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ARTICLE

# Efficient Green Synthesis, Molecular Modeling and Antimicrobial Investigations of Novel Chloroflavone Libraries

Santosh S. Chobe[1,✉], Nilesh J. Mali[2], Charushila K. Nerkar[1], Savita S. Chobe[1], Arvind M. Patil[3] and Trupti Tated[4]

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## ABSTRACT

In this article, a sequence of novel substituted 3-chloroflavones derivatives has been synthesized by using the inexperienced efficiency of solvent polyethylene glycol-400. This novelty of prepared derivatives was examined for their antifungal and their *in silco* docking study. Polyethylene glycol-400 is known as a green solvent to get to the bottom of the ecosystem's toxic solvent load. A collection of novel substituted 3-chloroflavones derivatives has been synthesized by using the inexperienced functionality of polyethylene glycol-400 solvent. These newly prepared formulations had been evaluated for their antifungal and their *in silico* docking study. The structures of all the synthesized compounds were characterized with FT-IR, $^1$H NMR and HRMS techniques.

## KEYWORDS

3-Chloroflavones, PEG-400, Biological activities.

## INTRODUCTION

Design, synthesis and growth of essential molecules as human therapeutics are some of the main goals for medicinal and organic chemistry. In last decade, combined chemical libraries focused on privileged systems have gained access to Horton *et al.* [1] with particular attention paid to heterocyclic structures. They are part of a class of substances with demonstrated effectiveness in medicinal chemistry [2]. Flavonoids are a popular product range found in plants' kingdom nearly exclusively. Several of them are colourful and thus play a crucial role in plant ecology. A fundamental cornerstone for the synthesis of bioactive compounds is also the flavone structure [3] (Fig. 1). Many natural and synthetic flavonoids have significant bioactivity [4-6].

There has been considerable research to improve the design of the flavones [7,8] and increase their bioactivity. Haloflavones are the useful intermediates among these changes in the synthesis of C3 replace flavones and C38-linked bioflavonoids. The biological activities *viz*. antimicrobial, antihypertensive [9] and antimalarial [10] is an integral part of flavone. Up to now, over 4000 different varieties have been reported in the literature [11]. Flavones and flavones have an anti-proliferative effect on MCF-7 cells for human breast

***Author affiliations:***

[1]Organic Research Laboratory, L.V.H. College, Panchvati, Nashik-422003, India
[2]Department of Chemistry, M.G.V's M.S.G. College, Malegaon Camp, Malegaon-423203, India
[3]Department of Chemistry, S.N.J.B. Arts, Science and Commerce College, Chandwad-423101, India
[4]Sinhgad Institute of Pharmacy, Narhe, Pune-411041, India

✉To whom correspondence to be addressed:

E-mail: chobesantoshs@gmail.com

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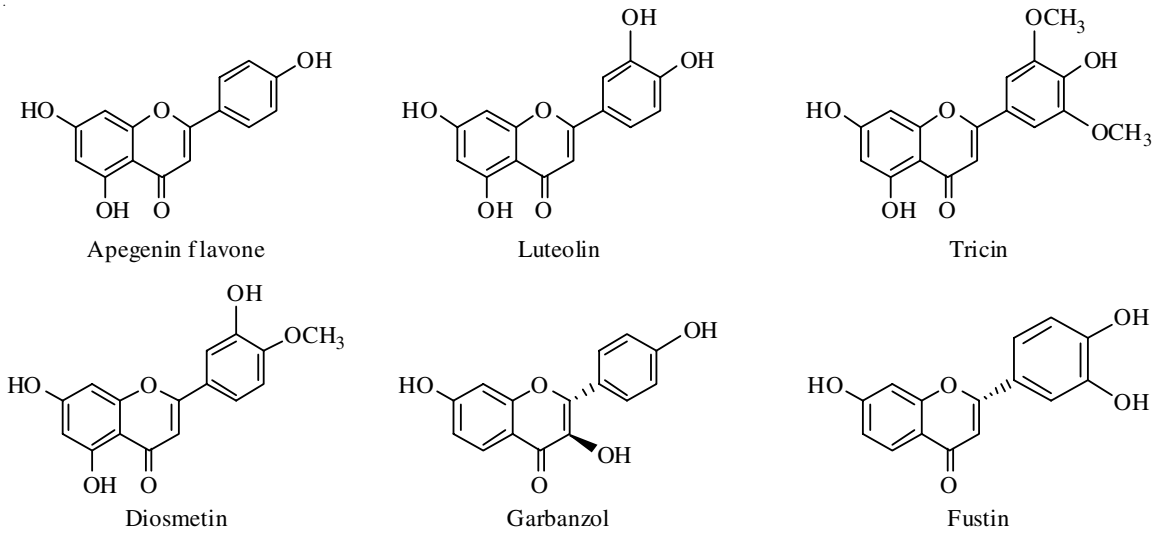



