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In-silico directions on Anti-diabetic and pkSCM Predictions of Novel Guanidinopyrimidines

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Abstract: Novel 2-(3-(4-methyl / 4-chlorophenyl)guanidine-1-yl)-4,6-disubstituted phenyl pyrimidine (7) were synthesized by simple condensation between therapeutic chalcone with bioactive biguanide derivatives. It was established by different spectral studies. Furthermore, subject to ADMET prediction using pkSCM server and molecular docking studies against human glucokinase protein (PDB ID: 1V4S) plays an important role in the novel drug development of type 2 diabetes and the synthesized compounds results are compared with currently used FDA approved drug and also the theoretical calculations were performed by DFT method. To learn the compound reactivity; HOMO – LUMO energy-gap, MEP surface and some other properties of the compound 7a were investigated.

Keywords: Pyrimidine, Anti-diabetic, ADMET-pkSCM, Molecular Docking, DFT.

1. INTRODUCTION

The International Diabetes Federation (IDF), 2019 Diabetes Atlas shows that there are 463 million people who have diabetes worldwide. Over the past 20 years, it has grown from 151 million in 2000 to 463 million in 2019. It is expected to increase by 578 million in 2030 and 700 million in 2045 [1]. The Centre for Disease and Control (CDC) Diabetes Statistics reports said that the 7th leading cause of death in the US population, it is estimated that 9.4% diabetes [2].

In recent years, type 2 diabetes (T_2DM) has become a serious global health problem bringing serious burdens to societies not only that many diabetes-related complications are cardiovascular, eye, kidney, vascular damage, pregnancy, children (type 1 and type 2), and the economic impact of complications [3]-[9]. Due to currently used first-line antidiabetic (T_2DM) medicine is not completely curable the disease. So a need for novel approaches for anti-T_2DM drug discovery [10].

Looking back at FDA's past path in introducing new drugs to the world, they have been prioritizing modifications to older drugs over new ones. So we started our new search with guanidine has been used extensively in the treatment of diabetes for the past 100 years [11]. The literature review reveals that guanidine (biguanidine, phenformin, buformin, and metformin) and pyrimidine derivatives are exhibited in tremendous biological activities [12]-[19]. For that highly therapeutic biguanidine derivatives are coupled with biologically active chalcone, to form novel guanidinopyrimidine derivatives.

Pyrimidine could be a basic nucleus in DNA & RNA; it is the one of the Nitrogen-containing heterocyclic compounds that has significantly a lot of pharmacological activity like anti-diabetic [20]-[24], anticancer [25],[26], anti-inflammatory [27],[28] antifungal [29], antibacterial [30]-[32], anti-tubercular [33], anti-malarial [34], anti-HIV [35], antiviral [36] and antioxidant [37]. To fulfil the critical necessity of drugs in the ground of chemotherapy the title compounds viz., 2-(3-(4-methyl and 4-chlorophenyl)guanidine-1-yl)-4,6-diarylpyrimidine (**7a-7l**) were synthesized from its relevant chalcone and 1-(4-methyl and 4-chlorophenyl)biguanide hydrochloride in the presence of a CH_3ONa catalyst.

Molecular docking study against glucokinase protein (1V4S) plays a vital role in the regulation of glucose metabolism and used for novel drug development in type 2 diabetes and ADMET (pkSCM) prediction [38]- [43] plays a critical role in the development of new drugs in the extraordinary conditions that currently exist in the world. The newly synthesized compound **7a** is subjected to DFT [44] (B3LYP) calculation for the optimized structure has been employed to quantify the electronic variables such as dipole moment, total energy, MEP surface, Frontier orbital surface and thermodynamic parameters were calculated which is highly useful the better understand the chemical reactivity of the structure.

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2. EXPERIMENTAL

All basic raw materials were bought from Avra synthetic compounds (p) ltd., FT-IR spectra were taken on an Agilent Resolutions Pro Cary-630 spectrophotometer utilizing the ATR strategy, ^{1}H and ^{13}C NMR spectra were recorded on Bruker Ultra shield TM 400 Advance - III spectrometer in chloroform-D ($CDCl_3$) with TMS as internal standard and the chemical shifts were reported in δ (ppm) scales. Melting points were taken deep vision (230V) melting points apparatus by the open tube capillary and are uncorrected.

A. General method for the synthesis of 1-(4-methyl / 4-chlorophenyl)biguanide hydrochloride: The syntheses of biguanidine derivatives are very simple cyano addition reaction between cyanoguanidine (dicyandiamide) and various *p*-substituted anilinium chlorides (4-Me and 4-Cl) (**Scheme -1**).

