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Molecular Docking, Synthesis, Structure Illucidation, Admet Analysis and Biological Activity Evaluation of Some Fluorinated Chromene Derivatives

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Abstract

The paper constitutes the exploration performed to developed new fluorinated chromene derivations by coupling response of separate fluorinated amino composites using suitable coupling reagents. The response is clean which enable too easy workup and good yield. Chromene derivations (3a- h) are synthesized by coupling response between different fluoro aniline derivations and 6-(trifluoromethyl) -3,4-dihydro-2H-chromene-2-carboxylic acid, N, N '- Dicyclohexylcarbodiimide(DCC) and(2-(1H- benzotriazol-1-yl) hexafluorophosphate(HBTU) are used as a coupling reagent. N, N '- Dicyclohexylcarbodiimide urea is formed as a side product during response which can remove by filtration. The response was rapid-fire and was conducted at room temperature with high- to- excellentyields, chromene derivations were assessed for tyrosinase and α- glucosidase inhibitory conditioning. Depended on IC50 values. All novel chromenes displayed significant α- glucosidase inhibition compared with reference (IC50 = 7.80 mM). Likewise, the capability of the studied composites to inhibit tyrosinase was estimated and set up to be moderate 'In silico studies were performed to explore the list modes of the chromenes at the list point of α- glucosidase and tyrosinase. Molecular docking results revealed the significance of hydrogen cling, hydrophobic, π- π mounding, πcation, and essence relations between the target enzymes and the synthesized composites. Inclusively, the results attained in the current work indicated that the studied chromenes may be regarded as supereminent composites for designing new chemicals potentially effective in conditions similar as skin diseases and diabetes mellitus.

Keywords: *6-(Trifluoromethyl) -3,4-Dihydro-2H-Chromene-2-Carboxylic Acid, DCC, HBTU and Different Fluoro Aniline*

1. Introduction

Chromene is a privileged heterocyclic emulsion that's set up in a variety of biologically active natural and synthetic products (1- 3). The synthetic chromene outgrowth has been shown to bind to the cellular protein and beget cell death. The natural chromene rhodomyrtone is known to showed potent antibacterial exertion (5) In addition, a number of styles have been developed for the conflation of substituted chromenes derivations (6). In this transition essence- intermediated cyclization (7) multicomponent responses (8), ring- closing metathesis approaches (9, 10) are included. Chromone derivations useful as balanced multifunctional agents against Alzheimer's complaint (11)

Also, the enzyme inhibitory exertion, along with antioxidant and antimicrobial goods of these composites were studied. Eventually, the relations and binding modes of the synthesized chromenes 3(a-l) and 4(a-c) with the list point of α- glucosidase and tyrosinase were estimated using molecular docking studies. To the stylish of our knowledge, this is the first report about the catalyst-free conflation and natural evaluation of these 4H-chromene derivations.

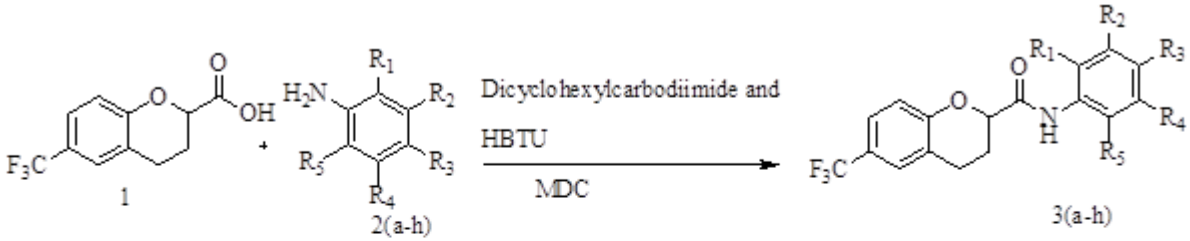
2. Materials And Methods

Chemistry

The reagents were bought from Merck (Germany) and used without farther sanctification. The IR scales were acquired on a Shimadzu FTIR- 8400S spectrophotometer (Japan) using KBr bullets. NMR ranges were recorded on Bruker Avance 300 and 400 MHz spectrometers(Bruker, Rheinstatten, Germany), operating at 300 and 400 MHz for 1H, as well as75.4 and 100 MHz for 13C. The CDCl3 was used as solvent and TMS as an internal reference. The elementary analysis for C, H, and N atoms was carried out using the Costech essential analyzer. Melting points were measured in open glass capillaries using Electro thermal melting point outfit.

General procedure for the synthesis of 6-(trifluoromethyl)-N-(Sustituted)phenyl)-3,4-dihydro-2H-chromene-2-carboxamide

These fluorine base composites are synthesized by undecorated coupling reaction by coupling reaction between fluoro aniline derivations 2(a-h) and 6-(trifluoromethyl) -3,4-dihydro-2H-chromene-2-carboxylic acid. N, N '- Dicyclohexylcarbodiimide(DCC) and(2-(1H- benzotriazol-1-yl) hexafluorophosphate (HBTU) are used as a coupling reagent. N, N '- Dicyclohexylcarbodiimide urea is formed as a side product during reaction which can remove by filtration.



Where 3a= R_1,R_2,R_3,R_4,R_5= H,H,CF_3,H,H
3b= R_1,R_2,R_3,R_4,R_5= H,CF_3,H,H,H
3c= R_1,R_2,R_3,R_4,R_5= CF_3,H,H,H,H
3d= R_1,R_2,R_3,R_4,R_5= H,CF_3,F,H,H
3e= R_1,R_2,R_3,R_4,R_5= H,F,CF_3,H,H
3f= R_1,R_2,R_3,R_4,R_5= CF_3,H,CF_3,H
3g= R_1,R_2,R_3,R_4,R_5= CF_3,H,CF_3,H,H
3h= R_1,R_2,R_3,R_4,R_5= F,F,F,H,H

Scheme 1: Scheme-1 reagents and condition (1) Dicyclohexylcarbodiimide and HBTU both 1.50Eq, dry MDC, 15 hrs at reflux

6-(trifluoromethyl)-N-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-chromene-2-carboxamide (3a)

^{1}H NMR (400 MHz, DMSO): δ =2.01 (m, 1H); 2.26 (m, 1H), 2.41-2.68 (m, 2H), 4.51 (dd, 1H), 7.33-8.87 (m, 7H, Aromatic proton) 8.76 (s, 1H), IR (cm-1): 3250 (N-H), 3021 (C-H aromatic ring), 2955 (C-H), 2865 (C-H), 1666 (C=O), 1422 (C=C), 1341 (C-H), 1324 (C-H), 1281 (C-N), 1072 (C-O), 1021 (C-F) cm^{-1}. Yield: 68%; mp 170-175 ^{o}C; MS (m/z): 389 (M+); Anal. calcd for $C_{18}H_{13}F_6NO_2$: C, 55.53; H, 3.37; F, 29.28; N, 3.60; Found: C, 55.54; H, 3.31; F, 29.23; N, 3.58.

6-(trifluoromethyl)-N-(3-(trifluoromethyl)phenyl)-3,4-dihydro-2H-chromene-2-carboxamide (3b)

^{1}H NMR (400 MHz, DMSO): δ =2.09 (m, 1H); 2.31 (m, 1H), 2.56-2.76 (m, 2H), 4.31 (dd, 1H), 7.30-8.67 (m, 7H, Aromatic proton) 8.77 (s, 1H), IR (cm-1): 3233 (N-H), 3023 (C-H aromatic ring), 2953 (C-H), 2864 (C-H), 1661 (C=O), 1425 (C=C), 1344 (C-H), 1320 (C-H), 1277 (C-N), 1067 (C-O), 1024 (C-F) cm^{-1}. Yield: 76%; mp 168-173 ^{o}C; MS (m/z): 389 (M+); Anal. calcd for $C_{18}H_{13}F_6NO_2$: C, 55.53; H, 3.37; F, 29.28; N, 3.60; Found: C, 55.54; H, 3.31; F, 29.23; N, 3.58.

6-(trifluoromethyl)-N-(2-(trifluoromethyl)phenyl)-3,4-dihydro-2H-chromene-2-carboxamide (3c)
^{1}H NMR (400 MHz, DMSO): δ =2.06 (m, 1H); 2.32 (m, 1H), 2.51-2.72 (m, 2H), 4.22 (dd, 1H), 7.32-8.61 (m, 7H, Aromatic proton) 8.70 (s, 1H), 8.69 (s, 1H), IR (cm-1): 3255 (N-H), 3027 (C-H aromatic ring), 2953 (C-H), 2861 (C-H), 1665 (C=O), 1424 (C=C), 1342 (C-H), 1323 (C-H), 1284 (C-N), 1075 (C-O), 1027 (C-F) cm^{-1}. Yield: 76%; mp 167-170ºC; MS (m/z): 389 (M+); Anal. calcd for $C_{18}H_{13}F_6NO_2$: C, 55.53; H, 3.37; F, 29.28; N, 3.60; Found: C, 55.54; H, 3.31; F, 29.23; N, 3.58.

N-(4-fluoro-3-(trifluoromethyl)phenyl)-6-(trifluoromethyl)chroman-2-carboxamide (3d)
^{1}H NMR (400 MHz, DMSO): δ =2.16 (m, 1H); 2.33 (m, 1H), 2.69-2.80 (m, 2H), 4.43 (dd, 1H), 6.86-8.78 (m, 6H, Aromatic proton) 8.97 (s, 1H), IR (cm-1): 3243 (N-H), 3033 (C-H aromatic ring), 2965 (C-H), 2868 (C-H), 1665 (C=O), 1426 (C=C), 1351 (C-H), 1334 (C-H), 1261 (C-N), 1065 (C-O), 1056 (C-F) cm-1. Yield: 77%; mp 163-67ºC; MS (m/z): 407 (M+); Anal. calcd for $C_{18}H_{12}F_7NO_2$: C, 53.08; H, 2.97; F, 32.65; N, 3.44; Found: C, 53.02; H, 2.92; F, 32.61; N, 3.43.

