RESEARCH ARTICLE

Synthesis, Characterisation, Molecular Docking Studies and Biological Evaluation of Novel Benzothiazole Derivatives as EGFR Inhibitors for Anti-breast Cancer Agents

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ABSTRACT

Novel (2-anilino-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide derivatives were synthesized and characterized by spectroscopy methods. All the compounds assessed for *in-vitro* antimicrobial activities on three strains are *S. aureus*, *S. epidermis* and *E. coli* by using disc plate method (25 µg/mL). Compounds 5a-5j showed good to excellent antimicrobial activity for three different strains compared to standard ciprofloxacin. Further screened by *in-vitro* cytotoxic activity against MCF-7 cell lines. Some compounds were 5i, 5c, 5b,5d and 5i showed high cytotoxic activities of IC_{50} values 73, 53,37,32 and 24 µg/mL, reference drug as Gefitinib against MCF-7 cell lines and MCF-12A. Further carried out docking studies using Schrodinger software to analyze the orientations, interactions and binding modes of these derivatives at the adenine -5-triphosphate binding site of EGFR (PDB ID: 2ITY), which indicated that the ligands show good interactions with active site residues in this structural benzothiazole class, and are considered lead compounds for further development as anti-breast cancer drugs.

Keywords: Benzothiazole, Cytotoxic activity, Breast cancer, MCF7 Cell lines, Antibacterial activity.

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INTRODUCTION

Cancer, which is responsible for most global deaths, is the leading cause of mortality worldwide. In 2020, 19.32 million new cancer cases were stated,[1] with a staggering death toll of around 10 million individuals. The perilous nature of this disease arises from the abandoned proliferation of cells that spread through the body. The causes of cancer are multifaceted and encompass a range of factors, including genetics and the environment. Additionally, certain human activities[3] such as alcohol consumption,[4] smoking,[5] and the consumption of red meat[6] contribute to the development of cancer. Furthermore, specific types of cancer can be attributed to infections caused by *Helicobacter pylori*,[7] human papillomavirus[8] (HPV), and hepatitis B virus[9] (HBV). Anticancer medications are used to stop the development and division of cancer cells, which usually results in the death of the tumor cells. For this reason, numerous studies have been conducted in an effort to create a more effective anti-cancerous medicine. The process of making significant progress towards creating a medicine with no side effects,[10] however, is ongoing. Nevertheless, the FDA has approved anticancer medications, including daunorubicin, trastuzumab,[11] sunitinib.[12] However, such medications have several severe, hard-to-diagnose adverse effects.

Benzothiazole has various pharmacologic activities of antimicrobial,[13] antimalarial,[14] anti-leishmanial,[15] anti-fungal[16] anti-cancer[17] and inhibit tyrosine kinase,[18] topoisomerase,[19] and DHODH kinase[20] in the latest research. The applications of benzothiazole derivatives as anticancer drugs are rapidly spreading to almost all the branches of pharmaceutical chemistry. These derivatives represent as large group of anti-proliferative agents that exhibit DNA-intercalating cytotoxicity, causing interference in replication. The EGFR

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receptor belongs to the tyrosine kinase receptor family. When a ligand binds with the receptor, major tyrosine groups are autophosphorylated, with stimulation of PI3K/AKT pathways. These pathways work synergistically to endorse cell persistence. USFDA permitted 21 previous studies on foretinib and cabozantinib 2012 for thyroid cancer[22] but it has always been a topic of debate around their use and high adverse effects were reported in the literature. In order to improve efficacy and reduce toxicity, cost-effective and innovative strategies are planned for modifying the SAR of cabozantinib and foretinib of our research work.

Hence, we have designed the synthetic compounds 5a to 5j from the substituted aromatic amines, respectively, (2-anilino-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide derivatives.

MATERIALS AND METHOD

Synthesis of General Procedure

An equimolar amount of 1.4 moles of 4,6-dimethyl-1,3-benzothiazole-2-amine[23-25] and (3.8 mL) of ammonium thiocyanate, 1-mL of glacial acetic acid and add 4 mL of concentrated HCl in a clean round bottom flask on reflux for 1-hour. Then, filter the solution, wash and dry the product. TLC does the conformation of the obtained product. weigh 1.8 mol of 4,6-dimethyl-1,3-benzothiazole-2-amine obtained from 1st step, then add 1-mL of chloro-acetyl chloride in 50 mL of dry benzene and 15 gm of KCO_3 in a clean round bottom flask on reflux for 12 hours then the solid product was stirred with ice water and filtered then washed through 5% sodium bicarbonate and subsequently with water. Further, weigh 3.38 mol of aniline and a quantity sufficient of ethanol in an RBF on reflux for 2 hours. This procedure was meticulously followed to achieve the compounds 5a-5j Substituted aromatic amines respectively (2-anilino-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide.

