Research Article

Synthesis, Antimicrobial Evaluation, and Docking Studies of Substituted New Chromone Linked 1,2,3-Triazoles

Amol S. Nipate, Chetan K. Jadhav, Asha V. Chate, Vidya S. Dofe, Prashant P. Dixit, Prachi Sharma & ...show all

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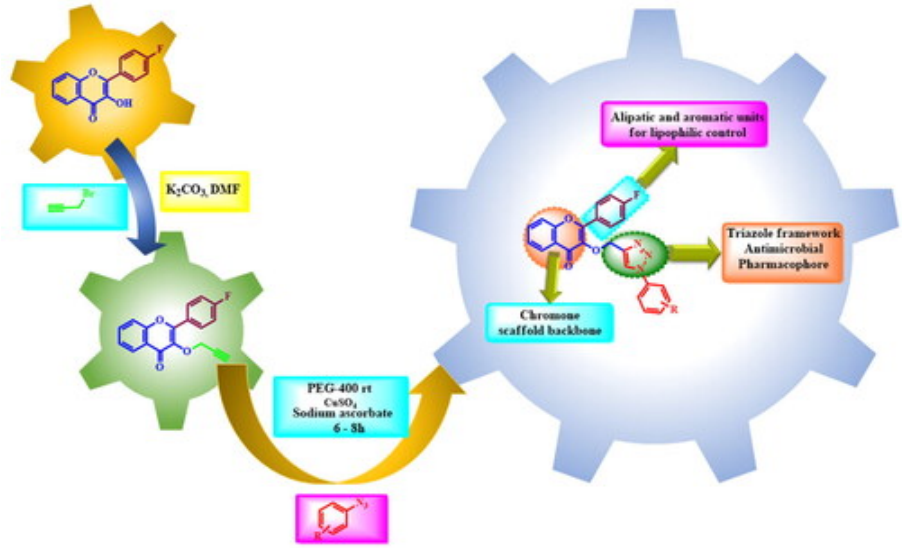
ABSTRACT:

In Search of new antibacterial, antifungal agents with improved potency, herein we report the synthesis of a series of new substituted 2-(4-fluorophenyl)-3-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one derivatives (**6a-q**), starting from acetophenone. All the synthesized compounds have been screened for *in vitro* antibacterial and antifungal activity by using the agar well diffusion method. Among fifteen synthesized compounds, four chromone derivatives i.e. (**6a-b), (6h**), and (**6i)** have shown proficient antimicrobial activities. Compound (**6a)** showed powerful inhibitory activity against all bacterial pathogens but it was not that effective against fungal pathogens on the other hand compound (**6b)** showed satisfactory

aureus was remarkable. Other compounds were found active against a few pathogens but activity was good. The compound (**6b)** was found very effective in inhibiting the growth of *S. aureus* ATCC 6538 at a low concentration with MIC 190 µg/ml.

Graphical abstract



Keywords: 123-Triazoles chromones antibacterial antifungal

Introduction

The continuous demand for biologically relevant heterocycles has been a source of inspiration and attracts the continuous attention of chemists and biologists all around the world.[1] Among various pharmaceutical drugs such as fludarabine,[2] panomifene,[3] flurocytosine,[4] diflunisal[5] contains fluorine and fluconazole,[6] voriconazole,[7] triozolam[8] etc (Figure 1) contains triazole. The introduction of fluorine into triazole-containing molecules may lead to improved pharmacological/physicochemical properties of compounds such as bioavailability solubility, manipulation of polarity, hydrogen bonding, and lipophilicity. Synthesizing new molecular assemblies with well-defined biological targets remains an extremely exigent task and requires refinements in conventional synthetic tactics.[9,10]

Figure 1. Structures of Bioactive heterocyclic compounds

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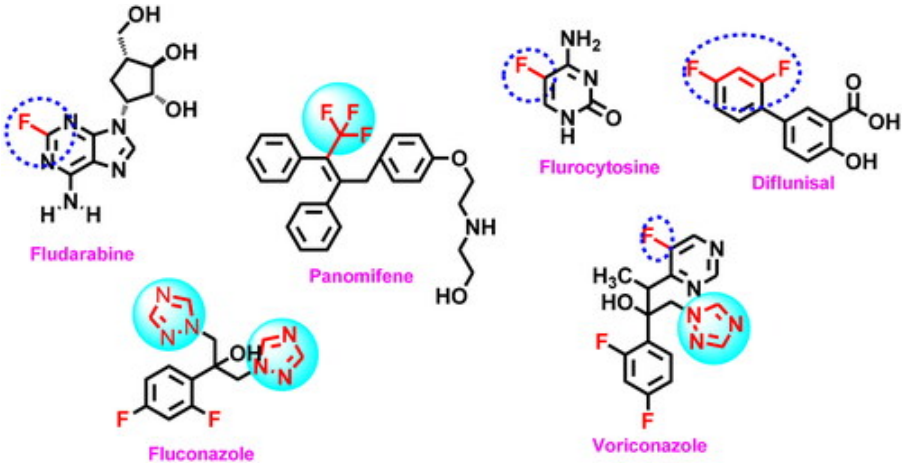

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In various drugs contains heterocycles are important molecules to design and discovery of drugs.