N-(3-fluoro-4-(trifluoromethyl)phenyl)-6-(trifluoromethyl)chroman-2-carboxamide (3e)
^{1}H NMR (400 MHz, DMSO): δ =2.18 (m, 1H); 2.46 (m, 1H), 2.61-2.80 (m, 2H), 4.63 (dd, 1H), 6.73-8.00 (m, 6H, Aromatic proton), 8.99 (s, 1H), IR (cm-1): 3256 (N-H), 3055 (C-H aromatic ring), 2978 (C-H), 2877 (C-H), 1674 (C=O), 1435 (C=C), 1323 (C-H), 1311 (C-H), 1266 (C-N), 1066 (C-O), 1020 (C-F) cm^{-1}. Yield: 75%; mp 165-167ºC; MS (m/z): 407 (M+); Anal. calcd for C18H12F7NO2: C, 53.08; H, 2.97; F, 32.65; N, 3.44; Found: C, 53.04; H, 2.90; F, 32.60; N, 3.40.

N-(2,4-bis(trifluoromethyl)phenyl)-6-(trifluoromethyl)chroman-2-carboxamide (3f)
1H NMR (400 MHz, DMSO): δ =2.11 (m, 1H); 2.41 (m, 1H), 2.60-2.77 (m, 2H), 4.60 (dd, 1H), 6.70-8.46 (m, 6H, Aromatic proton), 8.91 (s, 1H), IR (cm^{-1}): 3251 (N-H), 3050 (C-H aromatic ring), 2973 (C-H), 2874 (C-H), 1675 (C=O), 1436 (C=C), 1327 (C-H), 1318 (C-H), 1269 (C-N), 1061 (C-O), 1022 (C-F) cm-1. Yield: 77%; mp 163-165ºC; MS (m/z): 557 (M+); Anal. calcd for $C_{19}H_{12}F_9NO_2$: C, 49.90; H, 2.64; F, 37.39; N, 3.06;; Found: C, 49.88; H, 2.63; F, 37.32; N, 3.01.

N-(3,5-bis(trifluoromethyl)phenyl)-6-(trifluoromethyl)chroman-2-carboxamide (3g)
^{1}H NMR (400 MHz, DMSO): δ =2.21 (m, 1H); 2.49 (m, 1H), 2.74-2.86 (m, 2H), 4.44 (dd, 1H), 6.74-8.45 (m, 6H, Aromatic proton), 8.95 (s, 1H), IR (cm^{-1}): 3261 (N-H), 3070 (C-H aromatic ring), 2953 (C-H), 2874 (C-H), 1645 (C=O), 1466 (C=C), 1387 (C-H), 1368 (C-H), 1259 (C-N), 1051 (C-O), 1032 (C-F) cm^{-1}. Yield: 70%; mp 160-163ºC; MS (m/z): 557 (M+); Anal. calcd for $C_{19}H_{12}F_9NO_2$: C, 49.90; H, 2.64; F, 37.39; N, 3.06; Found: C, 49.83; H, 2.61; F, 37.30; N, 3.00.

6-(trifluoromethyl)-N-(2,3,4-trifluorophenyl)chroman-2-carboxamide (3h)
1H NMR (400 MHz, DMSO): δ =2.13 (m, 1H); 2.34 (m, 1H), 2.66-2.79 (m, 2H), 4.46 (dd, 1H), 6.74-8.45 (m, 5H, Aromatic proton), 8.87 (s, 1H), IR (cm-1): 3256 (N-H), 3046 (C-H aromatic ring), 2965 (C-H), 2864 (C-H), 1633 (C=O), 1438 (C=C), 1367 (C-H), 1377 (C-H), 1276 (C-N), 1046 (C-O), 1066 (C-F) cm^{-1}. Yield: 66%; mp 155-159ºC; MS (m/z): 375 (M+); Anal. calcd for $C_{17}H_{11}F_6NO_2$: C, 54.41; H, 2.95; F, 30.38; N, 3.73; Found: C, 54.40; H, 2.93; F, 30.34; N, 3.71.

Biological assays

Enzyme inhibitory exertion

The possible effectiveness of chromene derivations in skin diseases and diabetes mellitus were delved by assessing their inhibitory belongings against tyrosinase and αglucosidase, independently, using the preliminarily reported standard methodologies (12), as outlined below.

Tyrosinase inhibitory exertion

Tyrosinase inhibitory exertion of chromenes 3(a-h) was measured using the modified dopachrome system with L- DOPA as a substrate (13). Distant concentrations of chromene results (20µL) were associated with tyrosinase result and phosphate buffer (100 µL, pH = 6.5) in well microplate incubated for 20 min at room temperature. Additionally, the reaction was constituted with the extension of LDOPA (50 µL). A like, a blank was prepared by subjoining sampling solution to all reaction reagents without enzyme (tyrosinase) result. The ocular thickness of the sampling and blank was measured at 492 nm after incubation at 25 ˚C (10 min). The absorbance of the blank was abated from that of the sample and the tyrosinase inhibitory exertion was expressed as IC50 values.

α-Glucosidase inhibitory activity

The sample result (60 µL) with comprehended enthrallment was mixed with glutathione(60 µL), α-glucosidase result(from Saccharomyces cerevisiae)(60 µL) in phosphate buffer(pH = 6.5), and PNPG(p- nitrophenyl- α- D- glucopyranoside)(60 µL) in a well microplate and incubated for 15 min at 37 °C(14). Also, a blank was prepared by adding sample result to all response reagents without enzyme (α- glucosidase) result. Due to the addition of sodium carbonate (60 µL, 0.3M), the response was quenched. Ultimately, the UV absorbance of the composite and blank were determined at 400 nm. The absorbance of the blank was knocked off from that of the sample and α- glucosidase inhibitory exertion was expressed as IC50 values. Acarbose was applied as a positive control in this assay.

Antimicrobial Activity

The minimal inhibitory concentrations(MICs) of synthesized syntheses were carried out by broth microdilution system as described by Rattan Antibacterial exertion was screened against two gram positive(Staphylococcus aureus MTCC 96, Streptococcus pyogenus MTCC 443) and two gram negative(Escherichia coli MTCC 442, Pseudomonas aeruginosa MTCC 441) bacteria, ampicillin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species Candida albicans MTCC 227, Aspergillus niger MTCC 282 and Aspergillus clavatus MTCC 1323, Griseofulvin was used as a standard antifungal agent. All MTCC societies were collected from Institute of Microbial Technology, Chandigarh and Mueller Hinton broth was used as nutrient media to grow and adulterated the medicine suspense for the test. Inoculum size for test strain was acclimated to 108 CFU(Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used to adulterate to get asked attention of medicines to test upon standard bacterial strains. Periodical dilutions were prepared in primary and secondary webbing. The control tube containing no antibiotic was incontinently sub dressed(before inoculation) by spreading a loopful unevenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes were also incubated overnight. The MIC of the control organism was read to check the delicacy of the medicine attention. The smallest attention inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described over) were sub dressed and incubated overnight at 37 °C. The quantum of growth from the control tube before incubation (which represents the original inoculum) was compared. Mores might show analogous number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal exertion and no growth if the whole inoculum has been killed. The test must include a alternate set of the same dilutions invested with an organism of known perceptivity. Each synthesized medicine was adulterated for carrying 2000 µg/ ml attention, as a stock result. In primary webbing 500 µg/ ml, 250µg/ ml and 125 µg/ ml attention of the synthesized medicines were taken. The active synthesized medicines set up in this primary webbing were further tested in an alternate set of dilution against all microorganisms. The medicines set up active in primary webbing were also adulterated to gain 100 µg/ ml, 50 µg/ ml, 25 µg/ ml,12.5 µg/ ml,6.25 µg/ ml,3.12 µg/ ml and1.56 µg/ ml attention. The loftiest dilution showing at least 99 inhibition is taken as MIC.

ADME/ toxin Studies

A computer tool called ADMET Predictor was created for calculating the pharmacokinetic parameters and characteristics of medicine- suchlike composites grounded on their molecular structures. ADMET stands for immersion, Distribution, Metabolism, Excretion/ Elimination, and toxin. A patch doesn't automatically qualify as a promising seeker just because it's largely bioactive and has a low dangerous profile. In the process of discovering new medicines and medicines like composites, a new chemical should only be explored if it has a better pharmacokinetic profile. To help wasting time or coffers, it's pivotal to assess the ADMET profile of new composites as soon as possible. As a result, we used the online Swiss ADME software to prognosticate the ADMET parcels of our advanced motes (3a – 4h). The Lipinski" Rule of Five" was the" most extensively utilised rule- grounded sludge" of medicine-likeness and was used to determine whether a patch is well absorbed orally. Molecular weight (MW) ≤ 500, Octanol/ water partition measure (iLOGP) ≤ 5, Number of hydrogen bond benefactors (HBDs) ≤ 5, and Number of hydrogen bond acceptors (HBAs) ≤10.6 are the factors of the rule of five. The four rules of five(MW, iLOGP, HBAs, and HBDs) and four added parameters, including molecular

topological polar face area(TPSA), number of rotatable bonds(RB), number of sweet heavy tittles(nAH), and number of cautions for undesirable substructures, were generated by the quantitative estimate of medicine- likeness(QED) conception(cautions). Comparing the conception of QED to standard medicine- likeness principles, the ultimate is the more adaptable and extensively used (14-16). The ensuing list includes certain ADMET features and parameters along with their permitted limits.

Table 1: Permitted limits of ADMET parameters

ADMET parameter	Permitted limit
Molecular weight (MW)	50 to 100
octanol/water partition coefficient (iLOGP)	-2 to 10
Topological Polar Surface Area (TPSA)	20 to 130
Number of H-Bond acceptors (HBA)	0 to 10
Number of H-bond Donors (HBD)	0 to 5
Rotatable bonds (RB)	0 to 5
Number of aromatic heavy atoms (nAH)	15 to 50
Lipophilicity of the compound (LogP)	-0.7 to 50
Molar refractivity (MR)	40 to 130

Molecular docking

In order to identify possibility of-inflammatory medicines, molecular docking trials were carried out on the target proteins. Download the PDB lines for the 3D demitasse structures of The crystal clear structure of tyrosinase from Agaricus bisporus mushroom (PDB ID 2Y9X, chain A (17) of Saccharomyces cerevisiae isomaltase(PDB ID 3AXH)) from the RCBS Protein Data Bank(https//www.rcsb.org/). Using BIOVIA Discovery plant visualizer 2021, the attained proteins were made ready for docking by having water motes and heteroatoms removed. By adding Kollman charges, Gasteiger charges, and polar hydrogens, the protein structures were reduced to the smallest energy state for farther disquisition. ChemDraw Ultra12.0 was used to produce the intended and produced ligand structures, and Chem 3D- Pro12.0 was used to reduce and store the structures in SDF train format. Also, using the Open Babel software, all SDF format lines are restated to PDB format. Protein metamorphoses from PDB to PDBQT train format, grid- grounded docking studies using dereliction parameters, and docking by connecting the protein- ligand using MGL AutodockVina were all completed. Using command advisement, it was possible to see the docking positions of ligands that stylish linked to the active point areas of the proteins. The tapes of the ligands to the target proteins in two dimensional and three dimensional were viewed using BIOVIA Discovery Studio 2021.

