Original Article

In Silico Analysis of Flavonoid–Triazole Hybrid Inhibitors Targeting Neurodegenerative, Oncological, and Infectious Diseases

A. Immaculate, A. Kalpana*
PG & Research Department of Chemistry, Sri Sarada College for Women, Salem, Tamil Nadu 636 016, India.
***Corresponding author's E-mail:** kalpanaanbarasu@gmail.com

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ABSTRACT

This study computationally evaluates the ADME properties and binding potential of various flavonoid-triazole hybrids, including Chalcones, dimers, Flavanone (Hesperetin, Bavachinin), Flavone (Benzimidazole, Apigenin-7-methyl ether, Baicalein, Chrysin), Flavanol, Isoflavone (Daidzein), and Flavan, against five key therapeutic protein targets: GlcN-6-P (antimicrobial), mTOR (anticancer), BChE (anti-Alzheimer's), SARS-CoV-2 MPro (antiviral), and PGHS (anti-inflammatory). Molecular docking analyses reveal promising interactions with 37 compounds exhibiting exceptional anti-Alzheimer potential (-14 to -15 kcal/mol), alongside notable candidates for anticancer (28 compounds, -12 to -14 kcal/mol), anti-inflammatory (6 compounds, -9 to -10 kcal/mol), antimicrobial (21 compounds, -12 to -13 kcal/mol), and antiviral (24 compounds, -13 to -14 kcal/mol) activity. Despite strong experimental evidence supporting their pharmacological activity, our drug-likeness analysis uncovers notable limitations in some hybrids, including moderate to poor solubility, low GI absorption, violations of drug-likeness rules, and carcinogenicity concerns. Effect of skeletal changes in flavonoids has been studied. However, among all tested compounds, flavone apigenin-7-methyl ether triazole hybrids emerge as standout candidates, exhibiting both exceptional binding affinity and favourable drug-likeness properties. These findings highlight their potential as promising multi-targeted drug templates, warranting further investigation for therapeutic development.

Keywords: Apigenin-7-methyl ether triazole hybrids, Multitargeted drug, mTOR, GlcN-6-P synthase, BChE, SARS-CoV-2 MPro, PGHS.

INTRODUCTION

Flavonoids are a large class of plant-derived polyphenolic secondary metabolites characterized by C6-C3-C6 skeleton and classified according to the saturation & structural variation of the central pyran ring into flavonols, flavanones, isoflavones, flavones, flavans and anthocyanidins. Extensive in vivo and clinical studies have demonstrated their broad spectrum of pharmacological activities.[1] These activities are largely attributed to their ability to modulate multiple biological pathways through inhibition of key enzymes. Several flavonoid-based molecules have progressed to clinical evaluation or therapeutic use, underscoring their medicinal relevance. In recent years, molecular hybridization has emerged as an effective strategy in medicinal chemistry to enhance potency and pharmacokinetic properties by integrating two or more pharmacophores within a single framework. Among heterocyclic motifs, the 1,2,3-triazole ring has gained considerable attention due to its synthetic accessibility, metabolic stability, and strong hydrogen-bonding and electrostatic interaction capabilities. Incorporation of 1,2,3-triazole into bioactive scaffolds has been associated with improved antimalarial, antitubercular, anticancer, antidiabetic, anti-inflammatory, antimicrobial and antiviral activities. Therefore, flavonoid-triazole hybrids represent promising multifunctional scaffolds for the development of novel therapeutic agents.[2] Several major diseases including Alzheimer's disease, cancer, microbial & viral infections, inflammatory disorders are driven by distinct but well-characterized molecular targets. In the present study, 364 flavonoid-triazole hybrids were computationally evaluated for their multitarget therapeutic potential against GlcN-6-P synthase (antimicrobial), mTOR (anticancer), human BChE (anti-Alzheimer's), SARS-CoV-2 Mpro (antiviral), and PGHS (anti-inflammatory). Molecular docking was employed to analyse binding interactions and affinity toward these targets. Furthermore, in silico assessment of drug-likeness and medicinal chemistry parameters were performed to evaluate pharmacokinetic suitability. This integrated computational approach provides insights into the potential of flavonoid-triazole hybrids as multitarget drug candidates with favorable pharmacological profiles for diverse therapeutic applications.

MATERIALS AND METHODS

Chem 3D program employing the MM2 method was used to optimize the geometrical structures of flavonoid hybrids and selective drugs. The structure of GlcN-6-P (2vf5), mTOR (4drh), BChE (4tpk), SARS-Cov-2 MPro (6lu7) and PGHS (3ln1) proteins was drawn out from the protein data bank. To carry out docking studies, Auto dock tools were utilized. [3-4] Swiss ADME,[5] Pre ADME and ADMET lab web tools are employed to predict, drug-likeness, pharmacokinetics and medicinal chemistry friendliness [6-7].

RESULTS AND DISCUSSION

The binding energy of all the flavonoid hybrids were compared with drugs and the top hits are identified. The compound number, chemical structure, binding energy and the range are presented in Table S1-S6. The estimated data for flavonoid hybrids and pharmaceuticals parameters are presented in Table S7-S11.

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Docking against BChE

In order to know the anti-Alzheimer activity of the chosen flavonoid hybrids the molecular docking was performed with the BChE target (Table S2). 37 compounds manifest highest BE -14 to -15 kcal/mol indicating their admirable anti-Alzheimer capability. The FDA approved cholinesterase inhibitors (donepezil, galantamine and rivastigmine) was chosen and docked with the BChE enzyme (Figure S1).

