INSILICO DRUG DESIGING ON NOVEL QUINOLINE NITRATES

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ABSTRACT: -

This research paper presents a comprehensive study on the in-silico drug designing of novel quinoline nitrates, emphasising their potential pharmacological applications. Quinoline, a heterocyclic compound, has been recognised for its diverse biological activities including antibacterial, antifungal, antiviral, anticancer, and anti-inflammatory properties. The study systematically explores the synthesis of various quinoline derivatives, particularly focusing on their structural modifications to enhance biological activity. The research uses quantitative structure-activity relationship (QSAR) modelling to predict the biological efficacy of synthesised compounds based on their molecular descriptors. Molecular docking studies further elucidate the binding affinities and interactions of the designed quinoline nitrates with biological targets. The findings reveal that the synthesised compounds exhibit favourable drug-like properties, according to the Lipinski Rule of Five, supporting their potential as leads for further pharmacological exploration. Overall, this study contributes valuable insights into the design and development of quinoline-based drugs, highlighting their therapeutic potential across various diseases.

KEYWORDS: -

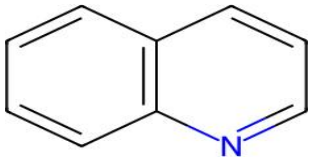
quinoline, activity, compounds, biological, molecular, derivatives, properties, docking, against, chemistry

1. INTRODUCTION

Quinoline is a heterocyclic compound having molecular equation C_9H_7N, characterized by a double-ring structure that contains a benzene ring combined with pyridine at two adjoining carbon particles. Quinoline is additionally known as, benzopyridine, benzo[b]pyridine 1-benzazine and benzazine. It may be a hygroscopic, yellowish oily liquid marginally dissolvable in water, dissolvable in liquor, ether and numerous other natural solvents. Isoquinoline could be a congener of quinoline and varies from quinoline in the nitrogen position (at 2nd position) **[1]**.

The clinical perception demonstrates that indeed when a human breathes in a 0.001 ppm level of quinoline for 8 h it is perfectly nontoxic and this case is very inverse to benzene; even a small concentration of benzene leads to different organic clutters like cancer.

It is exceptionally steady and is ordinarily utilized as tall bubbling dissolvable with a boiling point. of 237^0C. Since quinoline has an acidic pka of 4.85, it can frame salts with acids whose log P esteem is 2.04**[2]**. Quinoline framework is recognized as a prominent presence in different naturally dynamic plants (Cinchona), agrochemicals, Dyes, and pharmaceuticals.