Molecular Docking Study of EGFR with Inhibitors

The molecular dynamics simulation[26] analysis of remodeled and refined EGFR structure (Figure 1a), revealed that the protein has attained equilibrium and has maintained stability throughout the MD production with a minimal RMS deviation of ~ 0.35 nm (Figure 1b). The RMSF plot (Figure 1c), showed that except the C-terminal and N-terminal residues by higher fluctuation of ~ 0.6 nm, sheet II and III residues and the C-terminal loop residues has shown higher fluctuations of ~0.38 nm. However, a negligible degree of compactness was observed for the protein without any significant Rg deviations (Figure 1d). The minimum potential energy structure extracted at 86.8th ns (Figure S2) with a minimum potential energy of -7.062e+05 kJ/mol was considered further for docking studies (Table 1).

Biological Evaluation

Antimicrobial activity

Schiff bases derived from benzothiazoles 5a-5j were assessed for their *in-vitro* antibacterial effects[27,28] against three distinct

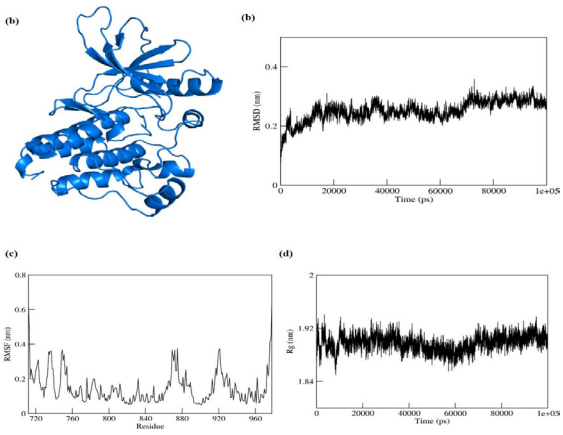


Figure 1: (b) Modelled and refined three-dimensional structure of EGFR shown in cartoon representation (Slate blue); Molecular dynamics simulation analysis of EGFR: RMSD plot: RMSF plot: Radius of gyration plot

strains: *S. aureus*, *S. epidermidis*, and *E. coli*. This evaluation was conducted using the disc plate method. After determining the MIC values, a fixed concentration of 25 µg/mL was established for all the compounds. Notably, 5a-5j exhibited significant antimicrobial efficacy against the aforementioned bacterial strains, a reference drug such as ciprofloxacin. The outcomes were quantified and the zone of inhibition (mm) against selected microorganisms were measured. Detailed results can be found in Table 2.

In-vitro cytotoxicity by MTT assay

The cytotoxicity of all the compounds against breast cancer cell lines and non-cancerous breast cell lines was screened by MTT assay method.[29,30] One of the most powerful anticancer medications, gefitinib, was employed as a reference medication in this study. The survival curve representing the MCF-7 cancer cell line was generated by plotting the connection between the surviving fraction and drugs concentration. As the response parameter, the IC_{50} values, which stand for the concentration necessary to decrease cell viability by 50% were computed. Table 3 lists the findings of the synthesized compounds' *in-vitro* cytotoxic activities. Additionally, these chemicals were evaluated against the normal epithelial cell MCF 12A in order to ascertain their selectivity for malignant versus normal cells.

Experimental Section

Chemistry

All chemicals used were acquired from SD Fine Chemicals Ltd (Mumbai). Readymade TLC plates from E. Merck were employed, and the TLC plates were subjected to development using both iodine and UV light. The mobile phase utilized for development was chloroform and methanol (1:1). Infrared (IR) spectra was using KBr pellets and a 1420 spectrometer.[24,25] ESI-MS was run negative mode using a ZQ-4000 single quadrupole mass spectrometer.[26-31] For ^{1}H-NMR ^{13}C-NMR (126MHz), $CDCl_3$, spectroscopy, Bruker Advance 500 MHz equipment was employed, and chemical shifts were recorded in ppm.

