinimbine [12], murryafoline A [13], mahaimboline, isomahanine [14], etc. which are the most potent anti-tumor principles against several cell lines or in animal models.

Schiff's base containing molecules are referred to those compounds having azomethine group (C=N), formed by the condensation of primary amines and active carbonyl groups. [15] Schiff's bases are well known for their anti-cancer potential.

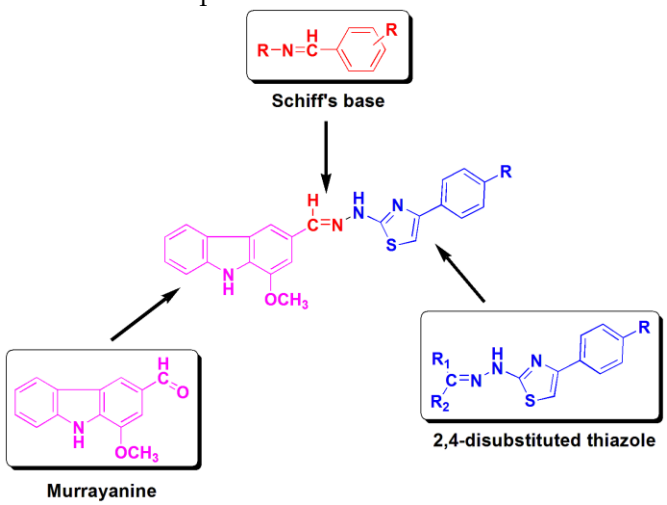



**Fig. 1. Rationale for the synthesis of substituted thiazole linked murrayanine-Schiff's base derivatives**

Compounds comprising of thiazole ring system have demonstrated tremendous anti-tumor prospective. [16] 2, 4-disubstituted thiazoles have been reported to exhibit impressive anti-cancer and nucleolytic activity. [17] In an exciting finding, 2, 4-disubstituted thiazoles are found to exhibit potentials for the treatment of osteoporosis and breast cancer as Src homology 2 (SH-2) inhibitors. [18]

Based on the fact that all the three scaffolds; viz. murrayanine, Schiff's base and thiazole have been reported to exhibit potent anti-proliferative activity, all three of them were integrated to form a hybrid molecule which is believed to demonstrate excellent anti-cancer (Figure 1). Thus, the present research involved rational designing of anti-cancer agents having murrayanine scaffold linked with 2,4-disubstituted thiazole moiety via Schiff's base linkage with an objective that the analogs will demonstrate enhanced anti-proliferative activity than their parents and also show comparable activity with the standard drug.

## MATERIALS AND METHODS

### Chemical and Instrumentation

All chemical derivatives, solvents, and analytical grade reagents employed in synthesizing the products were procured from Merck, HiMedia, and Sigma-Aldrich. The melting points of the synthesized derivatives were measured on Perfit melting point apparatus. Thin layer chromatography was carried out using silica gel G-coated TLC plates (Merck). The FT-IR spectra were recorded in KBr discs on the IRAffinity-1 instrument. The $^1$H-NMR (400 MHz) spectra were recorded using Bruker spectrospin NMR DPX-300. The TMS (Sigma-Aldrich) was used as an internal standard. The mass spectra were obtained on JEOL-JMS-DX 303 instrument. The elemental analyses were performed on Perkin-Elmer 240C analyzer. The microplate reader of BioTek Instruments Inc., USA was used for analysis of SRB Assay.

