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SYNTHESIS, MOLECULAR DOCKING, AND BIOLOGICAL EVALUATION OF SOME NOVEL INDOLE DERIVATIVES CONTAIN 1,3-THIAZOLE

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ABSTRACT

In present study, microwave assisted synthesis of some novel Indole derivatives contain 1, 3-thiazole was performed. All the synthesized products were purified through column chromatography and structures of these compounds were characterized by IR, ¹H NMR and mass spectral data. All the final derivatives were screened for their anticancer, antimicrobial activity and Molecular docking studies. All their efficacy was compared with standard drugs. The synthesized compound **4b**, **4e**, **4i** and **4j** are showed good Anticancer activities whereas others exhibited significant activities. The compound **4c**, **4d**, **4e** and **4i** are has showed maximum antibacterial activity compare with streptomycin as a standard drug. The molecular docking studies of these novel derivatives of indole showed good agreement with the biological results when their binding pattern and affinity towards the active site of EGFR was investigate. Molecular docking study has been performed for all the synthesized compounds with MCF Acetylcholine-binding protein (AChBP) and results obtained are quite promising.

Keywords: Indole, 1,3-thiazole, Molecular docking, Anti-bacterial, Anticancer activity

1. INTRODUCTION

The microwave assisted synthesis articulates an area of research, developing from scientific discoveries about pollution awareness and it exploits a set of principles that reduces or eliminates the generation of hazardous chemicals in all steps of synthetic process. Substituted 1,3-thiazole nucleus and Indole moiety has engaged a distinctive place in the field of medicinal chemistry due to widespread range of Pharmacological activities [1-3]. The Molecular design and the microwave synthesis of the bioactive nitrogen, sulphur-containing heterocycles are at the top of the drug discovery and development. Substituted heterocyclic fragments constitute the core structure of a large number of pharmacologically interesting medicinal scaffolds present in numerous life-saving drugs [4-5]. Among these, substituted 1,3-thiazole nucleus and Indole skeletons are widely well used on designing several medicinal frameworks with a large number of Pharmacological belongings such as antimicrobial, anti-inflammatory, anticancer, antitubercular, and antiviral activities [6-9].

In conventional devices such as oil bath and heating mantles, are not only show for heating responses but also it produces a hot surface area on the reaction vessel. In microwave power alternatively is brought right into the chemical reactor from another

location and travels through the walls of the response vessel, warming the reagents, catalysts, and solvents directly. Recently, a new technique such as microwave dielectric heating has actually concerned the leading edge of chemical investigation [10-12]. Microwaves assisted synthesis is a high-speed technic with has actually attracted a significant quantity of rate of interest in most recent years. The new scaffolds 1,3-thiazole moiety contain novel Indole derivatives possessing latent functional substituents appear promising to fulfil the objectives of our Pharmacological activities and the desired chemical transformations.

2. MATERIAL AND METHODS

Melting points were measured by using open capillaries, using Toshniwal melting point apparatus, expressed in °C and are uncorrected. IR spectra of the compounds were recorded using on thermo Nicolet Nexus 670S series, FT-IR spectrometer using KBr disc. ¹H NMR was scanned on Avance-400 MHz instrument and chemical shifts are expressed in δ (ppm) relative to TMS as an internal standard using DMSO-*d*₆ as solvent. The mass spectra were recorded on a LC-MSD-Trip-SL. The purity of the compounds was checked on silica gel-coated aluminium sheets (Merck, 1.005554, silica gel HF254–361, Type 60, 0.25 mm) by analytical thin-layer

chromatography (TLC). TLC was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with ultraviolet light (short wave length, 254 nm). Column chromatography was performed by using Qualigen's silica gel for column chromatography (60–120 mesh).

2.1. General procedure [13-16]

Step 1: Synthesis of 2-Amino 4-Aryl Thiazole (Cyclization reaction). A mixture of substituted acetophenone (0.1 mol), thiourea (0.2 mol) and Iodine (0.1 mol) were placed in an open vessel containing a Teflon coated stir bar. The vessel was placed in the microwave cavity (CEM, Discover) and subjected to MW irradiation at 140°C for 10 min. Then after the completion of the reaction crude mixture was cooled to 70°C and then it was triturated, filtered and washed with ethanol. The crude product was dissolved in hot water and the pH was adjusted to 11–12 with NH₄OH. The precipitate was filtered and crystallized from mixture of ethanol: water (1:4) to get the product.

