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IN SILICO STUDY OF N-(4-OXO-2-(4-(4-(2-(SUBSTITUTED PHENYL AMINO) ACETYL) PIPERAZIN-1-YL) PHENYL) QUINAZOLIN-3(4*H*)-YL) BENZAMIDE DERIVATIVES

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ABSTRACT

Derivatives of quinazolinone, piperazine, and amide have numerous significant medicinal applications, particularly in the pharmaceutical sector. As a result, the current *in silico* investigation attempted to use computational methods to determine the molecular properties, bioactivity score, and toxicity of various N-(4-oxo-2-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4*H*)-yl) benzamide derivatives. The investigation revealed that, except for molecular weight, the majority of the substances fitted Lipinski's rule of five, indicating drug-like properties. The bioactivity data revealed that the N-(4-oxo-2-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4*H*)-yl) benzamide derivatives were moderate active as GPCR ligand, Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor, and Enzyme inhibitor.None of the synthesized compounds were assessed to be cytotoxic and hepatotoxic based on the results of ProtTox-II.The evidence presented by the current study regarding the pharmacokinetic features and toxicity of recently synthesized derivatives& existing medications can be used to design and develop novel compounds that are more potent, more selective, and less toxic.

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Introduction

The invasion of harmful organisms is the cause of numerous diseases. Strong and broad-spectrum antibacterial medicines were developed to treat these infections. Antibiotics are life-saving medications in therapeutics, but they are also toxic and potentially dangerous. Among these adverse effects include allergic, and anaphylactic reactions, superinfections, resistance development, eradication of the normal non-pathogenic bacterial flora, and selective toxicity. Over the previous decade, the development of resistance in organisms that are often pathogenic in humans has surged. The number of antimicrobials that can be employed to treat particular species has been diminished because of this rising resistance. For specific classes of species, newer antimicrobials are also required. Antimicrobials that can treat infections caused by fungus and mycobacteria are extremely limited. The ongoing dispute against infectious diseases necessitates the development of new drugs, drugs with fewer side effects, and medications with shorter treatment times [1].

Quinazoline has a variety of pharmacological activity profiles, including those analgesic, anti-inflammatory, antimicrobic, diuretic, antihypertensive, antimalarial, sedative, hypoglycemic, and anti-carcinogenic [2].

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Piperazine nuclei are frequently found in compounds that seem to be pharmacologically active and have been designated as privileged structures. Among these significant biological functions is antimicrobial, antituberculosis, neuroleptic, anti-epileptic, anti-depressing, anti-inflammatory, antineoplastic, anti-malarial, anti-arrhythmic, anti-oxidant, and anti-viral action [3-7].
Amides were found to be good antimicrobial agents that have antimicrobial, antibacterial, antifungal, and photosynthesis inhibition activity, anti-inflammatory, and analgesic activities [8-13].
A common alteration technique is to combine these two or more effective moieties into one, which might also increase activity or eliminate undesirable side effects [14].
Such hybridization is proposed to explore the way this structural variation influences the anticipated biological properties. Given the significance of Quinazolinone, Piperazine, and Amide moieties in the field of medicinal chemistry, it was proposed to synthesize new hybrid molecules comprised of Quinazolinone, Piperazine, and Amide derivatives to study the molecular properties, bio-activity score, and toxicity study.

Materials and Methods

Developing Molecules and Naming of N-(4-oxo-2-(4-(4-(2-(substituted phenyl amino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4H)-yl) Benzamide Derivatives
Chem Draw Professional is a drawing program that enables users to represent biomolecules and biochemical pathways along with chemical structures and reactions. Moreover, users can see 3D structures, anticipate characteristics and spectra, and transform chemical structures into IUPAC names [15].
The chemical structures and nomenclature of N-(4-oxo-2-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4*H*)-yl) benzamide derivatives were produced utilizing Chem Draw Ultra 8.0.

