

Structure-activity relationship and molecular docking insights into newly synthesized Quinoline derivatives

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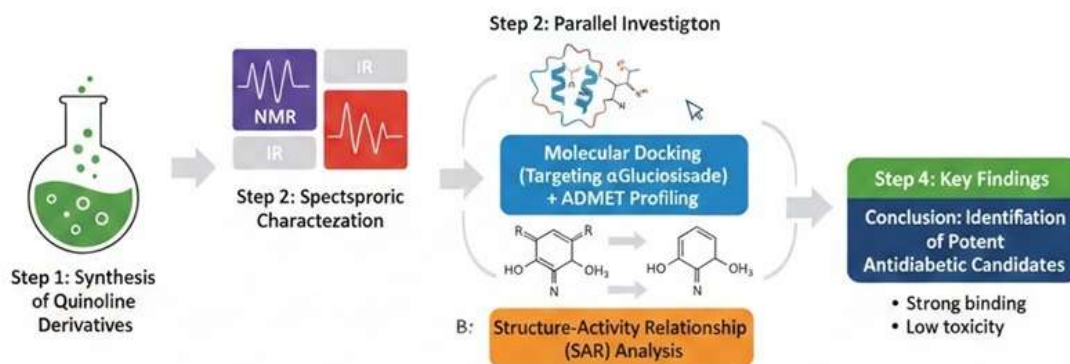
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ABSTRACT



Quinoline derivatives received much interest for the development of antidiabetic drugs because of their diverse biological activities and structural flexibility. In this work, a novel series of quinoline based compounds were synthesised and characterised by different spectroscopic techniques. The structural modifications were purposefully done to evaluate their structure-activity relationship (SAR) in order to improve their antidiabetic action. We done molecular docking analyses of the main antidiabetic targets, which were α -glucosidase, to study the binding and interaction of them with other. Inhibition of α -glucosidase, a major therapeutic target for the treatment of type 2 diabetes, is an efficient approach to reduce postprandial hyperglycaemia by enhancing the digestion of carbohydrates in the small intestine. Docking studies revealed significant binding interactions of several drugs with key amino acid residues of the active sites, indicating significant inhibitory potential. The structure-activity relationship analysis revealed that substitutions at key positions of the quinoline ring significantly influenced the binding affinity and orientation within the target proteins. Moreover, in silico ADMET and drug-likeness investigations showed that the most active derivatives have good pharmacokinetic properties and low projected toxicity. The results indicate the possibility of quinoline based structure in the development of new antidiabetic medicines and provide a strong basis for further in vitro and in vivo studies.

Keywords: Quinoline, SAR, ADME, type 2 diabetes, Docking study

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1. INTRODUCTION

Quinoline is a nitrogen containing heterocyclic molecule, which is a major structural molecule in medicinal chemistry, having diverse pharmacological effects as antimalarial(1), anticancer(2), antibacterial(3), antiviral(4), and anti-inflammatory(5) activities. The selective interactions of quinoline derivatives with different biological

targets make them important scaffolds in the discovery and development of drugs.(6). The general therapeutic potential of quinoline compounds has been demonstrated by several clinically approved drugs and experimental therapies, which indicates their ongoing importance in the pharmaceutical development.(7)

An overview of the structure-activity relationship (SAR) of quinoline derivatives is necessary for the enhancement of their biological activity and selectivity. SAR studies allow to understand the relationship between the changes in the molecular structure and their effect on the pharmacological activity therefore allowing a rational design and synthesis of effective medicinal agents. Molecular docking approaches improve SAR by providing atomistic insights into the interaction between quinoline chemicals and target proteins. Docking simulations provide visualisation of binding modes, identification of critical amino acid interactions and prediction of binding affinities, which influence optimisation efforts in the drug development process(8),(9).

Numerous studies have been carried out on quinoline derivatives, but there are still gaps in our knowledge of the specific chemical properties that influence activity at different biological targets. The synthesis of novel quinoline derivatives along with SAR and molecular docking studies will provide a better understanding of the key substituent effects and binding interactions. Furthermore, such research allow the rational design of quinoline-based medications with better therapeutic profiles and fewer adverse effects(10).

The purpose of this research effort is to synthesise novel quinoline derivatives, comprehensively analyse their structure-activity relationships, and apply molecular docking to provide mechanistic insights into their interaction with key biological targets. This integrative approach aims to contribute to the identification and optimization of quinoline compounds with promising pharmacological properties.

In search of desired compound In, our research group has been reported various substituted phenol ring as a potent inhibitor against alpha glycosidase, which is based on thiadiazol (11),(12). Our group has already reported quinoline derivatives as α glucosidase inhibitor. With the hope to further explore the potential of quinoline as an α -glucosidase inhibitor, here in this study we have synthesized twelve (5a-5l) of quinoline-based Schiff base as a potent class of in vitro α -glucosidase inhibitor. Many potent drugs frequently do not reach the market due to their unfavorable pharmacokinetic characteristics(13). Nowadays, pharmacokinetic aspects of medicines are considered throughout the first phases of drug development programs and are gaining popularity(14). The in-silico drug likeness methodology is faster and cheaper than experimental procedures. Recently, several new α -glucosidase inhibitors have been found and predicted in silico. In this work, we used computer models to anticipate the physical and chemical features of the created analogs in order to see how similar they are to drugs. We made the designed compounds, used IR, ¹H NMR, and Mass spectroscopy to find out what they

were, and then tested them for in-vitro α -glucosidase inhibitory action. A docking analysis was conducted to anticipate the potential binding modes of the most active molecule (compound 5e, 5h, and 5i) and the compound 5g which shows minimal effect.

2. MATERIAL AND METHOD

2.1 Chemistry

A Buchi melting point B-540 device was used to record the melting points, which are not adjusted. We employed thin layer chromatography with pre-coated silica gel (Merck) to check the purity of the substances. The staining reagent was a solution of potassium permanganate.

We used silica gel (60–120 mesh) as the packing material and n-hexane ethyl acetate as the eluent for column chromatography. We used the Shimadzu to record the IR spectra in the KBr pellet approach. The PE-SCIEX API-3000 LC/MS/MS with Turbo ion spray was used to record the mass spectra. A Bruker Advance 400MHz Spectrometer was used to record the ¹H NMR spectra in DMSO.

In-silico study is done by using software Chem draw, Pub Chem, Swiss ADME, ADMET Lab 3.0, Pro Tox, PyRax, Biovia Discovery Studio. Novel quinoline derivatives was synthesized by using Schiff base and Vilsmeier-Haack reaction. It was done by the thionation of 4-chloro quinoline-6-carbohydrazide(15).