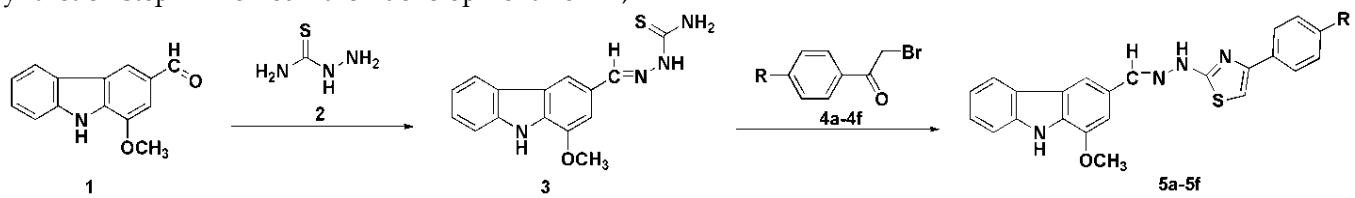
### Extraction of murrayanine

The murrayanine was extracted as per our previously mentioned protocol where using soxhlet apparatus, the powdered stem bark of *M. koenigii* was extracted with n-hexane. [19] The obtained extract was initially filtered through a cotton plug and successively with a Whatman filter paper. The concentrated plant extract was additional subjected to isolation by silica gel-based column chromatography technique using eluant mixtures in order; hexane, hexane/ethyl acetate, ethyl acetate, ethyl acetate/methanol and methanol to produce 75 fractions. All fractions were analyzed by TLC technique, where fractions $B_{21}$-$B_{37}$ of hexane extract were collectively taken to isolate the desired compound; murrayanine 1.

### Synthesis of target compounds

The novel molecules were developed from an active carbazole derivative present in *M. koenigii* L. known as murrayanine 1 which has a well known anti-cancer activity. The objective was to design few hybrid molecules having better anti-cancer activity than the parent murrayanine and to develop a series which will possess comparable activity like the standard drug. For the synthesis of derivatives 5a-5f, the active part (viz. –CHO part) of murrayanine 1 was focused exhaustively.

The -CHO (aldehyde) moiety of the carbazole was preferred where a Schiff's base function can be incorporated. Schiff's base, an important element of medicinal chemistry was introduced from a thiosemicarbazide 2 function for the synthesis of compound 3. The mechanism involved attack of electrophilic aldehydic carbon atom of 1 by the nucleophilic amine of 2, resulting in the substitution of carbonyl by an azomethine function. The terminal synthetic step involved the development of 2,4-disubstituted thiazoles over thiosemicarbazide template employing Hantzch's synthetic protocol. The name reaction involves cyclization of α-halo carbonyl compounds by reactants having N-C-S fragment of the ring. The final compounds 5a-5f were produced by condensation of 3 having the two heteroatoms on the same carbon with 4a-4f which comprise of one halogen and one carbonyl function on two neighboring carbons. Scheme 1 portrays the overall synthetic pathway.




**Scheme 1. Synthetic scheme for substituted thiazole linked murrayanine-Schiff's base derivatives**

**1-methoxy-9H-carbazole-3-carbaldehyde (1)**

m.p.: 165-167°C, $R_f$: 0.47, hexane: ethyl acetate: methanol (7:2:1). FTIR (KBr) υ ($cm^{-1}$): 3250 (-NH), 3081 (C-H, aromatic), 1722 (C=O), 1295 (C-O). $^1$H NMR (δ, ppm, DMSO-$d_6$): 10.4 (9, 1H), 9.81 (4, 1H), 7.2-8.8 (Aromatic, 6H), 3.86 (1, 3H). MS: [$M^+$ 225; 181 (30%)]. Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.56; H, 4.88; N, 6.03.

**Synthetic protocol for (E)-2-((1-methoxy-9H-carbazol-3-yl)methylene)thiosemicarbazide (3)**

Equimolar quantity of murrayanine (0.01 M) (1) and thiosemicarbazide (0.01 M) (2) was slowly added to ethanolic solution under continuous stirring and the content was refluxed for 12 hr. The reaction mixture was cooled; precipitate was collected, washed with ice cold water, dried properly and recrystallized with aqueous ethanol. [19]

67% yield; FTIR (KBr) υ ($cm^{-1}$): 3411 (-$NH_2$), 3250 (-NH, stretch), 3076 (C-H, aromatic), 1664 (C=N, azomethine), 1613 (C=C, aromatic), 1567 (-NH, bending), 1285 (C-O), 1162 (C=S). $^1$H NMR (δ, ppm, $CDCl_3$): 10.23 (9, 1H), 8.46 (azomethine, 1H), 7.1-8.6 (Aromatic, 6H), 3.97 (1, 3H), 2.2 (12, 1H). MS: [$M^+$ 298]. Anal. Calcd for $C_{15}H_{14}N_4OS$: C, 60.38; H, 4.73; N, 18.78. Found: C, 60.24; H, 4.70; N, 18.55.