Calculation of Molecular Properties of N-(4-oxo-2-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4H)-yl) Benzamide Derivatives and a Few Specific Antimicrobial Agents
The molecular properties that influence a compound's absorption, distribution, metabolism, and excretion serve as a qualitative index of its drug-likeness. Based on Lipinski's rule of five, the *in silico* drug-likeness properties of N-(4-oxo-2-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4*H*)-yl) benzamide, as well as some anti-microbial drugs, were reviewed using the Molinspiration online molecular property calculation toolkit [16, 17]. According to the rule, molecules with excellent membrane permeability have log P ≤ 5, molecular weight ≤ 500 Da, hydrogen bond acceptors ≤ 10, and hydrogen bond donors ≤ 5. The number of flexible bonds, topological polar surface area, and molecule volume are additional rules that are significant in the computational prediction of drug-likeness. The number of flexible bonds reflects a compound's conformational flexibility and, ultimately, its ability to bind to receptors or ion channels. The degree of molecular flexibility is indicated by this fundamental topological characteristic. It has been demonstrated to be a very good descriptor of a drug's oral bioavailability [18]. Every single non-ring bond bound to a nonterminal heavy (i.e., non-hydrogen) atom is referred to as a rotatable bond. Because of their large rotational energy barrier, amide C-N bonds are not taken into consideration. The TPSA has proven to be a very accurate description of the absorption of drugs, including intestinal absorption, bioavailability, Caco-2 permeability, and blood-brain barrier penetration. TPSA is however regarded as a reliable measure of medication penetration through the blood-brain barrier (TPSA < 60 $Å^2$) and intestinal drug permeation (TPSA < 140 angstroms squared $Å^2$). The Absorption percentage (% ABS), which may be computed utilizing the equation% ABS = 109-(0.345 x TPSA), can be used to express the amount of absorption. Hence, to model molecular properties and biological activity in QSAR research, Molecular Volume is frequently used [19].

Calculation of Bioactivity Score N-(4-oxo-2-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4H)-yl) Benzamide Derivatives and a Few Specific Antimicrobialagents
Table 3 lists the bio-activity ratings of the produced compounds towards GPCR ligands, ion channel modulators, nuclear receptor ligands, kinase inhibitors, protease inhibitors, and enzyme inhibitors. By computing the activity score of the GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, and enzyme inhibitor, it is possible to assess the drug's bioactivity. With the support of the online Molinspiration drug-likeness score, all the variables were determined (www.molinspiration.com).The drug-likeness score for each compound was obtained, compared to its distinct bodily function, and the outcomes were comparable to those of standard medicines. For organic molecules, the probability is that they are active if the bioactivity score exceeds 0, fairly active between -5.0 and 0.0, and Inactive if the value is below -5.0 [20].

Prediction of Toxicity of N-(4-oxo-2-(4-(4-(2-(substituted phenyl amino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4H)-yl) Benzamide Derivatives
ProTox-II, a digital laboratory for the estimation of small molecule toxicity, was used to analyze the toxicity of N-(4-oxo-2-(4-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4*H*)-yl) benzamide. ProTox-II incorporates molecular similarity, fragment propensities, most frequent features, and (fragment similarity based CLUSTER cross-validation) intelligent retrieval for the estimation of various toxicity end-points, which include acute toxicity, hepatotoxicity,

cytotoxicity, carcinogenicity, mutagenicity, immunotoxicity, adverse outcomes (Tox21) pathways, and toxicity targets. The LD_{50} values for toxic dosages are frequently expressed in mg/kg body weight. The dosage at which half of the test subjects die after being administered a drug is termed the median lethal dosage, or LD_{50} [21]. The Globally Harmonized System (GHS) for the classification and labeling of chemicals specifies toxicity classes.

LD_{50} data are reported in [mg/kg]:

Category1: Fatal if ingested ($LD_{50} \leq 5$)

Category2: Fatal if ingested ($5 < LD_{50} \leq 50$)

Category3: Toxic if ingested ($50 < LD_{50} \leq 300$)

Category4: Harmful if ingested ($300 < LD_{50} \leq 2000$)

Category5: May be harmful if ingested ($2000 < LD_{50} \leq 5000$)

Category6I: Harmless ($LD_{50} > 5000$) [21]

Results and Discussion

To develop new molecules, computer-aided drug design is essential in the field of medicinal chemistry. To discover and enhance physiologically active molecules, computational medicinal researchers can make utilization of a wide range of tools and programs in computer-aided drug design. Optimizing the chemical structure of lead components concerning ADME processes has become fundamental to the modern drug development strategy. In **Table 1**, a nomenclature as per IUPAC rules and molecular formlaof of N-(4-oxo-2-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4H)-yl) benzamide derivatives are presented.

Table 1. Nomenclature and molecular formula of N-(4-oxo-2-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4*H*)-yl) benzamide derivatives