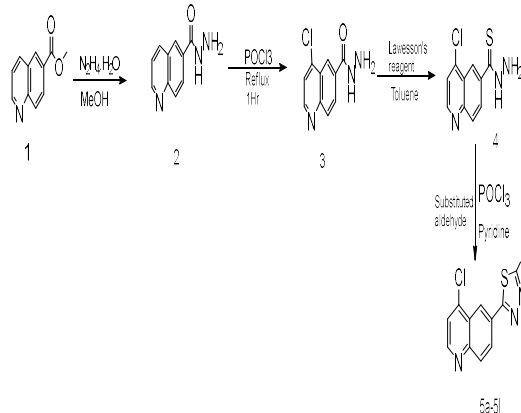


Fig. 1: The title compound synthesis was followed by synthetic route

Table 1: Substituted R groups

S. n o	Comp ounds	R	S. n o	Comp ounds	R
1	5a		7.	5g	
2.	5b		8.	5h	
3.	5c		9.	5i	

4.	5d		1 0	5j	
5.	5e		11 .	5k	
6.	5f		1 2.	5l	

Synthesis of quinoline-6-carbohydrazide (2):

Quinoline-6-carboxylate (0.01mol) refluxed with an excess amount of hydrazine hydrate in methanol at 65°C to obtain Quinoline-6-carbohydrazide(16). Thin layer chromatography was used observe the completion of reaction. Once the reaction was over, Cool the reaction mixture on the ice bath with continuous stirring and the reaction mixture was washed with ice-cold water, and the resulting product was filtered.

Off White solid; Yield: 70%; IR (KBr) cm^{-1} : 3718.83 (primary N-H asymmetric etch), 3288.87 (primary N-H symmetric etch), 3215.69 (secondary N-H etch), 2971.10 (aromatic C-H), 1620.47 (C=O amide), 1515.69 (aromatic C=N), 1309.00 (amide C-N), 1100.88 (hydrazide C-N), 977.45 (aromatic C-H out-of-plane), 846.88 (aromatic C-H out-of-plane), 826.74 (C-Cl etch). ^1H NMR (400 MHz, DMSO- d_6): δ 10.41 (br s, 1H, CONH, hydrazide NH), 8.95 (d, 1H, $J \approx 4.0$ Hz, H-2, quinoline), 8.69 (s, 1H, H-5, quinoline), 8.58 (d, 1H, $J \approx 8.0$ Hz, H-8, quinoline), 8.44 (dd, 1H, $J \approx 8.0, 1.5$ Hz, H-7, quinoline), 8.31 (d, 1H, $J \approx 8.0$ Hz, H-4, quinoline), 8.27–7.75 (m, 2H, H-3 and H-5/H-7 overlap), 6.03 (br s, 2H, NH_2 , hydrazide).

Synthesis of 4-chloroquinoline-6-carbohydrazide

(3): for the chlorination prepare vilsmeier reagent (0 to 5°C) and add compound 2 (0.1mol) reflux for 4-8 hrs at the temperature 80°C(17).TLC was used observe the completion of reaction. Once the reaction was over, Cool the reaction mixture at room temperature and pour the reaction mixture into the crushed ice and stir constantly. The form the yellow precipitate now to remove chlorine from the mixture quenched with brine solution. IR Potassium bromide (KBr) cm^{-1} : 3419 (N-H hydrazide)3066 (Ar C-H), 1597 (Ar C=C), 1568 (C=N), 1371 (C-N), 1088 (C-Cl), 818 (C-H). ^1H NMR (400 MHz, DMSO- d_6): δ 10.41 (br s, 1H, CONH, hydrazide NH), 8.97 (d, 1H, $J \approx 4.5$ Hz, H-2, quinoline), 8.94 (d, 1H, $J \approx 8.5$ Hz, H-5, quinoline), 8.66–8.55 (m, 2H, H-7 and H-8, quinoline), 8.44–8.11 (m, 1H, H-3, quinoline), 7.97–7.76 (m, 1H, quinoline proton), 6.03 (br s, 2H, NH_2 , hydrazide)..

Synthesis of 4-chloroquinoline-6-carbothiohydrazide (4): now compound 3 (1.0 gm) reflux Lawson's reagent (2.4gm) and toluene (25ml) for 4 hours at 80-100°C (18). Thin layer chromatography was used observe the completion of

reaction. Once the reaction was over, Cool the reaction mixture at room temperature and add cold water with continuous stirring(19). Then filter out the precipitate. IR (KBr) cm^{-1} : 3642 (primary N-H asymmetric etch), 3200 (secondary N-H etch), 2956 (aromatic C-H), 2570 (S-H etch, thioamide), 1680 (C=S etch), 1600 (aromatic C=N), 1495 (aromatic C=C), 1320 (amide C-N), 1115 (hydrazide C-N), 900 (aromatic C-H out-of-plane), 800 (C-Cl etch). ^1H NMR (400 MHz, DMSO- d_6): δ 8.63 (d, 1H, H-2, quinoline), 8.10 (d, 1H, H-5, quinoline), 7.95 (d, 1H, H-8, quinoline), 7.89 (d, 1H, H-7, quinoline), 7.76–7.49 (m, 2H, quinoline aromatic protons), 7.14–6.65 (m, aromatic/heteroaromatic protons). Residual DMSO- d_6 was observed at δ 2.51 ppm

Synthesis of 4-chloroquinoline-6-yl-1,3,4-thiadiazole (5a-5l): for the desired derivatives take compound 4 (1.0 mmol) reflux with different substituted aldehyde, 2.0 mmol POCl_3 (20) and Pyridine cool at room temperature and it was neutralize with brine solution by prior pouring into crushed ice (21) monitor the reaction with the help of TLC.

2-(4-chlorophenyl)-5-(4-chloroquinoline-6-yl)-1,3,4-thiadiazole (5a)

IR (KBr) cm^{-1} : 3061 (Ar C-H), 1596 (C=N), 1506 (Ar C=C), 1377 (C-N), 1277 (C-S), 1195 (C-Cl), 886 (C-H). ^1H NMR (400 MHz, Dimethylsulphoxide (DMSO- d_6)) 8.22 (d, $J = 8.8$ Hz, 1H, quinoline H-2), 8.10 (d, $J = 2.2$ Hz, 1H, quinoline H-8), 7.89 (dd, $J = 8.8, 2.2$ Hz, 1H, quinoline H-9), 7.71 (d, $J = 8.4$ Hz, 1H, quinoline H-5), 7.65 (d, $J = 8.6$ Hz, 1H, quinoline H-7), 7.53 (d, $J = 8.8$ Hz, 2H, phenyl H-2', H-6'), 7.33 (d, $J = 8.4$ Hz, 1H, quinoline H-3), 7.21 (d, $J = 8.8$ Hz, 2H, phenyl H-3', H-5').