Chalcone hybrids

A series of tetrazolo-quinoline-chalcones **1-12** and pyrazole-chalcones **13-22** conjugated with triazole ring displays appreciable BE -11 to -14 kcal/mol. 1,2,3-triazole-linked dehydro acetic acid chalcone hybrids **23-38** exhibit valuable BE -10 to -11 kcal/mol. Thiophene-chalcone hybrids consisting of a bis-triazole ring with phenyl/benzyl substituents **39-48**, exhibit outstanding BE -13 to -15 kcal/mol. A series of chalcone-1,2,3-triazole conjugates **49-66** exhibit exemplary BE -12 to -13 kcal/mol. Morpholino-quinolinyl chalcones conjugated with 1,2,3- triazole ring **67-78** manifest valuable BE -9 to -14 kcal/mol. Chalcone-based 1,4-disubstituted 1,2,3-triazole hybrids **79-99** express docking score -10 to -12 kcal/mol. Quinoline-based chalcone hybrids **100-111** display attractive BE -12 to -15 kcal/mol. Novel chalcone-triazole hybrids **112 & 113** with BE -9 to -10 kcal/mol exhibit moderate solubility, high GI absorption, mostly complies with all rules and no PAINS alert, yet show no BBB penetration, inhibitor of CYP2C19, CYPC9, CYP3A4 and carcinogenicity in mouse model in spite of literature support displaying neuro protective activity [8]. Two novel 1,2,3 triazole derivatives **114 & 115** reveal noticeable docking score of -11.22 & -12.8 kcal/mol which are inconsistent with the experimental evidence that they showed higher inhibitory activity for both AChE and BChE enzymes [9] though exhibit no PAINS alert, it shows poor solubility, low GI absorption, no BBB penetration, inhibitor of some CYPs, carcinogenicity in mouse model and contravene the rules except Veber. Chalcone hybrids with a triazole ring on the *ortho* position **116-118** and *meta* position **119-127** of the B ring of the chalcone scaffold reveals binding score -10 to -12 kcal/mol. Two series of 1,2,3-triazole-linked chalcone hybrids bearing a phenyl **128-137**; isatin **138-147** moiety displays BE -10 to -13 kcal/mol. A group of indoles chalcone hybrids with benzene sulfonamide through a 1,2,3-triazole linker **148-164** displays BE -8 to -12 kcal/mol.

Flavonoid dimers hybrids

A set of flavonoid dimers linked by triazole ring **165-189** indicate exquisite docking score -12 to -15 kcal/mol. The dimer **175** with R=F had an astonishing docking score of -15.38 kcal/mol and is stabilized by H-bonding with Thr120, His438, Ser198, Trp82, van der Waals interaction with Gly117, interaction of F with Glu197, π-anion interaction with Asp70, amide-π interactions with Ile69, Phe329, Gly116, Trp82 and triazole ring of the dimer forms π-alkyl interaction with Ala328 & His438. **184** that possess extraordinary BE -15.62 kcal/mol, establish H-bonds with Tyr128, Gly117, Ser287, Gly116, Halogen interaction with Glu197, π-cation & π-anion interactions with His438 & Glu197, π-lone pair interactions with Trp82 and π-π T-shaped interaction with Tyr332, Phe329 and Trp82 (Figure S1). It acts as a Pgp non-substrate, non-inhibitor of all CYPs and shows no PAINS alert. Datosativanone **190** express excellent BE -12.15 kcal/mol.

Flavanone hybrids

An array of hesperetin hybrids linked by the 1,2,3-triazole ring **191-209** with substituent such as F, Cl, Br, Me, CN, OMe, CF_3 and NO_2 display classic BE -11 to -13 kcal/mol. Four series of hesperetin derivatives **210-223; 224-228; 229-239 & 240-248** exhibit magnificent docking score of -8 to -13 kcal/mol. **210** that possess experimental evidence for its eight-fold higher activity than a positive control resveratrol [3] exhibit BE -12.97 Kcal/mol, moderate solubility, high GI absorption, complies with all five rules, accepted by Golden triangle rule, yet, no BBB penetration, inhibitor of CYP2C9, CYP2D6, CYP3A4, high risk in hERG and carcinogenicity in mouse model. **217**, **222**, **227** and **228** that possesses experimental evidence of having higher activity for BChE than donepezil [3] exhibit BE -12 to -13 Kcal/mol and shows moderate solubility, non-inhibitor of CYP1A2, CYP2C19 and follow Muegge criteria but does not show BBB penetration, rejected by Golden triangle rule and show carcinogenicity in mouse model. 1,2,3-triazole-linked bavachinin derivatives **249-259** exhibit wonderful BE -11 to -15 kcal/mol. **250** was found to be potent with the binding free energy of -15.34 kcal/mol and developed H-bond with His438. Further, benzene ring of the dimer exhibits π-σ interactions with Thr120, Tyr332, π-π T interactions with Phe329, Trp82 and π-alkyl interactions with Tyr128, Leu125, Trp430, Ala328, Phe329 & Pro285. In the sequence of 22 flavanone triazolyl hybrids **260-278** that exhibit outstanding BE -10 to -13 kcal/mol, the hybrids with substituents such as Me-, OMe-, NO_2-, F-, Cl-, Br- & CF_3-benzyl display higher binding affinity towards the target protein.