Chromone constitutes a naturally occurring oxygen-containing heteroatom with a benzoannelated γ-pyrone ring (4*H*-chromen-4-one, 4*H*-1-benzopyran-one) synthetic compound.[11] Chromones scaffolds and derivatives of chromones show the wide range of medicinal activities such as antimalarial, antimicrobial, antioxidant, anti-proliferation, antitumor, antiallergic, anti-inflammatory, antiplaque, and neuroprotection.[12–18]

The various synthetic routes were utilized for development of different class of heterocycles. Moreover, triazole based heterocycles have been commonly synthesized by most convenient and favorable synthetic route Click Chemistry. The term, “Click Chemistry” was introduced by Sharpless in 2001.[19] Click Reaction has become a synthetic/medicinal chemist’s favorite not only because of its ability to mimic different functional groups but also due to enhancement in the targeted biological activities and it also involves high-yielding reactions with wider scope, easily removable by-products, complete control of stereospecificity, and simplicity of the procedure. 1*H*-1,2,3-triazole, obtained by Click Reaction.[20] Triazole ring has also been shown to play a critical role in biomolecular mimetics, fragment-based drug design, and bio-orthogonal methodologies.[21] In addition, the availability of triazole containing various drug molecules such as Rufinamide,[22] Savolitinib,[23] Ticagrelor[24] and Tazobactam[25] (Figure 2) in the markets has underscored the potential of this biologically enriched core in expediting the development of new scaffolds. The most widely efficient route for the synthesis of 1,4 disubstituted 1,2,3 triazoles is copper/cu(I)- catalyzed Huisegn 1,3-dipolar (alkyne–azide) cycloaddition reaction [26]

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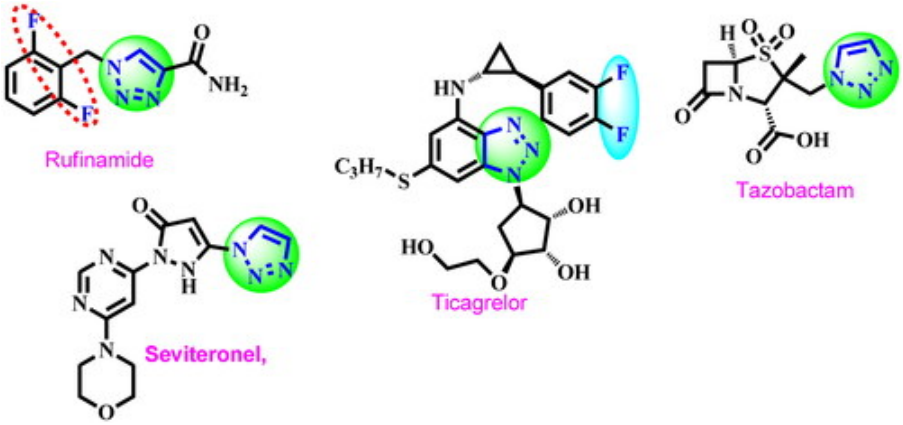
medicinal activities including anti-inflammatory, antimicrobial, anti-tuberculosis, antiplatelet, anticancer, and antiviral activity.[27–31]

Figure 2. Structures of 1,2,3-triazole-containing drugs.



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Owing to the significant features of nitrogen and oxygen containing heterocycles to modulate the physicochemical properties, we have synthesize chromone fused or linked with different heterocyclic derivatives in our earlier work.[31] Which have gained crucial importance over the last few decades in medical and chemical research.[32] Herein, we are reporting the synthesis of new chromone-based 1,2,3-triazole derivatives and their antimicrobial screening. Moreover, in addition to this, we have also performed molecular docking study and in silico ADME prediction for the synthesized compounds. Further, molecular docking study of the title compounds was carried out for the better understanding of the drug-receptor interaction and complements the results obtained from the antimicrobial screening. Here, we have described the syntheses of new substituted-2-(4-fluorophenyl)-3-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one using a chimeric approach.