Step: 2. 1-(1H-indol-3-yl)-N-(4-phenylthiazol-2-yl) methanimine (2a-2g). To a solution of equimolar quantity of compound (1a-1g) (0.01mol) and Indole-3-carboxaldehyde (0.01mol) was added into absolute ethanol (20ml) and 10ml of glacial acetic acid, then MW irradiation 300W for 8-10 min. Then after the completion of the

reaction mixture was cooled to room temperature and the solvent was then distilled off and the product obtained was recrystallized using ethanol. The progress of the reaction was monitored by TLC (n-Hexane: Ethyl acetate 7:3).

Step: 3: Preparation of (N-(1, 3-benzothiazol-2-yl)-2-chloroacetamide) (3a-3b).

To a solution of 2-amino benzothiazole (0.016mol) in (30ml) glacial acetic acid, chloroacetyl chloride (3.7g, 0.032mol) was added drop wise with constant stirring. The reaction mixture was MW irradiation 150W for 3-5 min, then it was powered in to crushed ice. The precipitated solid that obtained was filtered off, washed with cold water, dried and recrystallized from aqueous ethanol.

Step: 4. N-(benzo[d]thiazol-2-yl)-2-(3-((4-phenylthiazol-2-yl) imino) methyl)-1H-indol-1-yl) acetamide (4a-4l). To a solution of Compound (2a-2g) (0.016mol) in (30ml) glacial acetic acid, N-(benzo[d]thiazol-2-yl)-2-chloroacetamide (3a-3b) (0.032mol) was added drop wise with constant stirring. The reaction mixture was MW irradiation 150W for 3-5 min, then it was powered in to crushed ice. Then it was powered onto crushed ice. The precipitated solid that obtained was filtered off, washed with cold water, dried and recrystallized from aqueous ethanol.

2.2. Physical and Spectral data of the compounds:

4a: *N*-(benzo[d]thiazol-2-yl)-2-(3-(((4-phenylthiazol-2-yl)imino)methyl)-1H-indol-1-yl) acetamide: M.P. 187-

189°C; Mol. formula: C₂₇H₁₉N₅OS₂, yield 78%, IR (ν cm⁻¹): 3414(NH Str, -CO-NH-), 3062(C-H Str, Ar), 2992, 2842(C-H Str, Aliphatic), 2349 (C-S-C Str, Thazole), 1700(C=O Str, -CO-NH-), 1636(C=N Str), 1548(C=CH Str), 1484(C=C Str, Ar), 892(C-N Str). ¹H-NMR (DMSO) δδ ppm: 11.513(s, 1H, Acetamide), 8.997(s, Immine proton, CH=N), 8.371(s, 1H, Ar-H), 7.897-7.846(d, 2H, Ar-H), 7.798-7.780(d, 2H, Ar-H), 7.695-7.685(d, 2H, Ar-H), 7.601(s, 1H, Ar-H), 7.581-7.548(t, 2H, Ar-H), 7.498-7.480(t, 2H, Ar-H), 4.971-4.818(s, 2H, -CH₂-CO), 2.284-2.169(s, 1H, -CH-). Mass (LC-MS): m/z 493(M), 494(M + 1, 100%).

4b: *N*-(benzo[d]thiazol-2-yl)-2-(3-(((4-(p-tolyl)thiazol-2-yl)imino)methyl)-1H-indol-1-yl) acetamide: M.P. 203-205°C; Mol. formula: C₂₈H₂₁N₅OS₂, yield 84%, IR (ν cm⁻¹): 3423(NH Str, -CO-NH-), 3012(C-H Str, Ar), 2910, 2891, 2732(C-H Str, Aliphatic), 2323(C-S-C Str, Thazole), 1712(C=O Str, -CO-NH-), 1648(C=N Str), 1548(C=CH Str), 1485(C=C Str, Ar), 972(C-N Str). ¹H-NMR (DMSO) δδ ppm: 10.691(s, 1H, Acetamide), 8.893(s, Immine proton, CH=N), 7.979(s, 1H, Ar-H), 7.809-7.783(d, 2H, Ar-H), 7.658-7.631(d, 2H, Ar-

H), 7.520(s, 1H, Ar-H), 7.485-7.473(d, 2H, Ar-H), 7.443(t, 2H, Ar-H), 7.581-7.433(d, 2H, Ar-H), 7.392-7.388(t, 2H, Ar-H), 4.744-4.733(s, 2H, -CH₂-CO), 2.185(s, 1H, Ar-CH₃). Mass (LC-MS): m/z 507(M), 508(M + 1, 100%).