Table 1: Molecular docking analysis of compounds with EGFR

Compound Code	*docking score*	*glide score*	*Interactions*				
			Hydrogen bonds	*Halogen bond*	*Salt bridge*	*π-π stacking*	*π--cation*
5a	-5.561	-5.886	Asp855		Asp855		
5b	-6.161	-6.206	Asp855		Asp855		
5c	-6.113	-6.139	Asp855		Asp855		
5d	-4.841	-4.872	Asn842		Asp855		
5e	-5.361	-5.391			Asp855		
5f	-4.597	-4.597				Phe723	Lys745
5g	-4.559	-4.637	Lys745			Phe723	Lys745
5h	-5.243	-5.245		Cys797,Asp800			
5i	-3.805	-3.813	Lys745			Phe723	Lys745
5i	-3.805	-3.813	Lys745			Phe723	Lys745
std	-3.105	-3.232				Phe723	Lys745

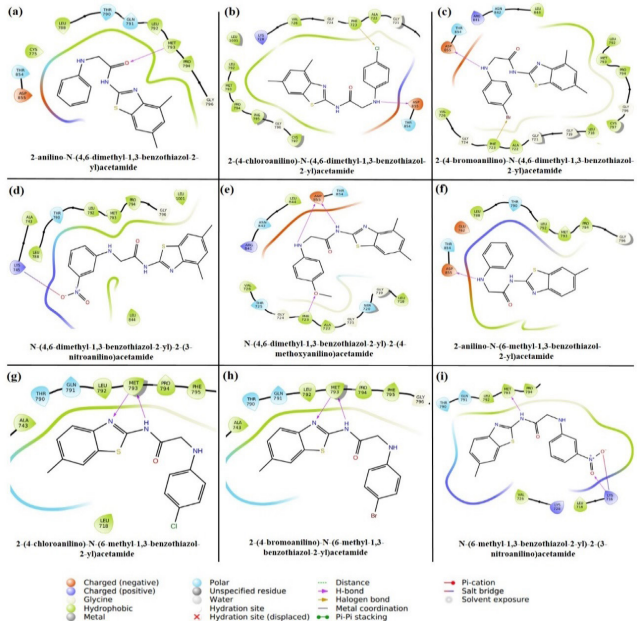


Figure 2: 2D interaction profiling of EGFR- inhibitor complexes (5a-5i) Compound 16-20

5a: (2-anilino-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide Green solid, Yield, 78%, m.p126ºC IR tmax, 3236 (-OH), 3104 (N–H), 2662.54(-CH2 str),1678(C-O),1332(C-N),1167.04(C–Nstr), ^{1}H-NMR(500MHz, DMSO), d12.01(s,2H), 7.5(s,1H), 8.03(d.2H), 8.1(d,8.0Hz,1H), 7.82(8.2Hz,1H), ^{13}C-NMR (126MHz), $CDCl_3$), d164.23, 162.63, 155.88, 153.72, 132.42, 139.22, 127.56, 123.20, 121.13, 118.21, 112.32, 107.321 ESI-MS (m/z) Molecular Formula $C_{19}H_{19}N_5O_4$, Molecular weight found: 382.

5b: 2-(4-bromoanilino)-*N*-(4,6-dimethyl-1,3-Benzo-sulfonazol-2-yl) ethanamide Dark brown solid, Yield, 76%, m.p143 ºC, (IR) tmax, 3182 (-OH), 3221 (N–H), 2584.14 (-CH2), 1598 (C-O), 1421(C-N), 1169.04 (C–N), ^{1}H-NMR(500MHzDMSO4.01(d,2H), 7.80(d,2H), 8.11(d.1H), 7.7(d,8.0Hz,2H), 7.69(8.2Hz,1H) ^{13}CNMR(126MHz), $CDCl_3$), d162.23, 161.63, 155.88, 153.72, 137.42, 139.22, 117.56, 126.20, 121.13, 118.21, 112.32, 107.321 ESI-MS (m/z) $C_{20}H_{22}N_6O_3S$ Molecular weight found 393.65.

Table 2: Antimicrobial activity of the synthesised compound

Compound code	*Zone of Inhibition(mm)/Conc of synthesised compounds 25 µg/mL*		
	S. aureus	*S. epidermis*	*E. coli*
5a	14	12	15
5b	16	13	13
5c	15	15	12
5d	14	14	13
5e	13	15	16
5f	16	13	13
5g	15	15	12
5h	14	12	13
5i	13	15	12
5j	15	13	14
Ciprofloxacin	28	29	28

5c: 2-(4-chloroanilino)-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide (5c) yellow soild, Yield, 78%, 143 ºC, IR tmax, 3236 (-OH), 3104 (N–H), 2662.54(-CH2 str),1678(C-O),1332(C-N),1167.04(C Nstr), ^{1}H-NMR(500MHz, DMSO), d12.01(s,2H), 7.5(s,1H), 8.03(d.2H), 7.9(d,8.0Hz,2H), 7.82(8.2Hz,1H) ^{13}CNMR(126MHz), $CDCl_3$), d164.23, 162.63, 155.88, 153.72, 132.42, 139.22, 127.56, 123.20, 121.13, 118.21, 112.32, 107.321 ESI-MS (m/z) [M+]. Molecular formula $C_{13}H_{15}N_5O_3S$ Molecular weight found 290.