Table 2: Tyrosinase and α-glucosidase inhibitory activity of chromenes

Compound	Tyrosinase	α-Glucosidase
3a	3.40±0.40	4.43±0.03
3b	4.01±0.20	6.01±0.01
3c	4.50±0.30	5.52±0.10
3d	3.15±0.01	5.14±0.20
3e	3.51±0.30	3.44±0.04
3f	4.80±0.10	3.50±0.04
3g	4.90±0.20	5.50±0.10
3h	5.12±0.30	3.51±0.05
Kojic Acid	NT	0.91±0.07
Ascabrose	7.80±0.30	NT

Antimicrobial assay

The antibacterial and antifungal conditioning of chromenes 3(a-h) were screened against gram-positive and gram-negative bacteria and fungal strains. The attained results revealed that some of these composites have antimicrobial goods at the tested attention preliminarily, the antibacterial

exertion of synthesized. The results of biological screening revealed that compound 3c showed very good antibacterial activity against Staphylococcus aureus bacterial strain. While compound 3b and 3f showed excellent activity against streptococcus pyogenus. Compound 3g showed excellent activity against E.coli bacterial species at 100 µg mL-1. Rest of the compounds were found to be good to moderate inhibitors against tested microbial strains. Antifungal screening of these compound results that compound 4d showed very good antifungal activity against candida albicans. Compound 4e exhibit good activity against Aspergillus niger. Compound 4g exhibit excellent antifungal activity against and Aspergillus clavatus. While remaining all compounds were good to moderate inhibitors.

3. RESULTS AND DISCUSSION

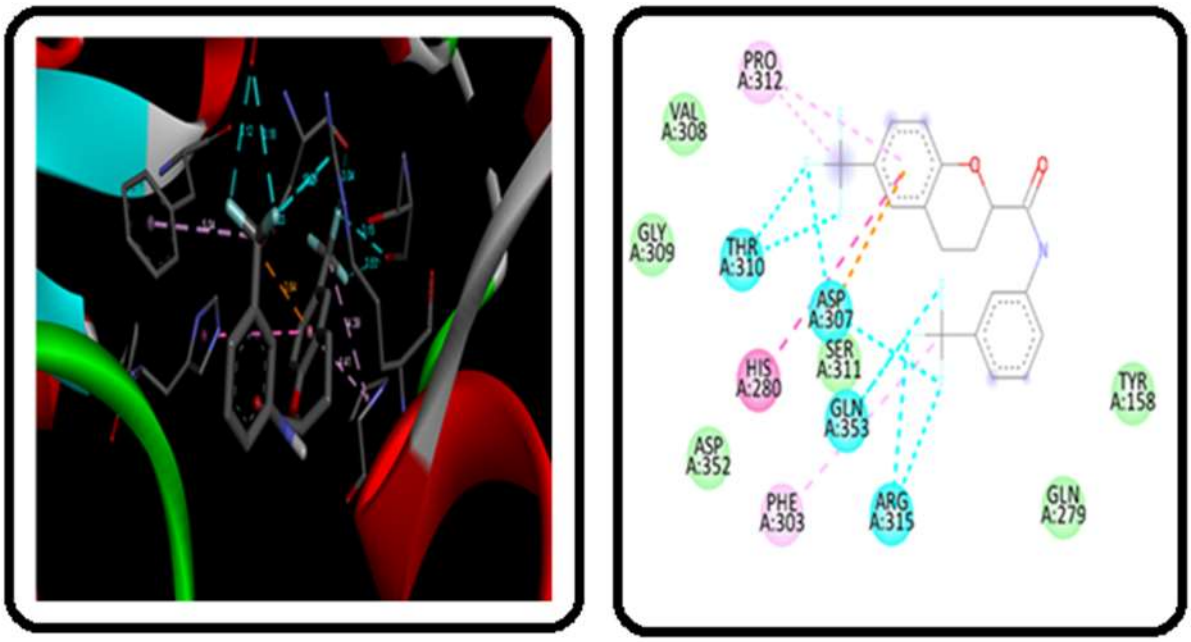
Results of ADMET The results of the ADMET revealed the physicochemical parcels of the designed composites, including molecular weight(MW), number of rotatable bonds(RB), number of hydrogen benefactors(HBD), number of hydrogen acceptors(HBA), topological polar face area(TPSA), octanol/ water partition measure (iLOGP), number of sweet heavy tittles (nAH), molar refractivity(MR), lipophilicity (LogP) and the number of cautions for undesirable substructures(PAINS and Brenk) were mentioned in Table- 3. All of the created composites agreed the rules by causing no further than one violation. All of the MW, RB, HBD, HBA, TPSA, iLOGP, nAH, and MR, in other words, are within the permissible bounds. Also, there's just 1 Brenk for composites 3h and no warning for PAINS, indicating the composites high particularity. Therefore, it's now possible to state that developed motes have a favorable pharmacokinetic profile.

Table 3: Predicted ADME parameters of Chromene 3(a-h)

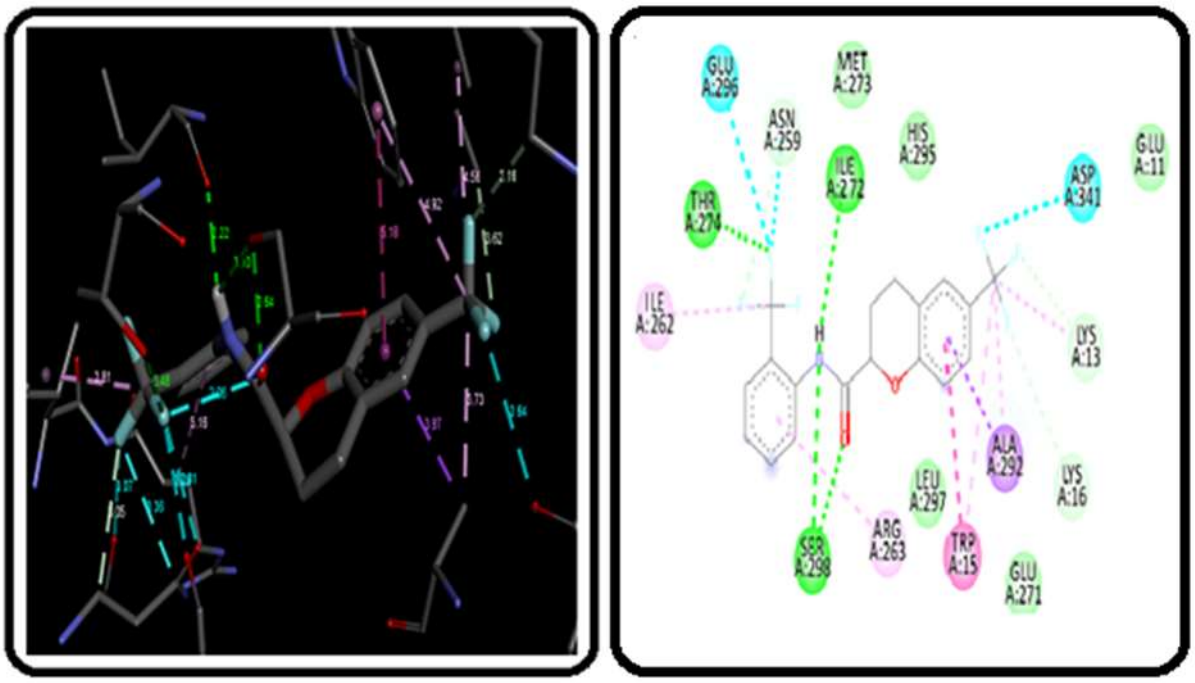
Comp.	MW	iLOGP	HBD	HBA	TPSA	RB	nAH	MR	LogP	PAINS	Brenk
3a	389.29	3.31	1	8	38.33	5	12	84.43	4.91	0	0
3b	389.29	3.04	1	8	38.33	5	12	84.43	4.89	0	0
3c	389.29	3.00	1	8	38.33	5	12	84.43	4.88	0	0
3d	407.28	2.98	1	9	38.33	5	12	84.39	5.12	0	0
3e	407.28	2.88	1	9	38.33	5	12	84.39	5.10	0	0
3f	457.29	3.23	1	11	38.33	6	12	89.43	5.87	0	0
3g	457.29	3.26	1	11	38.33	6	12	89.43	5.88	0	0
3h	375.27	2.89	1	8	38.33	4	12	89.33	4.75	0	1