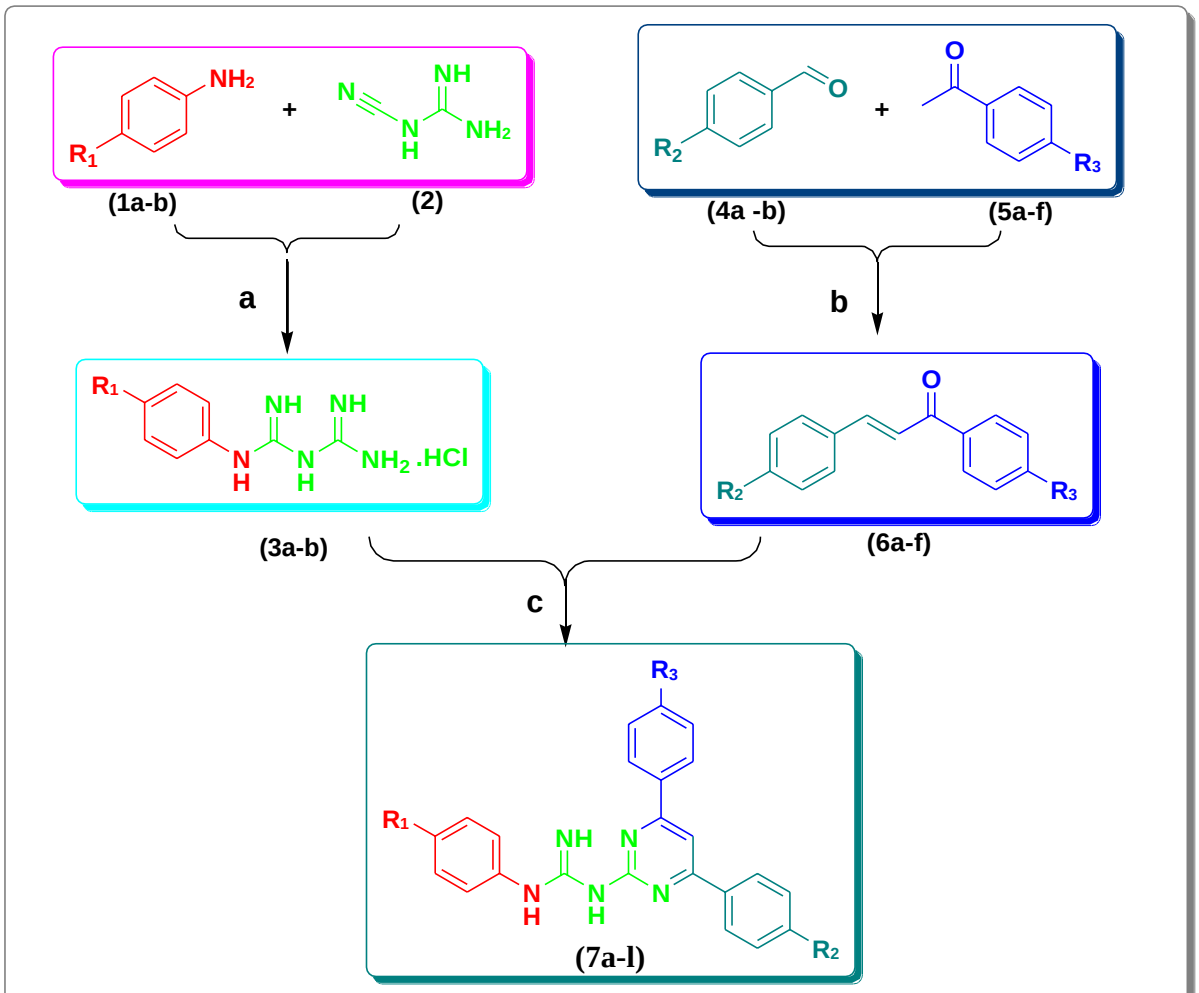
B. General method for the synthesis of various chalcone: The simple condensation reaction between various *p*-substituted aldehydes with *p*-substituted acetophenone in ethanol basic (NaOH) solution afforded chalcone.

*C. General method for synthesis 2-(3-(4-methyl and 4-chlorophenyl)guanidine-1-yl)-4, 6 diphenyl)pyrimidine. **(7a-7l)**:* A mixture of various chalcones (0.001mol) and 1-(4-methyl and 4-chlorophenyl)biguanide hydrochloride (0.001mol) in presences of CH_3ONa catalyst in methanol (25mL) medium. The reaction blend was refluxed for 24 hrs and the reaction progress observed by TLC. After completion of the reaction, it was permitted to achieve room temperature and poured into brain water with stirring. The product was filtered, dried and recrystallized using ethanol.

3. RESULT AND DISCUSSION

The novel guanidinopyrimidines **(7a-7l)** were synthesized as shown in **Scheme-1** by preparing 1-(4-methyl and 4-chlorophenyl)biguanide hydrochloride prepared by an addition reaction between *p*-substituted **(**4-methyl and 4-chloro) aniline and dicyandiamide and chalcone **(6a-e)** (preparation of various chalcone **(6a-e)** was carried out by the condensation of *p*-substituted aldehyde and acetophenone). The crude products were purified by recrystallization in ethanol. The structure of the compound **7a** was characterized by FT-IR and NMR (^1H &^{13}C) spectroscopy analysis. In FT-IR spectra show the incidence bands at 3465 and 1634 cm^{-1} where it indicates the presence of NH and C=N respectively in the newly synthesized compound. Then the disappearance of the sharp carbonyl group (C=O) band and these IR spectral data indicated the formation of compound **7a**.