Flavone hybrids

A set of 1,4-disubstituted 1,2,3-trizole flavone/hybrid heterocycles **279-292** exhibit BE -8 to -11 kcal/mol. Flavone hybrids **293-304** displays exceptional BE -13 to -15 kcal/mol. The hybrids **295, 296, 300 & 301** with substituents R_1=H/CH_3; R_2=2,6-Me-ph/4-NO_2-benzyl were shown to have higher docking sore of -15 kcal/mol. **295** formed hydrogen bonds with the surrounding amino acid residues Ser198, His438, Trp82, in addition to, side chain of the triazole ring have π-donor hydrogen bond with Thr120; flavone moiety, triazole moiety forms π-π T interactions with Phe329, Tyr332, Trp82, Trp231 and flavone moiety forms π-alkyl interaction with Ala328. **301** forms H-bonds with Thr122, Thr120, triazole moiety of compound express π-cation interaction with His438, a ring of the flavone moiety forms π-σ interaction with Trp82, in addition to side chain of flavone moiety exhibit π-π T interaction with Trp82 and π-alkyl interaction with Pro84 (Figure S1). Flavone derivatives of apigenin-7-methyl ether **305-311** exhibit BE -10 to -12

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kcal/mol. Baicalein hybrids **312-322** and Chrysin derivatives **323-325** exhibit BE -11 to -12 kcal/mol.

Flavonol, Isoflavone and Flavan hybrids

A series of 20 flavonol-linked 1,2,3-tiazole conjugates **326-345** reveal BE -10 to -12 kcal/mol. The 5,6-diaryl -1,2,4-triazine-isoflavone hybrid **346** exhibit admirable docking score of -15.02 kcal/mol. A group of daidzein bridged bis-[1,2,3]-triazole iso flavone hybrid **347-359** proclaim docking score -10 to -13 kcal/mol. Five 1,2,3-triazole linked flavan hybrids **360-364** display noticeable BE -8 to -11 kcal/mol which is supported by the experimental studies. The same study revealed that **363** showed activity being comparable with donepezil and does not show cytotoxicity even at higher concentration and increase the SH-SY5Y cell viability to a greater extent than Trolox suggesting its best neuro protective effect [10]. However, **363** shows poor solubility, low GI absorption, no BBB penetration, Pgp substrate, inhibitor of CYP2C19, CYP2C9, CYP2D6, CYP3A4, carcinogenicity in rat/mouse model and have violations in all the rules. The reference drug galantamine and the docked lead compounds **175** and **301** revealed interaction in common with the amino acid residue Thr120.

Docking against GlcN-6-P

In order to know the antimicrobial activity of the chosen flavonoid hybrids the molecular docking was performed with the Glucosamine-6-phosphate synthase (Glms) target (Table S3). 21 compounds show BE -12 to -13 kcal/mol indicating their admirable antimicrobial capability. Gentamicin **D4**, ciprofloxacin **D5** and fluconazole **D6** were chosen as reference and docked with GlcN6P synthase enzyme (Figure S2).

Chalcone hybrids

A series of **1-12** and **13-22** displays BE -10 to -12 kcal/mol. **8** with R=2-NO_2 -phenyl revealed a better docking score of -12.61 kcal/mol at the target protein site. Among them **13**, with Cl-ph group linked to pyrazole and triazole nucleus, which experimentally exhibit the highest antibacterial activity with reference to gentamicin and antifungal activity with reference to fluconazole [11] display admirable BE -10.9 kcal/mol in our study. **16**, with *p*-Cl-ph on pyrazole ring and *m*-CF_3-ph on the benzene ring that experimentally exhibit strong antibacterial and antifungal activities [11] show BE -11.08 kcal/mol signifying the role of electro withdrawing group for the antimicrobial activity, yet acts as non-inhibitors of CYPs, conform Veber, both **13** and **16** shows poor solubility, low GI absorption, carcinogenicity in both rat/mouse models. A docking score of -12.62 kcal/mol is expressed by **18** (R_1=CH_3; R_2=2-Cl-phenyl) forming H-bond interactions with Ser303, Thr352, Ser349, Ser604, Gln348, Lys603, Val399, π-anion interactions with Asp354, Glu488, π-sulfur interaction with Cys300, π-σ interaction with Val605 and π-alkyl interactions with Ala353, Leu484, Cys300, Leu601. **23-38** that exhibit BE -8 to -11 kcal/mol, **32**, (R=4-Br-benzyl) which experimentally revealed the highest activity against *E. coli, B. subtils, A. niger*, then the ciprofloxacin and fluconazole, perform good BE -10.3 kcal/mol. Experimentally proven most potent antibacterial and antifungal **36** (R=4-OCH_3-ph),[12] possess BE -8.99 kcal/mol. The presence of substituents such as Me, NO_2, F and Br on the benzene ring linked to the triazole moiety increases the binding energy from -8 to -11 kcal/mol. The position of the substituents has only small effect on the binding energy. **32** and **36** show moderate solubility, high GI absorption, mostly non-inhibitors of CYPs, in specific **36** follow all the rules, still, shows carcinogenicity in mouse model. Hybrids **39-48**, that possess experimentally proven antibacterial and antifungal effect but seems to be less than *streptomycin* [13] exhibit BE -10 to -12 kcal/mol. These hybrids are mostly non-inhibitors of CYPs nevertheless show poor solubility, low GI absorption, overstep all the rules and carcinogenicity. **49-66** [14] that reveals BE -9 to -11 kcal/mol indicates that the substituent such as OMe, NO_2, F, Br and CF_3 plays an important role for antimicrobial activity. **67-78** manifest valuable BE -9 to -12 kcal/mol which is in support with the experimental evidence [15] of showing antibacterial and antifungal activity with reference to ampicillin and griseofulvin respectively, however, are inhibitors of some CYPs, show poor solubility, and carcinogenicity in both rat/mouse model. In this series the substituents-Cl/NO_2 phenyl present in the triazole ring increases the binding energy. **79-99** express docking score -9 to -11 kcal/mol, from the results it is known that the substituents Br, OMe, NO_2, F plays important role in altering the binding energy. derivatives with Br in both benzene rings of chalcone scaffold and 1,2,3-triazole moiety or in any one ring has the higher binding energy. The docking results are in par with the experimental study [14] and **90, 93, 97-99** shows moderate solubility, high GI and abide by the rules, however, some of the hybrids (**79-99**) exhibit carcinogenicity. **100-111** that exhibit antibacterial and antifungal activity [16] display attractive BE -9 to -13 kcal/mol. **103** and **107** with R=4-NO_2-phenyl presented the highest docking score -12.87 & -13.35 kcal/mol which is in favour of the experimental evidence [16] though it only inhibits CYP3A4, it shows poor solubility, low GI absorption, carcinogenicity in both rat/mouse model and flout all the rules except Veber. **103** is stabilized by H-bonding interactions with Thr302, Lys603, Gln348, Ser401, Ser604. Its quinoline moiety forms π-lone pair interactions with Thr352, Ala602 and π-alkyl interactions with Cys300, Leu601, Val399, Leu484. **107** form H-bonding with the Thr302, Lys603, Gln348, Ser604. Its quinoline moiety displays π-lone pair interactions with Thr352, Ala602, π-alkyl interactions with Cys300, Leu601, Val399, Leu484. Hybrids **112- 164** shows binding score -8 to -11 kcal/mol.