Molecular docking

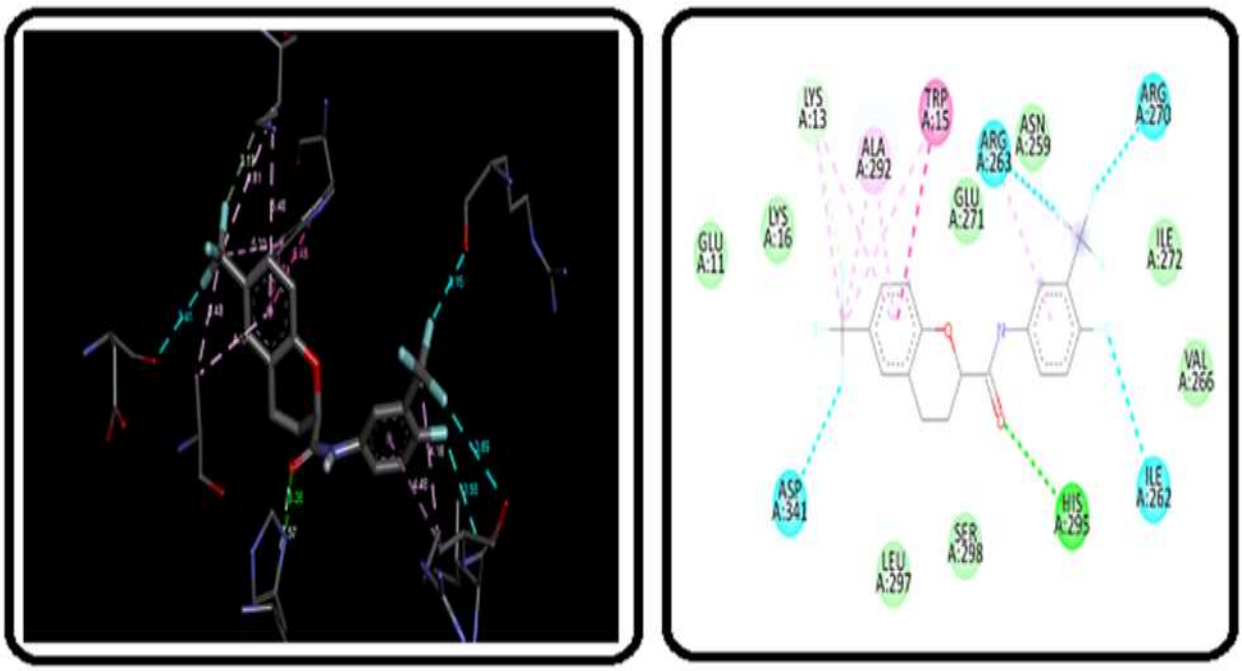
The molecular docking studies were performed to dissect the presumptive list modes of synthesized chromenes 3(a-h) against α- glucosidase and tyrosinase. The results of docking study were represented in tables 4 and 5. The analysis of the docking results for 3d as the most active emulsion against α- glucosidase showed that NH of 3d compound is involved in hydrogen bonds with amine group of his244[A]. Also, the hydrogen bond was observed between fluorine group with Ala323and Asn260 .The hydrophobic relations and π- π mounding were observed with His263 (A) His259 (A) Val 283(A) independently. All of these relations stabilize the list of 3d to the active point of α-glucosidase and the list energy of-9.7 kcal/ mole was calculated for α- glucosidase- 3d complex. The molecular relations between 3e,3f,3h (as the most active emulsion against tyrosinase) and binding point remainders of tyrosinase were represented in image As seen, the hydrogen bonds were formed between the NH and f atom of side chain amine groups of various chain. Likewise, the hydrophobic commerce was observed between the pi electrons. The estimated list energy for these relations was-11kcal/mole.



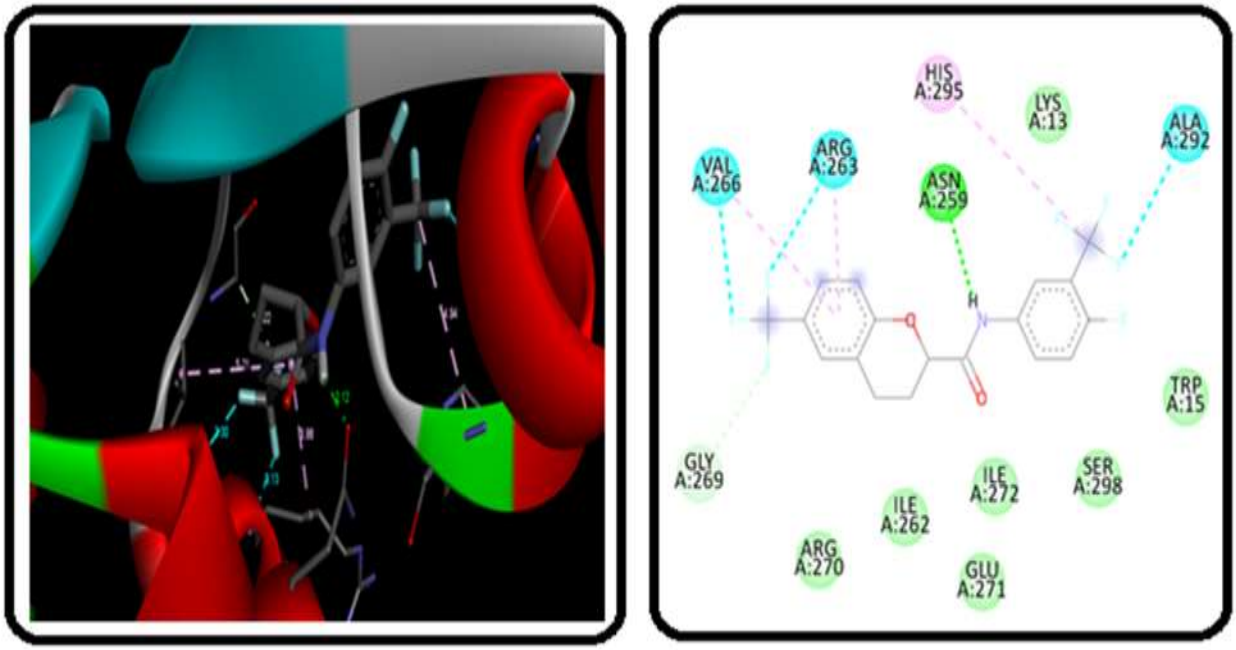
3D & 2D binding mode of synthesized ligand compounds 3a active site region of tyrosinase



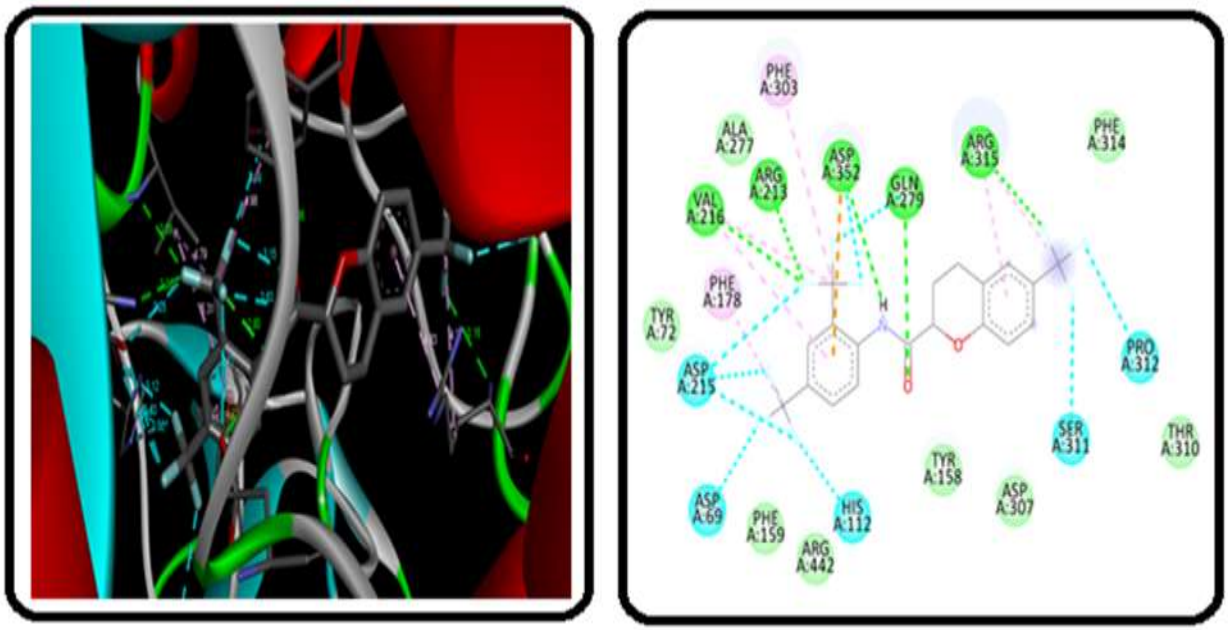
3D & 2D binding mode of synthesized ligand compounds 3b active site region of tyrosinase



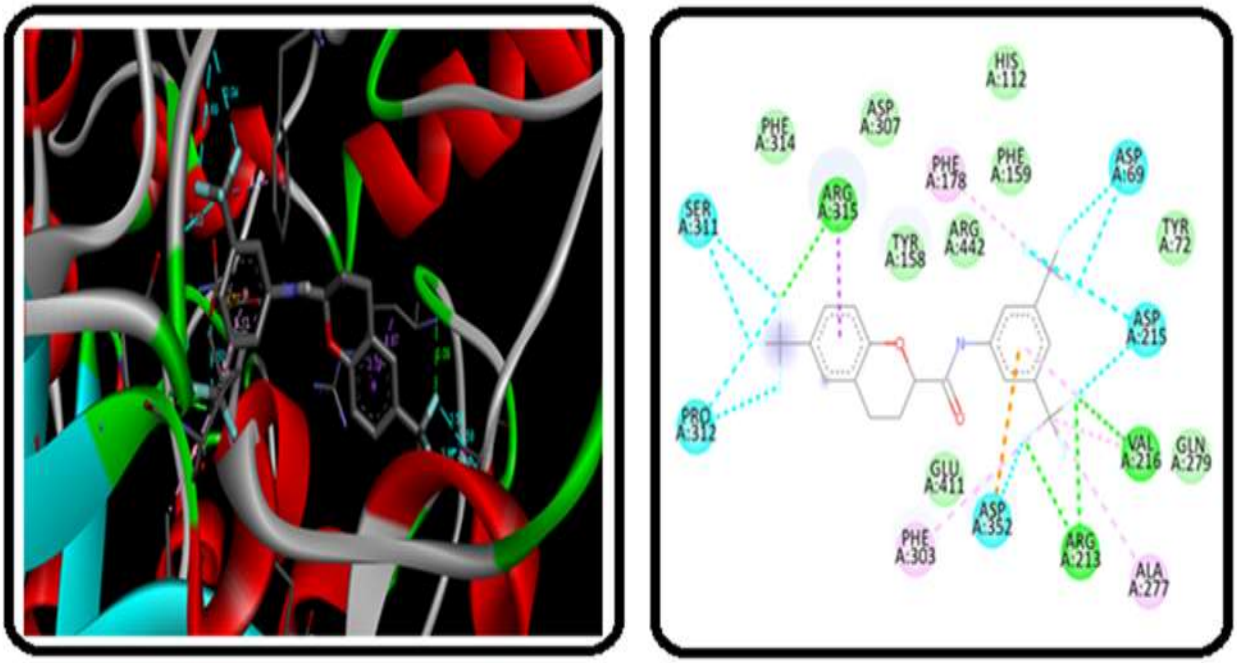
3D & 2D binding mode of synthesized ligand compounds 3c active site region of tyrosinase