From ^1H NMR spectra of compound **7a** revealed the following signals: a sharp singlet appeared in the region δ 7.22 ppm (due to HC=C confirmed the cyclization of the chalcone into pyrimidine ring.) was assigned to the H_5 proton of the pyrimidine ring. A broad singlet at δ 5.27 ppm assigned to the imine NH protons, the aromatic two methyl ($-CH_3$) groups six protons observed at two singlets at δ 2.25 (s, 3H) and 2.34 (s, 3H) ppm. A multiplet at δ 7.054-8.179 ppm characteristic of the aromatic protons. In the ^{13}C NMR spectra of compound **7a**, the chemical shift values of carbon atoms appear between δ 167.46 – 164.96 ppm due to pyrimidine ring ipso carbons, δ 171.92 ppm due to guanidine group ipso carbon, δ 142.05– 120.97 ppm due to aromatic carbon atoms, δ 104.03 ppm due to the C_5 carbon of the pyrimidine ring, δ 21.85 & 21.60 ppm due to aromatic ring methyl carbon atoms. All the above spectral data indicated the structure of the synthesized compound **7a**.



S.No	7a	7b	7c	7d	7e	7f	7g	7h	7i	7j	7k	7l
R_1 =	-4Me	-4Me	-4Me	-4Me	-4Me	-4Me	-4C	-4Cl	-4Cl	-4Cl	-4Cl	-4Cl
R_2 =	-4Me	-4Me	-4Me	-4Me	-4OMe	-4OMe	-4Me	-4Me	-4Me	-4Me	-4OM	-4OMe
R_3 =	-H	-4F	-4Cl	-4Me	-4Br	-4OMe	-H	-4F	-4Cl	-4Br	-H	-4OMe

Scheme 1: Synthetic pathway of derivatives **(7a-l).** Reagents and conditions: (a) Propan-1-ol, Con HCl, reflux, 3h; (b) Ethanol, NaOH, stirring RT; (c) Methanol, CH_3ONa, Reflux, 24h.

A 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-phenylpyrimidine (7a): Light yellow powder, yield: 60%; mp 130-132°C; FT- IR (ATR) cm^{-1}: 3465- 3186 (NH), 3142, 3022 (Ar CH), 2917, 2850 (Ali CH), 1634, 1603 (C=N), 1584, 1561 (C=C); ^1H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.25 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3), 5.27 (s, 2H, imine N-H), 7.22 (s, 1H, pyrimidine ring C_5-H), 7.05-8.17 (m, 14H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 171.92 (imine C=NH), 167.46 (pyrimidine ring C_4 & C_6), 164.96 (pyrimidine ring C_2), 142.05-120.97 (aromatic ring carbon atoms), 104.03 (pyrimidine ring C_5), 21.85 & 21.60 (aromatic ring methyl carbon).

B. 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-(4-fluorophenyl)pyrimidine (7b): Light yellow powder, yield: 73%; mp 142-144°**C**; FT- IR (ATR) cm^{-1}: 3465- 3190 (NH), 3123, 3019 (Ar CH), 2917 (Ali CH), 1634, 1598 (C=N), 1585, 1569 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.35 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3), 5.50 (s, 2H, imine N-H), 7.41 (s, 1H, pyrimidine ring C_5-H), 7.15-8.27 (m, 14H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 171.98 (imine C=NH), 167.43 (pyrimidine ring C_4 & C_6), 164.94 (pyrimidine ring C_2 and aromatic F-C_{ipso}), 142.12-114.12 (aromatic ring carbon atoms), 104.32 (pyrimidine ring C_5), 21.62 & 20.87 (aromatic ring methyl carbon).

C. 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-(4-chlorophenyl)pyrimidine (7c): Light yellow powder, yield: 75%; mp 168- 170°C; FT- IR (ATR) cm^{-1}: 3466- 3191 (NH), 3019 (Ar CH), 2918, 2852 (Ali CH), 1636, 1608 (C=N), 1585, 1561 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.23 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3), 5.52 (s, 2H, imine N-H), 7.44 (s, 1H, pyrimidine ring C_5-H), 6.98-8.16 (m, 14H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 171.81 (imine C=NH), 167.51, 164.95 (pyrimidine ring C_4 & C_6), 164.43 (pyrimidine ring C_2), 141.96-121.13 (aromatic ring carbon atoms), 105.65 (pyrimidine ring C_5), 21.61 & 20.96 (aromatic ring methyl carbon).

D. 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-(4-methylphenyl)pyrimidine (7d): Light yellow powder, yield: 67%; mp 158-160°C; FT- IR (ATR) cm^{-1}: 3466- 3186 (NH), 3144, 3019 (Ar CH), 2918, 2854(Ali CH), 1633, 1605 (C=N), 1584, 1561 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.23 (s, 3H, Ar-CH_3), 2.32 (s, 6H, Ar-CH_3), 5.49 (s, 2H, imine N-H), 7.47 (s, 1H, pyrimidine ring C_5-H), 6.96-8.16 (m, 14H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 171.89 (imine C=NH), 167.46, 165.66 (pyrimidine ring C_4 & C_6), 164.94 (pyrimidine ring C_2), 142.03-121.07 (aromatic ring carbon atoms), 106.22 (pyrimidine ring C_5), 21.62, 21.47 & 20.87 (aromatic ring methyl carbon).