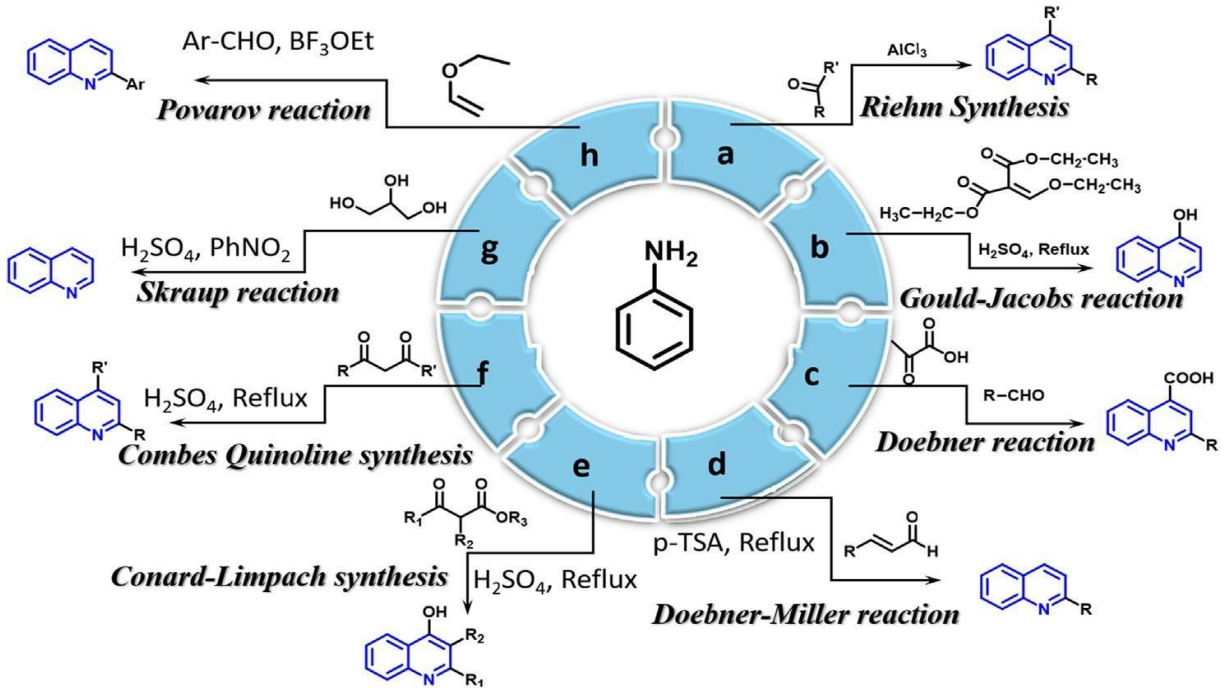


MOLECULAR WEIGHT:129

Quinoline framework is recognized as unmistakable presence in different naturally dynamic plants (Cinchona), agrochemicals, Dyes, pharmaceuticals. Quinoline could be a well-known chelating operator in coordination chemistry to chelate metallic particles and are connected as N-benefactor ligands. **[3]**

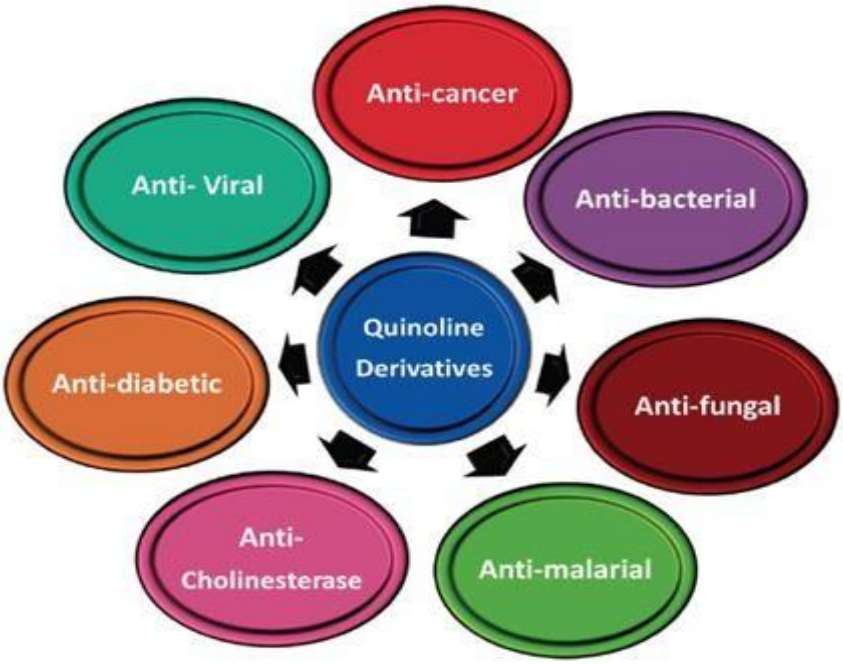
Quinoline subsidiaries are broadly utilized as "parental" compounds to synthesize atoms with restorative benefits, particularly with anti-malarial and anti-microbial exercises. It is well known that some quinolines and their derivatives have antibacterial, anticancer, antifungal, hypotensive, anti-HIV, analgesic, and anti-inflammatory properties. Quinoline and its analogues have as of late been inspected for their modes of work within the hindrance of tyrosine kinases, proteasome, tubulin polymerization, topoisomerase and DNA repair. Substitution of the bunch in an appropriate position of a bioactive particle is found to apply a significant pharmacological impact **[4].**

TRADITIONAL METHODS FOR SYNTHESIS OF QUINOLINES



Reference : Mohan Ilakiyalakshmi, Ayyakannu Arumugam Napoleon ; Review on recent development of quinoline for anticancer activities ; Arabian Journal of Chemistry (2022) 15, 104168

PHARMACOLOGICAL USES OF QUINOLINES



Synthetic quinoline derivatives.