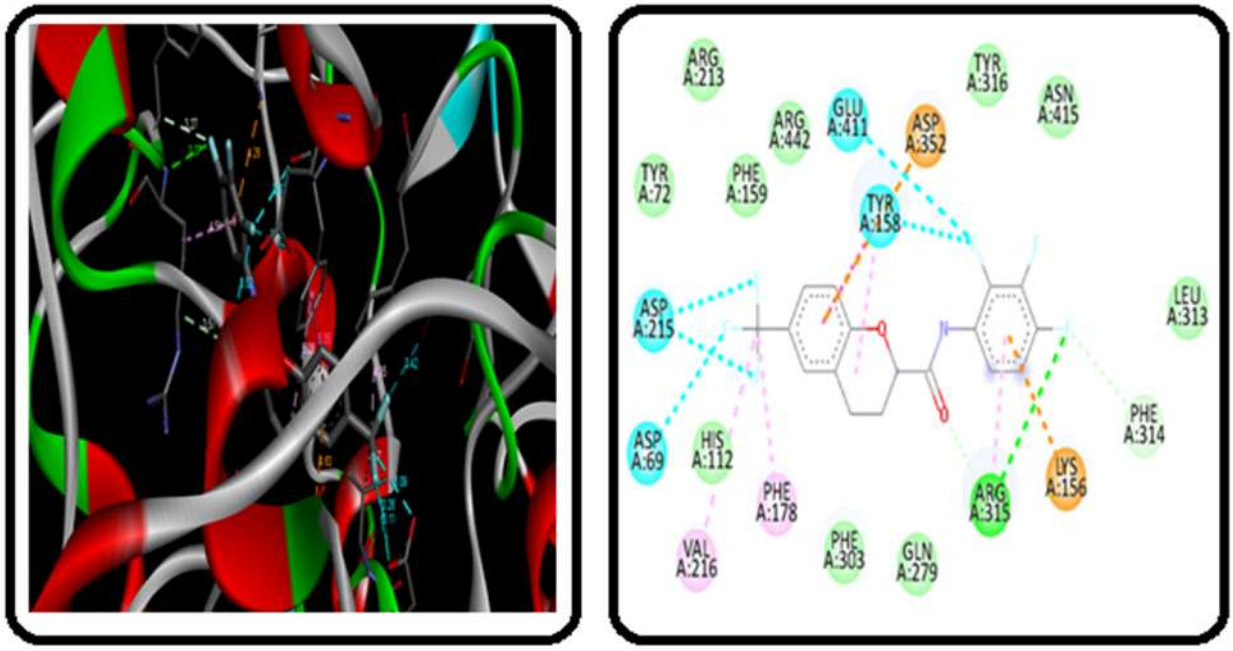
3D & 2D binding mode of synthesized ligand compounds 3d active site region of tyrosinase



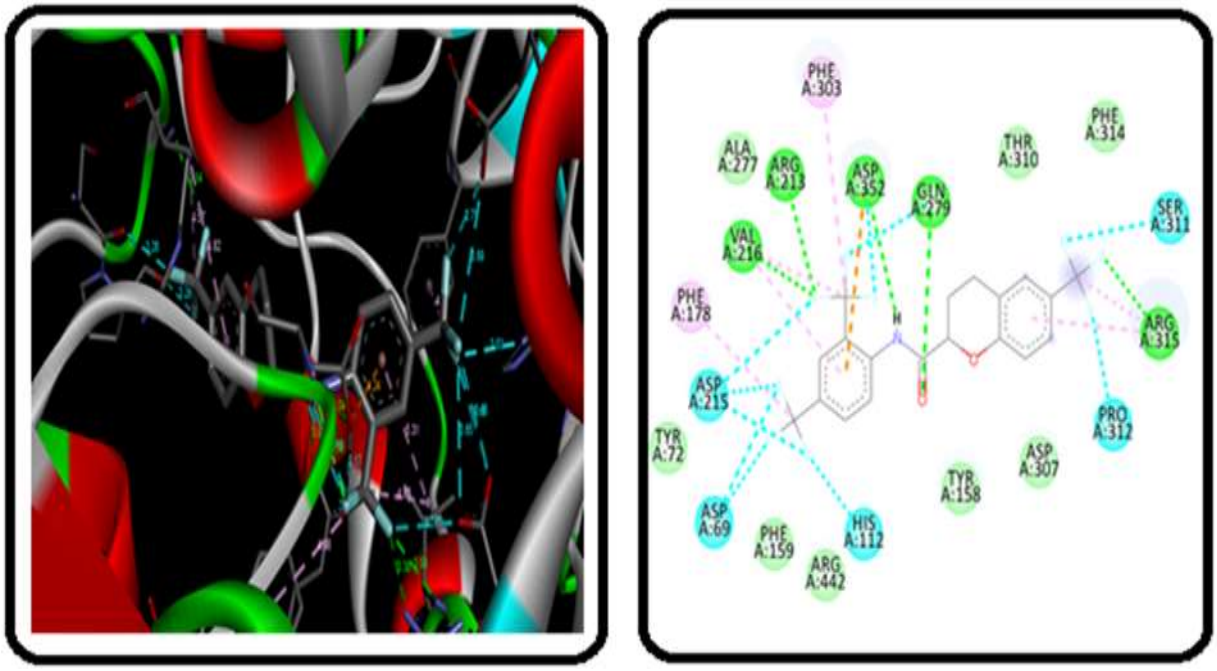
3D & 2D binding mode of synthesized ligand compounds 3e active site region of tyrosinase



3D & 2D binding mode of synthesized ligand compounds 3f active site region of tyrosinase



3D & 2D binding mode of synthesized ligand compounds 3g active site region of tyrosinase



3D & 2D binding mode of synthesized ligand compounds 3h active site region of tyrosinase

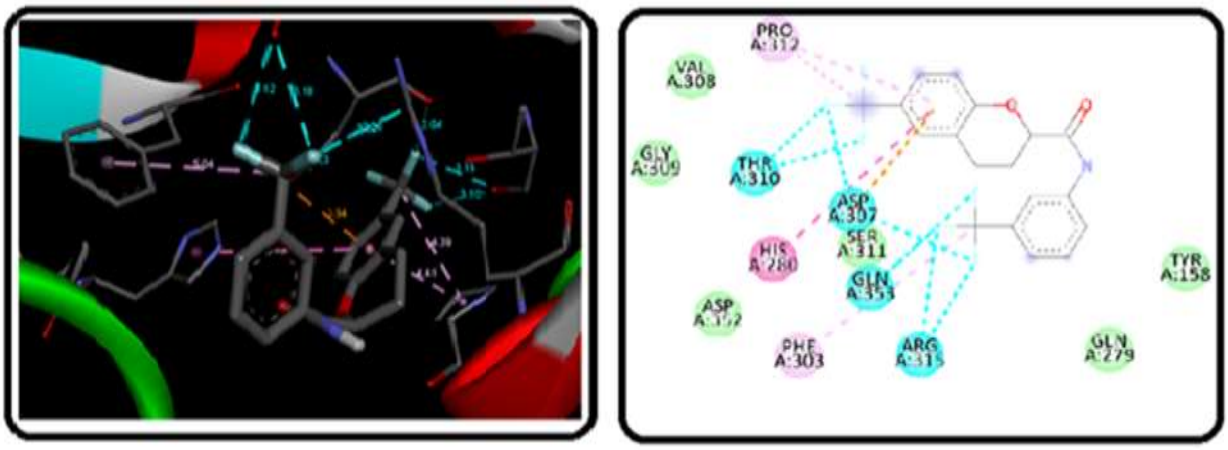
Table 4:- The molecular interaction between the synthesized Chromene 3(a-h) and tyrosinase resulted from the docking analysis

Compound	Energy score (S) Kcal/mol.	Type of interaction	Bond length	Interacting moiety in the drug	Amino acid involved (Chain Type)
3a	-10.4	Halogen bond	3.22	F	ARG(A)315
		Halogen bond	3.18	F	GLN(A)353
		Halogen bond	3.56	F	ASP(A)307
		Halogen bond	3.15	F	THR(A)310

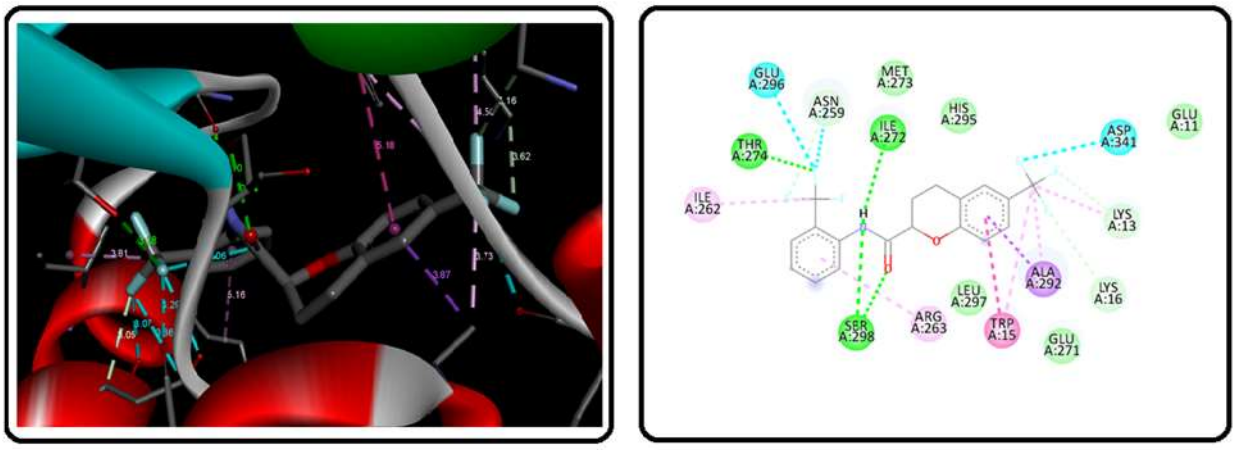
		Halogen bond	3.26	F	ARG (A) 315
		Halogen bond	3.12	F	GLN(A)353
		Halogen bond	3.04	F	ASP(A)307
		Pi-Anion	3.64	6 ring	ASP(A)307
		Pi-Pi Stacked	5.72	6 ring	HIS(A)208
		Pi-alkyl	4.41	6 ring	PRO(A)312
		Pi-alkyl	4.39	CH	PRO(A)312
		Pi-alkyl	5.04	CH	PHE(A) 303
3b	-9.9	Conventional H bond	2.64	O	SER(A) 298
		Conventional H bond	3.1	NH	SER(A) 298
		Conventional H bond	2.22	NH	ILE (A) 272
		Conventional H bond	3.48	F	THR(A)274
		Pi-Alkyl	3.81	CH	ILE (A) 262
		Pi-Alkyl	5.16	6 ring	ARF (A) 263
		Pi-Alkyl	4.92	CH	TRP (A) 15
		Pi-Alkyl	3.73	CH	ALA (A0 292
		Pi-Alkyl	4.56	CH	LYS (A) 13
		Pi-sigma	3.87	6 ring	ALA (A) 292
		C-H bond	3.62	C-F	LYS (A) 13
		C-H bond	3.16	C-F	LYS (A) 16
		C-H bond	3.05	C-F	ASN (A) 259
3c	-10.1	Halogen bond	3.41	F	ASP(A) 341
		Halogen bond	3.55	F	ILE (A) 262
		Halogen bond	3.15	F	ARG (A) 270
		Halogen bond	3.69	F	ARG (A) 263
		Conventional H bond	3.26	O	HIS (A) 295
		Pi-Pi T shape	5.46	6 ring	TRP (A) 15
		Pi-Pi T shape	4.74	6 ring	TRP (A) 15
		C-H bond		C-H	LYS (A) 13
		Pi-Alkyl	4.18	C-H	ARG (A) 263
		Pi-Alkyl	5.33	C-H	TRP (A) 13
		Pi-Alkyl	4.17	6 ring	ALA (A)A 292
		Pi-Alkyl	3.48	C-H	ALA (A)A 292
		Pi-Alkyl	4.81	C-H	LYS (A) 13
		Pi-Alkyl	3.4	6 ring	LYS (A) 13
3d	-10.3	Halogen bond	3.3	F	VAL (A) 266
		Halogen bond	5.21	F	ARG (A) 263
		Halogen bond	3.04	F	ALA (A) 292
		Conventional H bond		NH	ASN(A) 259
		Pi-Alkyl	4.94	C-H	HIS (A) 296
		Pi-Alkyl	5.21	6 ring	VAL (A0 266
		Pi-Alkyl	3.86	6 ring	ARG (A) 263
3e	-11	Conventional H bond	3.54	F	VAL (A) 216
		Conventional H bond	3.36	F	ARG (A) 213
		Conventional H bond	3.03	NH	ASP (A) 352
		Conventional H bond	3.06	O	GLN (A) 274
		Conventional H bond	3.16	F	ARF (A) 315
		Pi-Anion	4.07	C-H	PHE (A) 178
		Pi-Alkyl	5.31	6 ring	VAL (A) 216
		Pi-Alkyl	4.98	C-H	PHE (A) 303
		Pi-Alkyl	4.83	6 ring	ARG (A) 315
		Pi-Alkyl	4.53	C-H	ARG (A) 316
		Pi-Alkyl	4.79	C-H	VAL (A) 216
		Halogen bond	3.52	F	HIS (A) 112
		Halogen bond	2.69	F	ASP (A) 69