Fig. 1. Structures of some drugs containing flavone moiety

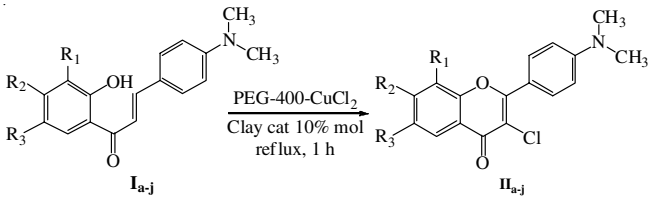
cancer. The most potent ant proliferative active agents are 5-methoxy flavones and 7,8-dihydroxy flavones [12].

The use and alteration of the traditional techniques are a requisite for the current context because of the ever-greater need to use greener methods. Poly(ethylene glycol) (PEG) can be a better choice of solvent because of its efficient benefits as a green reaction route. Several green chemistry strategies have been implemented since green chemistry so that a wide range of compounds can be synthesized without ecological risks [13-20]. It is well-known that PEG solvents are easily accessible, cheap, reusable, thermally stable, biocompatible and non-lethal [21]. With this objective and keeping with it, a novel alternatives for significant bioactive haloflavone derivatives with the design of safe, simplistic and eco-sustainable protocols for the synthesis of pharmacologically active 3-chloroflavone derivatives is reported.

## EXPERIMENTAL

Thin-film chromatography (TLC) of the aluminium foil (silica-gel 60 $F_{254}$ 0.25 mm) was monitored on a pre-linear aluminium foil plate observed in iodine vapour. The melting points were determined on the Kofler micro-melting plate and are uncorrected. The $^1H$ & $^{13}C$ NMR spectra were recorded in DMSO-$d_6$ at 25 ºC using Bruker 300MHz spectrophotometer. The mass analysis was conducted on MS-JEOL SX102 Mass spectroscopy by using Argon/Xenon (6Kv, 10mA) as the FAB gas and and mass values are recorded as *m/z*.

**General procedures for the synthesis of chloroflavone derivatives:** A solution of 1-(5-chloro-2-hydroxy-4-methyl-phenyl)-3-(4′-(dimethylaminophenyl)prop-2-en-1-one (**2i**) (0.315 g, 0.001 mol) was dissolved as an electrocatalyst in PEG-400. To this reaction mixture, excess of $CuCl_2$ (10% mol) was added and heated for 1 h under moderate reflux. The response has been tested *via* TLC; after completion, the reaction has been extracted from diethyl ether (2 × 20 mL) (TLC). The combined organic solvents have been soaked over anhydrous $Na_2SO_4$, beneath lower pressure until the solvent disappear. The solid substance precipitated with the ethanol to provide for 3,6-dichloro-2-(4′-(dimethylphenyl)-7-methyl-4*H*-chromen-4-one was washed with cold water, dried and recrystallized. Similarly, the same process has followed for all of the derivatives as shown in **Scheme-I**.