Compound No.	Nomenclature	Molecular formula	R
PRP7A1	N-(4-oxo-2-(4-(4-(2-(phenylamino)acetyl)piperazin-1-yl)phenyl)quinazolin-3(4*H*)-yl)benzamide	$C_{33}H_{30}N_6O_3$	H
PRP7A2	N-(2-(4-(4-(2-(o-toluidino)acetyl)piperazin-1-yl)phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzamide	$C_{34}H_{32}N_6O_3$	2-CH_3
PRP7A3	N-(2-(4-(4-(2-(2-methoxyphenylamino)acetyl)piperazin-1-yl)phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzamide	$C_{34}H_{32}N_6O_4$	2-OCH_3
PRP7A4	N-(2-(4-(4-(2-(4-methoxyphenylamino)acetyl)piperazin-1-yl)phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzamide	$C_{34}H_{32}N_6O_4$	4-OCH_3
PRP7A5	N-(2-(4-(4-(2-(p-toluidino)acetyl)piperazin-1-yl)phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzamide	$C_{34}H_{32}N_6O_3$	4-CH_3
PRP7A6	N-(2-(4-(4-(2-(4-chlorophenylamino)acetyl)piperazin-1-yl)phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzamide	$C_{33}H_{29}ClN_6O_3$	4-Cl
PRP7A7	N-(2-(4-(4-(2-(4-hydroxyphenylamino)acetyl)piperazin-1-yl)phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzamide	$C_{33}H_{30}N_6O_4$	4-OH
PRP7A8	N-(2-(4-(4-(2-(4-nitrophenylamino)acetyl)piperazin-1-yl)phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzamide	$C_{33}H_{29}N_7O_5$	4-NO_2
PRP7A9	N-(2-(4-(4-(2-(m-toluidino)acetyl)piperazin-1-yl)phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzamide	$C_{34}H_{32}N_6O_3$	3-CH_3
PRP7A10	N-(2-(4-(4-(2-(3-methoxyphenylamino)acetyl)piperazin-1-yl)phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzamide	$C_{34}H_{32}N_6O_4$	3-OCH_3
PRP7A11	N-(2-(4-(4-(2-(2-chlorophenylamino)acetyl)piperazin-1-yl)phenyl)-4-oxoquinazolin-3(4*H*)-yl)benzamide	$C_{33}H_{29}ClN_6O_3$	2-Cl

The results of computing the molecular characteristics of all the synthesized substances using molecular inspiration Cheminformatic are presented in **Table 2**. The drug-likeness score of the N-(4-oxo-2-(4-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4*H*)-yl) benzamide were good and it obeyed Lipinski's rule **(Table 2)**. Most of the compounds exhibited MiLog P values below 5, while the methyl and chloro analogs showed higher values, indicating that these compounds possessed good permeability. All of the derivatives had TPSA values between 99.57 and 145.39. (well below 160). Each agent seems to have a molecular weight of ≤ 600. As compared to higher molecular weight compounds, molecules with such a minimal molecular weight are very efficiently absorbed, diffused, and transported. The bulkiness of the molecules likewise increases in proportion to the rise in molecular weight, to a certain extent [22].

Table 2. Scores for the compounds' drug-likeness

Comp.	MW	miLogP	TPSA	natoms	nON	nOHNH	n violations	nrotb	Vol.	% ABS
PRP7A1	558.64	4.76	99.57	42	9	2	1	7	503.6	74.64
PRP7A2	572.67	5.16	99.57	43	9	2	2	7	520.52	74.64
PRP7A3	588.67	4.77	108.80	44	10	2	1	8	529.51	71.46
PRP7A4	588.67	4.82	108.80	44	10	2	1	8	529.51	71.46
PRP7A5	572.67	5.21	99.57	43	9	2	2	7	520.52	74.64
PRP7A6	593.09	5.44	99.57	43	9	2	2	7	517.50	74.64
PRP7A7	574.64	4.28	119.80	43	10	3	1	7	511.98	67.66
PRP7A8	603.64	4.72	145.39	45	12	2	2	8	527.30	58.84
PRP7A9	572.67	5.18	99.57	43	9	2	2	7	520.52	74.64
PRP7A10	588.67	4.79	108.80	44	10	2	1	8	529.51	71.46
PRP7A11	593.09	5.39	99.57	43	9	2	2	7	517.50	74.64
Ciprofloxacin	331.35	-0.70	74.57	24	6	2	0	3	285.46	83.27
Fluconazole	306.28	-0.12	81.66	22	7	1	0	5	248.96	80.82

It was discovered that the hydrogen bond donors (≤5) and acceptors (≤ 10), i.e., less than 5 and 10, respectively, fit in Lipinski's rule of five. All of the above-mentioned components exhibited n violations of 1 to 2 and were flexible (< 10 rotatable bonds). Six distinct protein structures were utilized to evaluate the bioactivity of all N-(4-oxo-2-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4*H*)-yl) benzamide analogs. A bioactivity score is shown in **Table 3**.
Bioactivity scores, which are categorized into three ranges, are utilized to measure biological activity.

1. If the bioactivity score is greater than 0, there is significant biological activity.
2. If the bioactivity score is between -5.0 to 0.00, there is moderate biological activity.
3. If the bioactivity score is less than -5.0, biological activity is not detected [23].