**Synthetic protocol for (E)-4-(4-substituted-phenyl)-2-(2-((1-methoxy-9H-carbazol-3-yl)methylene) hydrazinyl)thiazole (5a-5f)**

Equimolar quantity of *(E)*-2-((1-methoxy-9H-carbazol-3-yl)methylene)thiosemicarbazide (0.01 M) (3) and substituted phenacyl bromide (0.01 M) (4a-4f) were dissolved in ethanol or methanol solution, and the solution was slowly stirred for 10 min to promote complete dissolution. The content was refluxed on a water bath for 10-12 hr and the progress of the reaction was monitored by TLC. The obtained product was suitably recrystallized from chloroform or ethanol. [20]

**(E)-2-(2-((1-methoxy-9H-carbazol-3-yl)methylene) hydrazinyl)-4-phenylthiazole (5a)**

81% yield; FTIR (KBr) υ ($cm^{-1}$): 3194 (-NH, stretch), 3146 (C-H, aromatic), 1651 (C=N, azomethine), 1623 (C=C, aromatic), 1552 (-NH, bending), 1274 (C-O). $^1$H NMR (δ, ppm, $CDCl_3$): 10.13 (9, 1H), 8.03 (azomethine, 1H), 7.2-8.7 (Aromatic, 12H), 4.24 (12, 1H), 3.84 (1, 3H). MS: $M^+$ 398. Anal. Calcd for $C_{23}H_{18}N_4OS$: C, 69.32; H, 4.55; N, 14.06. Found: C, 69.19; H, 4.47; N, 13.89.

**(E)-4-(4-chlorophenyl)-2-(2-((1-methoxy-9H-carbazol-3-yl)methylene)hydrazinyl)thiazole (5b)**

72% yield; FTIR (KBr) υ ($cm^{-1}$): 3264 (-NH, stretch), 3069 (C-H, aromatic), 1672 (C=N, azomethine), 1611 (C=C, aromatic), 1564 (-NH, bending), 1253 (C-O), 676 (C-Cl). $^1$H NMR (δ, ppm, $CDCl_3$): 10.29 (9, 1H), 8.09 (azomethine, 1H), 7.1-8.9 (Aromatic, 11H), 4.19 (12, 1H), 3.77 (1, 3H). MS: $M^+$ 432, M+2 434. Anal. Calcd for $C_{23}H_{17}ClN_4OS$: C, 63.81; H, 3.96; N, 12.94. Found: C, 63.29; H, 3.92; N, 12.52.

**(E)-4-(4-bromophenyl)-2-(2-((1-methoxy-9H-carbazol-3-yl)methylene)hydrazinyl)thiazole (5c)**

56% yield; FTIR (KBr) υ ($cm^{-1}$): 3257 (-NH, stretch), 3124 (C-H, aromatic), 1669 (C=N, azomethine), 1626 (C=C, aromatic), 1594 (-NH, bending), 1295 (C-O), 612 (C-Br). $^1$H NMR (δ, ppm, $CDCl_3$): 10.37 (9, 1H), 8.07 (azomethine, 1H), 7.2-8.8 (Aromatic, 11H), 4.33 (12, 1H), 3.96 (1, 3H). MS: $M^+$ 477, M+2 479. Anal. Calcd for $C_{23}H_{17}BrN_4OS$: C, 57.87; H, 3.59; N, 11.74. Found: C, 57.21; H, 3.46; N, 11.55.