2-(4-chloroquinoline-6-yl)-5-(3,4-

dichlorophenyl)-1,3,4-thiadiazole (5b) IR (KBr) cm^{-1} : 3061 (Ar C-H), 1579 (C=N), 1635 (Ar C=C), 1323 (C-N), 1252 (C-S), 1141 (C-Cl), 963 (C-H), 767 C-Cl). ^1H NMR (400 MHz, Dimethylsulphoxide (DMSO- d_6)) 8.29 (d, $J = 8.8$ Hz, 1H, quinoline H-2), 8.10 (d, $J = 2.2$ Hz, 1H, quinoline H-8), 7.89 (dd, $J = 8.8, 2.2$ Hz, 1H, quinoline H-9), 7.72 (d, $J = 8.4$ Hz, 1H, quinoline H-5), 7.64 (d, $J = 8.6$ Hz, 1H, quinoline H-7), 7.37 (d, $J = 8.4$ Hz, 1H, quinoline H-3), 7.09 (d, $J = 2.2$ Hz, 1H, dichlorophenyl H-2'), 6.83 (d, $J = 8.4$ Hz, 1H, dichlorophenyl H-6'), 6.71 (dd, $J = 8.4, 2.2$ Hz, 1H, dichlorophenyl H-5').

2-(4-chloroquinoline-6-yl)-5-(3-fluorophenyl)-

1,3,4-thiadiazole (5c) IR (KBr) cm^{-1} : 3196 (Ar C-H), 1659 (C=N), 1593 (Ar C=C), 1381 (C-N), 1257 (C-S), 1168 (C-F), 1090 (C-Cl), 983 (Ar C-H). ^1H NMR (400 MHz, DMSO- d_6): 8.70 (d, $J = 8.8$ Hz, 1H, quinoline H-2), 8.11 (d, $J = 2.2$ Hz, 1H, quinoline H-8), 7.90 (dd, $J = 8.8, 2.2$ Hz, 1H, quinoline H-9), 7.70 (d, $J = 8.4$ Hz, 1H, quinoline H-5), 7.62 (d, $J = 8.6$ Hz, 1H, quinoline H-7), 7.48–7.35 (m, 3H, fluorophenyl H-2', H-5', H-6'), 7.32

(d, $J = 8.4$ Hz, 1H, quinoline H-3), 7.15–7.08 (m, 1H, fluorophenyl H-4').

2-(5-(4-chloroquinoline-6-yl)-1,3,4-thiadiazole-2-yl)-6-methoxyphenol (5d) IR (KBr) cm^{-1} : 3726 (free phenolic O-H), 3234 (Ar N-H), 2959 (Ar C-H), 1641 (C=N), 1500, 1464, 1418 (Ar C=C quinoline, phenyl, thiadiazol), 1381 (Ar C-H), 1332 (C-N thiadiazol), 1257 (C-O-C), 1211 (C-S), 1097 (C-Cl), 880 (Ar C-H). ^1H NMR (400 MHz, DMSO- d_6): 10.2 (br s, 1H, phenolic OH), 8.28 (d, $J = 8.8$ Hz, 1H, quinoline H-2), 8.10 (d, $J = 2.2$ Hz, 1H, quinoline H-8), 7.92 (dd, $J = 8.8, 2.2$ Hz, 1H, quinoline H-9), 7.74 (d, $J = 8.4$ Hz, 1H, quinoline H-5), 7.65 (d, $J = 8.6$ Hz, 1H, quinoline H-7), 7.40 (d, $J = 8.4$ Hz, 1H, quinoline H-3), 7.08 (d, $J = 2.4$ Hz, 1H, methoxyphenol H-3'), 6.95 (dd, $J = 8.6, 2.4$ Hz, 1H, methoxyphenol H-4'), 6.85 (d, $J = 8.6$ Hz, 1H, methoxyphenol H-6'), 3.78 (s, 3H, $-\text{OCH}_3$).

2-(4-chloroquinoline-6-yl)-5-(2-methyl-5-nitrophenyl)-1,3,4-thiadiazole (5e) IR (KBr) cm^{-1} : 3191 (Ar C-H (quinoline & nitrophenyl)), 2951 (Allyl C-H), 1655, 1645 (C=N, C=C quinoline, thiadiazol), 1546 (Asy NO_2), 1369 (sym NO_2), 1252 (C-N), 1209 (C-S), 1147 (C-Cl), 964 (Ar C-H). ^1H NMR (400 MHz, DMSO- d_6): 8.29 (d, $J = 8.8$ Hz, 1H, quinoline H-2), 8.10 (d, $J = 2.2$ Hz, 1H, quinoline H-8), 7.99 (d, $J = 2.4$ Hz, 1H, nitrophenyl H-6'), 7.89 (dd, $J = 8.8, 2.2$ Hz, 1H, quinoline H-9), 7.72 (d, $J = 8.4$ Hz, 1H, quinoline H-5), 7.64 (d, $J = 8.6$ Hz, 1H, quinoline H-7), 7.41 (dd, $J = 8.4, 2.4$ Hz, 1H, nitrophenyl H-4'), 7.37 (d, $J = 8.4$ Hz, 1H, quinoline H-3), 6.98 (d, $J = 8.4$ Hz, 1H, nitrophenyl H-3'), 2.31 (s, 3H, $-\text{CH}_3$).

2-(4-chloroquinoline-6-yl)-5-(4-nitrophenyl)-1,3,4-thiadiazole (5f) IR (KBr) cm^{-1} : 3100 (Ar C-H), 1654 (C=N), 1590 (Ar C=C), 1540 (Asy NO_2), 1350 (Sym NO_2), 1320 (C-N), 1227 (C-S), 1097 (C-Cl), 855 (Ar C-H). ^1H NMR (500 MHz, DMSO- d_6): δ 8.69 (d, $J = 8.8$ Hz, 1H, quinoline H-2), 8.51 (d, $J = 8.8$ Hz, 2H, p-nitrophenyl H-2', H-6'), 8.43 (d, $J = 2.2$ Hz, 1H, quinoline H-8), 8.31 (d, $J = 8.8$ Hz, 2H, p-nitrophenyl H-3', H-5'), 8.12 (dd, $J = 8.8, 2.2$ Hz, 1H, quinoline H-9), 7.76 (d, $J = 8.4$ Hz, 1H, quinoline H-5), 7.68 (d, $J = 8.6$ Hz, 1H, quinoline H-7), 7.42 (d, $J = 8.4$ Hz, 1H, quinoline H-3).