E. 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methoxyphenyl)-6-(4-bromophenyl)pyrimidine (7e): Light yellow powder, yield: 76%; mp 154-156°C; FT- IR (ATR) cm^{-1}: 3366-3161 (NH), 3081, 3026 (Ar CH), 2954-2850 (Ali CH), 1666-1637 (C=N), 1600-1559 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.24 (s, 3H, Ar-CH_3), 3.78 (s, 3H, Ar-OCH_3), 5.47 (s, 2H, imine N-H), 7.41 (s, 1H, pyrimidine ring C_5-H), 6.85-8.24 (m, 14H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 171.41 (imine C=NH), 167.47, 164.95 (pyrimidine ring C_4 & C_6), 164.25 (pyrimidine ring C_2), 162.60 (aromatic ring methoxy C_{ipso}), 162.60-113.60 (aromatic ring carbon atoms), 105.17 (pyrimidine ring C_5), 55.33 (aromatic ring methoxy carbon), 20.77 (aromatic ring methyl carbon).

F. 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methoxyphenyl)-6-(4-methoxyphenyl)pyrimidine (7f): Light yellow powder, yield: 62%; mp 138-140°C; FT- IR (ATR) cm^{-1}: 3365-3155 (NH), 3005 (Ar CH), 2954-2838 (Ali CH), 1666-1636 (C=N), 1598-1559 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.34 (s, 3H, Ar-CH_3), 3.87 (s, 6H, Ar-OCH_3), 5.58 (s, 2H, imine N-H), 7.55 (s, 1H, pyrimidine ring C_5-H), 6.81-8.34 (m, 14H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 171.48 (imine C=NH), 167.34, 164.87 (pyrimidine ring C_4 & C_6), 163.44 (pyrimidine ring C_2), 162.63, 158.15 (aromatic ring methoxy C_{ipso}), 162.63-113.66 (aromatic ring carbon atoms), 102.91 (pyrimidine ring C_5), 55.47, 55.39 (aromatic ring methoxy carbon), 20.86 (aromatic ring methyl carbon).

G. 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-phenylpyrimidine (7g): Light yellow powder, yield: 60%; mp 84-86°C; FT- IR (ATR) cm^{-1}: 3467-3202 (NH), 3057 (Ar CH), 2920 (Ali CH), 1640 (C=N), 1585, 1562 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.34 (s, 3H, Ar-CH_3), 7.50 (s, 1H, pyrimidine ring C_5-H), 6.89-8.51 (m, 17H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 171.90 (imine C=NH), 167.46 (pyrimidine ring C_4 & C_6), 164.86 (pyrimidine ring C_2), 142.23-122.06 (aromatic ring carbon atoms), 106.53 (pyrimidine ring C_5), 21.62 (aromatic ring methyl carbon).

H. 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-(4-fluorophenyl)pyrimidine (7h): Light yellow powder, yield: 60%; mp 184-186°C; FT- IR (ATR) cm^{-1}: 3479-3182 (NH), 3123, 3037 (Ar CH), 2954-2869 (Ali CH), 1652, 1638 (C=N), 1596, 1567 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.31 (s, 3H, Ar-CH_3), 5.48 (s, 2H, imine N-H), 7.63 (s, 1H, pyrimidine ring C_5-H), 6.84-8.28 (m, 14H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 171.01 (imine C=NH), 167.35 (pyrimidine ring C_4 & C_6), 166.56 (pyrimidine ring C_2), 164.79 (aromatic F-C_{ipso}), 164.79-114.20 (aromatic ring carbon atoms), 103.42 (pyrimidine ring C_5), 21.64 (aromatic ring methyl carbon).

I. 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-(4-chlorophenyl)pyrimidine (7i): Light yellow powder, yield: 74%; mp 194-196°C; FT- IR (ATR) cm^{-1}: 3494-3243 (NH), 3020 (Ar CH), 2920 (Ali CH), 1652 (C=N), 1578, 1563 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.32 (s, 3H, Ar-CH_3), 7.44 (s, 1H, pyrimidine ring C_5-H), 6.92-7.87 (m, 15H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 165.72 (imine C=NH), 165.66, 164.53 (pyrimidine ring C_4 & C_6), 164.37 (pyrimidine ring C_2), 141.69-125.01 (aromatic ring carbon atoms), 105.66 (pyrimidine ring C_5), 21.49 (aromatic ring methyl carbon).

J. 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-(4-bromophenyl)pyrimidine (7j): Light yellow powder, yield: 76%; mp 220-222°C; FT- IR (ATR) cm^{-1}: 3499-3131 (NH), 3021 (Ar CH), 2917

(Ali CH), 1671-1637 (C=N), 1579, 1559 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 2.36 (s, 3H, Ar-CH_3), 7.49 (s, 1H, pyrimidine ring C_5-H), 6.96-7.84 (m, 16H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 165.68 (imine C=NH), 164.46 (pyrimidine ring C), 141.75-125.01 (aromatic ring carbon atoms), 105.65 (pyrimidine ring C_5), 21.50 (aromatic ring methyl carbon).