4c: *N*-(benzo[d]thiazol-2-yl)-2-(3-(((4-(4-chlorophenyl)thiazol-2-yl)imino)methyl)-1H-indol-1-yl) acetamide: M.P. 254-256°C; Mol. formula: C₂₇H₁₈N₅OClS₂, yield 76%, IR (ν cm⁻¹): 3403(NH Str, -CO-NH-), 3082(C-H Str, Ar), 2952, 2810(C-H Str, Aliphatic), 2351 (C-S-C Str, Thazole), 1712(C=O Str, -CO-NH-), 1653(C=N Str), 1532(C=CH Str), 1405(C=C Str, Ar), 1083(C-N Str), 794(Cl Str, Ar-Cl). ¹H-NMR (DMSO) δδ ppm: 11.498(s, 1H, Acetamide), 8.916(s, Immine proton, CH=N), 7.978(s, 1H, Ar-H), 7.902-7.876(d, 2H, Ar-H), 7.848-7.795(d, 2H, Ar-H), 7.785(s, 1H, Ar-H), 7.695-7.686(d, 2H, Ar-H), 7.606-7.596(t, 2H, Ar-H), 7.583-7.518(d, 2H, Ar-H), 7.491-7.488(t, 2H, Ar-H), 4.769-4.768(s, 2H, -CH₂-CO). Mass (LC-MS): m/z 527(M), 528(M + 1, 100%), 529(M + 2, 30%).

4d: *N*-(benzo[d]thiazol-2-yl)-2-(3-(((4-(4-fluorophenyl)thiazol-2-yl)imino)methyl)-1H-indol-1-yl) acetamide: M.P. 213-215°C; Mol. formula: C₂₇H₁₈N₅O₂FS₂, yield 77%, IR (ν cm⁻¹): 3422(NH Str, -CO-NH-), 3010(C-H Str, Ar), 2991, 2842(C-H Str, Aliphatic), 2323 (C-S-C Str, Thazole),

1713(C=O *Str*, -CO-NH-), 1636(C=N *Str*), 1542(C=CH *Str*), 1383(C=C *Str*, Ar), 930(C-N *Str*), 851(F *Str*, Ar-F). ¹H-NMR (DMSO) $\delta\delta$ ppm: 10.958(s, 1H, Acetamide), 8.671(s, Immine proton, CH=N), 8.105(s, 1H, Ar-H), 7.886-7.878(d, 2H, Ar-H), 7.843(d, 2H, Ar-H), 7.685-7.658(d, 2H, Ar-H), 7.638-7.581(t, 2H, Ar-H), 7.574-7.556(d, 2H, Ar-H), 7.516-7.146(t, 2H, Ar-H), 7.16(s, 1H, Ar-H), 4.567-4.565(s, 2H, -CH₂-CO). Mass (LC-MS): m/z 511(M), 512(M + 1, 100%), 513(M + 2, 30%).

4e: N-(benzo[d]thiazol-2-yl)-2-(3-(((4-(4-methoxyphenyl)thiazol-2-yl)imino)methyl)-1H-indol-1-yl)acetamide

acetamide: M.P. 187-189°C; Mol. formula: C₂₇H₁₉N₂OS, yield 78%, IR (ν cm⁻¹): 3414(NH *Str*, -CO-NH-), 3062(C-H *Str*, Ar), 2992, 2842(C-H *Str*, Aliphatic), 2349(C-S-C *Str*, Thazole), 1700(C=O *Str*, -CO-NH-), 1636(C=N *Str*), 1548(C=CH *Str*), 1484(C=C *Str*, Ar), 972(C-N *Str*), 809(Cl *Str*, Ar-Cl). ¹H-NMR (DMSO) $\delta\delta$ ppm: 12.304(s, 1H, Acetamide), 9.839(s, Immine proton, CH=N), 8.456(s, 1H, Ar-H), 8.183-8.058(d, 2H, Ar-H), 7.969-7.694(d, 2H, Ar-H), 7.591-7.534(d, 2H, Ar-H), 7.525-7.5059(t, 2H, Ar-H), 7.5057(s, 1H, Ar-H), 7.4904-7.4900(d, 2H, Ar-H), 7.474-7.470(t, 2H, Ar-H), 4.7951-4.7950(s, 2H, -CH₂-CO), 3.795-3.794(s, 1H, -OCH₃). Mass (LC-MS): m/z 493(M), 494(M + 1, 100%).