**(E)-2-(2-((1-methoxy-9H-carbazol-3-yl)methylene) hydrazinyl)-4-(p-tolyl)thiazole (5d)**

70% yield; FTIR (KBr) υ ($cm^{-1}$): 3291 (-NH, stretch), 3111 (C-H, aromatic), 1656 (C=N, azomethine), 1631 (-NH, bending), 1609 (C=C, aromatic), 1211 (C-O). $^1$H NMR (δ, ppm, $CDCl_3$): 10.25 (9, 1H), 8.04 (azomethine, 1H), 7.1-8.6 (Aromatic, 11H), 4.21 (12, 1H), 3.83 (1, 3H), 2.38 (18, 1H). MS: $M^+$ 412. Anal. Calcd for $C_{24}H_{20}N_4OS$: C, 69.88; H, 4.89; N, 13.58. Found: C, 69.76; H, 4.77; N, 13.27.

**(E)-2-(2-((1-methoxy-9H-carbazol-3-yl)methylene) hydrazinyl)-4-(4-methoxyphenyl)thiazole (5e)**

63% yield; FTIR (KBr) υ ($cm^{-1}$): 3232 (-NH, stretch), 3055 (C-H, aromatic), 1671 (C=N, azomethine), 1629 (-NH, bending), 1616 (C=C, aromatic), 1263 (C-O). $^1$H NMR (δ, ppm, $CDCl_3$): 10.28 (9, 1H), 8.04 (azomethine, 1H),

7.1-8.9 (Aromatic, 11H), 4.03 (12, 1H), 3.85 (1, 3H). MS: $M^+$ 428. Anal. Calcd for $C_{24}H_{20}N_4O_2S$: C, 67.27; H, 4.70; N, 13.07. Found: C, 66.87; H, 4.33; N, 12.79.

**(E)-4-(4-fluorophenyl)-2-(2-((1-methoxy-9H-carbazol-3-yl)methylene)hydrazinyl)thiazole (5f)**

52% yield; FTIR (KBr) υ ($cm^{-1}$): 3244 (-NH, stretch), 3127 (C-H, aromatic), 1662 (C=N, azomethine), 1618 (-NH, bending), 1601 (C=C, aromatic), 1259 (C-O), 1012 (C-F). $^1H$ NMR (δ, ppm, $CDCl_3$): 10.22 (9, 1H), 8.05 (azomethine, 1H), 7.3-8.5 (Aromatic, 11H), 3.98 (12, 1H), 3.79 (1, 3H). MS: $M^+$ 416. Anal. Calcd for $C_{23}H_{17}FN_4OS$: C, 66.33; H, 4.11; N, 13.45. Found: C, 65.96; H, 4.02; N, 13.14.

***In silico* molecular docking**

The *in silico* docking protocol was performed as per our previous reported paper. [21] All the molecules were fabricated using Chem Draw Ultra v. 8.0 and Merck Molecular Force Field application was run to minimization the energy. The 3-D X-ray structure of EGFR kinase (PDB ID: 2J5F) was obtained from RCSB Protein Data Bank and molecular docking of the selected ligands was performed employing AutoDock Vina. The ligand–protein complex was generated by keeping the program parameter to their default preferences. The docking was executed by MDS into the 3D model of the enzyme implementing Genetic Algorithm (GA) functions. A comparison of docking experiment was done with a well-known EGFR kinase inhibitor gefitinib to determine and compare the pharmacophoric features of synthesized molecules. The achieved outcomes were evaluated in terms of the binding score. An RMSD value inferior or close to 2A° was considered as a successful docking.

**Anticancer screening**

The anti-cancer screening was performed as per the protocol by Wei *et al.* [22] The breast cancer cell lines; MCF-7 and MDA-MB-231 were procured from NCCS, Pune. The cells were cultured in RPMI1640 media complemented by 10% fetal bovine serum at 37°C and 5% $CO_2$ and preserved in a humidified atmosphere. Sulforhodamine B (SRB) assay was employed to measure the *in vitro* cell sensitivity towards the test compounds using doxorubicin as the positive control. According to the protocol, the living cells were harvested, counted and plated using 96-well plates. After treating the cells with the compound of interest, 10% trichloroacetic acid solution was used to fix at 4°C. Further, the cells were treated with deionized water continuously and suitably stained with 0.4% SRB solution prepared in glacial acetic acid for 15 min. In order to remove unbound stain, the wells were washed thoroughly with the glacial acetic acid solution and allowed to dry at room temperature. Tris-base (tris(hydroxymethyl)aminomethane) solution was employed to solubilize the bound protein stain. Using microplate reader, the optical density was measured at 540 nm. The $IC_{50}$ values were determined accordingly. Capecitabine was employed as the standard drug for comparative study against the newly synthesized analogs.