		Halogen bond	3.12	F	ASP (A) 215
		Halogen bond	5.75	F	ASP (A) 215
		Halogen bond	3.25	F	ASP (A) 215
		Halogen bond	3.59	F	VAL (A) 216
		Halogen bond	3.36	F	ARG (A) 213
		Halogen bond	3.17	F	ASP (A) 352
		Halogen bond	3.69	F	GLN (A) 274
		Halogen bond	3.16	F	ARF (A) 315
		Halogen bond	3.24	F	PRO (A) 312
		Halogen bond	3.31	F	SER (A) 311
3f	-11	Conventional H bond	3.09	F	ARG (A) 315
		Conventional H bond	3.21	F	ARG (A) 213
		Conventional H bond	3.11	F	ARG (A) 213
		Conventional H bond	3.2	F	VAL (A) 216
		Pi-Anion	4.07	6-ring	ASP (A) 352
		Pi-Sigma	4.5	6 ring	ARG (A) 315
		Pi-Alkyl	4.21	C-H	PHE (A) 178
		Pi-Alkyl	5	C-H	PHE (A) 303
		Pi-Alkyl	4.01	C-H	ALA (A) 277
		Pi-Alkyl	4.04	C_H	VAL (A) 216
		Pi-Alkyl	5.13	6-ring	VAL (A) 216
3g	-10.1	Conventional H bond	3.37	F	ARG (A) 315
		Halogen bond	3.11	F	ASP (A) 215
		Halogen bond	4.92	F	ASP (A) 69
		Halogen bond	3.42	F	ASP (A) 215
		Halogen bond	3.2	F	GLU (A) 411
		Halogen bond	4.63	F	ARG (A) 315
		Pi-Alkyl	4.87	C-H	VAL (A) 216
		Pi-Alkyl	4.35	C-H	PHE (A) 178
		Pi-Alkyl	4.51	6 ring	ARG (A) 315
		Pi-Alkyl	5.28	6 ring	TYR (A) 315
		Pi-Cation/anion	4.63	6-ring	ASP (A) 352
		Pi-Cation/anion	4.26	6-ring	LYS (A) 158
		C-H bond	3.27	CH	PHE (A) 314
3h	-11	Halogen bond	3.27	F	ARG (A) 315
		Halogen bond	5.77	F	ASP (A) 215
		Halogen bond	3.11	F	ASP (A) 215
		Halogen bond	3.69	F	ASP (A) 69
		Halogen bond	2.7	F	ASP (A) 69
		Halogen bond	3.53	F	HIS (A) 112
		Halogen bond	3.28	F	PRO (A) 312
		Halogen bond	3.26	F	SER (A) 311
		Halogen bond	3.68	F	GL (A) 279
		Halogen bond	3.17	F	ASP (A) 352
		Halogen bond	3.14	F	ARG (A) 315
		Halogen bond	3.39	F	ARG (A) 213
		Halogen bond	3.54	F	VAL (A) 216
		Conventional H bond	3.59	F	VAL (A) 216
		Conventional H bond	3.39	F	ARG (A) 213
		Conventional H bond	3.04	NH	ASP (A) 352
		Conventional H bond	3.08	O	GLN (A) 279
		PI- Anion	4.24	C-H	ASP (A) 352
		PI-Alkyl	4.07	C-H	PHE (A) 178
		PI-Alkyl	5.31	C-H	VAL (A) 216
		PI-Alkyl	4.8	C-H	VAL (A) 216

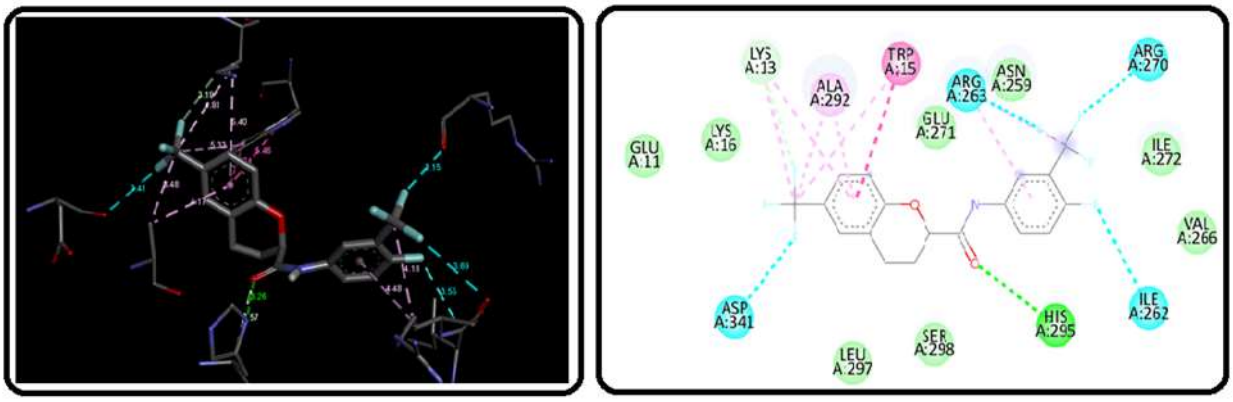
	PI-Alkyl	4.98	C-H	PHE 303 (A)



3D & 2D binding mode of synthesised ligand compounds 3a active site region of α-glucosidase



3D & 2D binding mode of synthesised ligand compounds 3b active site region of α-glucosidase