K. 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-(4-methoxyphenyl)-6-phenylpyrimidine (7k): Light yellow powder, yield: 61%; mp 84-86°C; FT- IR (ATR) cm^{-1}: 3308, 3190 (NH), 3056 (Ar CH), 2921, 2849 (Ali CH), 1647 (C=N), 1606, 1561 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 3.79 (s, 3H, Ar-OCH_3), 5.36 (s, 2H, imine N-H), 7.43 (s, 1H, pyrimidine ring C_5-H), 6.87-8.24 (m, 15H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 171.59 (imine C=NH), 167.31, 164.75 (pyrimidine ring C), 162.76 (aromatic methoxy C_{ipso}), 162.78-113.72 (aromatic ring carbon atoms), 105.99 (pyrimidine ring C_5), 55.41 (aromatic ring methoxy carbon).

L. 2-(3-(4-chlorophenyl)guanidine-1-yl)-4-(4-methoxyphenyl)-6-(4-methoxyphenyl)pyrimidine (7l): Light yellow powder, yield: 67%; mp 180-182°C; FT- IR (ATR) cm^{-1}: 3461, 3160 (NH), 3001 (Ar CH), 2956, 2933 (Ali CH), 1647, 1637 (C=N), 1600, 1561 (C=C); ^{1}H NMR (400 MHz,$CDCl_3$) δ, ppm: 3.80 (s, 6H, Ar-OCH_3), 5.22 (s, 1H, imine N-H), 7.15 (s, 1H, pyrimidine ring C_5-H), 6.65-8.25 (m, 15H, Ar-H & NH); ^{13}C NMR (100 MHz, $CDCl_3$): 171.57 (imine C=NH), 167.27, 164.70 (pyrimidine ring C_4 & C_6), 162.78 (pyrimidine ring C_2), 160.55 (aromatic ring methoxy C_{ipso}), 160.55-113.72 (aromatic ring carbon atoms), 102.14 (pyrimidine ring C_5), 55.47, 55.41 (aromatic ring methoxy carbon).

4. ADMET PREDICTION.

Medication revelation is an enormously difficult and costly endeavour, which includes disease choice, target recognition, and validation, lead finding and optimization, preclinical and medical trials. In recent times, in-silico methods are used for novel molecular entities approved by the FDA has risen clearly. Nowadays in-silico predictions are playing a major in the pharmaceutical research and development field. In 2018, the FDA permitted only fifty-nine (64%) fresh molecular. Drug-likeness rules: Past few decades, several rules were developed in order to drug discovery pipeline and the few well-known rules are Lipinski"s „rule-of-five" (The RO5 states that the following criteria are MW ≤ 500; log P ≤ 5; HBDs ≤ 5 and HBAs ≤ 10), the Golden Triangle and the Pfizer's rule.

Currently, freely available the pkCSM serve is extremely useful for determining molecular (MW, log P, HBDs, HBAs & TPSA) and the ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity)

properties. Water solubility and toxicity calculation are highly essential in the drug discovery process because about 30% of drug molecules did not clear the clinical trials because of their toxicity. The pkSCM several is highly useful for determining in-silico water solubility, which highly uses full for the Biopharmaceutics Drug Distribution and Classification System (BDDCS). The BDDCS system to split into four classes (class1, 2, 3 & 4) based on their solubility and permeability properties. Considering oral drugs, once they reach the gastrointestinal tract, they must be able to move through biological membranes to enter the systemic circulation. Furthermore, it has been reported that BBB/CNS (blood-brain barrier/ central nervous system penetration), P-glycoprotein, renal clearance as well as toxicity and clinical safety concerns are a significant problem in drug discovery.

Table 1: Molecule Properties of Synthesised Compounds (7a-7l).

Ligand	**Molecule properties**					
	Molecular Weight	**LogP**	**Rotatable Bonds**	**H-Bond Acceptors**	**H-Bond Donors**	**Polar Surface area**
7a	393.49	5.8862	4	3	3	175.92
7b	411.48	6.0253	4	3	3	180.09
7c	427.94	6.5396	4	3	3	186.22
7d	407.52	6.1946	4	3	3	182.29
7e	488.39	6.3489	5	4	3	194.90
7f	439.52	5.5950	6	5	3	192.51
7g	413.91	6.2312	4	3	3	179.86
7h	431.90	6.3703	4	3	3	184.03
7i	448.36	6.8846	4	3	3	190.16
7j	492.81	6.9937	4	3	3	193.73
7k	429.91	5.9314	5	4	3	184.97
7l	459.94	5.9400	6	5	3	196.45

The drug development failure is due to their toxicity, which can damage an organism (cells and organs). Toxicity issues like hERG inhibition, phospholipidosis or cytochrome P450 (CYP) inhibitions are more likely to be problematic for compounds with high lipophilicity values for the synthesized compounds. The synthesized compounds **(7a-7l)** (molecular and ADMET properties) are analyzed and their results are fulfilled the drug-like properties. The molecule properties are shown in **Table (1).** It was concluded that synthesized pyrimidine derivative (**7a-7l**) may be a promising hit molecule for the development of future anti-diabetic drugs.