## RESULT AND DISCUSSION

**Chemistry**

The IR spectra verified several imperative characters of the fabricated compounds. The stretching of the amides was principally exemplified by peaks in range 3194-3291 $cm^{-1}$. The amide bending was mainly observed in the range 1552-1631 $cm^{-1}$. Two important aspects of the aromatic ring were detected in the spectra. A C-H stretching in the range 3055-3146 $cm^{-1}$ and C=C stretching was recognized in the range 1609-1631 $cm^{-1}$. A prominent Schiff's base feature was observed in the range of 1651-1672 $cm^{-1}$. The $^1H$ NMR suggested the well-known structural attribute. The amide proton emerges in the spectrum at two different places. The protons of carbazole were noticed in the range 10.1-10.4 ppm, whereas the protons of aliphatic amide were positioned at 3.9-4.4 ppm. The peaks signifying the aromatic protons were observed at 7.1-8.9 ppm, symbolizing the 11 aromatic protons. The mass spectra depicted that all the observed base peaks were either corresponding or similar to their molecular weight. The isotopic forms of chlorine and bromine were also detected in the spectra as +2 molecular mass of abundance >30%. Numerous fragment peaks were also found in the m/z range of 100-200. The elemental analysis highlighted the % estimation of elements in close agreement with the theoretical value.

**Anti-proliferative activity**

The anti-cancer SRB assay of the hybrid compounds revealed that all compounds exhibited anti-cancer activity to their certain extent. Analog 5b having chloro substitution displayed most potent anti-proliferative activity with $IC_{50}$ values of 23.41μM against MCF-7 cell line and 32.15μM against MDA-MB-231 cell line. Compound 5f also demonstrated good activity with $IC_{50}$ values of 34.18μM against MCF-7 cell line and 43.66μM against MDA-MB-231 cell line. The derivatives 5a, 5d and 5e displayed poor anticancer with $IC_{50}$ values >50 μM against both the cell lines. However, an average anti-tumor activity was observed for the bromo moiety containing compound 5c having an $IC_{50}$ value of 39.74μM against MCF-7 cell line and 45.32μM against MDA-MB-231 cell line. Based on the Structure Activity Relationship (SARs) and rational designing of this hybrid scaffold, the substituents, and their positions played an imperative role in exhibiting anti-proliferative activity by modulating the biological target. The SAR highlighted that unsubstituted analog 5a expressed the lowest cytotoxic effect, however, the molecule showed better activity against MDA-MB-231 cell line as compared to MCF-7. The analogs 5d and 5e with electron-donating group have average activity. It has also been observed that analogs possessing electron withdrawing substituents (Cl, Br, and F) results in an increase in anticancer potential as indicated by their $IC_{50}$ values. The anti-proliferative activity might be

correlated with log P (lipophilicity) since all compounds with log P value greater than 6 displayed the highest activity among all candidates. Therefore, it could be exploratory of the fact that lipophilicity may be the decisive aspect for enhanced activity that influences bilipid membrane permeation and deeper access to molecular targets. The $IC_{50}$ values of the synthesized compounds are depicted in Table 1.