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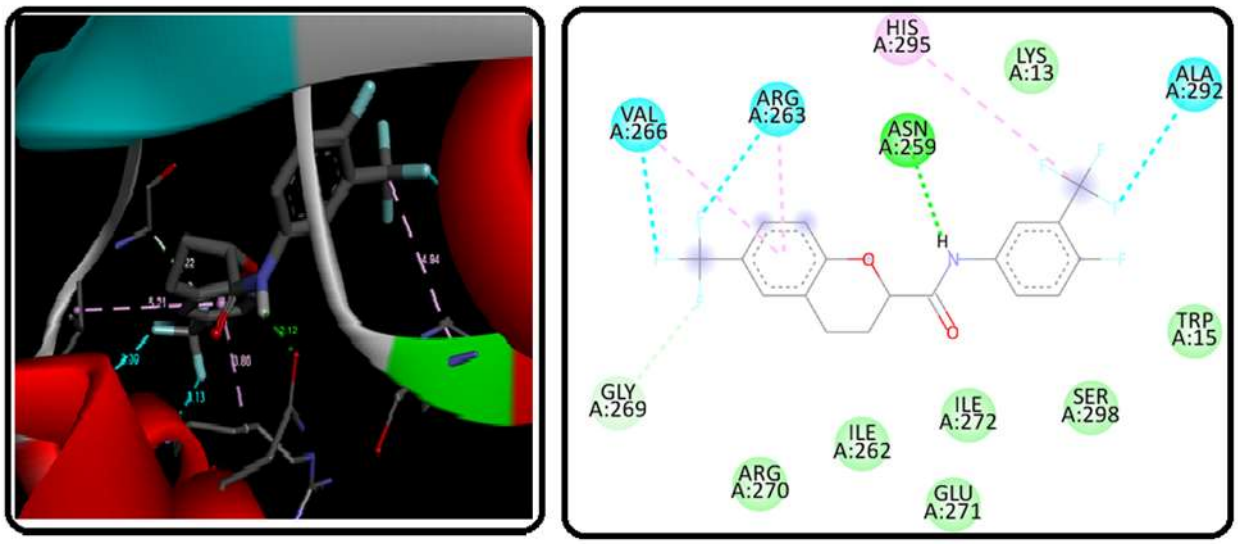
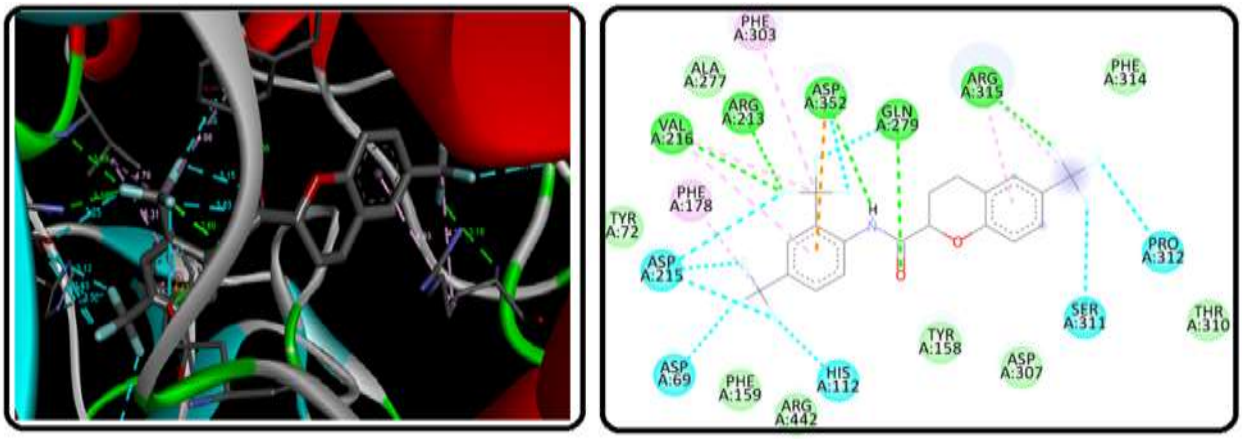
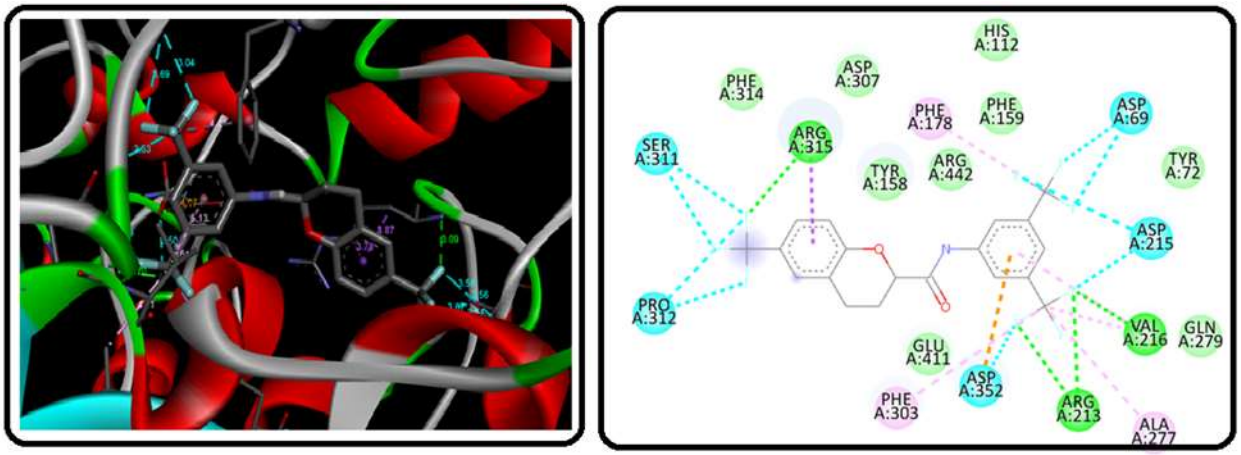


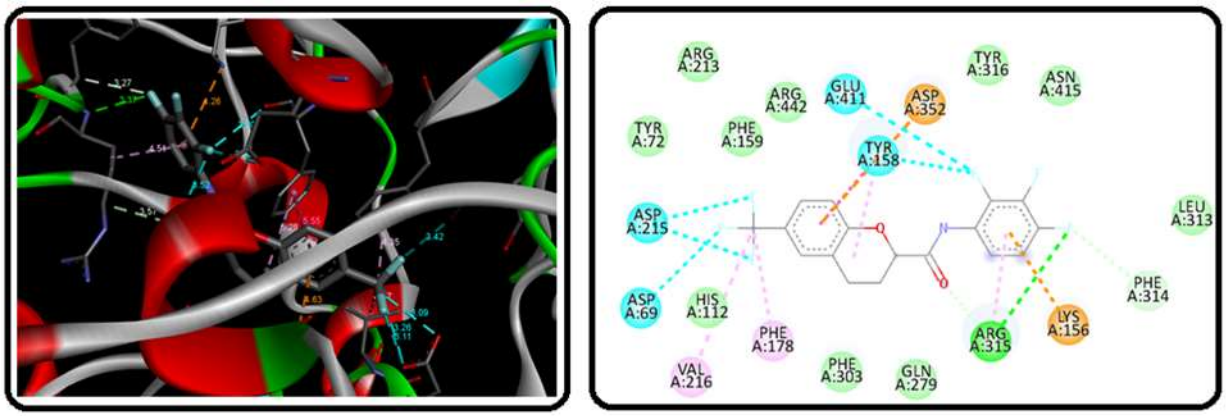
3D & 2D binding mode of synthesised ligand compounds 3d active site region of α-glucosidase



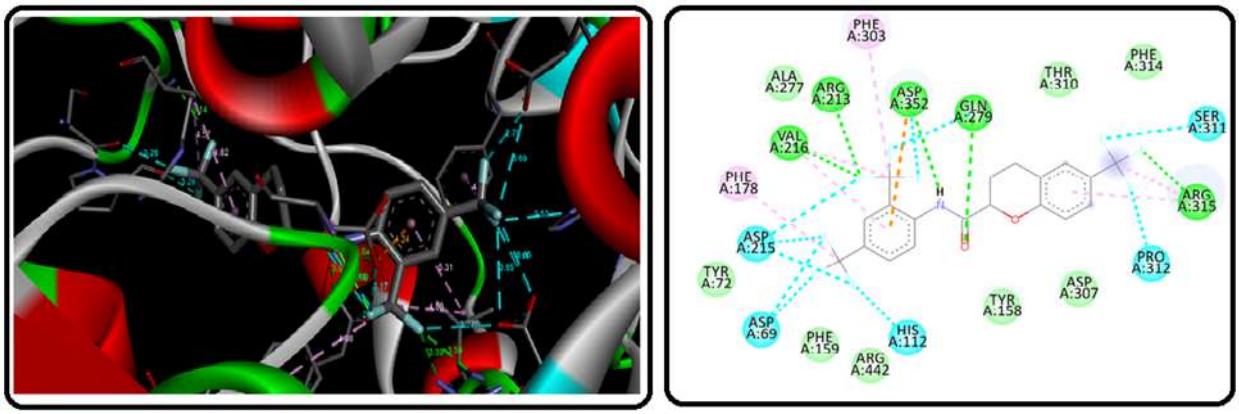
3D & 2D binding mode of synthesised ligand compounds 3e active site region of α-glucosidase



3D & 2D binding mode of synthesised ligand compounds 3f active site region of α-glucosidase



3D & 2D binding mode of synthesised ligand compounds 3g active site region of α-glucosidase



3D & 2D binding mode of synthesised ligand compounds 3h active site region of α-glucosidase

References colour of the bond

Table 5: The molecular interaction between the synthesized chromenes 3(a-h) and α- glycosidase resulted from the docking analysis

Compound	Energy score (S) Kcal/mol	Type of interaction	Bond length	Interacting moiety in the drug	Amino acid involved (Chain Type)
3a	-8.9	Conventional H bond	3.37	F	LYS (A) 379
		Conventional H bond	3.48	F	LYS (A) 379
		Conventional H bond	3.14	F	ASP (A) 357

		Conventional H bond	3.39	F	GLU (A) 356
		Pi-Alkyl	4.95	CH	TRP (A) 358
		Pi-Anion	4.06	6-ring	ASP (A) 357
		Pi-Anion	4.4	6-ring	GLU (A) 356
		Halogen bond	5.27	F	GLU (A) 354
		Halogen bond	3.2	F	GLU (A) 359
		Halogen bond	3.5	F	ASP (A) 357
		Halogen bond	3.1	F	ASP (A) 354
		Halogen bond	3.11	F	ASP (A) 353
		Halogen bond	3.39	F	ASP (A) 353
3b	-8.7	Halogen bond	3.5	F	HIS (A) 263
		Halogen bond	3.96	F	HIS (A) 263
		PI-PI- Shaped	4.77	6-ring	HIS (A) 244
		PI- Alkyl	4.92	6-ring	VAL (A) 248
		PI- Alkyl	3.5	CH	VAL (A) 283
		PI- Alkyl	5.2	CH	HIS (A) 259
		PI- Alkyl	3.96	CH	HIS (A) 263
		PI- Sigma	3.5	6-ring	VAL (A) 283
		CH-Bond	3.52	CH	HIS (A) 61
		CH-Bond	2.99	CH	HIS (A) 259
3c	-8.4	Conventional H bond	3.27	F	ARG(A) 268
		Hydrogen bond	3.14	F	ARG (A) 268
		CH-Bond	3.27	F	HIS (A) 61
		CH-Bond	3.13	F	HIS (A) 85
		CH-Bond	3.22	F	HIS (A) 263
		PI-PI- T Shaped	5.35	6-ring	PHE (A) 264
		PI-PI- T Shaped	4.27	6-ring	HIS (A) 263
		PI- Sigma	3.88	CH	VAL (A) 283
		PI- Alkyl	4.86	CH	HIS (A) 259
		PI- Alkyl	4.36	CH	HIS (A) 85
		PI- Alkyl	4.33	CH	ASN (A) 260
		PI- Alkyl	5.28	CH	HIS (A) 61
		PI- Alkyl	4.21	6-ring	VAL (A) 283
3d	-9.7	Conventional H bond	2.48	NH	HIS(A) 244
		Halogen bond	3.19	F	ALA (A) 323
		Halogen bond	3.01	F	ALA (A) 323
		Halogen bond	2.83	F	ASN (A) 260
		C-H-Bond	3.53	6-ring	ASN (A) 81
		C-H-Bond	3.37	F	HIS (A) 85
		C-H-Bond	3.46	F	HIS (A) 259
		C-H-Bond	3.37	F	HIS (A) 259
		C-H-Bond	3.77	F	HIS (A) 263
		PI- Alkyl	4.66	CH	HIS (A) 263
		PI- Alkyl	5	CH	HIS (A) 259
		PI- Alkyl	4.52	CH	VAL (A) 283
3e	-8.1	Conventional H bond	3.28	F	ARG (A) 301
		Conventional H bond	3.08	F	ARG (A) 301
		PI- Alkyl	4.89	CH	HIS (A) 390
		PI- Alkyl	5.28	CH	PHE (A) 135
		PI- Alkyl	4.62	CH	LEU (A) 24
		PI- Alkyl	3.98	6-ring	LEU (A) 24
		PI- Alkyl	4.31	CH	LEU (A) 24
		CH-Bond	3.87	6-ring	ASN(A) 22
		Halogen bond	2.97	F	ASP (A) 367
		Halogen bond	3.44	F	ASP (A) 367