Flavonoid dimers hybrids

A set of flavonoid dimers linked by triazole ring **165-189** indicate exquisite docking score -9 to -13 kcal/mol. The dimer **172** was found to be the most potent inhibitor with a highest docking score of -13.42 kcal/mol and it forms H-bonds with Ser401, Ala602, Thr302, Ser303, Gly301. C ring of its flavonoid moiety shows π-σ and π-sulfur interactions with Leu484 & Cys300 respectively. Triazole moiety and C ring of the flavonoid moiety displays π-alkyl interaction with

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Leu601, Val605, Cys300 (Figure S2). Datosativanone **190** reveal excellent BE -12.15 kcal/mol.

Flavanone hybrids

191-209 with substituent such as F, Cl, Br, Me, CN, OMe, CF_3 and NO_2 display the BE -9 to -11 kcal/mol. The hybrid with NO_2 substituent **(209)** binds strongly with the target protein with the score of -11.03 kcal/mol. Four series of hesperetin derivatives **210-223; 224-228; 229-239 & 240-248** exhibit magnificent docking score of -9 to -11 kcal/mol. 1,2,3-triazole-linked bavachinin derivatives **249-259** exhibit wonderful BE -9 to -13 kcal/mol. **258** shows higher binding affinity with BE -13.32 kcal/mol and its acyl chain made hydrogen bond with Thr302, B chain of the flavanone moiety exhibit π-anion interaction with Glu488. It also displays π-alkyl interactions with Val605, Cys300, Lys487, Leu484, Leu601 (Figure S2). **260-278** that exhibit BE -9 to -11 kcal/mol, the hybrids with substituents such as Me, OMe, NO_2, F, Cl, Br & CF_3 benzyl display higher binding affinity towards the target protein.

Flavone hybrids

A set of flavone hybrids **279-311** exhibit BE -8 to -11 kcal/mol. The hybrid with R=4-OH-ph **306** exhibit -10 kcal/mol. **312-322** exhibit BE -9 to -10 kcal/mol, specifically higher binding affinity for **321** with R=2-OH. The binding energy increases as the substituents varies viz., R=2-OH, 4-CF_3 < 2-F < 2-Cl < 3-CF_3 < 4-F < 2-CN < 4-Me,2-CF_3 < 2-Br < OH. **323-325** that displayed antibacterial activity against *E. coli* with reference to chrysin and gentamycin [17] exhibit BE -9 to -10 kcal/mol. **323, 325** show moderate solubility, high GI absorption, no PAINS alert, non-inhibitor of some CYPs and observe all the rules, yet carcinogenicity in mouse model.

Flavonol, Iso flavone and Flavan hybrids

A series of 20 flavonol-linked 1,2,3-triazole conjugates **326-345** synthesised by Claisen-Schmidt condensation followed by Algare-Flynne-Oyamada displays BE -8 to -10 kcal/mol. The 5,6-diary-1,2,4-triazine-isoflavone hybrid **346** exhibit admirable docking score of -12.42 kcal/mol. A group of daidzein bridged bis [1,2,3]-triazole iso flavone hybrid **347-359** proclaim docking score -9 to -12 kcal/mol and 1,2,3-triazole linked flavan hybrids **360-364** display BE -7 to -9 kcal/mol.

Docking against mTOR

In order to know the anti-cancer activity of the chosen flavonoid hybrids the molecular docking was performed with the Mammalian target of rapamycin (mTOR) target (Table S4). 28 compounds reveal -12 to -14 kcal/mol indicating their admirable anti-cancer capability. Doxorubicin, mubritinib and fluorouracil are chosen as references (Figure S3).