Reference: Ruksana Tabbassum, Muhammad Ashfaq, Current Pharmaceutical aspects of synthetic quinoline derivatives. vol 21; issue 10, 2021 ,pg (1152 -1172)

ANTIBACTERIAL ACTIVITY:

Annulated new quinoline analogues' antibacterial properties in combination with triazole, pyrazole, imidazole and pyrrole frameworks which were at that point tried against different bacterial strains, counting B. sphaericus, B. subtilis, S. aureus, C. violaceum and P. aeruginosa. Recently synthesized quinoline derivatives were demonstrated to have strength against the M. tuberculosisH37Rv strain.**[5]**

ANTIFUNGAL ACTIVITY:

Groupings of antifungal quinoline compounds were arranged with terbinafine as the lead compound and side chain display within the compounds incorporate different bulky fragrant rings

inspected against A. flavus, A. niger, P. citrinum and M. purpureus and demonstrated to have strong action.20 Novel quinoline subordinates were arranged and examined for micro biological action towards E. coli and C. albicans utilizing the channel paper circle strategy. The comes about illustrated that azetidine-containing quinoline derivatives completely ruled both sorts of life forms in restricting development.**[6]**

ANTIMYCOBACTERIAL ACTIVITY:

A novel engineered strategy for the Union of melded thieno/ furo-quinoline compounds and anti mycobacterial power of the compounds were detailed and evaluated, showing the most extreme movement and the pre-eminent MIC value achieved was 5.6 µmol, which when compared to ethambutol (To begin with line against-tubercular sedate) was found to be prevalent (7.6 µmol). Quinoline related molecules with side chain and isoxazole unit were produced and assessed for antimycobacterial activity.**[7]**

ANTIVIRAL ACTIVITY:

A few mono and poly substituted quinolines were created and detailed to haveanti-HIV-1 activity.35Anilido quinoline compounds illustrated great antiviral adequacy towards the Japanese strain of encephalitis virus.36 A promising course of drugs synthesized by focussing on the N-1 and C-6 locations for treating HIV infections. Novel quinoline compound 23was planned and synthesized, which works as an inhibitor against HIV-1 Tat-Tar interaction.**[8]**

ANTIPROTOZOAL ACTIVITY:

A single-step union of aryl quinoline constituting carboxylates was detailed and evaluated for antiprotozoal activity against T. gondii.40 Nakayama et al. It was discovered that alkenyl and alkynyl quinolones exhibited

antiprotozoal activity against Chagas disease, cutaneous leishmaniasis, visceral leishmaniasis, and African trypanosomiasis.[9]

ANTIMALARIAL ACTIVITY:

Reactivity considers of two quinoline subsidiaries **[10]** were detailed as potential lead compounds as antimalarials utilizing Discrete Fourier Change (DFT)and Atomic Elements (MD)reenactments.

The novel compounds were found to be as compelling as or more compelling than primaquine against P. falciparum cellproliferation.48 Novel 4-anilinoquinolinecompounds were synthesized, illustrating powerful antimalarial action against P. falciparum strains.

ANTICANCER ACTIVITY:

Unused chloro/ phenoxyquinoline compounds were arranged, and the recently shaped atomic substances were surveyed in vitro for cytotoxic adequacy against different cancer cell lines.54 A arrangement of unused quinoline subordinates were synthesized by utilizing the MTT strategy. The focused on modern compounds were screened against 4 human cancer cores invitro specifically U2OS, HCT 116, A549 and MCF 7.55. A grouping of modern benzo-[h]quinolines were planned and synthesized with ethyl carboxamide side chain show at4th position of quinoline. Significant arrangement of tetracyclic quinoxalines was planned, synthesized and evaluated, which appears topoisomerase II inhibitory movement.