		Halogen bond	3.65	F	HIS (A) 390
		Halogen bond	3.01	F	ASP (A) 137
		Halogen bond	3.61	F	LEU (A) 266
3f	-8.8	Conventional H bond	3.07	O	VAL (A) 283
		Conventional H bond	3.15	O	SER (A) 282
		Conventional H bond	3.05	O	SER (A) 282
		PI- Alkyl	5.5	6-ring	PRO (A) 277
		PI- Alkyl	4.64	CH	PHE (A) 264
		PI- Alkyl	4.49	CH	HIS (A) 263
		PI- Alkyl	5.18	CH	VAL (A) 283
		CH-Bond	3.58	O	PRO (A) 284
		PI-PI T Shaped	4.96	CH	PHE (A) 192
		PI-PI T Shaped	5.32	6-ring	PHE (A) 192
		PI-Sigma	3.52	6-ring	VAL (A) 283
		Halogen bond	3.32	F	ASN (A) 260
		Halogen bond	3.36	F	MFT (A) 280
		Halogen bond	3.6	F	GLY (A) 281
		Halogen bond	3.33	F	MFT (A) 280
		Halogen bond	3.29	F	GLY (A) 281
		Halogen bond	3.31	F	SER (A) 282
		Halogen bond	3.32	F	ASN (A) 260
		Halogen bond	3.08	F	GLU (A) 189
3g	-8.3	Conventional H bond	3.3	F	GLN (A) 413
		C-H bond	3.52	F	LYS (A) 180
		PI-PI Stacked	3.88	6-ring	HIS (A)182
		PI-Alkyl	3.39	F	PRO (A) 175
		Halogen bond	3.3	F	ASN (A) 174
		Halogen bond	3.55	F	GLU (A) 173
		Halogen bond	2.83	F	GLU (A) 173
		Halogen bond	3.57	F	PRO (A) 175
		Halogen bond	5.26	F	PRO (A) 175
3h	-8.2	Halogen bond	3.49	F	GLN (A) 173
		Halogen bond	3.1	F	ASN (A) 174
		Halogen bond	3.1	6-ring	HIS (A) 178
		Halogen bond	3.4	F	GLN (A) 44
		Halogen bond	3.44	F	ARG (A) 38
		Halogen bond	3.68	F	GLN(A) 41
		Conventional H bond	5.06	O	GLN (A) 41
		Conventional H bond	3.14	F	TYR (A) 165
		Conventional H bond	3.51	F	ARG (A) 115
		Conventional H bond	3.48	F	ARG (A) 115

Table 6: In vitro Antibacterial Screening Results for (3a-h)

Compound	**Minimum inhibition concentration (ug ml-1)**			
	Gram-positive		**Gram-negative**	
	Sa	Sp	Ec	Pa
3a	500	500	450	550
3b	1000	100	900	1000
3c	250	900	500	550
3d	1000	250	350	350
3e	500	500	350	900
3f	500	100	500	500
3g	1000	500	100	550

3h	500	550	550	450
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Norfloxacin	10	10	10	10

Antibacterial Activity

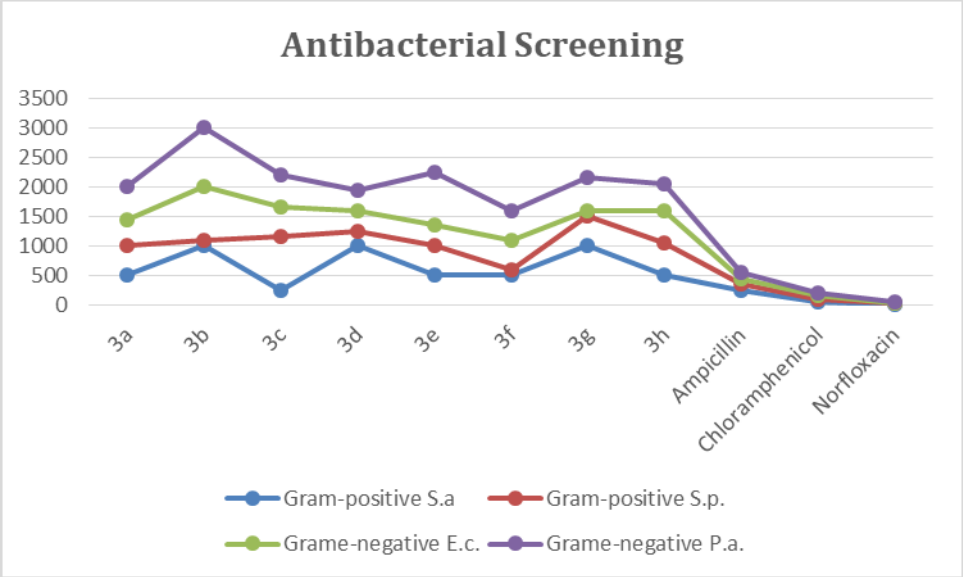
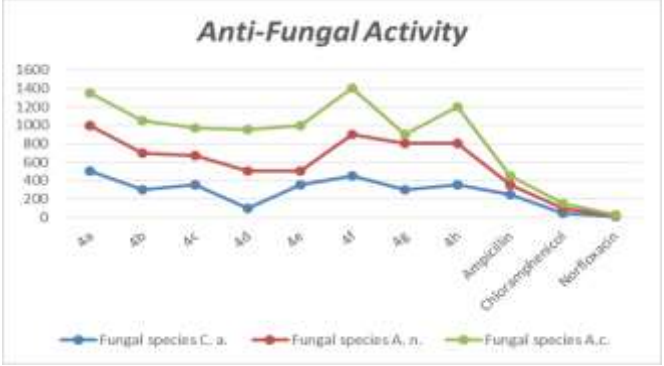


Fig 1: Antibacterial Activity of Chromene derivatives 3a-h

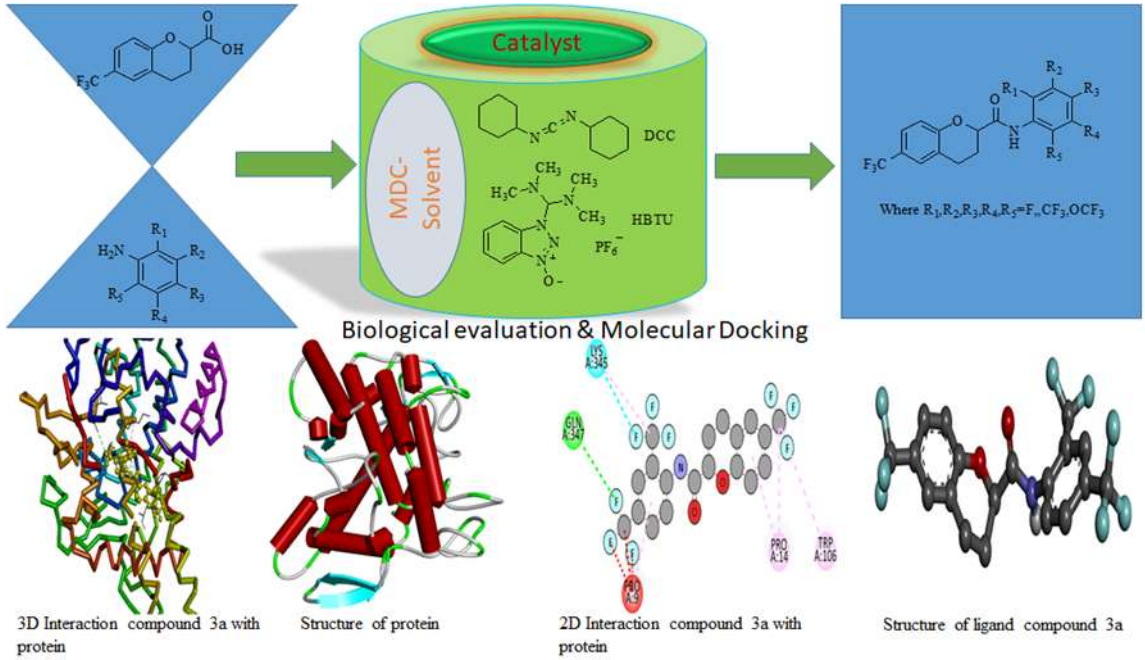
Table 7: In vitro Anti-Fungal Activity Screening Results for 3a-h

Compound	**Minimal inhibition concentration (ug ml-1)**		
	Fungal species		
	C.a.	A.n.	A.c.
3a	500	500	350
3b	300	400	350
3c	350	320	300
3d	100	400	450
3e	350	150	500
3f	450	450	500
3g	300	500	100
3h	350	450	400
Ampicillin	250	100	100
Chloramphenicol	50	50	50
Norfloxacin	10	10	10

Antifungal Activity



Graphical Abstract



4. Conclusion

In the present study, a new environmentally benign methodology was developed for the conflation of preliminarily known chromene derivations 3(a-h) grounded on the green chemistry principles. To this end, the composites were synthesized in high yield, with short response times, and straightforward work- up, using simple catalyst and media, by one- pot and one- step response. Also, the attained products were purified only by recrystallization system without employing any chromatographic ways. In the coming step, for the first time, some natural parcels similar as, ADMET analysis, enzyme inhibitory eventuality, and antimicrobial goods of these chromenes were delved. Findings verified the eventuality of this class of chromenes to be regarded as new impediments of α- glucosidase with anti-diabetic exertion. Chromene derivations were docked into the active spots of α- glucosidase and tyrosinase. The results revealed the actuality of H- bond, hydrophobic, π- π mounding, π- cation, and essence relations between the enzymes and the studied chromenes. Further structural variations on the studied chromenes are demanded to further ameliorate their natural conditioning at the asked targets. The results attained in this work can pave the way for unborn medicine design studies, and pharmacological examinations on chromene derivations.

Acknowledgement

The authors are thankful to Tolani College of art & science, adipur & Shri Ramji Ravji (R R) Lalan College, Bhuj, for providing laboratory facilities.

References:

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