Table 3. Bioactivity score of the compounds

Comp.	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
PRP7A1	-0.13	-0.83	-0.21	-0.77	-0.34	-0.35
PRP7A2	-0.20	-0.95	-0.29	-0.83	-0.39	-0.45
PRP7A3	-0.25	-1.08	-0.37	-0.93	-0.42	-0.53
PRP7A4	-0.24	-1.05	-0.38	-0.90	-0.39	-0.51
PRP7A5	-0.19	-0.95	-0.30	-0.84	-0.38	-0.45
PRP7A6	-0.17	-0.92	-0.29	-0.84	-0.37	-0.43
PRP7A7	-0.14	-0.89	-0.25	-0.74	-0.34	-0.38
PRP7A8	-0.36	-1.14	-0.53	-1.03	-0.46	-0.62
PRP7A9	-0.20	-0.96	-0.30	-0.84	-0.38	-0.46
PRP7A10	-0.25	-1.06	-0.37	-0.92	-0.42	-0.52
PRP7A11	-0.19	-0.92	-0.27	-0.86	-0.40	-0.45
Ciprofloxacin	0.12	-0.04	-0.07	-0.19	-0.20	0.28
Fluconazole	0.04	0.01	-0.09	-0.23	-0.09	0.03

The synthesized compounds' bioactivity scores revealed the following outcomes.

- GPCR Ligand: All substances were shown to exhibit a moderate active (≤0) for GPCR ligands.
- Ion channel modulator: All substances were shown to exhibit a moderate active (≤0) for the Ion channel modulator.
- Kinase inhibitor: It was revealed that all substances have a moderate affinity (≤ 0) for kinase inhibitors.
- Nuclear receptor ligand: The activity of all substances was found to be moderate (≤ 0).
- Protease inhibitor: Against the protease inhibitor, all substances proved to be relatively moderately active (≤ 0).
- Enzyme inhibitor: Regarding enzyme inhibitory activity, all substances were rated as being just moderately active (≤ 0).

Table 4. Toxicity Profile of the Compounds

Comp.	LD_{50} (mg/kg)	Toxicity Category	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
PRP7A1	1500	IV	(-)	(+)	(-)	(-)	(-)
PRP7A2	1500	IV	(-)	(+)	(-)	(+)	(-)
PRP7A3	1500	IV	(-)	(-)	(+)	(+)	(-)
PRP7A4	1500	IV	(-)	(-)	(+)	(+)	(-)
PRP7A5	1500	IV	(-)	(+)	(-)	(+)	(-)
PRP7A6	1500	IV	(-)	(-)	(+)	(-)	(-)
PRP7A7	1500	IV	(-)	(-)	(-)	(-)	(-)
PRP7A8	1500	IV	(-)	(+)	(+)	(+)	(-)
PRP7A9	1500	IV	(-)	(+)	(-)	(+)	(-)
PRP7A10	1500	IV	(-)	(-)	(+)	(+)	(-)
PRP7A11	1500	IV	(-)	(-)	(+)	(-)	(-)
Ciprofloxacin	2000	IV	(-)	(-)	(-)	(+)	(-)
Fluconazole	1271	IV	(+)	(-)	(-)	(-)	(-)

[Active: (+), Inactive: (-)]

All the synthesized comppounds were evaluated to toxicity profile and given in **Table 4**. None of the ligands have exhibited acute toxicity according to toxicity class classification [24, 25], and they were shown to be similar to standard drugs. All synthetic substances exhibit category 4 toxicity. Endpoint results for the toxicological prediction include cytotoxicity, mutagenicity, carcinogenicity, immunotoxicity, and hepatotoxicity. None of the synthetic compounds were expected to be cytotoxic orhepatotoxic. The non-carcinogenic effects of the compounds PRP7A3, PRP7A4, PRP7A6, PRP7A7, PRP7A10, and PRP7A11 were indicated. It was predicted that the compounds PRP7A1, PRP7A2, PRP7A5, PRP7A7, and PRP7A9 were going to be non-immunotoxic. The predicted non-mutagenic properties of the synthesized substances PRP7A1, PRP7A6, PRP7A7, and PRP7A11 were confirmed.

Conclusion

In conclusion, the bioactivity scores for all eleven substances are moderate. All components, except molecular weight, fulfill the rule of five for the drug-likeness activity of compounds. For GPCR ligand, Ion channel modulator, Kinase inhibitor, Nuclear receptor ligand, Protease inhibitor, and Enzyme inhibitor, all drugs have moderate activity (≤0). It was predicted that none of the synthesized molecules would be cytotoxic orhepatotoxic.
To examine the molecular characteristics, bioactivity score, and toxicity studies of N-(4-oxo-2-(4-(4-(4-(2-(substituted phenylamino) acetyl) piperazin-1-yl) phenyl) quinazolin-3(4*H*)-yl) benzamide derivatives with some selected anti-microbial agents such as Ciprofloxacin and Fluconazole.

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