5. MOLECULAR DOCKING

Molecular docking is a beneficial method for the drug development process and the result is highly useful in the drug discovery pipeline. It reduces the time and cost of the researcher. AutoDock vina is consumer-friendly, freely available software and the results speed up the development of novel drugs at a significantly lower cost. Furthermore, Glucokinase protein (1V4S) plays an important role in the regulation of glucose metabolism and thus represents a novel molecular target for drug discovery in type 2 diabetes. We currently identified little molecule synthetic activators that activated glucokinase and lowered blood glucose levels in numerous murine models of diabetes. The crystal structures clearly showed that one of these activators binds to an allosteric site in the active form of glucokinase and allosterically activates the enzyme. The outcomes are highly valuable for the improvement of novel glucokinase activators as a recent treatment for type 2 diabetes [45, 46].

Table 2: Docking Results of the Designed Compounds (7a-7l) Towards 1V4S Protein.

Ligand	Binding energy (k.cal/mol)	No of Hydrogen bonding	Residues	Distance (A°)
7a	-8.3	1	Arg 327	2.09
7b	-8.5	2	Ser 336, Thr 228	2.42, 1.92
7c	-8.5	1	Arg 327	2.16
7d	-8.6	1	Arg 327	2.09
7e	-8.2	1	Ser 336	2.57
7f	-8.2	2	Ser 336, Thr 228	2.33, 1.99
7g	-8.2	1	Thr 228	1.99
7h	-8.2	2	Thr 228 Ser 336	2.02, 2.40
7i	-7.7	1	Arg 327	2.12
7j	-8.5	1	Thr 228	2.00
7k	-7.9	-	-	-
7l	-8.2	2	Ser 336, Thr 228	2.32, 2.01
Metformin	-5.3	2	Asp 78	2.52, 2.28

The target protein structure (1V4S) was downloaded from the protein data bank (PDB) and then converted into pdbqt format. The newly synthesized ligands (**7a-7l**) were subjected in molecular docking study against the 1V4S protein. Protein and ligands preparations and their docking process are followed regular protocol [47, 48] and the discovery studio 4.5 (viewer) is used for the imaging process. Among the sequence of compounds, **7d** delivered outstanding binding energy against 1V4S protein with binding energy is -8.6 k.cal/mol. The docking result was compared with metformin, which is currently used for type -2 diabetic persons. The outcome gives information to show an excellent result on 1V4S proteins. The

docking results were illustrated in **Table 2**. The docking images of compound **7d** (2D & 3D) were given in **Figure. 1 & 2.**