ANTIOXIDANT ACTIVITY:

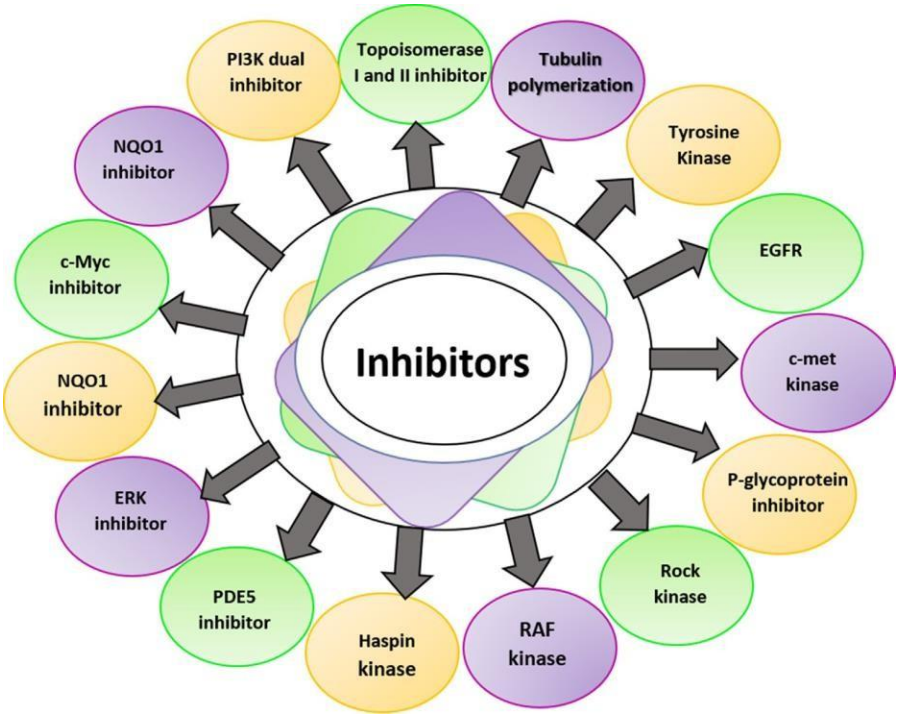
An arrangement of quinoline carbaldehyde hydrazone subordinates was found as the bioisosteric subordinate of Melatonin, characterized and tried in vitro for antioxidant movement. MTT test and Lactate dehydrogenase spillage test was utilized to evaluate the cytotoxicity of all substances.82,83Bactericidal and antioxidant properties of quinoline subordinates of zingerone and tetrahydro curcumin were investigated.84Quinoline subordinates were synthesized by the interaction between aldehyde, and pyruvic corrosive yielded quinoline having carboxylic corrosive **[11]**. In vitro and in silico antioxidant tests were performed on recently synthesized atoms.

ANTIINFLAMMATORY ACTIVITY:

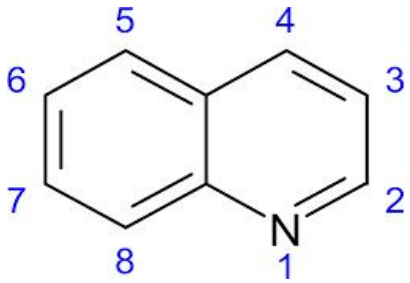
Several phenoxyquinoline compounds were produced and tested for anti-inflammatory activity.91 Novel quinoline derivatives were synthesized with a COX-2 methyl sulfonyl pharmacophore as selective COX-2 inhibitors.

