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

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Submitted for the partial fulfillment of the
Master degree

In pharmaceutical sciences
(Pharmaceutical Chemistry)

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Many Thanks

Acknowledgement

Words can't help me in expressing my deep appreciation, respect and gratitude to my great supervisors "Prof.Dr. Dalal A. Abou El-Ella and Prof.Dr. Khaled A. M. Abouzid" for their great support, kind help, work design, valuable Ideas, precious guidance and continuous encouragement during all stages of this work. Thank you for your great efforts and tremendous support which allowed this thesis to appear in its final form. Also, I would like to express my gratefulness to Prof.Dr. Mahmoud M. A. Hassan for his kindness, continuous support and fruitful opinions throughout the whole practical work.

It also gives me pleasure to express my appreciation to Dr. Nadia Hamdy, lecturer of biochemistry, Faculty of Pharmacy, Ain Shams University, for carrying out the enzyme inhibition assay for the new hits. Additionally I should not forget the great help in docking study introduced by Dr. Moustafa El-Araby, lecturer of the pharmaceutical chemistry, Faculty of Pharmacy, Helwan University. and Dr. Nasser Saad, lecturer of the pharmaceutical chemistry, Faculty of Pharmacy, Ain Shams University

I'm also indebted to my parents, my wife and my daughter for their continuous help, understanding, patience and cooperation. Finally, I must thank my upper guide, god father & the kind manager Prof.Dr. Mohammed Ihab Fetouh, the dean of faculty of pharmacy at Egyptian Russian University for his kindness, great assistance & wonderful personality.

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List of Abbreviations.

- **ABL** Abelson Murine Leukemia Viral Oncogene Homologue
- **2D** Two Dimensional
- **3D** Three Dimensional
- **A°** Angstrom
- **ATP** Adinosine Tri Phosphate
- **BSA** Bovine Serum Albumin
- **CADD** Computer Aided Drug Design
- **Calcd** Calculated
- **CDK** Cyclin Dependant Kinase
- **Cpd** Compound
- **DCC** *N,N'*-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
- **TGFα** 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-anilino-quinazolines **(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 (**VId**)
2) m-(2-(Morpholin-4-yl)ethoxy)acetanilide (**VIf**)
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-di methoxyquinazoline (**Xb**)
3) 4-(3-(Benzylaminocarbonyl)anilino)-2-chloro-6,7-dimeth oxyquinazoline (**Xc**)
4) 2-Chloro-6,7-dimethoxy-4-(3-((ethyl piperazin-1-ylcarbox-ylate)-4-ylcarbonyl)anilino)quinazoline (**Xd**)
5) 2-Chloro-6,7-dimethoxy-4-(3-(piperidin-1-ylcarbonyl)ani-lino)quinazoline (**Xe**)
6) 2-Chloro-6,7-dimethoxy-4-((3-(2-phenylethyl)aminocarbon-yl)anilino)quinazoline (**Xf**)
7) 2-Chloro-6,7-dimethoxy-4-(3-(isopropylaminocarbonyl)an-ilino)quinazoline (**Xg**)
8) 2-Chloro-6,7-dimethoxy-4-(3-(t-butylaminocarbonyl)anil-ino)quinazoline (**Xh**)
9) 2-Chloro-6,7-dimethoxy-4-(3-((1-phenylpiperazin)-4-ylcarb-onyl)anilino)quinazoline (**Xi**)
10) 4-(3-(Benzyloxy)anilino)-2-chloro-6,7-dimethoxyquinazol-ine (**XIa**)
11) 4-(3-(Allyloxy)anilino)-2-chloro-6,7-dimethoxyquinazoline (**XIb**)
12) 2-Chloro-4-(3-(3,4-dichlorobenzyloxy)anilino)-6,7-dimeth-oxyquinazoline (**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(*1H*)-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.