Chalcone hybrids

A series of tetrazolo-quinoline-chalcones **1-12** that showed strong anti-tumour activity higher than the positive control doxorubicin [18] displays notable BE -8 to -13 kcal/mol, however, shows poor solubility and carcinogenicity in mouse model. **2** (R=4-Cl-ph) bind to the active pocket of BChE with the docking score of -13.59 Kcal/mol, its triazole moiety form H-bond with Ser2035, π-anion interaction with Glu2032, π-π T interactions with Trp2101, Phe2039, Phe2108 & Tyr2105 and π-alkyl interactions with Leu2031, Arg2036, Tyr2105, Arg2109. **3** (R=4-NO_2-ph) BE -12.79 kcal/mol, is greater than the reference doxorubicin and is stabilized by H-bond with Ser2035, π-anion interaction with Glu2032. Furthermore, its quinoline moiety forms π-π T interactions with Phe2039, Trp2101, Phe2108, π-alkyl interactions with Leu2031, Tyr2105, Arg2109, Phe2108, Arg2036. This finding is in good agreement with the experimental results [19]. **13-66** displays appreciable BE -8 to -13 kcal/mol. Among them **62** (R_1= NO_2, R_2=2-F-benzyl) binds effectively in to the active site of mTOR (BE -13.2 kcal/mol) establishing π-donor H-bond with Ser2035, π-π T interactions with Phe2108, Tyr2105 and π-alkyl interactions with Leu2031, Arg2109 (Figure S3). Compounds **67- 147** express docking score -7 to -12 kcal/mol. A group of 17 hybrids of indole chalcones with benzene sulfonamide through a 1,2,3-triazole linker **148-164** that showed moderate inhibition of the tumour associated isoforms [19] exhibit BE -8 to -11 kcal/mol, are Pgp non-substrates, non-inhibitors of CYP1A2, CYP2D6 shows moderate solubility and no PAINS alert, yet high risk in hERG, low GI absorption and carcinogenicity in mouse model.

Flavonoid dimers hybrids

A series of flavonoid dimers connected by triazole **165-185** that showed a significant modulatory impact on MRP1 than verapamil and low toxicity [20] are Pgp non-substrates and display a docking score of -8 to -11 kcal/mol with no PAINS alert, however show low solubility/GI absorption, carcinogenicity and defy all the rules. **186-189** that showed moderate antiproliferative activity [21] exhibit appreciable BE -10 to -12 kcal/mol, no PAINS alert but poor solubility, low GI absorption, carcinogenicity, breach all the rules though they are Pgp non-substrates and non-inhibitors of some CYPs. Datosativanone **190** reveal BE -7.83 kcal/mol.

Flavanone hybrids

Hesperetin hybrids linked by the 1,2,3-triazole ring **191-209** displayed moderate antiproliferative activity with bearable toxicity [22] exhibit BE -9 to -11 kcal/mol. It shows no PAINS alert, moderate to poor solubility, mostly high GI absorption carcinogenicity in mouse model and are Pgp subtrates/non-inhibitors of two CYPs. **191** obey all the rules yet have high risk in hERG parameter. **210-248** exhibit magnificent docking score of -8 to -11 kcal/mol. 1,2,3-triazole-linked bavachinin derivatives **249-259** that exhibited antiproliferative activity [23] exposes wonderful BE -9 to -11 kcal/mol, shows no PAINS alert, however have poor solubility and carcinogenicity. In the sequence of 22 flavanone triazolyl hybrids **260-278** that exhibit BE -9 to -12 kcal/mol.

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Flavone hybrids

Hybrids **279-292** that displayed antiproliferative activity compared to doxorubicin and paclitaxel [24] exhibit BE -8 to -11 kcal/mol fortunately have no PAINS alert, moderate solubility, high GI absorption, except **292** all other complies with the rules. **293-304** that showed antiproliferative activity [25] shows meritable BE -11 to -14 kcal/mol, no PAINS alert, Pgp non-substrates, yet, tragically exhibit poor solubility, low GI absorption and carcinogenicity. **301**, the experimentally proven as the most promising compound [25] display highest BE -14.04 kcal/mol and is Pgp non-substrate, non-inhibitor of CYPs except CYP3A4. It has no PAINS alert and no evidence of carcinogenicity. And also, it is noted that, the presence of electron withdrawing group on C-4 of the benzene ring allied to the unsubstituted R_1 of the flavones scaffold is associated with increase in the binding affinity and stabilized by forming π-donor hydrogen bonds with Glu2032, Ser2035, π-σ interaction with Gln85, π-π T interactions with Phe2039, Tyr2105, Phe2108 and π-alkyl interaction with Arg2036 (Figure S3). **295** unveil BE -12.76 kcal/mol, its imidazole and flavone moiety exhibit H-bonds with Arg2036, Gln85, Ser2035, Glu2032, it possesses π-σ interaction with Gln85, π-π T and π-alkyl interaction with Trp2101, Tyr2105, Phe2108. **305-311** that displayed antiproliferative activity [26] exhibits BE -8 to -10 kcal/mol, the hybrid with R=2-(2-hydroxymethyl)-phenyl **305** show BE -10.21 kcal/mol. These hybrids show moderate solubility, high GI absorption, no PAINS alert, conform all rules and except **307** all other does not show carcinogenicity in mouse model. The hybrids **312-325** exhibit BE -9 to -11 kcal/mol.