ANALGESIC ACTIVITY:

Trifluoromethyl quinolines were arranged and found to have conclusive pain-relieving activity and nitric oxide-releasing subordinate was created, and its movement stems from its opposing impact on vanilloid receptors.89 Quinoline compounds were made that have pain relieving activity and are particular agonists at CB2 Cannabinoid receptors. **[12]**



1.1 : STRUCTURAL ACTIVITY RELATIONSHIP OF QUINOLINE



1. SUBSTITUTION PATTERNS:

The biological activity of quinoline derivatives can be significantly altered by substituents on the aromatic rings.substituents on the benzene ring can effect the compounds ability to interact with biological targets. Substituents on the pyridine ring can influence electronic properties and binding affinity.

2. POSITION OF SUBSTITUENTS:

The position of substituents on the quinoline ring such as 2,4,8, positions can impact the compounds activity. for instance,8 substituted quinolines often show better antimalarial activity compared to others.

3. RING MODIFICATION:

Modifying the quinoline core by introducing additional rings or hetero atoms can enhance or alter biological activity.Examples include quinoline-based compounds with additional pyrimidine or oxazole rings,which can show varied pharmacological properties.

4. ELECTRON WITHDRAWING/ELECTRON DONATING GROUPS:

The presence of electron withdrawing /electron donating groups can influence the reactivity and interaction of quinoline derivatives with their targets.For example,electron -withdrawing groups might enhance anti-cancer activity while electron- donating groups could affect anti-microbial properties.

5. CONFORMATIONAL FLEXIBILITY:

The ability of quinoline derivatives to adopt different conformations can impact their binding to biological targets, influencing their efficacy and selectivity.

1.2 : QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP [QSAR]

Building prediction models of biological activities based on the structural and molecular details of a compound library is known as quantitative structure-activity relationship, or QSAR, modelling. The term quantitative structure-property relationship (QSPR) refers to the broad application of QSAR, which was initially applied in drug development and discovery to correlate molecular data with biological activities as well as other physicochemical properties. For the purpose of determining correlations between chemical structures and biological activity, QSAR is a widely recognized prediction and diagnostic method. In an effort to satisfy the requirement and desire of medicinal chemists to forecast biological reaction, QSAR has developed overtime **[13]**

The outcome of computer procedures that begin with an appropriate molecular structure description and conclude with some deductions, theories, and forecasts regarding the behaviour of molecules in the environmental, physicochemical, and biological systems that are being studied is quantitative structural

analysis, or QSAR. A series of mathematical formulas connecting chemical structure to biological activity are the ultimate results of QSAR calculations **[14]**. Using all of the molecular descriptors from a molecule's 1D, 2D, and 3D representations, multivariate QSAR analysis computes a model by looking for the best descriptors that are valid for the property under study. The principles, background, and procedures related to the creation of QSAR models are covered in this review.

2D Chem Draw could be used to draw the structures of the complexes that are being studied. These could be transformed into 3D objects by applying the CS Chem 3D ultra's preset conversion process. Spartan was then used to optimize the complex's shape and minimize energy in the 3D structures that were created. Chemical software such as Dragon, Gaussian, PADEL, and so forth can be used to compute molecular descriptors. The fundamental details of a molecule's physicochemical characteristics, such as its constitutional, electronic, geometrical, hydrophobic, lipophilicity, solubility, steric, quantum chemical, and topological descriptors, are known as molecular descriptors **[15**]. Multivariate analysis could be used to correlate molecular descriptors with observed activity, such as partial least squares and multilinear regression.

1.3 : MOLECULAR DOCKING:

Within the field of molecular modelling, docking is a method that anticipates a molecule's preferred route when it jumps to another to form a stable complex **[16]**. In order to predict the degree of participation or binding affinity connecting two molecules with each other, for instance, score function, information about the selected rotation direction may be worn.

A key component of signal transduction is the interactions between physically suitable substances including proteins, peptides, nucleic acids, carbohydrates, and lipids. Moreover, the kind of signal that forms—such as antagonism vs agonistism—may be influenced by the relative orientation of the two interact associates. Docking is therefore useful in predicting the type and potency of the signal that is created. The capacity of molecular docking to predict the binding-conformation of small molecule ligands to the appropriate target binding site makes it one of the most widely utilized techniques in structure-based drug design. The characterization of binding performance is important for both the rational design of pharmaceuticals and the understanding of basic biochemical processes.