5d: 2-(2,6-dimethylanilino)-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide light orange solid,

Table 3: Inhibition growth IC_{50} data for 5a-5j

	IC_{50} (in μM)	
Compound	*MCF-7*	*MCF 12A*
5a	61.1 ± 0.42	Non-toxic
5b	42.2 ± 0.61	Non-toxic
5c	85.2 ± 0.58	Non-toxic
5d	73.2 ± 0.83	Non-toxic
5e	67.2 ± 0.64	82.2 ± 0.53
5f	53.2 ± 0.39	Non-toxic
5g	74.2 ± 0.53	Non-toxic
5h	41.2 ± 0.74	71.2 ± 0.40
5i	37.2 ± 0.33	Non-toxic
5j	85.2 ± 0.48	Non-toxic
Gefitinib	33.2 ± 0.92	Non-toxic

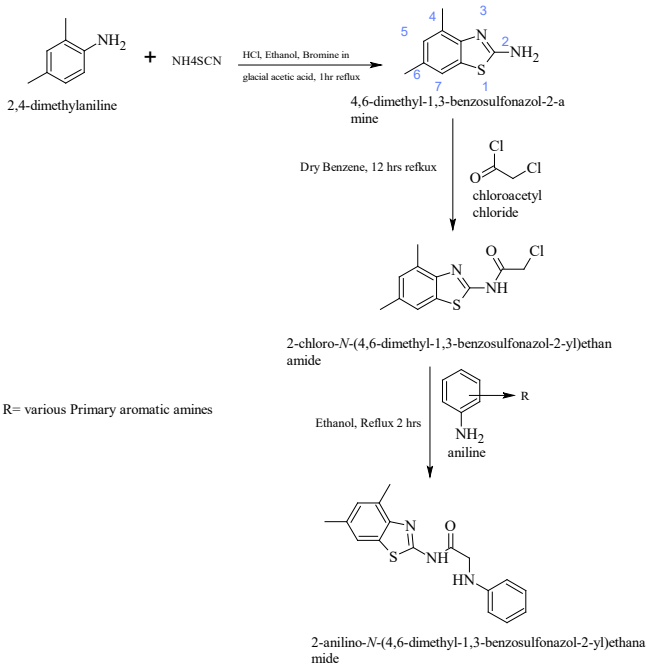
Yield, 85%, m.p., 176ºC, (IR) tmax, 3241 (-OH), 3362 (N–H str), 2584.14 (-CH2), 1598 (C-O), 1421(C-N), 1169.04 (C–N), ^{1}H-NMR(500MHz, DMSO) 14.01(d,2H), 7.76(s,1H), 8.42(d.1H)7.7(d,8.0Hz,2H), 7.69(8.2Hz,1H) ^{13}CNMR(126MHz), $CDCl_3$), d162.23, 161.63, 155.88, 153.72, 137.42, 139.22, 117.56, 126.20, 121.13, 118.21, 112.32, 107.321 ESI-MS (m/z) Molecular Formula $C_{11}H_{12}N_4O_3S$ Molecular weight found 354

5e: 2-(2,4-dimethylanilino)-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide white solid, Yield, 78%, m.p., 126 ºC, (IR) tmax, 3110 (-OH), 3426 (N–H), 2584.14 (-CH2 str), 1598 (C-O), 1421(C-N), 1169.01 (C–N),^{1}HNMR(500MHz,DMSO)d 14.01(d,2H), 7.82(s,1H), 8.3(d.1H) 7.7(d,8.0Hz,2H), 7.69(8.2Hz,2H) ^{13}CNMR(126MHz), CDCl,d162.23, 161.63, 155.88, 153.72, 137.42, 139.22, 117.56, 126.20, 121.13, 118.21, 112.32, 107.321 ESI-MS (m/z) Molecular Formula $C_{20}H_{22}N_6O_3S$ Molecular weight found 395.

5f: 2-(2methoxyanilino)-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide light orange solid, Yield, 88%, m.p., 106ºC(IR) tmax, 3216 (-OH), 3420 (N–H), 2584.14 (-CH2), 1598 (C-O), 1421(C-N), 1169.04 (C–N),^{1}H-NMR (500MHz, DMSO)d 14.01(d,2H), 7.62(s,1H), 8.53(d.2H) 7.6(d,8.0Hz,2H), 6.99(8.2Hz,2H) ^{13}CNMR(126 MHz), $CDCl_3$), d162.23, 161.63, 155.88, 153.72, 137.42,139.22,117.56,126.20,121.13,118.21,112.32,107.321 ESI-MS (m/z) Molecular Formula $C_{11}H_{11}N_5O_4S$ Molecular weight found 310.