Flavonol, Iso flavone and Flavan hybrids

326-345 that exhibited cytotoxic activity against ovarian cancer cell lines [27] express BE -9 to -11 kcal/mol, however show poor solubility, low GI absorption, violates all rules except Veber, regardless of showing non-inhibiting capacity of CYP1A2, CYP2C19, CYP2D6, majority of them are found to be non-carcinogenic in mouse model and none show PAINS alert. The isoflavone hybrid **346** that showed strong anti-cancer activity higher than fluorouracil [28] exhibit admirable docking score of -10.79 kcal/mol, however show poor solubility, low GI absorption, violates all the rules, carcinogenicity, in spite of showing non-inhibiting capacity of majority of CYPs. **347-359** that are active against cancer cell lines [29] proclaim docking score -8 to -11 kcal/mol, nevertheless show poor solubility (except **356** & **359**), low GI absorption (except **356**), violates all the rules, all other show carcinogenicity (except **353, 354**) despite not showing PAINS alert. Five flavan hybrids **360-364** display BE -7 to -10 kcal/mol.

Docking against PGHS

In order to know the anti-inflammatory activity of the chosen flavonoid hybrids the molecular docking was performed with the Prostaglandin G\H Synthase (PGHS) target (Table S5). 6 compounds reveal -9 to -10 kcal/mol indicating their admirable anti-inflammatory capability. Indomethacin **D10**, sulindac **D11** and celecoxib **D12** were chosen as reference and docked with Prostaglandin G\H Synthase (Figure S4).

Chalcone hybrids

A series of **1-22** displays BE -6 to -9 kcal/mol. Among them **6** with good binding free energy of -9.14 kcal/mol forms Vanderwal's interaction with Glu443, Leu157, amide-π interaction with Arg442 and side chain of triazole moiety forms π-alkyl interactions with Pro148, Lys445, Arg442. **23-115** express docking score BE -6 to -8 kcal/mol. Chalcone hybrids with a triazole **116-127** that possess moderate to weak 15-lipoxigenase inhibitory activity [30] express binding score -6 to -8 kcal/mol, majority show moderate solubility, high GI absorption, adhere most of the rules and carcinogenicity. Two series of 1,2,3-triazole-linked chalcone hybrids bearing a phenyl **128-147** that endowed with higher inhibitory capacity against ovine COX-1 and human recombinant COX-2 [31] when compared to celecoxib and indomethacin exposes BE -6 to -7 kcal/mol. These hybrids despite showing moderate solubility, high GI absorption, stick to major rules, non-substrates of Pgp/non-inhibitors of majority of CYPs and exhibit carcinogenicity. A group of indole chalcones **148-164** illustrate BE -5 to -7 kcal/mol.

Flavonoid dimers hybrids

A set of flavonoid dimers **165-189** indicate exquisite docking score -6 to -10 kcal/mol. The dimer **184** reveal highest docking score -10.86 kcal/mol and forms H-bond with Leu157, π-anion interaction with Asp143 and π-alkyl interactions with Pro148 & Arg442 (Figure S4). Datosativanone **190** display good BE -7.87 kcal/mol.

Flavanone hybrids

Hesperetin hybrids **191-209** display noticeable BE -6 to -7 kcal/mol. **210-248** exhibit magnificent docking score of -6 to -8 kcal/mol. The compound **217** that exerted an anti-neuroinflammatory effect display BE -8.05 kcal/mol, moderate solubility, high GI absorption yet display carcinogenicity. **249-278** exhibit substantial BE -6 to -8 kcal/mol.

Flavone hybrids

279-304 exhibit meritable BE -5 to -10 kcal/mol. Among them **296**(R_1=CH_3, R_2=4-NO_2-benzyl) displays BE -10.27 kcal/mol and forms H-bonds with Arg442, Lys445, π-anion interaction with Glu443, π-σ interaction with Arg442 and π-alkyl interactions with Pro148, Lys445 (Figure S4). **301**(R_1=H, R_2=4-NO_2-benzyl) exhibit BE -9.39 kcal/mol and made H-bonds with Leu157, Glu443, π-σ interaction with Glu443, amide-π and π-alkyl interactions with Thr147, Arg442, Pro148, Lys445. **302**(R_1=H, R_2=4-F-benzyl) express BE -9.2 kcal/mol and forms H-bond Leu157, F interaction with Glu56 and π-alkyl interaction with Arg442. **305-325** shows BE -6 to -7 kcal/mol.

Flavonol, Iso flavone and Flavan hybrids

A series of Flavonol hybrids **326-345** reveal BE -6 to -8 kcal/mol, A group of daidzein bridged bis [1,2,3]-triazole iso

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flavone hybrid **346-359** proclaim docking score -5 to -8 kcal/mol, among them **346** exhibit admirable docking score of -8.41 kcal/mol and 1,2,3-triazole linked flavan hybrids **360-364** display BE -5 to -6 kcal/mol.

Docking against SARS-CoV-2 MPro

In order to know the anti-viral activity of the chosen flavonoid hybrids the molecular docking was performed with the (SARS-Cov-2 MPro) Covid target (Table S6). 24 compounds reveal -13 to -14 kcal/mol indicating their admirable anti-viral capability (Figure S5).

Chalcone hybrids

A series of **1- 48** displays excellent BE -8 to -13 kcal/mol. The hybrid **44** with R=4-F-phenyl had a docking score of -13.86 kcal/mol and forms H-bonds with His163, Arg188, His164, Cys145, Gln189, F interactions with Asp187, Thr190, π-cation interaction with His41, π-σ interaction with Asn142, π-sulfur interactions with Met49, His41, Cys145, π-π T interaction with His41 and π-alkyl interactions with Met165, Pro168, Leu141. **49-111** display attractive BE -9 to -14 kcal/mol. The hybrid **101** with R=3-Cl-phenyl with the binding free energy of -14.34 kcal/mol develop H-bonds with Glu166, Gly143, π-cation interaction with His41, π-sulfur interaction with Met165, Met49 and π-alkyl interactions with Pro168, Leu167, Leu27, Cys145 (Figure S5). **112-164** moiety show attractive BE -8 to -12 kcal/mol.