4f: N-(benzo[d]thiazol-2-yl)-2-(3-(((4-(4-nitrophenyl)thiazol-2-yl)imino)methyl)-1H-indol-1-yl)acetamide. M.P. 211-213°C; Mol. formula: C₂₄H₁₈N₆O₃S₂, yield 74%, IR (ν cm⁻¹): 3402(NH *Str*, -CO-NH-), 3054(C-H *Str*, Ar), 2987, 2865(C-H *Str*, Aliphatic), 2340(C-S-C *Str*, Thazole), 1702(C=O *Str*, -CO-NH-), 1632(NO₂), 1621(C=N *Str*), 1535(C=CH *Str*). ¹H-NMR (DMSO) $\delta\delta$ ppm: 11.763(s, 1H, Acetamide), 8.671(s, Immine proton, CH=N), 8.281(s, 1H, Ar-H), 7.763-7.673(d, 2H, Ar-H), 7.434-7.402(d, 2H, Ar-H), 7.320-7.243(d, 2H, Ar-H), 7.102(s, 1H, Ar-H), 7.043-7.002(t, 2H, Ar-H), 6.873-6.801(t, 2H, Ar-H), 4.893-4.801(s, 2H, -CH₂-CO), 2.453-2.324(s, 1H, -CH-). Mass (LC-MS): m/z 538.09(M), 539(M + 1, 100%).

4g: N-(benzo[d]thiazol-2-yl)-2-(3-(((4-(4-ethylphenyl)thiazol-2-yl)imino)methyl)-1H-indol-1-yl)acetamide. M.P. 201-203°C; Mol. formula: C₂₉H₂₃N₅OS₂, yield 78%, IR (ν cm⁻¹): 3401(NH *Str*, -CO-NH-), 3072(C-H *Str*, Ar), 2932, 2856, 2798(C-H *Str*, Aliphatic), 2343(C-S-C *Str*, Thazole), 1723(C=O *Str*, -CO-NH-), 1632(C=N *Str*), 1532(C=CH *Str*), 973(C-N *Str*). ¹H-NMR (DMSO) $\delta\delta$ ppm: 11.532(s, 1H, Acetamide), 8.893(s, Immine proton, CH=N), 7.893(s, 1H, Ar-H), 7.789-7.698(d, 2H, Ar-H), 7.345-7.231(d, 2H, Ar-H), 7.291(s, 1H, Ar-H), 7.172-7.132(d, 2H, Ar-

H), 7.101(t, 2H, Ar-H), 6.892-6.802(d, 2H, Ar-H), 6.543-6.211(t, 2H, Ar-H), 4.673-4.592(s, 2H, -CH₂-CO), 2.234-2.201(s, 2H, Ar-CH₂). 2.012-2.002(s, 1H, Ar-CH₃). Mass (LC-MS): m/z 521.13(M), 522(M + 1, 100%).

4h: N-(6-methylbenzo[d]thiazol-2-yl)-2-(3-(((4-phenylthiazol-2-yl)imino)methyl)-1H-indol-1-yl) acetamide. M.P. 183-185°C; Mol. formula: C₂₈H₂₁N₅OS₂, yield 81%, IR (ν cm⁻¹): 3412(NH Str, -CO-NH-), 3027(C-H Str, Ar), 2987, 2856(C-H Str, Aliphatic), 2345(C-S-C Str, Thazole), 1712(C=O Str, -CO-NH-), 1626(C=N Str), 1546(C=CH Str), 1410(C=C Str, Ar), 1021(C-N Str). ¹H-NMR (DMSO) δδ ppm: 12.092(s, 1H, Acetamide), 8.938(s, Immine proton, CH=N), 7.998(s, 1H, Ar-H), 7.890-7.783(d, 2H, Ar-H), 7.673-7.663(d, 2H, Ar-H), 7.543(s, 1H, Ar-H), 7.495-7.439(d, 2H, Ar-H), 7.236-7.201(t, 2H, Ar-H), 7.103-7.012(d, 2H, Ar-H), 6.980(t, 2H, Ar-H),

4.854-4.802(s, 2H, -CH₂-CO). Mass (LC-MS): m/z 507.12(M), 508(M + 1, 100%).

