

Molecular Design and Synthesis of Fused Pyrimidine Derivatives with Potential Anti-Cancer Activity

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List of Abbreviations.

• ABL	Abelson Murine Leukemia Viral Oncogene Homologue
• 2D	Two Dimensional
• 3D	Three Dimensional
• Å	Angstrom
• ATP	Adenosine Tri Phosphate
• BSA	Bovine Serum Albumin
• CADD	Computer Aided Drug Design
• Calcd	Calculated
• CDK	Cyclin Dependant Kinase
• Cpd	Compound
• DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
• DMF	Dimethylformamide
• DMSO	Dimethylsulfoxide
• EGFR	Epidermal Growth Factor Receptor
• FAK	Focal Adhesion Kinase
• FGFR	Fibroblast Growth Factor Receptor
• hr	Hour
• HRP	Horseradish Peroxidase
• I.R.	Infrared
• IC	Inhibitory Concentration
• IGFR	Insulin Like Growth Factor Receptor
• M.	Molecular
• M.P.	Melting Point
• M.Wt	Molecular weight
• NMR	Nuclear Magnetic Resonance
• NRTK	Non-Receptor Tyrosine Kinase
• PBS	Phosphate Buffered Saline
• Pdb	Protein data bank
• PDGFR	Platelet Derived Growth Factor Receptor
• QSAR	Quantitative Structure Activity Relationship

- **RMSD** Root Mean Square Deviation
- **rt** room temperature
- **RTK** Receptor Tyrosine Kinase
- **SRB** Sulfo-Rhodamine-B stain
- **SRC** Sarcoma (Schmidt-Ruppin A-2) Viral Oncogene
- **TGF α** Tumor Growth Factor alpha
- **TK** Tyrosine Kinase
- **TMB** 3,3',5,5'-Tetramethylbenzidine
- **VEGFR** Vascular Endothelial Growth Factor Receptor



Abstract

Abstract:

In recent years, 4-anilinoquinazolines have emerged as a versatile template for inhibition of a diverse range of receptor tyrosine kinases. Epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitors are the most widely studied compounds among all tyrosine kinases. In this work, we present a new sub-family of compounds containing 4-anilinoquinazoline, core as promising potent and selective EGFR inhibitors. Our strategy is directed toward designing a variety of ligands with bulky substituents at the anilino moiety, mimicking that of Lapatinib which is recently launched as potent inhibitor for both EGFR and erbB2.

Three series of new 6,7-dimethoxy-4-substituted-anilinoquinazolines (**Xa-i**, **XIa-g**, **XII**) were designed and synthesized from 4,5-dimethoxyanthranilic acid. EGFR inhibitory activity of the final compounds was assessed. Moreover, the *in vitro* activities of the most active hits were assessed on human breast carcinoma cell line (MCF-7) where the EGFR is highly expressed. Fortunately, compound **XIb** and **XIg** displayed highest activity for cell line test. Finally, the active hits and some of the inactive ones were docked to the active site pocket of the EGFR-TK enzyme for investigation of their binding mode to the receptor active site.

This thesis comprises the synthesis of the following unavailable unreported starting materials and intermediates:-

- 1) m-(3-Methylbenzyloxy)acetanilide (**VIId**)
- 2) m-(2-(Morpholin-4-yl)ethoxy)acetanilide (**VIIf**)
- 3) m-(3-Fluorobenzyloxy)acetanilide (**VIg**)
- 4) 4-(3-Carboxyanilino)-2-chloro-6,7-dimethoxyquinazoline (VIII).

In addition the study comprises the synthesis of the following new compounds:-

- 1) 2-Chloro-6,7-dimethoxy-4-(3-(morpholin-4-ylcarbonyl)anilino)quinazoline (**Xa**)
- 2) 2-Chloro-4-(3-(cyclohexylaminocarbonyl)anilino)-6,7-dimethoxyquinazoline (**Xb**)
- 3) 4-(3-(Benzylaminocarbonyl)anilino)-2-chloro-6,7-dimethoxyquinazoline (**Xc**)
- 4) 2-Chloro-6,7-dimethoxy-4-(3-((ethyl piperazin-1-ylcarboxylate)-4-ylcarbonyl)anilino)quinazoline (**Xd**)
- 5) 2-Chloro-6,7-dimethoxy-4-(3-(piperidin-1-ylcarbonyl)anilino)quinazoline (**Xe**)
- 6) 2-Chloro-6,7-dimethoxy-4-((3-(2-phenylethyl)aminocarbonyl)anilino)quinazoline (**Xf**)
- 7) 2-Chloro-6,7-dimethoxy-4-(3-(isopropylaminocarbonyl)anilino)quinazoline (**Xg**)
- 8) 2-Chloro-6,7-dimethoxy-4-(3-(t-butylaminocarbonyl)anilino)quinazoline (**Xh**)
- 9) 2-Chloro-6,7-dimethoxy-4-(3-((1-phenylpiperazin)-4-ylcarbonyl)anilino)quinazoline (**Xi**)
- 10) 4-(3-(Benzyloxy)anilino)-2-chloro-6,7-dimethoxyquinazoline (**XIa**)
- 11) 4-(3-(Allyloxy)anilino)-2-chloro-6,7-dimethoxyquinazoline (**XIb**)
- 12) 2-Chloro-4-(3-(3,4-dichlorobenzyloxy)anilino)-6,7-dimethoxyquinazoline (**XIc**)
- 13) 2-Chloro-6,7-dimethoxy-4-(3-(3-methylbenzyloxy)anilino)quinazoline (**XId**)

- 14) 4-(4-(Benzyloxy)anilino)-2-chloro-6,7-dimethoxyquinazoline (**XIe**)
- 15) 2-Chloro-6,7-dimethoxy-4-(3-(2-(morpholin-4-yl)ethoxy)anilino)quinazoline (**XIf**)
- 16) 2-Chloro-4-(3-(3-fluorobenzyloxy)anilino)-6,7-dimethoxyquinazoline (**XIg**)
- 17) 4-(3-(Benzyloxy)anilino)-6,7-dimethoxyquinazolin-2(1*H*)-one (**XII**)

The structures of the synthesized compounds were confirmed by the spectral and micro-analytical analysis. Additionally, the references reviewed were listed at the end of thesis & the whole thesis was summarized in Arabic.