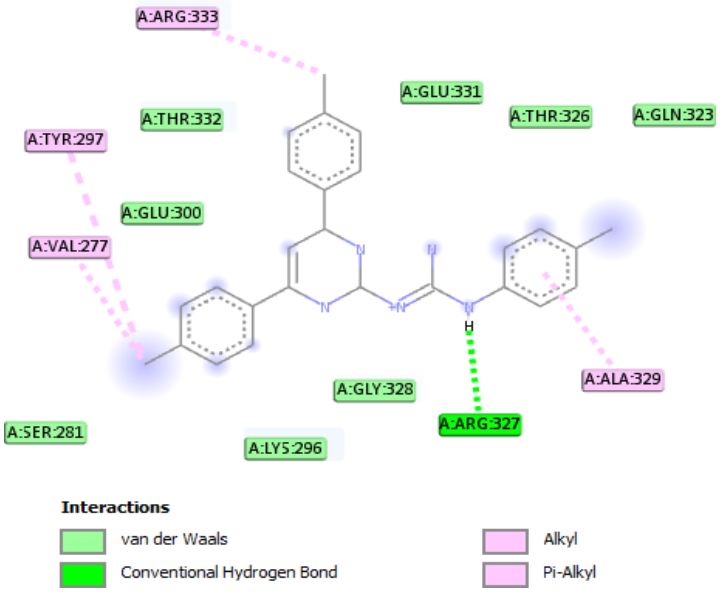


Fig. 1. 2D Images of compound 7d docked with human glucokinase (1V4S) protein

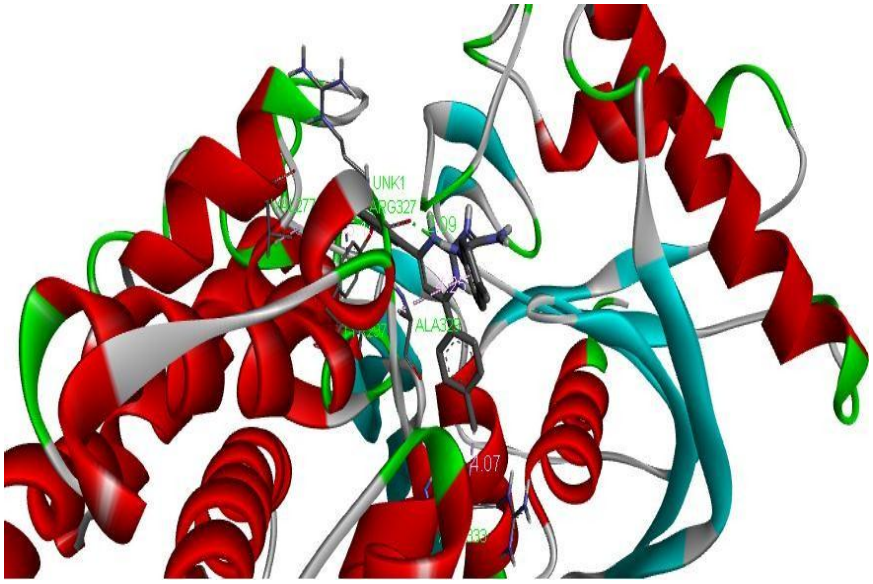


Fig. 2 3D Images of compound 7d docked with human glucokinase (1V4S) protein

6. DENSITY FUNCTIONAL THEORY (DFT) ANALYSIS

DFT studies were performed with GAUSSIAN-09 [49] software with the aid of the Gauss view (5.0) visualization program [50], utilizing B3LYP/6-31G(d,p) as basis set and determine the improved calculation. The input file is generated and run the program to obtain the optimized structure is shown in **Figure. 3** and the total energy, HOMO and LUMO energies of the 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-phenyl pyrimidine shown in **Table 3**.

Table 3: The Total Energy, HOMO and LUMO Energies of the 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-phenyl Pyrimidine.

Parameters	**DFT**
Molecular weight (g/mol)	393.494
Chemical Formula	C25H23N5
Total energy E (a.u.)	2542.1117
Dipole moment (Debye)	3.4782 (X = -2.9892 Y = 1.4516 =-1.0274)
HOMO energy (a.u.)	-0.18756
LUMO energy (a.u.)	-0.06965
HOMO-LUMO energy gap (a.u.)	0.11791

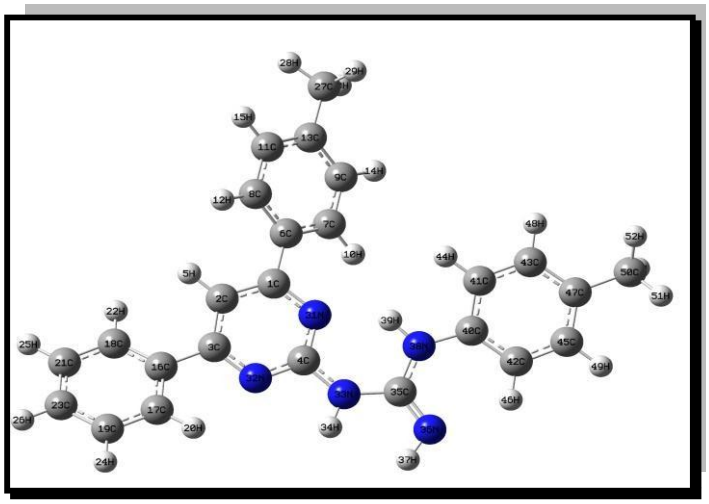


Fig. 3. Optimized geometry of the 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-phenyl pyrimidine.

A. Frontier Molecular Orbital: Change in the energy difference (ΔE) is calculated between HOMO & LUMO and this value is highly used full for classification of the molecule, the energy gap between the HOMO (-0.18756 au) and LUMO (-0.06965 au) is 0.11791au (3.2083 eV) (1 au = 27.210 eV). The ΔE is low so the molecule is more reactive and less stable [51, 52]. The HOMO and LUMO band-gap energy shown in **Figure 4**.

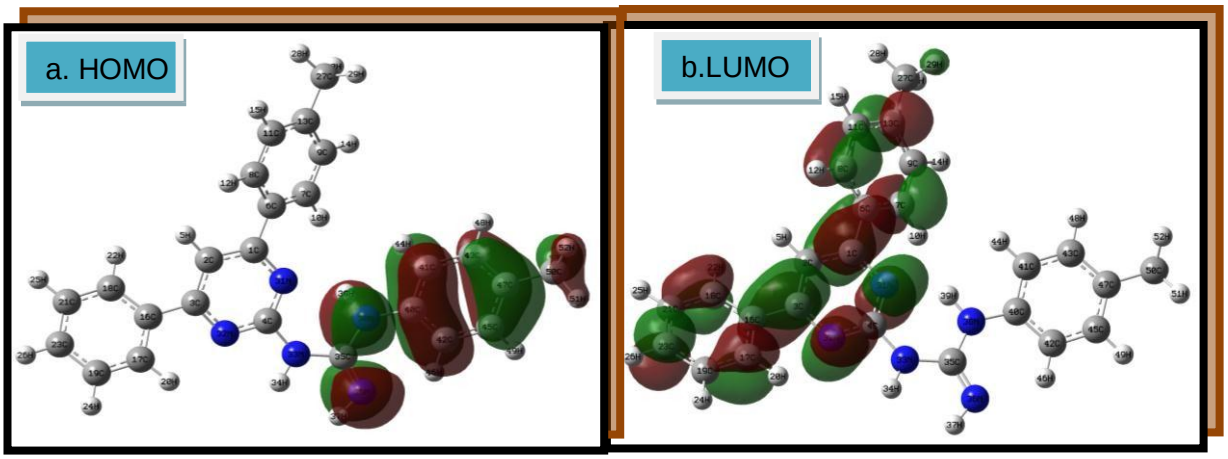


Fig. 4. Energy level of HOMO and LUMO of the 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-phenyl pyrimidine.

B. Molecular electrostatic potential (MEP) surface: Molecular electrostatic potential (MEP) surface area is shown in **Figure 5**. MEP surface area different colours are highly useful for the identifications of the molecule. The red colour (negative) region indicates the electrophilic while the blue colour (positive) region indicates the site for the nucleophilic reaction centres.