In order to decrease the free energy of the typically approach, the goal of molecular docking is to achieve an optimal conformation for both the protein and ligand as well as a fundamental direction between the two. Drug-protein, drug-nucleic acid, and enzyme substrate interactions are examples of basic bimolecular processes that are aided by molecular recognition. A thorough understanding of the universal principles governing the types of connections (hydrogen bonding, van der Waals, electrostatic) between ligands and their protein or nucleic acid targets may provide a framework for creating drug leads with the desired potency and specificity for a particular therapeutic target **[17]**.

Practical application of this information requires structural data for the goal of significance and a progression for evaluating candidate ligand. A variety of computational docking methods are accessible.

TYPES OF DOCKING

1. RIGID DOCKING:

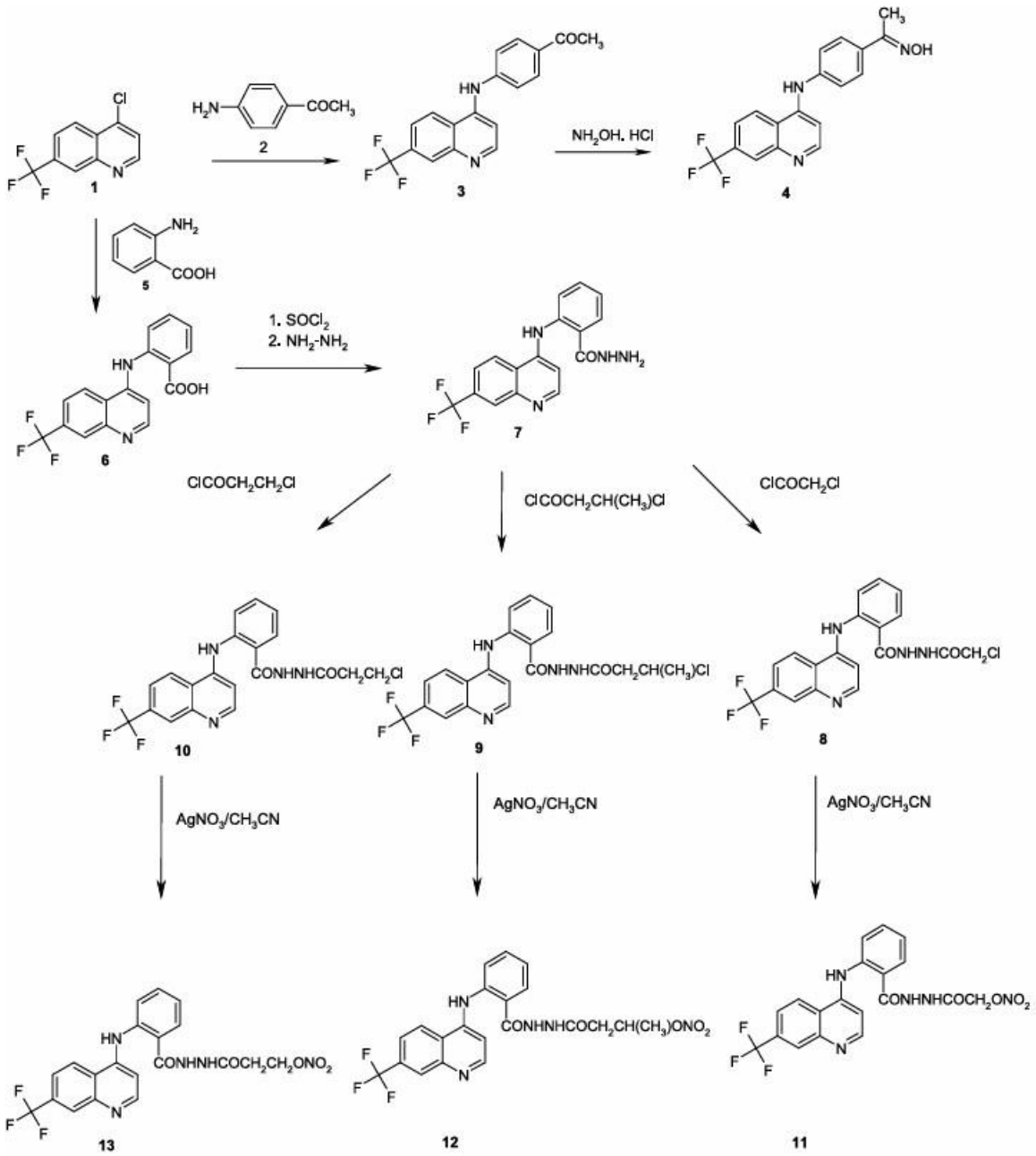
If we think that the molecules are rigid, then we are looking for a conversion in 3D space of one of the molecules which bring it to a most favourable fit inside the parameters of a scoring function with the other molecules. The ligand's conformation may be changing when the receptor is not present or when receptor binding activity is occurring.