4i: 2-(3-(((4-(4-ethylphenyl)thiazol-2-yl)imino)methyl)-1H-indol-1-yl)-N-(6-methyl benzo [d]thiazol-2-yl) acetamide. M.P. 173-175°C; Mol. formula: C₃₀H₂₅N₅OS₂, yield 76%, IR (ν cm⁻¹): 3442(NH Str, -CO-NH-), 3072(C-H Str, Ar), 2967, 2867(C-H Str, Aliphatic), 2365(C-S-C Str, Thazole), 1722(C=O Str, -CO-NH-), 1627(C=N Str), 1532(C=CH Str), 1398(C=C Str, Ar). ¹H-NMR (DMSO) δδ ppm: 12.053(s, 1H, Acetamide), 8.892(s, Immine proton, CH=N), 8.321(s, 1H, Ar-H), 8.092-8.002(d, 2H, Ar-H), 7.982(d, 2H, Ar-H), 7.873-7.783(d, 2H, Ar-H), 7.574-7.473(t, 2H, Ar-H), 7.342-7.301(d, 2H, Ar-H), 7.320-7.302(t, 2H, Ar-H), 7.201(s, 1H, Ar-H), 4.672-4.601(s, 2H, -CH₂-CO), 2.320(q, 2H, -CH₂-), 2.021-2.001(s, 2H, -CH₃). Mass (LC-MS): m/z 535(M), 536(M + 1, 100%).

Table 1: Physical data of Novel Indole derivatives (4a-4l)

Code	R	R ₁	Mol. Formula	Mol. wt (g.mol ⁻¹)	M.P (°C)	R _f Value
4a	-H	-H	C ₂₇ H ₁₉ N ₅ OS ₂	493.10	187-189	0.65
4b	CH ₃	-H	C ₂₈ H ₂₁ N ₅ OS ₂	507.12	203-205	0.77
4c	-Cl	-H	C ₂₇ H ₁₈ N ₅ OCIS ₂	527.06	254-256	0.63
4d	-F	-H	C ₂₇ H ₁₈ N ₅ O ₂ FS ₂	511.09	213-215	0.71
4e	-OCH ₃	-H	C ₂₈ H ₂₁ N ₅ O ₂ S ₂	523.11	167-169	0.58
4f	-NO ₂	-H	C ₂₄ H ₁₈ N ₅ O ₃ S ₂	538.09	211-213	0.63
4g	-C ₂ H ₅	-H	C ₂₉ H ₂₃ N ₆ OS ₂	521.13	201-203	0.59
4h	-H	-CH ₃	C ₂₈ H ₂₁ N ₅ OS ₂	507.12	183-185	0.61
4i	-C ₂ H ₅	-CH ₃	C ₃₀ H ₂₅ N ₅ OS ₂	535.15	173-175	0.79
4j	-CH ₃	-CH ₃	C ₂₉ H ₂₃ N ₅ OS ₂	521.13	223-225	0.65
4k	-F	-CH ₃	C ₂₈ H ₂₀ N ₅ OFS ₂	525.11	251-253	0.70
4l	-OCH ₃	-CH ₃	C ₂₉ H ₂₃ N ₅ O ₂ S ₂	537.13	177-179	0.82

4j: N-(6-methylbenzo[d]thiazol-2-yl)-2-(3-(((4-(p-tolyl)thiazol-2-yl)imino)methyl)-1H-indol-1-yl) acetamide. M.P. 223-225°C; Mol. formula: C₂₉H₂₃N₂OS, yield 75%, IR (ν cm⁻¹): 3421(NH Str, -CO-NH-), 3082(C-H Str, Ar), 2989, 2874(C-H Str, Aliphatic), 2332 (C-S-C Str, Thazole), 1723(C=O Str, -CO-NH-), 1628(C=N Str), 1525(C=CH Str). ¹H-NMR (DMSO) $\delta\delta$ ppm: 12.021(s, 1H, Acetamide), 8.909(s,

Immine proton, CH=N), 8.372(s, 1H, Ar-H), 8.327-8.281(d, 2H, Ar-H), 7.803-7.801(d, 2H, Ar-H), 7.453-7.401(d, 2H, Ar-H), 7.320-7.301(t, 2H, Ar-H), 7.290(s, 1H, Ar-H), 7.203-7.201(d, 2H, Ar-H), 6.873-6.820(t, 2H, Ar-H), 4.543-4.483(s, 2H, -CH₂-CO), 2.063-2.003(s, 6H, -CH₃). Mass (LC-MS): m/z 521.13(M), 522(M + 1, 100%).