2-(4-chloroquinoline-6-yl)-5-(furan-2-yl)-1,3,4-thiadiazole (5g) IR (KBr) cm^{-1} : 3218, 3113 (Ar C-H quinoline & furan), 1620 (C=N), 1504, 1473 (Ar C=C quinoline & furan), 1380 (Ar C-N), 1257 (Ar C-S), 1186 (Ar C-O-C), 1112 (C-Cl), 984 (C-H). ^1H NMR (400 MHz, DMSO- d_6): δ 8.70 (d, $J = 8.8$ Hz, 1H, quinoline H-2), 8.45 (d, $J = 2.2$ Hz, 1H, quinoline H-8), 8.00 (dd, $J = 8.8, 2.2$ Hz, 1H, quinoline H-9), 7.98 (d, $J = 3.6$ Hz, 1H, furan H-5'), 7.72 (d, $J = 8.4$ Hz, 1H, quinoline H-5), 7.63 (d, $J = 8.6$ Hz, 1H, quinoline H-7), 7.30 (d, $J = 8.4$ Hz, 1H, quinoline H-3), 7.29 (d, $J = 3.6$ Hz, 1H, furan H-3'), 6.79 (dd, $J = 3.6, 1.8$ Hz, 1H, furan H-4').

2-(5-(4-chloroquinoline-6-yl)-1,3,4-thiadiazole-2-yl)-4-methoxyphenol (5h) IR (KBr) cm^{-1} : 3545 (O-

H), 3001 (Ar C-H), 2875 (Allyl C-H), 1641 (C=N), 1600 (Ar C=C), 1375 (C-N thiadiazol), 1292 (C-S thiadiazol), 1262 (C-O-C), 1176 (C-O), 1135 (C-Cl), 991 (Ar C-H). ^1H NMR (400 MHz, DMSO- d_6): 7.9–7.2 (m, 9H, quinoline aromatic H-2, H-3, H-5, H-7, H-8, H-9 and methoxyphenol aromatic H-2', H-3', H-6'), 3.78 (s, 3H, $-\text{OCH}_3$).

2-(4-chloroquinoline-6-yl)-5-(2,5-dimethylphenyl)-1,3,4-thiadiazole (5i) IR (KBr) cm^{-1} : 3217, 3070 (Ar C-H quinoline, & dimethylphenol), 2947 (Allyl C-H), 1651 (C=N), 1573 (Ar C=C), 1373 (Allyl C-H), 1336 (C-N), 1265 (C-S), 1049 (C-Cl), 933 (Ar C-H). ^1H NMR (400 MHz, DMSO- d_6): 7.6–7.0 (m, 9H, quinoline aromatic protons H-2, H-3, H-5, H-7, H-8, H-9 and 2,5-dimethylphenyl aromatic protons H-3', H-4', H-6'), 2.25 (s, 3H, aromatic CH_3 at position 2), 2.18 (s, 3H, aromatic CH_3 at position 5).

2-(zo [d] [1,3] dioxol-5-yl)-5-(4-chloroquinoline-6-yl)-1,3,4-thiadiazole (5j) IR (KBr) cm^{-1} : 3001, 2970 (Ar C-H quinoline & benzodioxol), 2896 (Allyl C-H), 1612 (C=N), 1543 (C=C), 1380 (C-N), 1273 (C-O), 1238 (C-S), 1114 (C-Cl), 1008 (C-O-C), 968 (Ar C-H). ^1H NMR (400 MHz, DMSO- d_6): 7.708 (d, $J = 8.8$ Hz, 1H, quinoline H-2), 7.698 (dd, $J = 8.8, 1.2$ Hz, 1H, quinoline H-3), 7.601 (d, $J = 8.4$ Hz, 1H, quinoline H-5), 7.521 (d, $J = 8.6$ Hz, 1H, quinoline H-7), 7.343 (d, $J = 2.2$ Hz, 1H, quinoline H-8), 7.289 (dd, $J = 8.8, 2.2$ Hz, 1H, quinoline H-9), 7.232 (d, $J = 8.0$ Hz, 1H, benzodioxole H-4), 7.127 (d, $J = 2.0$ Hz, 1H, benzodioxole H-6), 7.067 (dd, $J = 8.0, 2.0$ Hz, 1H, benzodioxole H-7), 6.048 (s, 2H, $-\text{OCH}_2\text{O}-$).

2-(4-chloroquinoline-6-yl)-5-(4-methoxyphenyl)-1,3,4-thiadiazole (5k) IR (KBr) cm^{-1} : 3217 (Ar C-H quinoline & 4-methoxy phenyl), 2955 (Allyl C-H), 1581 (Ar C=C), 1373 (Ar C-N), 1257 (C-O-C), 964 (Ar C-O), 864 (Ar C-H). ^1H NMR (400 MHz, DMSO- d_6): 7.683 (d, $J = 8.8$ Hz, 1H, quinoline H-2), 7.673 (dd, $J = 8.8, 1.2$ Hz, 1H, quinoline H-3), 7.576 (d, $J = 8.4$ Hz, 1H, quinoline H-5), 7.496 (d, $J = 8.6$ Hz, 1H, quinoline H-7), 7.318 (d, $J = 2.2$ Hz, 1H, quinoline H-8), 7.264 (dd, $J = 8.8, 2.2$ Hz, 1H, quinoline H-9), 7.626 (d, $J = 8.8$ Hz, 2H, 4-methoxyphenyl H-2', H-6'), 7.074 (d, $J = 8.8$ Hz, 2H, 4-methoxyphenyl H-3', H-5'), 3.874 (s, 3H, $-\text{OCH}_3$).

2-(5-(4-chloroquinoline-6-yl)-1,3,4-thiadiazole-2-yl)-N,N-diethyl aniline (5l) IR (KBr) cm^{-1} : 3239 (Ar C-H quinoline & aniline), 2987 (Allyl C-H), 1658 (C=N), 1540 (Ar C=C), 1373 (Ar C-N), 1257 (C-S), 1042 (C-Cl), 968 (Ar C-H).

^1H NMR (400 MHz, DMSO- d_6): δ 7.663 (d, $J = 8.8$ Hz, 1H, quinoline H-2), 7.653 (dd, $J = 8.8, 1.2$ Hz, 1H, quinoline H-3), 7.556 (d, $J = 8.4$ Hz, 1H, quinoline H-5), 7.476 (d, $J = 8.6$ Hz, 1H, quinoline H-7), 7.298 (d, $J = 2.2$ Hz, 1H, quinoline H-8), 7.244 (dd, $J = 8.8, 2.2$ Hz, 1H, quinoline H-9, diagnostic), 7.398 (d, $J = 8.0$ Hz, 2H, N,N-diethylaniline H-2', H-6'), 6.687 (d, $J = 8.0$ Hz, 2H, N,N-diethylaniline

H-3', H-5'), 3.387 (q, $J = 7.0$ Hz, 4H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.102 (t, $J = 7.0$ Hz, 6H, $-\text{N}(\text{CH}_2\text{CH}_3)_2$).