**Scheme-I:** Synthesis of substituted 3-chloroflavone

**3-Chloro-2-(4-(dimethylamino)phenyl)-6,8-diiodo-4*H*-chromen-4-one ($II_a$):** White crystals, m.p.: 167-169 ºC; Elemental analysis calcd. (found) % for $C_{17}H_{12}NO_2ClI_2$: C, 37.02 (37.00); H, 2.19 (2.15); N, 2.54 (2.51); O, 5.80 (5.78); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3024 (C–H), 1624 (C=O), 1412 (C=C), 721(C-Cl); $^1H$ NMR ($CDCl_3$, 300 MHz, δ ppm): 3.1 (s, 6H, $(CH_3)_2$), 6.8-7.8 (m, 6H, Ar-H); MS (*m/z*): 350 (M+1), 322, 278, 230, 151, 114, 77, 65, 56.

**3-Chloro-2-(4-(dimethylamino)phenyl)-8-iodo-6-methyl-4*H*-chromen-4-one ($II_b$):** Pale yellow crystals, m.p.: 155-157 ºC; Elemental analysis calcd. (found) % for $C_{18}H_{15}NO_2ClI$: C,49.17 (49.14); H, 3.44 (3.43); N, 3.19 (3.20); O, 7.28 (7.26); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3115(C–H), 1626 (C=O), 1422 (C=C), 730 (C-Cl); $^1H$ NMR ($CDCl_3$, 300 MHz, δ ppm): 2.26 (s, 3H, $CH_3$), 3.0 (s, 6H, $(CH_3)_2$), 6.7-7.8 (m, 6H, Ar-H); MS (*m/z*): 338 (M+1), 318, 270, 235, 148,116, 77, 66, 56,41.

**3,6,8-Trichloro-2-(4-(dimethylamino)phenyl)-4*H*-chromen-4-one ($II_c$):** Yellow crystals, m.p.: 146-148 ºC; Elemental analysis calcd. (found) % for $C_{17}H_{12}NO_2Cl_3$: C, 55.39 (55.36); H, 3.28 (3.76); N, 3.79 (3.78); O, 8.68 (8.65); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3124 (C–H), 1628 (C=O), 1421(C=C), 732(C-Cl); $^1H$ NMR ($CDCl_3$, 300 MHz, δ ppm): 3.21(s, 6H, $(CH_3)_2$), 6.7-7.82 (m, 6H, Ar-H); MS (*m/z*): 366 (M+1), 322, 276, 236, 152, 115,78, 66, 41.

**3,6-Dichloro-2-(4-(dimethylamino)phenyl)-8-iodo-4*H*-chromen-4-one ($II_d$):** Cremy white crystals, m.p.: 152-154 ºC; Elemental analysis calcd. (found) % for $C_{17}H_{12}NO_2Cl_2$: C,

44.38 (44.35); H, 2.63 (2.62); N, 3.04 (3.02); O, 6.95 (6.92); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3132 (C–H), 1626 (C=O), 1418 (C=C), 736 (C-Cl); $^1$H NMR ($CDCl_3$, 300 MHz, δ ppm): 3.2 (s, 6H, $(CH_3)_2$), 6.7-7.8 (m, 6H, Ar-H); MS (*m/z*): 358 (M+1), 326, 278, 242, 150, 119, 78, 65.

**8-Bromo-3-chloro-2-(4-(dimethylamino)phenyl)-6-methyl-4*H*-chromen-4-one ($II_e$):** Brown crystals, m.p.: 168-170 ºC; Elemental analysis calcd. (found) % for $C_{18}H_{15}NO_2BrCl$: C, 55.06 (55.04); H, 3.85 (3.80); N, 3.57 (3.55); O, 8.15 (8.14); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3133 (C–H), 1628 (C=O), 1424 (C=C), 740 (C-Cl); $^1$H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.3 (s, 3H, $CH_3$), 3.28(s, 6H, $(CH_3)_2$), 6.7-7.9 (m, 6H, Ar-H); MS (*m/z*): 391 (M+1), 346, 326, 279, 242, 165, 118, 78.