Figure 1: Scheme of synthesis for some novel Indole derivatives

4k: 2-(3-(((4-(4-fluorophenyl) thiazol-2-yl) imino) methyl)-1H-indol-1-yl)-N-(6-methyl benzo[d]thiazol-2-yl) acetamide. M.P. 251-253°C; Mol. formula: $C_{28}H_{20}N_5OFS_2$, yield 72%, IR (ν cm^{-1}): 3403(NH Str, -CO-NH-), 3035(C-H Str, Ar), 2969, 2833(C-H Str, Aliphatic), 2387(C-S-C Str, Thazole), 1705(C=O Str, -CO-NH-), 1628(C=N Str), 1532(C=CH Str), 1354(C=C Str, Ar), 867(F Str, Ar-F). 1H -NMR (DMSO) $\delta\delta$ ppm: 11.932(s, 1H, Acetamide), 8.782(s, Imine proton, CH=N), 8.231(s, 1H, Ar-H), 7.902-7.900(d, 2H, Ar-H), 7.872(d, 2H, Ar-H), 7.547-7.582(d, 2H, Ar-H), 7.434-7.403(t, 2H, Ar-H), 7.321-7.300(d, 2H, Ar-H), 7.219-7.201(t, 2H, Ar-H), 7.031(s, 1H, Ar-H), 4.347-4.286(s, 2H, -CH₂-CO), 2.043-2.001(s, 3H, -CH₃). Mass (LC-MS): m/z 525.11(M), 526(M + 1, 100%), 527(M + 2, 30%).

4l: 2-(3-(((4-(4-methoxyphenyl) thiazol-2-yl) imino) methyl)-1H-indol-1-yl)-N-(6-methyl benzo [d]thiazol-2-yl)acetamide. M.P. 177-179°C; Mol. formula: $C_{29}H_{23}N_5O_2S_2$, yield 80%, IR (ν cm^{-1}): 3428(NH Str, -CO-NH-), 3087(C-H Str, Ar), 2984, 2873(C-H Str, Aliphatic), 2332 (C-S-C Str, Thazole), 1716(C=O Str, -CO-NH-), 1621(C=N Str), 1543(C=CH Str), 1482(C=C Str, Ar), 998(C-N Str). 1H -NMR (DMSO) $\delta\delta$ ppm: 12.432(s, 1H, Acetamide), 9.865(s, Imine proton, CH=N), 8.542(s, 1H, Ar-H), 8.281-8.201(d, 2H, Ar-H), 7.832-7.802(d, 2H, Ar-H), 7.656-7.632(d, 2H, Ar-H), 7.473-7.422(t, 2H, Ar-H), 7.320(s, 1H, Ar-H), 7.281-7.201(d, 2H, Ar-H), 7.109-7.001(t, 2H, Ar-H), 4.832-4.802(s, 2H, -CH₂-CO), 3.810-3.802(s, 1H, -OCH₃), 1.899-

1.802(s, 3H, -CH₃). Mass (LC-MS): m/z 537.13(M), 538(M + 1, 100%).

2.3. Pharmacological Evaluation:

2.3.1. Anti-bacterial-activity [18]: All the novel synthesized compounds (4a-4l) were evolved for their antibacterial activity against gram-positive strains such as *Bacillus subtilis*, and *Staphylococcus aureus*, were as gram-negative strains such as *Escherichia coli* and *Salmonella paratyphi* species (Table 2) by using the agar disc cup plate diffusion method. All the synthesized compounds were dissolved in Ethanol and methanol (2:8) to get a solution of 1 mg mL⁻¹. Streptomycin used as a standard drug. After incubation period the zone of inhibition was measured in millimetres for sample and standard drugs. Controlled solution alone showed no inhibition zone.