**Table 1: $IC_{50}$ values of synthesized derivatives against MCF-7 and MDA-MB-231 cell lines**

| Compound | $IC_{50}$ (µM) against | |
|---|---|---|
| | MCF-7 | MDA-MB-231 |
| **3** | 109.42 | 127.74 |
| **5a** | 83.47 | 70.11 |
| **5b** | 23.41 | 32.15 |
| **5c** | 39.74 | 45.32 |
| **5d** | 59.63 | 68.29 |
| **5e** | 79.44 | 86.12 |
| **5f** | 34.18 | 43.66 |
| **Capecitabine** | 6.98 | 9.77 |

**Table 2: Docking Score of the synthesized derivatives**

| Compound | Dock Score (kcal/mol) |
|---|---|
| **3** | -8.46 |
| **5a** | -10.54 |
| **5b** | -13.21 |
| **5c** | -10.97 |
| **5d** | -10.74 |
| **5e** | -10.33 |
| **5f** | -11.59 |
| **Gefitinib** | -13.48 |

## In silico docking

The molecular docking of ligands into the active site of EGFR kinase divulged several features. Compound 5b demonstrated the highest docking score -13.21 kcal/mol which suggests the highest affinity for the enzyme as compared to other compounds in the series. The compound interacted strongly with the amino acid residues (Figure 2). Numerous alkyl interactions were displayed by thiazole (with VAL726), phenyl (with LEU743), and carbazole (with LEU788) moieties. The carbazole moiety displayed a strong Pi-Sulfur interaction with MET766. The nitro atom of thiazole group exhibited a strong pi-Sigma interaction with LEU844 whereas the sulfur exhibited a pi-Sulfur interaction with CYS797. The chloro group at the para position of phenyl moiety exhibited hydrogen bonding with MET793 and alkyl interaction with three amino acid residues; ALA743, LEU718, and LEU792, respectively. The molecule 5b expressed a comparable docking score as the standard drug, gefitinib (-13.48 kcal/mol). The analog 5f exhibited good affinity for the enzyme with docking score -11.59 kcal/mol just next in gradation to 5b. Compound 5f, although displayed exactly similar interaction like 5b, however, the affinity was found to be low as compared to both 5b and standard drug. The other derivatives 5c-5e displayed the dock score more than -10 kcal/mol, representing moderate affinity for EGFR. In compound 5d and 5e, the thiazole ring interacted with MET793, LEU844, and ALA743, whereas, the phenyl ring interacted with LEU718 in common to exhibit antagonistic activity on EGFR. The methyl group (of tolyl moiety) of compound 5d demonstrated successful interactions with amino acid residues LEU844 and CYS797, respectively. It was strangely noticed that in compound 5e, no interaction took place between methoxy group and kinase residues. This may be the probable reason for lowest anti-cancer activity owing to lesser affinity towards the target. The docking score of the synthesized compounds is described in Table 2.