**8-Bromo-3,6-dichloro-2-(4-(dimethylamino)phenyl)-4*H*-chromen-4-one ($II_f$):** Light brown crystals, m.p.: 166-168 ºC; Elemental analysis calcd. (found) % for $C_{17}H_{12}NO_2BrCl_2$: C,49.43 (49.40); H, 2.93 (2.90); N, 3.39 (3.35); O, 7.75 (7.74); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3120 (C–H), 1622 (C=O), 1422(C=C), 724(C-Cl); $^1$H NMR ($CDCl_3$, 300 MHz, δ ppm): 3.26 (s, 6H, $(CH_3)_2$), 6.76-7.85 (m, 6H, Ar-H); MS (*m/z*):410 (M+1), 348, 324, 272, 222, 158, 76.

**6,8-Dibromo-3-chloro-2-(4-(dimethylamino)phenyl)-4*H*-chromen-4-one ($II_g$):** Brown crystals, m.p.: 162-164 ºC; Elemental analysis calc. for $C_{17}H_{12}NO_2Br_2Cl$: C,44.63 (44.60); H, 2.63 (2.62); N, 3.06 (3.05); O, 6.99 (6.99); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3124 (C–H), 1626 (C=O), 1432 (C=C), 712 (C-Cl); $^1$H NMR ($CDCl_3$, 300 MHz, δ ppm): 3.26 (s, 6H, $(CH_3)_2$), 6.8-7.8 (m, 6H, Ar-H); MS (*m/z*): 456 (M+1), 352, 318, 270, 212, 146, 76, 41.

**6-Bromo-3-chloro-2-(4-(dimethylamino)phenyl)-8-iodo-4*H*-chromen-4-one ($II_h$):** Light brown crystals, m.p.: 157-159 ºC; Elemental analysis calcd. (found) % for $C_{17}H_{12}NO_2BrClI$: C, 40.47 (40.42); H, 2.40 (2.38); N, 2.78 (2.75); O, 6.34 (6.32); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3135 (C–H), 1624 (C=O), 1430 (C=C), 716 (C-Cl); $^1$H NMR ($CDCl_3$, 300 MHz, δ ppm): 3.28 (s, 6H, $(CH_3)_2$), 6.7-7.8 (m, 6H, Ar-H); MS (*m/z*): 502 (M+1), 360, 324, 258, 213,146,77.

**3,6-Dichloro-2-(4-(dimethylamino)phenyl)-7-methyl-4*H*-chromen-4-one ($II_i$):** Yellow crystals, m.p.: 151-152 ºC; Elemental analysis calcd. (found) % for $C_{18}H_{15}NO_2Cl_2$: C, 62.09 (62.08); H, 4.34 (4.32); N, 4.02 (3.99); O, 9.19 (9.17); IR (KBr, $\nu_{max}$, $cm^{-1}$): 2929 (C–H), 1612 (C=O), 1410 (C=C), 717(C-Cl); $^1$H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.2 (s, 3H, $CH_3$), 3.0 (s, 6H, $(CH_3)_2$), 6.7-7.8 (m, 6H, Ar-H); MS (*m/z*): 347 (M+1), 319, 304, 281, 228, 151, 128, 114, 89, 77, 65, 51, 41.