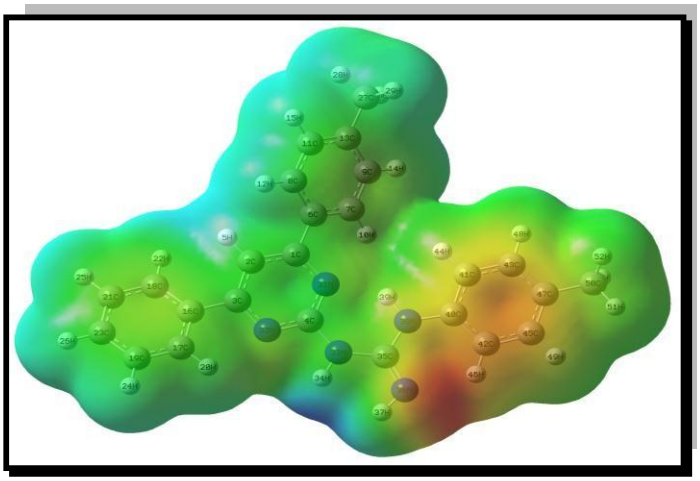


Fig. 5. MEP formed by mapping of total density over electrostatic potential in the gas phase for the synthesized compounds

The Mulliken population analysis value is clearly assigned each and every atoms electron density as shown in **Figure 6** as well as **Table 4** of compound **7a**. All the nitrogen atoms and few carbon atoms (C2, C7, C8, C9, C11, C17, C18, C19, C21, C23 C27, C41, C42, C43, C45, and C50) have negative charge behaved as electron donors and the remaining (carbon and hydrogen) atoms are positive behaved like an electron acceptor.

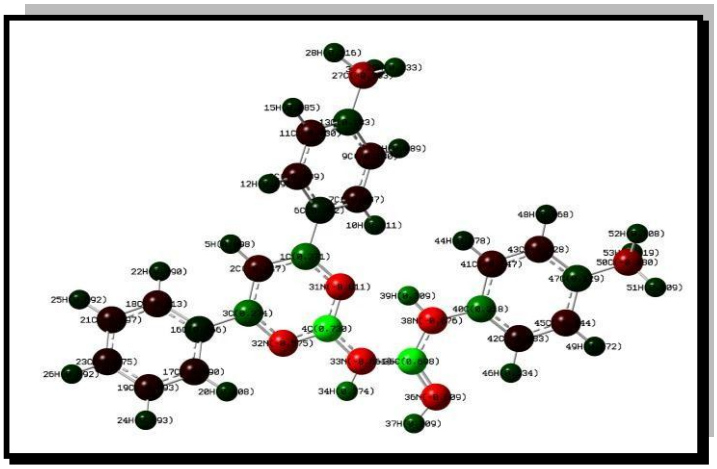


Fig. 6. The Mulliken atomic charges using DFT of 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-phenyl pyrimidine.

Table 4: Mulliken Atomic Charges of the Designed Compound (7a).

Atoms	Charges	Atoms	Charges	Atoms	Charges	Atoms	Charges	Atoms	Charges
C1	0.2514	H12	0.0791	C23	-0.0741	H34	0.2778	C45	-0.1391
C2	-0.1047	C13	0.1126	H24	0.0918	C35	0.4738	H46	0.0806
C3	0.2546	H14	0.0849	H25	0.0889	N36	-0.4830	C47	0.1044
C4	**0.4748**	H15	0.0821	H26	0.0885	H37	0.2444	H48	0.0727
H5	0.0878	C16	0.0837	C27	-0.3758	**N38**	**-0.5870**	H49	0.0722
C6	0.0824	C17	-0.0998	H28	0.1176	H39	0.2755	C50	-0.3751
C7	-0.1060	C18	-0.1092	H29	0.1332	C40	0.2722	H51	0.1108
C8	-0.1104	C19	-0.0910	H30	0.1194	C41	-0.1291	H52	0.1105
C9	-0.1210	H20	0.1139	N31	-0.5050	C42	-0.0347	H53	0.1252
H10	0.1164	C21	-0.0997	N32	-0.4934	C43	-0.1226		
C11	-0.1300	H22	0.0800	N33	-0.5446	H44	0.0722		

7. CONCLUSION

The novel pyrimidine derivatives were prepared in a well-organized manner and characterized by spectral studies and afterward exposed to the pkSCM prediction highly useful for the classifications of drugs to the pharmahopers. The molecular docking study results reviewed that compound 7d show excellent binding energy and other ligands also better than the FDA approved drug metformin. Recently synthesized ligands

establish to be with the best results when compared to the above medicine. We have carefully analyzed the geometrical parameters, HOMO-LUMO and MEP surface of 2-(3-(4-methylphenyl)guanidine-1-yl)-4-(4-methylphenyl)-6-phenyl pyrimidine utilizing DFT B3LYP/6-31 G(d, p). The smallest measure of the Frontier orbital energy difference has shown, the molecule is very reactive. MEP map reveals clearly the nucleophilic and electrophilic center of the molecule. In the future, those further potential remedial are investigated.

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