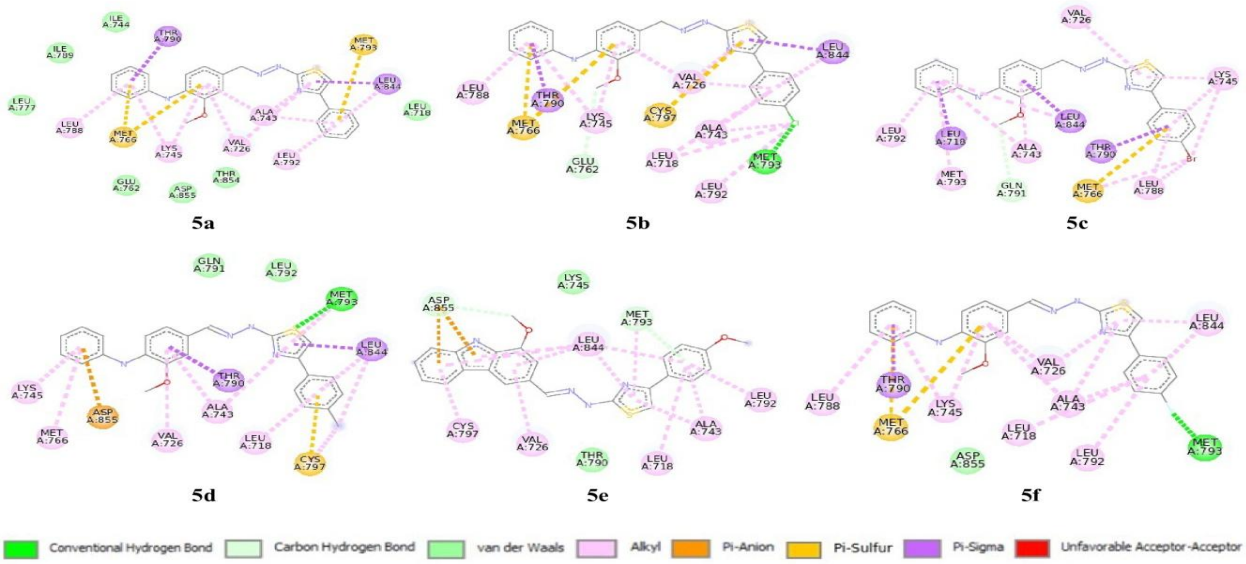



**Fig. 2. Docking poses of synthesized analogs against EGFR Kinase**

The study revealed the potential of substituted thiazole linked murrayanine-Schiff's base derivatives as active anti-breast cancer candidates. The research highlighted the intense role of substitution on the phenyl moiety of

the phenyl system of 2,4-disubstituted thiazole ring. The docking study was found to be in full agreement with the cytotoxic study, depicting access of molecules into the active sites of the enzyme. The compound 5b displayed most potent anti-proliferative activity with $IC_{50}$ values of 23.41µM against MCF-7 cell line and 32.15µM against MDA-MB-231 cell line. It might be understood that all the novel synthesized derivatives showed cytotoxic outcome by EGFR inhibitory mechanism. The research will surely encourage (medicinal) chemists for rationally designing of semi-synthetic analogs of heterocyclic prototype which will have pronounced anti-cancer activity. The well-defined mechanism of action (MOA) and structure-activity relationship (SAR) of the heterocyclic linked natural product will open new avenues in designing more effective inhibitors in future having diverse biological activities.

## ACKNOWLEDGEMENT

Authors are highly thankful to Savitribai Phule Pune University, Pune, Maharashtra, India for providing research grants (Grant No. 13PHM000126).