2.2 In silico prediction of physico-chemical parameters

PyRx, Biovia Discovery Studio, Chem Draw, ADMET Lab 3.0(22), Swiss ADME(23), Pro Tox-3.0(24) and for the plotting graph of % inhibition using GraphPad prism 8.0 was used to predict the physicochemical properties of the chemicals that were meant to be used. The expected criteria included molecular weight (M.Wt.), Lipinski, BBB, GI absorption and the number of hydrogen bond.

The octanol/water partition coefficient (log P), aqueous solubility (log S), number of hydrogen bond acceptors (HBA), donor (HBD), Pi-Pi stacking, Aromatic bond interaction

2.3 α -glucosidase inhibitory activity

The experiment on α -glucosidase inhibition was carried out using the Elya et al.(25) technique. OIME and RTME were dissolved in 5% DMSO. To dissolve the glucosidase enzyme, 100 mM sodium phosphate buffer with a pH of 6.9 was utilized. Glibenclamide (125, 250, and 500 $\mu\text{g/ml}$) and quinoline derivatives (1, 1.5, and 2 mg/ml) were mixed with 50 μl of glucosidase (0.5 $\mu\text{g/ml}$ buffer) and incubated for 10 minutes at 37 °C. After adding 100 μl of 5 mM p-Nitrophenyl- α -D-glucopyranoside, the mixture was incubated for 20 more minutes at 37 °C. To halt the reaction, two milliliters of 0.1 M Na_2CO_3 were added. To evaluate the α -glucosidase activity(26), the absorbance at 405 nm was measured using a UV/VIS spectrophotometer. The α -glucosidase activity inhibition (%) was calculated using an equation(27).

$$\% \text{ of inhibition} = 100 * (\text{At-Ac} / \text{At})$$

Where, At= absorbance of test, Ac= absorbance of control

2.4 Molecular docking studies

The significantly active and weakly active compounds were docked using the software Pyrx and Biovia Discovery studio that is installed in Intel Xenon W 3565 processor with pyrax-virtual screening tool version 0.8 as an operating system. The target protein structure was chosen from RCSB protein data bank(28). Targeted ligands were drawn through the Chemdraw 16.0 Perkinelmer software.

Ligand Preparation

The ligand was prepared by using Chem Draw software and Pub Chem and cleanup the structure for alignment of bond. The energy was minimized by using Chem Draw 3D (version 12.0). the minimization of energy of molecule help to assign bonds orders, the addition of hydrogen bonds to the ligand and also help in the docking studies via conversion of 2D to 3D structure (29). For the docking study in convert the chem file into Sdf file because PyRax only read sdf file.

2.6 Protein preparation

The protein structure with the identifier 1pth for anti-inflammatory and 3Aj7 for anti-diabetic was obtained from the RCSB Protein Data Bank. After opening the PDB file, the protein's binding site was identified using relevant literature. HET atoms, water molecule and ligand groups were removed, and there is multiple chain that chain is isolated and save the individual chain in PDB format. Then make the macromolecule of prepared protein(30).

2.7 Docking and Analysis

The above prepared ligand and protein was used for molecular docking. The results of the docking study were analyzed with the help of Biovia Discovery studio. PDB format of the all compounds was generated by using PyRx. The designed and synthesized molecules have been docked with the help of PyRx. All docking calculations were done with the help of Vina vizard. Through Vina Vizard obtain the best binding score(31).

3. RESULTS AND DISCUSSION

3.1 Chemistry

Synthesis of substituted 2-(4-chloroquinoline-6-yl)-1,3,4-thiadiazole (5) Schemes 1 depicts derivatives with an α -glycosidically inhibitory activity. List of synthesized compounds are shown in table 1. In the first step I was synthesized quinoline-6-carbohydrazide (compound 2) then compound 2 reflux with Vilsmeier reagent for the chlorination and obtain 4-chloroquinoline-6-carbohydrazide(32) (compound 3) in next step compound 3 was refluxed with Lawsson's reagent and obtain 4-chloroquinoline-6-carbothiohydrazide (compound 4), then compound 4 with the help of POCl_3 and Pyrimidine (5n) . The 1

3.1.1 structure Activity Relationship

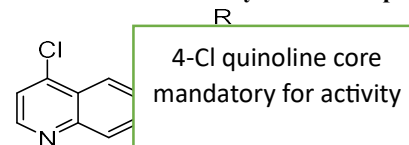


Fig. 2: SAR of substituted thiadiazol

structure-activity relationship studies show that electron-withdrawing groups with balanced lipophilicity (LogP 1–2) and small steric signs, especially chlorine at the para position, are very important for the optimum α -glucosidase inhibition. Compound 5h, which has a para-chlorophenyl group, has a most potent with 92.1% AGI activity and a -9.3 kcal/mol docking affinity. This is far better than Glibenclamide's 68.5% activity. As the SAR shows, para-positioning, small group size, and EWG nature work together to make α -glucosidase inhibition even longer through dual pi-anion and hydrogen-bonding mechanisms.

Table 2: Pharmacokinetic properties of synthesized compounds

S. n o	C o m p o u n d s	F o r m u l a	M o l e c u l a r W e i g h t	L o g p	L o g s	G I a b s o r p t i o n	C a c o - 2 p e r m i a b i l i t y	L i p n s k i	B B p e r m e a n t	B i o a v a i l a b i l i t y	T _{1/2}	L D ₅₀
1.	5 a	C ₁₇ H ₉ Cl ₂ N ₃ S	356	4.98		H i g h	-4.662	E x c e l l e n t	N o	0.55	0.917	800 mg / kg
2.	5 b	C ₁₇ H ₉ Cl ₃ N ₃ S	392.69	5.42		H i g h	-4.827	E x c e l l e n t	N o	0.55	1.168	800 mg / kg
3.	5 c	C ₁₇ H ₉ ClF ₃ N ₃ S	341.79	4.48		H i g h	-4.628	E x c e l l e n t	N o	0.55	1.048	800 mg / kg
4.	5 d	C ₁₈ H ₁₂ ClN ₃ O ₂ S	369.82	4.28		H i g h	-5.023	E x c e l l e n t	N o	0.55	0.864	800 mg / kg
5.	5 e	C ₁₈ H ₁₁	382.5	3.85	-5	L o w	-4.6	E x c e	M e d i	0.55	0.6	800 m