Flavonoid dimers hybrids

A set of flavonoid dimers linked by triazole **165-189** indicate exquisite docking score -10 to -13 kcal/mol. The dimer **183** shows the outstanding binding free energy of -13.98 kcal/mol and develop H-bonds with His163, Gly143, π-sulfur interactions with Cys145, Met165, π-alkyl interactions with Leu141, Met49 (Figure S5). Datosativanone **190** shows excellent BE -9.73 kcal/mol.

Flavanone hybrids

191-259 display the outstanding BE -9 to -13 kcal/mol. Flavanone triazolyl hybrids **260-278** that endowed with antiviral activity [32] exhibit outstanding BE -10 to -13 kcal/mol, solubility, high GI absorption, still demonstrate carcinogenicity.

Flavone hybrids

279-304 exhibit BE -9 to -13 kcal/mol. Flavone hybrids **296** (R_1=CH_3, R_2=4-NO_2-benzyl) with BE -13.86 kcal/mol establish H-bonds with Gly143, Cys145, π-donor H-bond with Glu166, π-cation interactions with His163, His41 and π-alkyl interactions with Met49, His41, Cys145. **301** (R_1=H, R_2=4-NO_2-benzyl) with BE -13.75 kcal/mol forms H-bonds with Glu166, Cys145, Gln189, Gly143, Ser144, Leu141. Benzene ring of the hybrid display π-cation interaction with His163, in addition to B ring of the flavone moiety shows π-sulfur interactions with His163, Met49. Furthermore, B & C ring of the flavone moiety and triazole moiety exhibit π-alkyl interactions with Met165, Cys145. **305-325** exhibit BE -9 to -12 kcal/mol. Among them **312-322** that possess ability to prevent infection by the respiratory syncytial virus comparable to the ribavirin [33] exhibit excellent BE -10 to -12 kcal/mol, moderate solubility, non-inhibitors of CYP1A2, CYP2C19 and stick to all the rules (except **317-319, 322**).

Flavonol, Iso flavone and Flavan hybrids

20 flavonol-linked 1,2,3-tiazole conjugates **326-345** displays BE -10 to -11 kcal/mol, Isoflavone hybrids **346- 359** exhibit admirable docking score of -9 to -13 kcal/mol and 1,2,3-triazole linked flavan hybrids **360-364** display BE -10 to -11 kcal/mol.

Drug-likeness

91% of the chalcone hybrids **1-164**, other flavonoid dimers **165-189**, flavanones **191-208, 210-226, 228-278,** Flavones **279-292, 294-295, 297-300, 302, 325**, Flavonols **326-345**, Isoflavones **347-349, 351** and flavans **360-364** hybrids shows TPSA value less than 140$Å^2$ indicating its good penetrating ability (Table S7 and Figure 1).

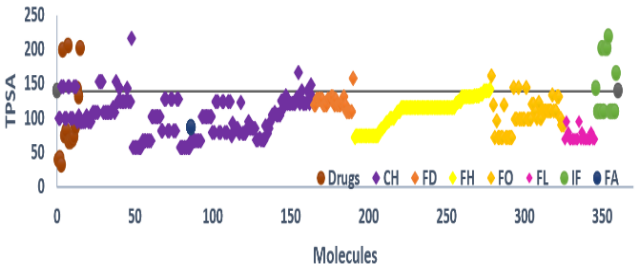

Figure 1: TPSA of the flavonoid hybrids (1-364) and the drugs (D1-D15)

Among 364 flavonoids, hesperetin hybrids **229, 238, 239, 245** and daidzein hybrid **359** display solubility, 167 flavonoids that includes hesperetin, baicalein hybrids, 1,2,3-triazole/indole-chalcone, -flavone hybrids show moderate solubility and 192 flavonoids comprising pyrazole/thiophene/1,2,3-triazole/morpholino-quinolinyl/quinoline chalcones, flavonoid dimers, bavachinin derivatives show poor solubility under Esol class. None of the flavonoids show insolubility under Esol class (Table S8). From the above discussion, it is evident that solubility presents a major challenge, despite the hybrids exhibiting high binding affinity with target proteins. While poor solubility leads to downsides such as low bioavailability, higher dosage requirements, and slow onset of action, it also provides benefits like sustained release, reduced toxicity, and enhanced stability. However, we suggest that the following methods could address solubility limitations, enhance pharmacokinetic profiles, and optimize the therapeutic potential of these hybrids (Table 1).

Majority of triazole-linked dehydro acetic acid chalcones, chalcone-based 1,4-disubstituted triazoles, hesperetins, 1,4-disubstituted triazole flavones, flavone derivatives of apigenin-7-methyl ether and chrysin derivatives exhibit high GI absorption (Table S9). Chalcone-based 1,4-disubstituted triazoles (**79, 86, 90-92**), 1,2,3-triazole-linked chalcone hybrids (**128-131**), flavanone triazolyl hybrids (**260-261**), flavone hybrids (**279-290**) show BBB penetration and it correlates well with its corresponding lower TPSA

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value. 123 hybrids are found to be P-gp substrates and 241 hybrids, including bavachinin, flavone/flavanone /flavan/flavonoid dimers-triazolyl, hesperetin, baicalein, pyrazole, thiophene, DHA, and quinoline-chalcone derivatives, are identified as non-substrates and are generally more advantageous for CNS-targeted and anticancer therapies due to improved bioavailability and reduced resistance (Boiled Egg Model- Figure S6).