2.3.2. Anticancer activity [19]: The anticancer activity of synthesized compounds was determined in vitro by MTT Assay, and Cell viability was once evaluated with three experiments with six concentrations in triplicates. All test compounds were weighed separately and dissolved in DMSO and with media make up the final concentration to 1 mg/ ml and the cells were treated with series of concentrations from 0.5, 10, 15, 25, 50, 75 and 100 μ g/ ml. Cells were counted by haemocytometer and seeded at density of 5.0×10^3 cells / well in 100 μ l media in 96 well plate

culture medium and incubated overnight at 37 °C. At the end of incubation time, precipitates are formed as a result of the reduction of the MTT salt to chromophore formazan crystals by the cells with metabolically active mitochondria. The optical density of solubilized crystals in DMSO was measured at 570 nm on a microplate reader. The percentage growth inhibition was calculated using the following formula (Table 2).

$$\% \text{ Inhibition} = \frac{100 (\text{Control} - \text{Treatment})}{\text{Control}}$$

The IC_{50} value was determined by using linear regression equation i.e. $y = mx + c$. Here, $y = 50$, m and c values were derived from the viability graph.

2.3.3. Molecular docking [20]: The binding of novel synthesized indole derivatives to aromatase was investigated in a docking procedure by applying a combined quantum mechanical/ molecular mechanical method. 2D structures of the compounds were converted to 3D using potential algorithms and application of high efficient force fields. Initial geometrical optimization and energy minimization of molecules were performed by using the Ligprep tool of Schrodinger suite. The digital structure of the Acetylcholine-binding protein (AChBP) was retrieved from the Protein databank website with PDB Id: 2ZJU and the structure was optimized by deleting unbound water molecules which are over 1 Å, adding hydrogen atoms to satisfy the valences,

adding missing amino acids to stabilize side chains and energy of the whole structure was minimized using OPLS-2005 force field using Protein Preparation Wizard tool of Schrodinger Suite. Thus structurally optimized protein structure was used to examine protein-ligand interactions of the dataset ligands using Glide Xp docking protocol. Initially, a 3D grid was established to the binding pocket (active site) of the protein, into which all the dataset ligands were docked into. Binding interactions and efficiency of the binding were calculated in terms of Glide Score, which is a combination of hydrophilic, hydrophobic, metal binding groups, Van der Waals energy, freezing rotatable bonds and polar interactions with receptor.

3. RESULTS AND DISCUSSION

3.1. Chemistry: The protocol for all the synthesized novel indole derivatives is depicted in Scheme. In first step, a mixture of substituted acetophenone reacts with thiourea in the presence of Iodine to give 2-amino 4-aryl thiazole, then it can be undergoing Schiff's base reaction with Indole-3-carboxaldehyde to produce 1-(1H-indol-3-yl)-N-(4-phenylthiazol-2-yl) methanimine (**2a-2g**). Were as in step-3, 2-amino benzothiazole reacts with chloroacetyl chloride to give (N-(1, 3-benzothiazol-2-yl)-2-chloroacetamide) (**3a-3b**). Finally, **3a-3g** compounds reacts with **2a-2g** to give the title of the

compounds. The chemical structures of all the synthesized compounds (**4a-4l**) were established by IR, NMR and Mass spectroscopic techniques and the yield of the compound ranges from 64%-83%. The mass spectra of all the synthesized compounds (**4a-4l**) are in accordance with their molecular weights. Detailed spectral data is given in experimental protocols.

3.2. Pharmacological Evaluation

3.2.1. Antibacterial activity: Antibacterial activity of the synthesized compounds (**4a-4l**) was compared with standard “Streptomycin” and the results are presented in **Table 2**. The most of the synthesized compounds like **4c**, **4d**, **4f** and **4k** are showed potent antibacterial activity against all the tested bacterial strains and **4b**, **4e**, **4g**, **4i** and **4l** are showed moderate antibacterial activity.

3.2.2. Anticancer activity: Novel Indole derivatives contain 1,3-thiazole were evaluated for cytotoxicity by MTT assay against human breast cancer cells (MCF7), and comparison with doxorubicin as standard. The results (**Table 3**, **Figure 3**) proposed that both cell lines were susceptible to the evaluated novel compounds. Compounds **4a-4l** showed IC₅₀ values in the range of 43.83 μ M to 84.44 μ M against MCF7 cell line. From the results, compounds **4b**, **4e** and **4l** are the most active analogs in this study and showing broad spectrum activity toward the

tested cell lines, whereas, remaining all other compounds showed moderate activity. All the test compounds results were shown in the table and expressed as a mean $\pm$ SEM of five concentrations.