2. FLEXIBLE DOCKING:

We think molecule flexibility then in adding to transformation, our aspire to locate the confirmations of the receptor and the ligand molecules, as they emerge in complex **[18]**.

4.METHODOLOGY:

SCHEME:



METHODOLOGY

Synthesis of1-[4-(7-Trifluoromethylquinolin-4-ylamino) Phen yl] ethanone oxime (4).

A mixture of an equimolar amount of 3 (5 mmol) and hydroxylamine hydrochlo ride in ethanol (20 ml) was refluxed for 3 h and left to cool. The separated solid was filtered, washed with di lute ammonia solution and water, dried, and crystallized.

General procedure for the preparation of compound 7

General procedure for the preparation of compound 7. A mixture of (5 g, 15 mmol) of 6 or 15 and excess of thionyl chloride was refluxed for 4 h, excess thionyl chloride was removed under reduced pressure, and the residue was refluxed for six hours in alcohol (30 ml) containing excess hydrazine hydrate. After cooling, the mixture was allowed to evaporate at a lower pressure. The resulting residue underwent filtering, water washing, drying, and crystallization.

Synthesis of 2-(7-Trifluoromethylquinolin-4-ylamino) benzoic acid hydrazide (7).

General procedure for the preparation of compounds 8–10

A mixture of (0.35 g, 1 mmol) of 7 or 16 was refluxed with (1.2 mmol) of the appropriate acid chloride, viz., acetyl chloride, 2-chloropropionyl chloride, and 3 chloropropionyl chloride in dry benzene (15 ml) and in the presence of triethylamine (0.1 ml) for 10 h. The solution was evaporated to dryness; the residue obtained was filtered, washed with water, and crystallized.

General procedure for the preparation of compound 11–13

A solution of the appropriate chloroalkyl derivative 8- 10 (1.8 mmol) in dry acetonitrile (2 ml) was treated portion wise with a solution of AgNO3 (0.34 g, 2 mmol) in Five milliliters of dry acetonitrile were added, and the mixture was agitated for three hours at room temperature. The mixture was then filtered, evaporated to dryness, and the residue was crystallized from absolute ethanol.

5.RESULTS AND DISCUSSION

5.1 LIPINSKYI RULE OF 5 OR FIVE:

Great efforts are being made to assess the similar "drug-like" qualities of molecules in the early phases of the discovery-research process in order to progress the discovery and development of new medications. There are other ways to tackle this issue, but the most popular and straightforward one was created by Chris Lipinski and his Pfizer colleagues. It is often known as the Rule of Five (ROF) or the Lipinski Rules **[19]**.

Rule of five (ROF) is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans **[20]**.

For a biologically active molecule to be considered for use as an oral medication, it must meet five requirements. Poor absorption or permeation are most likely if:

➢ Molar mass >500,

➢ Number of H-bond acceptors >10,

➢ Number of H-bond donors > 5,

➢ LogP> 5 (or MlogP>4.15)

An oral active drug's rating on the ROF ranges from "0" to "4", indicating that there isn't more than one infraction of the exposed criteria. But Lipinski notes that since several medications are known to not undergo ROF, such compounds shouldn't be entirely disregarded for additional research.