Table 1: Suggestive methods for solubility enhancement strategy

Target Protein	Application of Solubility Enhancement Strategy
GlcN-6-P (Antimicrobial)	Nanocrystals, salt formation
mTOR (Anticancer)	Amorphous dispersions, lipid nanoparticle
BChE (Anti-Alzheimer's)	Cyclodextrins, micellar solubilization
SARS-CoV-2 MPro (Antiviral)	Nanoparticles, PEGylation, prodrug approach
PGHS (Anti-inflammatory)	Liposomes, co-crystallization

Human intestinal absorption (HIA %), 70-100 is observed for all the flavonoids and 12 drugs signifying its good characteristics for oral therapy. 345 flavonoids and 13 drugs show medium permeability (Caco-2: 4-70 nm/s). 19 flavonoids, **D11** & **D12** exhibit low permeability (Caco-2<4 nm/s). 91% flavonoids, **D8** & **D12** bound strongly with plasma protein (PPB). The non-inhibiting capacity of flavonoids with CYPs are presented in Table S9 and Figure 2.

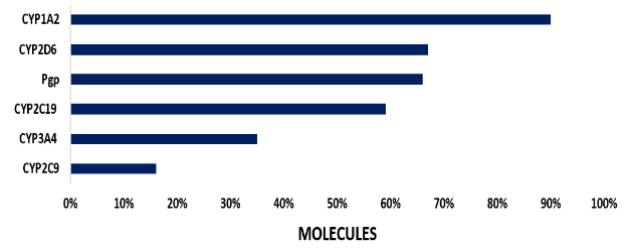

Figure 2: Non inhibiting capacity of the Flavonoid hybrids (1-364) against CYPs

The skin permeability parameter (Log Kp) for flavonoid hybrids **(1-364)** ranges from -4 to -12 cm/s which is similar to the drugs **(D1-D15)** -5 to -12 cm/s (Table S9). The percentage of compounds that obey various rules/criteria are depicted in Figure 3.

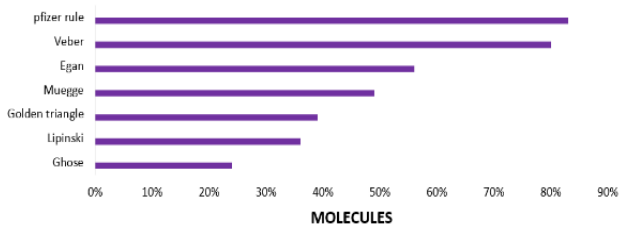

Figure 3: Drug likeness of Flavonoid hybrids 1-364

77% of flavonoids exhibit bioavailability score 0.55. 96% of flavonoids does not divulge PAINS alert. Regarding hERG parameter, 320 flavonoid hybrids:11 drugs unveil low-medium risk. Synthetic accessibility of all the flavonoid hybrids and the drugs considered for study ranges from 1 to 6 (Table S10) indicating that they are easy to synthesize and it is evident from the literatures. The examination of the drug likeness scores utilized from MolSoft indicates that the majority of the flavonoid hybrids belong to the class of drugs (Figure S7). From the preceding analysis, it is evident that flavone hybrids **279-292** and **305-311** exhibit strong binding energy and promising drug-likeness, making them potential multitargeted drug templates for future research. These top leads are stabilized by various interactions such as H-bonds, π-σ, π-sulfur, π-lone pair, alkyl, π-alkyl and amide-π stacked interactions Figure 4.

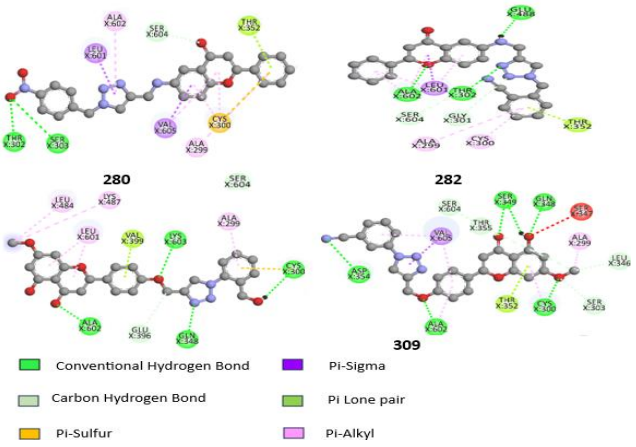

Figure 4: 2D interactions of flavone Triazole hybrids

CONCLUSION

Molecular modelling studies indicate that all screened hybrids exhibit strong binding affinity, often surpassing reference drugs in their interaction with target proteins. This discovery paves the way for novel therapies incorporating flavonoid-triazole hybrids in diverse configurations, as these enhance binding affinity. Notably OMe, F, Cl, Br, CN, NO_2 and CF_3 substituents strengthen interactions with key amino acid residues in the active site through hydrogen bonding, hydrophobic forces, and electrostatic interactions. Preliminary ADME studies provide valuable insights into drug-likeness but also highlight the moderate to poor solubility of certain hybrids as a limitation. This correlation suggests that while these compounds exhibit promising bioactivity, their pharmacokinetic and safety profiles may require further optimization for drug development. Flavone apigenin-7-methyl ether hybrids exhibit exceptional binding affinity and favourable drug-likeness properties, making them promising multi-targeted drug templates for further investigation.

Supplementary File

Detailed results, including Supplementary Tables and Figures are provided in the Supplementary Information available via Google Drive at https://shorturl.at/BbLYP.

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