**6-Bromo-3-chloro-2-(4-(dimethylamino)phenyl)-4*H*-chromen-4-one ($II_j$):** Cremy white crystals, m.p.: 158-160 ºC; Elemental analysis calcd. (found) % for $C_{17}H_{13}NO_2BrCl$: C, 53.92 (53.90); H, 3.46 (3.43); N, 3.70 (3.68); O, 8.45 (8.44); IR (KBr, $\nu_{max}$, $cm^{-1}$): 3032 (C–H), 1618 (C=O), 1412 (C=C), 712(C-Cl); $^1$H NMR ($CDCl_3$, 300 MHz, δ ppm): 3.2 (s, 6H, $(CH_3)_2$), 6.7-7.86 (m, 6H, Ar-H); MS (*m/z*): 376 (M+1), 322, 310, 278, 230, 157, 114, 89, 77, 51, 41.

**Antimicrobial activity:** Compounds have been screened for antimicrobial activity using the agar diffusion method [22,23]. The pathogens of bacteria and fungi were procured from The Institute of Microbial Technology in Chandigarh and the National Industrial Microorganism Collection (NCIM) in Pune, India, respectively. Antimicrobial effect *versus* certain human beings was investigated for molecules $\mathbf{II_{a-j}}$. The selected pathogens were *Bacillus subtilis* (MTCC 1789), *Klebsiella pneumoniae* (NCIM 2957), *Escherichia coli* (MTCC 1650), *Staphylococcus aureus* (MTCC 96), *Pseudomonas aeruginosa* (MTCC 2488) and fungi *Proteus vulgaris* (MTCC 1771), *Aspergillus flavus* (MTCC 2501), *Aspergillus niger* (MTCC 1781), *Trichoderma viridae* (MTCC 167), *Penicillium chrysogenum* (MTCC1996), *Candida albicans* (MTCC 227). In DMSO, stock solutions of compounds have been diluted to offer final levels of 50 to 1000 mg/mL. Reaction progress was supervised by thin-film chromatography (TLC) on a pre-lined Merck aluminium foil plate (silica gel 60 $F_{254}$, 0.25 mm thick) observed using iodine vapours. The melting factors for the Kofler micro-melting factor were measured and are incorrect. $^1$H NMR spectra were reported for the Bruker 300 MHz spectrophotometer. Both NMR spectra have been recorded; Muller Hinton Utilizing agar. This was filled with 0.1 mL of a suspension of related bacterial species are being cultivated in $10^5$ CFU/mL dilution sterile saline (0.85%). In each fungal and bacterial strain test, the wells of 6 mm in diameter were filled with 0.1 mL of each drug dilution separately. Only the DMSO has been used as a trigger. Antibiotic nystatin (30 mg/mL) and tetracycline (10 mg/mL) employed as an antifungal guide. This was packed with 0.1 mL of suspension of the related bacterial species were prepared in $10^5$ CFU/mL dilution sterile saline (0.85%). Antibiotic nystatin (30 mg/mL) and tetracycline (10 mg/mL) were employed as antifungal guide for fungal and bacterial development even after the time of incubation.

## Molecular docking study

**Ligand preparation:** In ChemDraw® 8.0 (Cambridge Soft, Cambridge, USA), 2D structures of all chloroflavon derivatives were drawn for 3D conformers in mol size of these compounds. For analysis of molecular docks, Maestro, version 9.0; Schrodinger was used. Import all molecules in Mestro Schrodinger 9.0 to minimize the energy of all ligand molecules by using OPLS force fields. Minimized structure of ligands were used for molecular docking.

**Protein preparation:** The 3D crystallographic structure for the Sterolcomplex with VT1161 (PDB ID 5Tz1) was obtained from Structural Bioinformatics Research Collaboratory (RCSB) (www.rcsb.org). Import downloaded protein (PDB ID 5Tzl) with Mestro Schrodinger to prepare protein for docking and it was performed with protein preparation wizard in Schrodinger.