3.2.3. Molecular docking studies:

Molecular docking studies were performed in order to find the possible protein ligand interactions of the dataset ligands. Additionally, these also assisted in identifying the conformational changes of the ligand in the protein environment. About generates 100 different protein ligand complex conformations for each docked complex were generated through Glide XP module. Based on the EModel energy, only one was displayed in the result. Glide dock scores of the dataset ligands were shown in **Table 4**, **Figure 5**, along with the interaction amino acids and number of amino acids.

Among the docked ligands, compound **4c** reported highest dock score of -5.86 with Glide binding energy of -38.599 Kcal/mol. Compounds **4c**, **4l** and **4k** possessed 3 hydrogen bonds, with Alanine 881 amino acid (2 bonds) and Glutamine 119 (1 bond). Dock scores of all the compounds ranged from -5.861 (compound **4c**) to -2.261 (compound **4i**). Nitrogen in the benzothiazole moiety and the amine group attached to the benzothiazole moiety are responsible for the H-bond interaction. Hydrophobic interactions were identified

between Tryptophan 143 amino acid and indole moiety of compounds 4c and 4f. Indole moiety of compound 4i had hydrophobic interaction with Histidine 145.

Benzothiazole moiety of compounds 4f and 4k showed hydrophobic interactions with Tryptophan 143 and Tyrosine 185, respectively.

Table 2: Antibacterial activity of novel indole derivatives by zone of inhibition (in mm)

Compound	Zone of Inhibition (in mm)			
	<i>B. subtilis</i>	<i>St. aureus</i>	<i>E. coli</i>	<i>Salmonella paratyphi</i>
Streptomycin	33	31	33	35
4a	18	22	09	18
4b	25	23	21	09
4c	30	25	19	29
4d	29	28	28	26
4e	28	26	22	23
4f	30	29	16	29
4g	23	22	17	17
4h	20	23	09	21
4i	21	22	20	20
4j	23	25	18	14
4k	30	29	18	29
4l	25	22	28	19

Figure 2: Graphical representation of antibacterial activity of novel indole compounds (4a-4l) – Zone of Inhibition (mm)

Table 3: Cytotoxic Activity of novel indole derivatives on MCF-7 Cells

S. No	Sample Name	IC ₅₀ (μg)
1	4a	83.21±0.321
2	4b	53.01±0.842
3	4c	84.44±0.032
4	4d	88.21±0.002
5	4e	51.04±0.631
6	4f	49.03±0.031
7	4g	70.46±0.183
8	4h	58.32±0.031
9	4i	90.23±0.005
10	4j	70.32±0.103
11	4k	69.92±0.204
12	4l	43.83±0.702
13	Doxorubicin	15.43±0.142

Figure 3: Graphical representation of anticancer activity of novel indole compounds (4a-4l)

Figure 4: The cytotoxic activities of the synthesized indole derivatives against breast MCF7 cancer cell line

Table 4: Insilico EGFR Inhibition of Novel Indole Derivatives-Glide dock scores of the dataset ligands

Compound No	Dock score XP GScore	No of H-bonds	Interacting amino acids	H-bond lengths (Å)	Emodel energy	Glide energy
4c	-5.861	3	ALA 88 GLN 119	2.11, 1.99 2.17	-60.578	-38.599
4l	-5.032	3	ALA 88 GLN 119	2.64, 2.00 2.00	-65.678	-41.979
4k	-4.825	3	ALA 88 GLN 119	2.47, 1.98 2.29	-53.043	-38.509
4f	-2.315	1	TRP 143	1.81	-53.837	-37.222
4i	-2.261	1	PRO 16	2.14	-63.732	-46.504

Figure 5: Molecular docking structures of Indole derivatives (Docking Pose between the Ligand and the Protein)

4. CONCLUSION

A series of novel indole derivatives was synthesized and their structures were established by means of IR, ¹HNMR and mass spectral data as well as elemental analysis. All the synthesized compounds were screened for antibacterial, anticancer activities. In addition to molecular docking studies, a study was performed to depict the essential structural components contributing to their pharmacological activity. Most of the compounds like **4c**, **4d**, **4f** and **4k** showed potent antibacterial activity against all the

tested bacterial strains and **4b**, **4e** and **4l** are the most active analogs in this study and showing broad spectrum activity toward the tested anticancer cell lines. Docking scores of all the synthesized novel indole derivatives were ranged between -2.261 to -5.861.

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