IDENTIFICATION OF DRUGLIKE PROPERTIES FOR COMPOUNDS (11 – 13)

COMPOUND CODE	MOL.FORMULA	MOL.Wt	NO. OF ROTATABLE BONDS	H-BOND ACCEPTORS	H-BOND DONARS	MOL REFRACTIVITY	TAPSA ^{0}	LOG P	LIPINSKYI RULE of 5
11	$C_{19}H_{14}F_3N_5O_5$	449.34	10	9	3	106.28	138.17A^0	1.68	YES
12	$C_{21}H_{18}F_3N_5O_5$	477.39	11	9	3	115.90	138.17A^0	1.89	YES
13	$C_{20}H_{16}F_3N_50_5$	463.37	11	9	3	111.09	138.17A^0	1.96	YES

5.2 CHEMISTRY:

The synthesis of the final compounds 4, 11–13 is outlined in Schemes 1 and 2. Briefly, 4-chloro-7-tri Fluoro methylquinoline was reacted with 4-aminoace tophenone, anthranilic acid, and p-aminobenzoic acid to give the corresponding anilino derivatives 3, 6, respectively. The equivalent oxime 4 was obtained by condensing 3 with hydroxylamine hydrochloride. In the meantime, the equivalent hydrazides 7 were produced via the reaction of 6 with thionyl chloride and then hydrazine hydrate. The matching haloalkyl derivatives 8–10 were produced when these hydrazides reacted with the proper acid chloride, specifically acetyl chloride, 2-chloropropionyl chloride, and 3-chloropropionyl chloride.

The terminal chloro function is then converted to the target nitrate derivatives with AgNO3 and acetonitrile.

To evaluate the thiol-induced nitric oxide generation, compounds 4, 11–13, were dissolved in phosphate buffer (pH 7.4), methanol, and H2O mixture at 37 C for 1h in the presence of 1:5 molar ratio of cysteine, the produced nitrite which is a convenient index of nitric oxide production trend was determined by Griess reagent. **[21]** These compounds were unable to generate nitrite under the same conditions at pH 1.

Melting points were determined on the Electrothermal Melting Point apparatus and were uncorrected. Infrared spectra were recorded on the Shimadzu-470 infrared spectrometer. 1HNMR spectra were recorded in DMSO-d6 on Varian XL-200MHz spectrometers (chemical shifts are given in parts per million (PPM) downfield from TMS). Elemental analyses (C, H, N) were performed by the Micro analytical Unit, Faculty of Science, Cairo University; the values were found to bewithin±0.4%of the theoretical ones, unless otherwise indicated. Mass spectra were made on Hewlett Packard GC–MS, model 5890, series II. Intermediates 3, 6,were prepared by reported procedures. All the new com pounds were crystallized from ethanol.

PHYSICAL CHARACTERISATION OF COMPOUNDS [4,7,8,9,10]

COMP.NO	MOL.FOR	MOL.WT	M.P	%YIELD
4	$C_{18}H_{14}F_3N_3O$	345.31	328–330 C	90%
7	$C_{17}H_{13}F_3N_4O_2$	362.3	233–235 C	95%
8	$C_{20}H_{14}F_3N_5O_3$	429.35	235–237 C	43%
9	$C_{22}H_{18}F_3N_5O_3$	457.4	205–207 C	36%
10	$C_{20}H_{18}ClF_3N_4O_3$	452.81	116–118 C	33%

CONCLUSION:

In this study a series of QUINOLINE NITRATE derivatives were designed and studied for DRUGLIKE PROPERTIES. All the designed compounds are having druglike properties conformed from SWISS ADME software. These finding support further exploration of designed quinoline nitrate derivatives as potential leads for various pharmacological activities like Anticancer agent, Antioxidants, Anti-inflammatory, Anti-microbial etc.

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