**Molecular docking:** Molecular simulation trials have been conducted using Schrodinger, LLC, New York, NY, United States Maestro 9.0 software (Maestro, version 9.0; Schrodinger, LLC). In Maestro 9.0 software, the compound designs were developed and fixed up. The OPLS 2005 Force field of LigPrep Maestro9.0 Software was used to minimize the power of designs using the energy [24]. These reduced structures have also been used for molecular dynamics. The analysis of molecular docking was conducted out using Maestro 90's Glide Norm 5.5 option [25]. The sterol crystallographic 3D structure (PDB code 5Tz1) has been derived from RCSB and prepared for the docking of the Schrodinger Protein Preparation guide. False atomic repre-

sentations were corrected with a protein preparation guide. The final step is to improve the structure of the protein. Imperf minimization of 2005 OPLS (Optimized Potentials for Liquid Simulations) was used to generate a molecular dynamics force field with a fall off RMSD (Root Mean Square Deviation) of 0.3 Å.

## RESULTS AND DISCUSSION

A simple method was utilized to synthesize 3-chloroflavones using green solvent (PEG-400) (**Scheme-I**) resulted in the formation of derivatives of 3-chloroflavone. After the recrystallization, all the compounds were separated to an 80-85% yield. The spectral analysis explained the characteristics features of the synthesized compounds.

Reference substances dissolved in 1 % DMSO for measuring the bioactivity. In contrast, DMSO without a reference substances were used as a monitor, which brought about an inhibition zone against various microbial strains mentioned in Table-1. The data comprised of three sets. The findings showed that compounds **II$_c$**, **II$_g$**, **II$_f$** and **II$_h$** exhibited a good inhibition zone (9-28 mm) against all selected bacterial strains and therefore exhibited good antifungal activity. The remaining two compounds (**II$_d$** and **II$_e$**) were found to have mild activity, while compound **II$_a$** was found to have moderate activity. Out of six selected bacterial strains of *S. aureus*, *K. pneumoniae* and *B. subtilis* were more susceptible to compounds **II$_d$**, **II$_h$** and **II$_i$** as shown by the maximum inhibition zone MIC (50 mg/mL). Compounds **II$_e$**, **II$_j$** and **II$_i$**, were found to be less active in *Klebsiella pneumoniae*, while **II$_a$**, **II$_c$**, **II$_f$** and **II$_g$** were found to be inactive in *Bacillus subtilis* strains.

Intense activity against *E. coli*, *K. pneumonia*, *B. subtilis* was shown by compounds **II$_c$**, **II$_f$**, **II$_g$**, **II$_h$** and found comparable to tetracycline standard. Also, all tested compounds were found to have antifungal capabilities against pathogenic fungi *viz*. *A. niger*, *T. viridae*, *C. albicans*, *P. chrysogenum* and *A. flavus*. In comparison with nystatin, most compounds displayed active antifungal activity at MIC concentrations of 250 mg/mL. Compound **II$_c$**, **II$_f$**, **II$_g$**, **II$_h$** exhibited excellent activity against fungal strains in *A. niger*, *T. viridae* and *P. chrysogen* (12-28 mm).

**Docking studies:** The coupled crystal-structure of sterol with VT1161 was used to conduct docking studies by a sterol blocker sequence with PDB ID 5Tz1. Structural similarity to fluconazole is observed in VT1161. The docking studies with the G value (Table-2), few of the chloroflavone pharmacophore containing binding sites is reported. An orientation of co-crystallized ligand was studied and understood initially. It was observed that most of the designed derivatives showed the same binding orientation, except for compounds **II$_b$** and**II$_e$**, were found communicating with HIS 377 (bond distance with hydrogen 2.352 Å and 2.110 Å, respectively) (Fig. 2).