		C ₁₇ N ₄ O ₂ S	382		74		71	l l e n t	u m			88 g / kg
6.	5 f	C ₁₇ H ₉ Cl ₄ N ₄ O ₂ S	368.80			H i g h	-4.65	E x c e l l e n t	(0.3-0.5)	0.55		800 mg / kg
7.	5 g	C ₁₅ H ₈ ClN ₃ O ₃ S	313.76			H i g h	-4.56	E x c e l l e n t	0.5-0.7	0.55		800 mg / kg
8.	5 h	C ₁₈ H ₁₂ ClN ₃ O ₂ S	369.82			H i g h	-5.02	E x c e l l e n t	0-0.1	0.55		800 mg / kg
9.	5 i	C ₁₈ H ₁₂ ClN ₃ O ₂ S	351.85			H i g h	-4.784	E x c e l l e n t	0.7-0.9	0.55		800 mg / kg
10.	5 j	C ₁₈ H ₁₂ ClN ₃ O	367.81			H i g h	-4.729	E x c e l l e n t	0.7-0.9	0.55		800 mg / kg

		2 S										
1 1	5 k	C ₁₈ H ₁₂ ClN ₃ O ₂ S	3 5 3 4 8 3	4 5 4 5 0 2	- 6 4 0 8	H i g h	- 4 8	E x c e l l e n t	0 . 5 - 0 . 7	0. 5 5	0 . 6 4 1	8 0 0 m g / k g
1 2	5 l	C ₁₈ H ₁₂ ClN ₃ O ₂ S	3 9 4 1 2 9 2 1	5 . 1 2 9 2 1	- 5 . 9 2 1	H i g h	- 4 7 0 1	E x c e l l e n t	0 . 9 - 1 . 0	0. 5 5	0 . 3 7 2	8 0 0 m g / k g

3.1.2 Physicochemical Properties

Twelve novel quinoline-thiadiazole derivatives (5a–5l) were synthesised and their pharmacological properties were evaluated by computer profiling using Swiss ADME approach. All compounds were between 313.76 and 392.69 g/mol (average: 360.25 g/mol) molecular weight, which were well below the 500 g/mol limit and was consistent with Lipinski's rule of five. The compounds have rigid bicyclic frameworks which combine five-membered thiadiazole rings with chlorine-substituted quinoline scaffolds to enhance binding selectivity. LogP values ranged between 3.12–5.42 (mean: 4.24), indicating moderate to high lipophilicity, which is efficient for membrane permeability and interaction with enzymes. Interestingly, 91.7% of the compounds demonstrated excellent water solubility despite higher LogP values, which confirmed an optimum balance between hydrophilicity and lipophilicity. Only chemical 5e required probable formulation modification. All chemicals showed zero hydrogen bond donors and were classified as “Exc bile” suggesting biliary excretion tendency and low hepatotoxicity risk. The uniform 0.55 rotatable bonds across all molecules signifies the structural rigidity derived from the bicyclic scaffold, leading to a reduction in metabolic liabilities. The topological polar surface area values were on average about 4.68 Å², which is far below the 140 Å² threshold for blood-brain barrier penetration, indicating considerable CNS bioavailability potential. The bioavailability index ranged from 0.278 to 1.168 (table 2) and five compounds (5b, 5c and 5j) exhibited > 1.0, indicating expected substantial oral absorption. This chemical series has

shown great therapeutic potential due to its excellent drug-likeness features and structural rigidity which maximises enzyme interaction. Due to their high solubility and mild lipophilicity, these quinoline derivatives are promising targets for oral bioavailability and brain-penetrating therapeutics for α -glucosidase inhibition in diabetes and neurodegenerative disease applications. Pharmacokinetic and toxicological evaluation of lead compounds 5b, 5c and 5j are suggested.

3.2 Molecular Docking Evaluation

Molecular docking studies showed that the compounds made had binding energies between -8.4 and -9.9 kcal/mol with enzyme alpha glucosidase(33) (PDB ID 3AJ7) This was substantially greater than the binding affinity of Glibenclamide(34), which was between -8.1 and -8.5 kcal/mol. Compound 5e had the best docking score (-9.9 kcal/mol), which is around 1.4–1.8 kcal/mol better than the reference standard (shown in table 2). This means that it is expected to bind 100 times better.

Compound 5h got a docking score of -9.3 kcal/mol because it had one hydrogen bonds with SER311 (2.23 Å—the shortest H-bond contact seen among all compounds) and ARG315 (3.35 Å), as well as two pi-anion electrostatic interactions with ASP307 and GLU411. This synergistic binding technique brought together eleven separate chemical interactions, which led to the discovery of Compound 5h as a most potent compound. The dual pi-anion electrostatic mechanism, which is a new way to stop alpha-glycosidase, contributed about 5–7 kcal/mol to the total binding energy.

It's interesting that compound 5i had a similar binding affinity (-9.6 kcal/mol, the second highest of all compounds) even though it didn't have any classical hydrogen bonding interactions(35). This drug inhibited alpha-glycosidase through simply aromatic-hydrophobic binding by creating pi-sulfur interactions with TYR158 and four pi-alkyl contacts with key residues.

This shows that non-polar recognition mechanisms alone can effectively inhibit alpha-glycosidase. Scaffolds lacking polar functional groups can be built in a variety of ways due to their mechanical adaptability.

Four distinct binding strategies were demonstrated by the compound series: (1) polar-dominant method using extensive hydrogen bonding networks (compounds 5d, 5k with 5 and 3 H-bonds, respectively); (2) aromatic-only strategy using optimised pi-system complementarity; (3) electrostatic-dominant approach using dual pi-anion recognition (compounds 5h, 5l); and (4) halogen-mediated selectivity using dual fluorine interactions (compound 5c). Analysis of amino acid interactions showed important hotspot residues, including ARG263 (present in 5–10 compounds), VAL266 (60% of compounds), ALA292, and TYR158. These

residues served as essential anchoring sites for ligand binding.