5g:2-(4-methoxy)-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide Green solid, Yield, 82%, m.p., 166 ºC, (IR) tmax, 3118(-OH), 3127 (N–H), 2566.14 (-CH2str), 1598 (C-O), 1421(C-N), 1169.04 (C–N),^{1}HNMR(500MHz,DMSO) d 14.01(d,2H), 7.73(s,1H), 8.62(s.1H) 7.7(d,8.0Hz,2H), 7.69(8.2Hz,1H) ^{13}C-NMR(126MHz), $CDCl_3$), d162.23, 161.63, 155.88, 153.72, 137.42, 139.22, 117. 56, 126.20, 121.13, 118.21, 112.32, 107.321 ESI-MS (m/z) Molecular Formula $C_{11}H_{11}BrN_4O_2S$ Molecular weight found 344.02.

5h: 2-(2-chloroanilino)-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide Dark yellow solid, Yield,80%, m.p., 162ºC (IR) tmax, 3114 (-OH), 3339 (N–H str), 2584.14 (-CH2), 1598 (C-O), 1421(C-N), 1169.04 (C–N),^{1}HNMR(500MHz,DMSO)d 14.01(d,2H),7.43(s,1H),8.91(d.1H)7.7(d,8.0Hz,2H),7.69(8.2Hz,1H)^{13}CNMR(126MHz),CDCl_3),d162.23,161.63,155.88,153.72,137.42,139.22,117. 56,126.20, 121.13,118.21,112.32,107.321 ESI-MS (m/z) Molecular Formula $C_{12}H_{12}N_4O_4S$ Molecular weight found 309.31.



Scheme1: Synthesis of Novel Benzothiazole Derivatives 5a-5i

5i: 2-(2-Bromo anilino)-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide yellow solid, Yield, 89%, m.p., 173ºC, (IR) tmax, 3144 (-OH), 3420 (N–H), 2584.14 (-CH2str), 1598 (C-O), 1421(C-N), 1169.04 (C–N),^{1}HNMR(500MHz,DMSO)d 14.01(d,2H),7.66(s,1H),8.11(d.1H)8.3(d,8.0Hz,2H),7.69(8.2Hz,1H)^{13}CNMR(126MHz),$CDCl_3$),d162.23,161.63,155.88,153.72,137.42,139.22,117.56, 126.20,121.13, 118.21,112.32,107.321 ESI-MS (m/z) Molecular Formula $C_{11}H_{11}BrN_4O_2S$ Molecular weight found 353.06.

5j: 2-(3-methoxyanilino)-*N*-(4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide Pale yellow solid, Yield, 94%, m.p., 162ºC IR) t_{max}, 3241 (-OH), 3362 (N–H), 2584.14 (-CH_2 str), 1598 (C-O), 1421(C-N), 1169.04(C–N), ^{1}H-NMR (C–N), ^{1}H-NMR (500 MHz, DMSO)d) 14.01(d,2H), 7.23(s,1H), 8.90(d.1H) 8.4(d,8.0Hz,1H), 7.69(8.2Hz,1H) ^{13}CNMR(126MHz), $CDCl_3$), d162.23, 161.63, 155.88, 153.72, 137.42, 139.22, 117.56, 126.20, 121.13, 118.21, 112.32, 107.321 ESI-MS (m/z) Molecular Formula $C_{11}H_{11}N_5O_4S$ Molecular weight found 310.02.

CONCLUSION

In this study, we have successfully synthesized Schiff base containing benzothiazole derivatives, all the compounds characterized by spectroscopy (Scheme 1). The empirical evidence of the present study revealed that the 4,6-dimethyl-1,3-Benzosulfonazol-2-yl) ethanamide compounds 5a-5j. All the compounds screened by *in-vitro* antimicrobial activities on three different strains are *S. aureus*, *S. epidermis* and *E. coli* by using disc plate method (25 μg/mL). 5a-5j compounds showed

good to excellent antimicrobial activity for three different strains compared to standard ciprofloxacin. Among all the compounds 5c, 5f, 6b, and 5d showed excellent activity against the MCF-7 cell lines. In this structural benzothiazole class, they are considered lead compounds for further development as anti-breast cancer drugs.

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