## REFERENCES

1. http://www.who.int/mediacentre/factsheets/fs297/en/ (accessed 11April, 2017).
2. Asati V, Mahapatra DK, Bharti SK. Thiazolidine-2, 4-diones as multi-targeted scaffold in medicinal chemistry: potential anticancer agents. European Journal of Medicinal Chemistry. 2014; 87:814-33.
3. Mahapatra DK, Bharti SK, Asati V. Anti-cancer chalcones: Structural and molecular target perspectives. European Journal of Medicinal Chemistry. 2015; 98:69-114.
4. Iyer D, Devi U. Phyto-pharmacology of Murraya koenigii (L.). Pharmacognosy Reviews. 2008; 2(3):180.
5. Nayak A, Mandal S, Banerji A, Banerji J. Review on chemistry and pharmacology of Murraya koenigii Spreng (Rutaceae). Journal of Chemical and Pharmaceutical Research. 2010; 2(2):286-99.
6. Adebajo AC, Olayiwola G, Eugen Verspohl J, Iwalewa EO, Omisore NO, Bergenthal D, Kumar V, Kolawole Adesina S. Evaluation of the Ethnomedical Claims of Murraya koenigii. Pharmaceutical Biology. 2005; 42(8):610-620.
7. Rao KV, Schwartz SA, Nair HK, Aalinkeel R, Mahajan S, Chawda R, Nair MP. Plant derived products as a source of cellular growth inhibitory phytochemicals on PC-3M, DU-145 and LNCaP prostate cancer cell lines. Current Science. 2004; 87(11):1585-1588.
8. Ajay S, Rahul S, Sumit G, Paras M, Mishra A, Gaurav A. Comprehensive review: Murraya koenigii Linn. Asian Journal of Pharmacy and Life Science 2011; 2231:4423.
9. Nagappan T, Ramasamy P, Wahid ME, Segaran TC, Vairappan CS. Biological activity of carbazole alkaloids and essential oil of Murraya koenigii against antibiotic resistant microbes and cancer cell lines. Molecules. 2011; 16(11):9651-9664.
10. Sukari M, Aspollah M, Ismail N, Bakar A, Haslizawati N, Ithnin NL. Cytotoxic carbazole alkaloids from Murraya koenigii (Rutaceae). Research Journal of Chemistry and Environment. 2014; 18(11):8-11.
11. Fiebig M, Pezzuto JM, Soejarto DD, Kinghorn AD. Koenoline, a further cytotoxic carbazole alkaloid from Murraya koenigii. Phytochemistry. 1985; 24(12):3041-3.
12. Mohan S, Abdelwahab SI, Cheah SC, Sukari MA, Syam S, Shamsuddin N, Rais Mustafa M. Apoptosis effect of girinimbine isolated from Murraya koenigii on lung cancer cells in vitro. Evidence-Based Complementary and Alternative Medicine. 2013; 2013.
13. Kok YY. Cytotoxicity of Mahanimbine, Murryafoline A and S-Benzyldithiocarbazate on Human Leukemic Cell Line, CEM-SS (Doctoral dissertation, Universiti Putra Malaysia).
14. Handral HK, Pandith A, Shruthi SD. A review on Murraya koenigii: multipotential medicinal plant. Asian Journal of Pharmaceutical and Clinical Research. 2012; 5(4):5-14.
15. Mahapatra DK, Bharti SK. Computer assisted rational design and synthesis of some novel 2, 4-di-substitued thiazole derivatives and their metal complexes (copper, cobalt, and nickel) as inhibitor of bacterial metabolic enzymes. International Journal of Infectious Diseases. 2016; 45:126-7
16. Bharti SK, Mahapatra DK, Singh SK. Thiazole: A Simple Scaffold with Tremendous Therapeutic Potential. In: Chemical and Biochemical Engineering: New Materials and Developed Components. Apple Academic Press. 2015, pp. 43-64.
17. Bharti SK, Patel SK, Nath G, Tilak R, Singh SK. Synthesis, characterization, DNA cleavage and in vitro antimicrobial activities of copper (II) complexes of Schiff bases containing a 2, 4-disubstituted thiazole. Transition Metal Chemistry. 2010; 35(8):917-25.
18. Bharti SK, Nath G, Tilak R, Singh SK. Synthesis, anti-bacterial and anti-fungal activities of some novel Schiff bases containing 2, 4-disubstituted thiazole ring. European Journal of Medicinal Chemistry. 2010; 45(2):651-60.
19. Shivhare RS, Mahapatra DK, Nair RR, Deshmukh SN. Schiff's base derivatives of murrayanine demonstrated enhanced anti-oxidant activity than its parent moiety. Indian Journal of Pharmaceutical Education and Research 2016; 50(3):9-15.
20. Bharti SK, Singh SK. Design, synthesis and biological evaluation of some novel benzylidene-2-(4-phenylthiazol-2-yl) hydrazines as potential anti-inflammatory agents. Medicinal Chemistry Research. 2014; 23(2):1004-15.
21. Asati V, Bajaj S, Mahapatra DK, Bharti SK. Molecular modeling studies of some thiazolidine-2, 4-dione derivatives as 15-PGDH inhibitors. Medicinal Chemistry Research. 2016; 25(1):94-108.
22. Wei H, Zhang X, Wu G, Yang X, Pan S, Wang Y, Ruan J. Chalcone derivatives from the fern Cyclosorus parasiticus and their anti-proliferative activity. Food and Chemical Toxicology. 2013; 60:147-52.

**HOW TO CITE THIS ARTICLE:** Mahapatra DK, Das D, Shivhare R. Substituted thiazole linked murrayanine-Schiff's base derivatives as potential anti-breast cancer candidates: Future EGFR Kinase inhibitors. Int. J. Pharm. Sci. Drug Res. 2017; 9(3): 139-144. **DOI: 10.25004/IJPSDR.2017.090307**