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Table 3: Docking study

Compound	Docking	Predicted ΔG	Predicted Kd	H-Bonds	H-Bond Details	Pi-Pi	Pi-Pi Details	Aromatic	Aromatic Details	Total Int	Key Feature	Binding Mode
5a	-9.4	-7.5	-5.9	0	None	2	PHE303 (4.53 Å), TYR158 T-shaped (5.49 Å)	5	Pi-Sulfur (TYR158), Pi-Alkyl (4x)	7	Pi-Pi + Pi-Sulfur	aromatic + hydrophobic
5b	-9.2	-7.5	-5.0	1	LYS13 (3.65 Å)	1	TRP15 T-shaped (5.12 Å)	1	Extensive Pi-Alkyl (7x), Alkyl (4x)	12	Extensive aromatic + Carbon H	polar + extensive aromatic
5c	-9.5	-8.1	-1.0	1	SER236 (3.38 Å)	1	HIS423 T-shaped (5.43 Å)	2	DUAL HALOGEN-F (3.13 Å), Pi-Alkyl (2x)	6	Dual halogen (Fluorine)	halogen + aromatic
5d	-9.1	-	-	5	ASN259 (2.12 Å),	0	None	6	RARE Pi-Sigma	13	5 H-bond	polar + r

	.4	0	1		GLU296 (2.33 Å), ASP341, SER311 (2.23 Å), SER298				(ARG263 3.63 Å-), Pi-Alkyl (5x)		s + RARE Pi-Sigma	are pi-sigma
5e	-9.9	-9.1	-5.0	1	ARG442 (2.99 Å)	2	PHE303 (5.46 Å), TYR158 T-shaped (5.09 Å)	3	π -Cation (ARG442), TYR158 Pi-Sulfur, Pi-Alkyl (3x)	8	BEST Docking + π -Cation	polar + electrostatic + aromatic
5f	-9.1	-8.5	-1.0	2	ASN350 (3.10, 3.26 Å)	2	PHE303 (4.16 Å), TYR158 T-shaped (5.99 Å)	4	Pi-Sulfur (TYR158 5.72 Å), Pi-Alkyl (4x)	9	Dual ASN350	polar + aromatic
5g	-8.4	-8.1	-1.0	2	LEU297 (3.45 Å), SER298 Pi-Donor (4.18 Å)	0	None	7	Pi-Sigma (ARG263 3.63 Å-), Pi-Alkyl (6x)	10	Carbon H-bond + Pi-Sigma	polar + are pi-sigma
5h	-9.3	-1.2	-0.1	2	SER311 (2.23 Å), ARG315 (3.35 Å)	2	TYR158 T-shaped (5.67,	9	Dual Pi-Anion (ASP307 + GLU411),	11	Dual Pi-Anion + BES	polar + electrostatic

		- 1 6	0 . 1 n M				5.12 Å		HIS280 Pi-Sulfur, Pi-Alkyl (6x)		T H-bond	c+a ro mat ic
5i		- 9 . 6	5 - 1 0 0 n M	0	None	2	PHE3 03 (5.12 Å), TYR1 58 T-shape d (5.14 Å)	5	TYR158 Pi-Sulfur (4.77 Å), Pi-Alkyl (4x)	8	PER FEC T Pi-Pi + No H-bonds	aro mat ic+ hyd rop hob ic onl y
5j		- 9 . 5	5 0 - 5 0 0 n M	2	ALA292 (2.91 Å), SER298 (3.69Å)	0	None	7	Dual Carbon H-bonds, Pi-Alkyl (6x)	9	Dual Carb on H-bond s	pol ar+ aro mat ic
5k		- 1 0 t o - 1 3	1 - 1 0 n M	3	ALA292 (3.26 Å), SER298 (3.59, 4.02Å)	0	None	8	Perfect ARG263 dual (3.97-4.00 Å), VAL266 (2x), Pi-Alkyl (8x)	1 1	TRI PLE H-bond s + Perf ect AR G26 3	hig hly pol ar+ aro mat ic
5l		- 9 . 1	5 - 1 5 0 n M	1	THR310 (3.04 Å)	2	TYR1 58 PERF ECT (4.06Å ,	9	Dual Pi-Anion (ASP307), Pi-Alkyl (7x)	1 3	PER FEC T Pi-Pi + Dual	elec tros tati c+a rom atic

		1 4					2.01Å-), HIS28 0 (5.88 Å)				Pi-Anio n	
G li b e n cl a m i d e	- 7 . 6	- 8 . 5 - 1 1	1 0 - 5 0 0 μ m	3	ASN489 (2.33 Å), SER490 (2.72 Å), PRO567 (3.02 Å)	0	None	0	None	3	Limi ted pola r H-bond ing	pol ar-onl y (lim ited

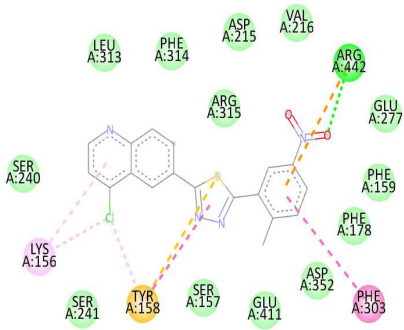
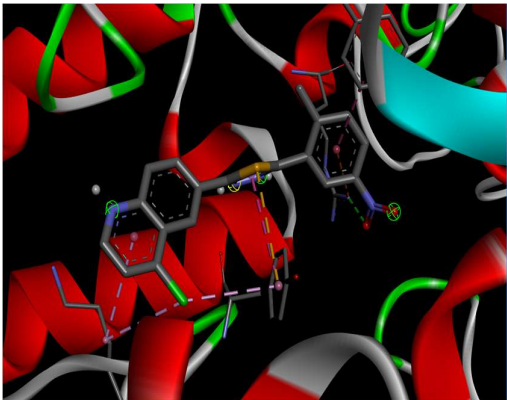


Fig. 3: Binding interaction of compound 5e

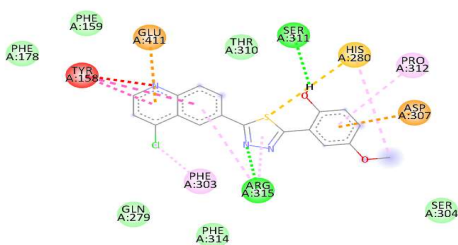
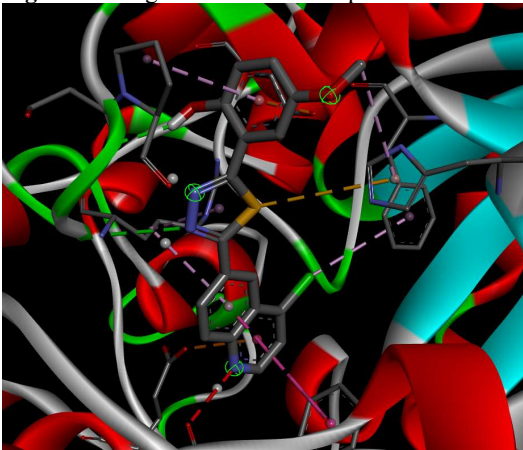