TABLE-2
G-SCORE OF DESIGNED
CHLOROFLAVONE DERIVATIVES **II$_a$-II$_j$**

| Compd. | $R_1$ | $R_2$ | $R_3$ | G-Score |
|---|---|---|---|---|
| **II$_a$** | I | H | I | -6.39808 |
| **II$_b$** | I | H | $CH_3$ | -7.60851 |
| **II$_c$** | Cl | H | Cl | -7.82083 |
| **II$_d$** | I | H | Cl | -7.57135 |
| **II$_e$** | Br | H | $CH_3$ | -7.89303 |
| **II$_f$** | Br | H | Cl | -3.10087 |
| **II$_g$** | Br | H | Br | -2.17807 |
| **II$_h$** | I | H | Br | -5.04346 |
| **II$_i$** | H | $CH_3$ | Cl | -6.9562 |
| **II$_j$** | H | H | Br | -5.47305 |
| Fluconazole | – | – | – | -7.19009 |

### Conclusion

To navigate novel chloroflavone derivatives using green PEG-400 medium, a cost-effective and highly viable protocol was established. This protocol has a remarkably high use of friendly and cost-effective solvents, extensive substrate coverage and straightforward activity. The synthesized compounds also displayed a promising the antimicrobial activity. Substitution of halo-group antibacterial and antifungal screening was shown to be of benefit.

TABLE-1
ANTIMICROBIAL ACTIVITY OF CHLOROFLAVONE DERIVATIVES (ZONE OF INHIBITION IN mm)

| Compd. | $R_1$ | $R_2$ | $R_3$ | Bacteria (MIC 50 mg/mL) | | | | | | Fungi (MIC 250 mg/mL) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EC | PA | PV | SA | KN | BS | AN | TV | PC | AF | CA |
| **II$_a$** | I | H | I | – | ± | – | 12 | 9 | – | 18 | 22 | 28 | 11 | 19 |
| **II$_b$** | I | H | $CH_3$ | – | ± | – | 10 | ± | 16 | ± | ± | – | 14 | 15 |
| **II$_c$** | Cl | H | Cl | 13 | ± | 9 | 16 | 9 | – | 26 | 22 | 28 | 11 | 16 |
| **II$_d$** | I | H | Cl | – | – | ± | 10 | 12 | 14 | 22 | 16 | ± | – | 10 |
| **II$_e$** | Br | H | $CH_3$ | ± | – | ± | 9 | ± | 15 | ± | – | 12 | – | ± |
| **II$_f$** | Br | H | Cl | 15 | 9 | – | 14 | 12 | – | 16 | 16 | 28 | 11 | 16 |
| **II$_g$** | Br | H | Br | 16 | 8 | 14 | 16 | 9 | – | 20 | 26 | 28 | 11 | 16 |
| **II$_h$** | I | H | Br | 18 | ± | – | 18 | 14 | 18 | – | 26 | 28 | 11 | 16 |
| **II$_i$** | H | $CH_3$ | Cl | ± | ± | ± | 14 | 13 | 15 | 22 | – | ± | 14 | ± |
| **II$_j$** | H | H | Br | ± | 9 | 10 | 10 | ± | 16 | 15 | ± | 24 | 18 | 14 |
| Tetracyclin | – | – | – | – | 32 | 20 | 25 | 17 | 20 | – | – | – | – | – |
| Nystatin | – | – | – | – | – | – | – | – | – | 14 | 18 | 17 | 14 | 17 |
| Control | – | – | – | – | – | ± | – | ± | ± | – | ± | ± | ± | – |

EC = *Escherichia coli* (MTCC 1650); PA = *Pseudomonas aeruginosa* (MTCC 2488); PV = *Proteus vulgaris* (MTCC 1771); SA = *Staphylococcus aureus* (MTCC 96); KN = *Klebsiella pneumoniae* (NCIM 2957); BS = *Bacillus subtilis* (MTCC 1789); AN = *Aspergillus niger* (MTCC 1781); TV = Trichodermaviridae (MTCC 167); PC = *Penicillium chrysogenum* (MTCC 1996); AF = *Aspergillus flavus* (MTCC 2501), CA = *Candida albicans* (MTCC 227); – = Not detected; ± = Trace activity