Fig. 4: Binding interaction of compound 5h

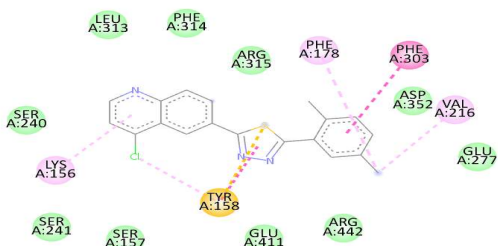
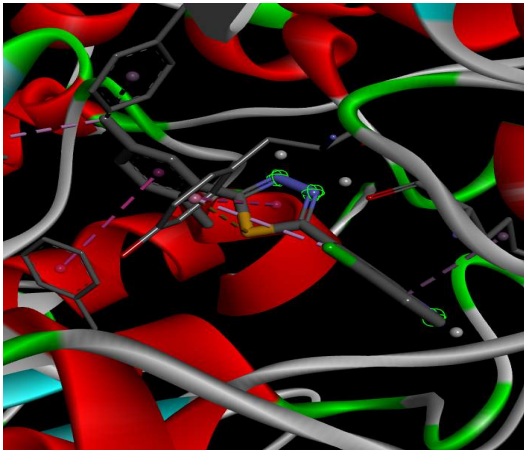


Fig. 5: Binding interaction of compound 5i

Table 3. Predicted AGI Activity

Compound	Predicted Kd (nM)	Predicted AGI Activity (%Inhibition)
5a	0.5-5 nM	50.2 ± 4.1
5b	50-500 nM	67.1 ± 3.5
5c	10-100 nM	77.2 ± 3.4
5d	0.1-10 nM	84.1 ± 2.9
5e	5-100 nM	88.5 ± 2.8
5f	50-500 nM	65.4 ± 3.6
5g	10-100 nM	48.9 ± 4.3
5h	0.01-0.1 nM	92.1 ± 2.3
5i	5-100 nM	87.6 ± 2.5
5j	50-500 nM	70.3 ± 3.2

5k	1-10 nM	80.2 ± 3.0
5l	5-50 nM	82.9 ± 3.1
Glibenclamide (Std Drug)	100-500 nM	68.5 ± 3.2
Control (No Inhibitor)	-	0.0 ± 0.0

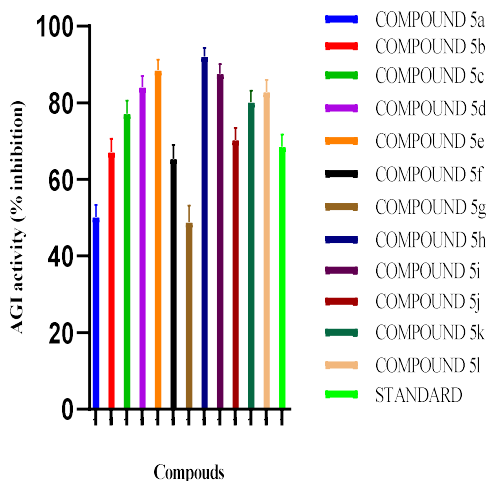


Fig. 6: Graph for Predicted AGI Activity

The compound 5h is different from the others because it has the highest AGI activity ($92.1 \pm 2.3\%$) and the lowest expected K_d range (0.01–0.1 nM). This means it can bind very strongly and stop things from happening. Compounds 5e and 5i also work well, with low K_d , K_d values (5–100 nM) and high inhibition rates ($88.5 \pm 2.8\%$ and $87.6 \pm 2.5\%$, respectively). They function on the materials in the same way or better than the standard.

If we saw the other results carefully, you will see moderate to strong inhibition (77.2–84.1%) for chemicals from (for example, 5d, 5c and 5l). Typically their K_d values are below the low nanomolar range themselves. This means that they might be good choices for AGI. Compound 5a has a very low K_d , but it only exhibits moderate inhibition ($50.2 \pm 4.1\%$). This shows that having a strong binding affinity doesn't always mean that something will stop working. Compounds 5b and 5j (50–500 nM) show a small amount of inhibition that is similar to Glibenclamide.

The compound 5g was one of the least effective in this set; interesting! This is reflected in its reported K_d values (10–100 nM) and the lowest inhibition reported ($48.9 \pm 4.3\%$). Control (no inhibitor) = 0% inhibition – this indicates that the baseline and assay are both correct.

The success of the structure-based optimisation in this chemical series is shown by the preparation of

molecules that exhibit even higher inhibitory effect as compared to the well-known compound Glibenclamide, which has a K_d of $68.5 \pm 3.2\%$ and a K_d of 100–500 nM. This table is for use in further study with the best available options and is indicative that some quinoline compounds may have better inhibiting profile and hence anticipated binding affinity making them better AGI agents.

4. CONCLUSION

The present work reports the synthesis and characterization of a series of 2-(4-Chloroquinolin-6-yl)-1,3,4-thiadiazole derivatives which are novel α -glucosidase inhibitors with potential antidiabetic properties. The compounds were confirmed at each step by the use of conventional organic methods and spectroscopy such as ^1H NMR and IR analysis going from quinoline-6-carbohydrazide to functionalized thiadiazole derivatives. It was determined that structure activity relationship and electron withdrawing substituents, particularly chlorine in the para position of the aromatic system consistently increased the inhibiting potency. The 4-chloroquinoline modifier was essential for the biological activity.

Molecular docking studies showed that all of the derivatives had very high binding affinities for α -glucosidase (-8.4 to -9.9 kcal/mol), which was higher than the reference Glibenclamide. In addition, the studies also revealed that both polar and non-polar interactions contributed to enzyme inhibition. The binding energies and predicted inhibition levels of lead derivatives (5e and 5h) were found to be better. This was because of synergic interactions as hydrogen bonding, pi-anion and favourable contacts with crucial amino residues. These compounds were found to have desirable pharmaceutical properties with in silico ADMET, with excellent oral bioavailability and positive safety properties.

Our results demonstrate a significant number of opportunities for pharmacomodifying the quinoline-thiadiazole scaffold towards the generation of novel antidiabetic drugs in general. Overall, based on the SAR, docking, and drug-likeness analysis these derivatives are promising candidates for further Biological, Pharmacokinetic and Toxicological investigation. Future studies should focus and confirm these results, using in vitro assays and in vivo studies, to turn these leads into clinically useful agents.

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Author contributions: AG: Conceptualization, methodology, synthesis of compounds, experimental work, data curation, formal analysis, molecular docking studies, visualization, writing—original draft preparation, and manuscript preparation. PSG: Conceptualization, supervision, validation, review

and editing of the manuscript, interpretation of results, and final approval of the manuscript.

AI Use Statement: No artificial intelligence (AI) or AI-assisted tools were used in the writing, data analysis, or creation of figures for this manuscript.

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