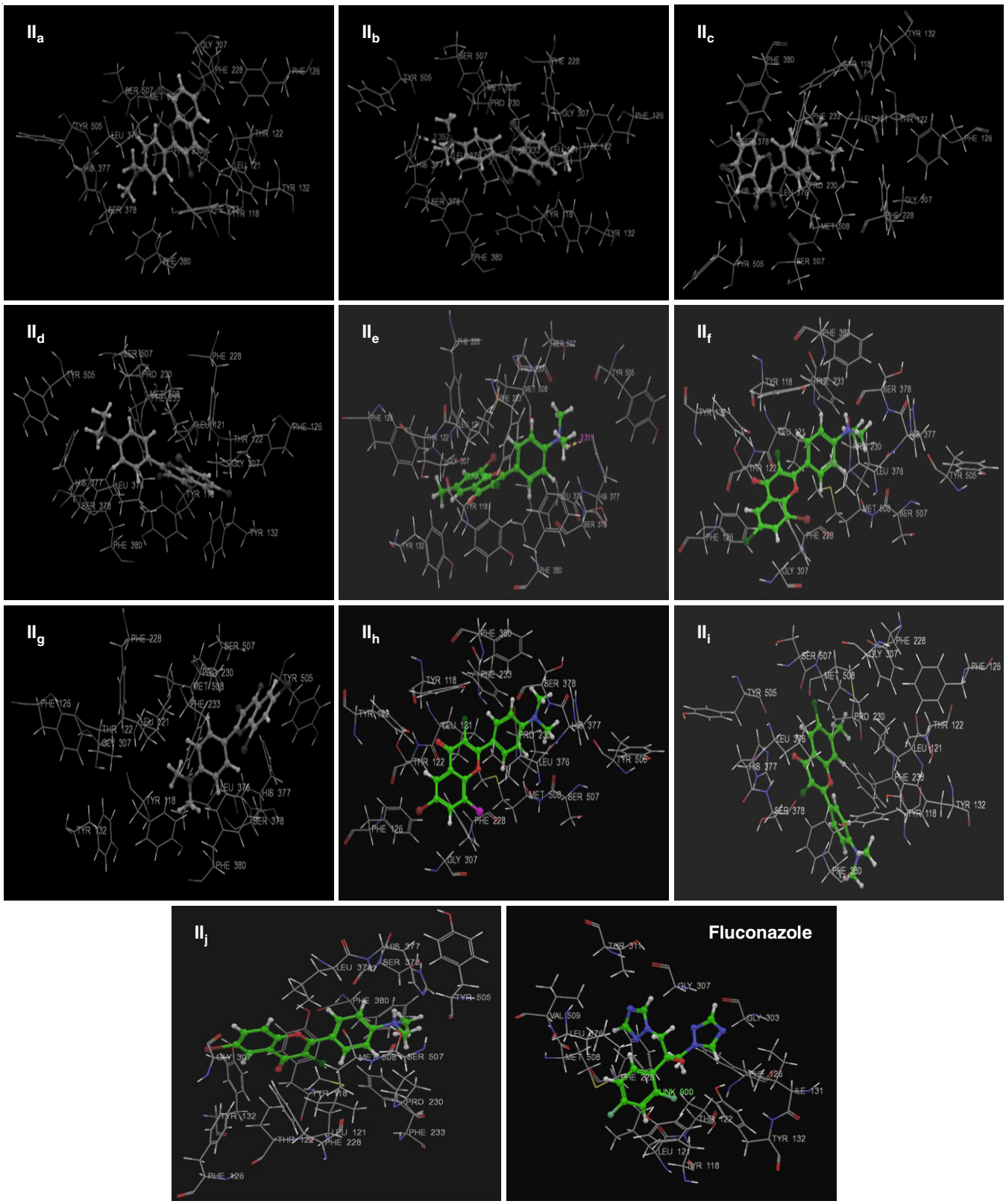



Fig. 2. Visual representation of synthesized compounds and standard drugs docked with VT1161, showing hydrogen bonding interactions with HIS377

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