2. Results and discussion

2.1. Chemistry

The desired compounds substituted 2-(4-fluorophenyl)-3-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (**6a-q**) were synthesized in four steps using various synthetic

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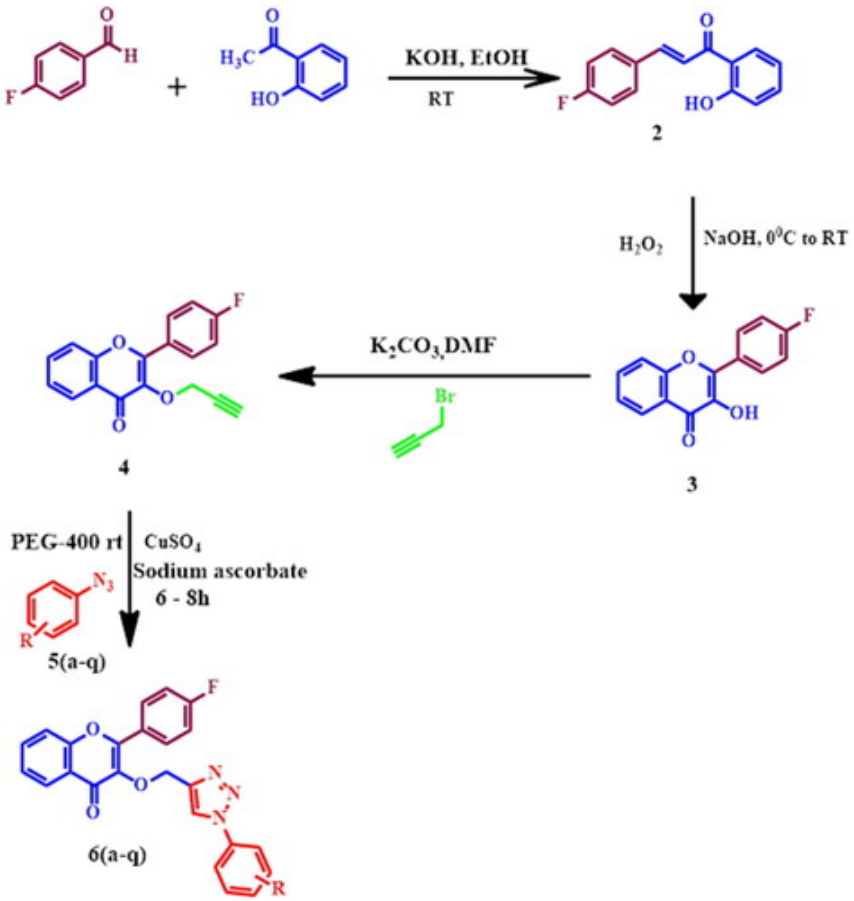
commercially available 2-hydroxyactopheone with 4-fluorobenzaldehyde in ethanol in presence of potassium hydroxide at room temperature for 2–4 h with 75% yield. Further, 4-fluro chalcone was treated with 30% hydrogen peroxide in ethanol in presence of 10% KOH. These reaction mixture was stirred vigorously for 30 min and kept for 2–3 h in ice cold conditions to yield 3-hydroxy chromone which was subsequently reacts with propargyl bromide (**2**) in *N,N*-dimethylformamide in the presence of potassium carbonate at room temperature for 4h to obtain a key chromone embedded intermediate i.e. 2-(4-fluorophenyl)-3-(prop-2-yn-1-oxy)-4*H*-chromen-4-one. Finally, the [1,2,3]-triazole core was incorporated through copper catalyzed 1,3 dipolar cycloaddition of 2-(4-fluorophenyl)-3-(prop-2-yn-1-oxy)-4*H*-chromen-4-one with freshly prepared substituted azide in the presence of a catalytic amount of $CuSO_4{\cdot}5H_2O$(1:1) and sodium ascorbate in PEG 400 and furnished the desired chromone linked 1,4 disubstituted 1,2,3-triazole compounds (**6a–q**), in good to excellent yields.

Scheme 1. General Scheme for synthesis of chromone linked 1,4-disubstituted 1,2,3-triazole derivatives (6a-q).



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All newly synthesized compounds were confirmed by using different spectroscopic technique such as IR, ^{1}H NMR, ^{13}C NMR, and Mass spectral data. In ^{1}H NMR spectra of compound (**6a**) (representative example) displays peaks signal corresponding to the CH_2 protons that bridge the chromone with triazole moiety was observed at δ 5.41 ppm and triazolyl-H was observed at δ 8.32 ppm as a singlet and a multiplet in the region δ 7.13 to 8.13 ppm due to the merged signals of 13 aromatic-H. In addition, the appearance of a sharp singlet for 1 proton observed at δ 8.22 ppm in the PMR, suggested the presence of 1,2,3 triazole C–H. The appearance of a sharp singlet (1H) observed at δ 8.13 ppm in the PMR, suggested the presence olefinic C–H. The presence of three characteristics of carbon signals, are observed at 21.09, 65.09, and 175.05 ppm in ^{13}C NMR spectrum of compound (**6a**). The signal of carbons at 175.05 ppm was due to the chromone carbonyl carbon, confirming the formation of a 1,2,3-triazole ring in(**6a**). The HRMS (ESI) for (**6a**) shows the m/z at 414.1176 for for $C_{24}H_{16}FN_3O_3$ $[M + H]^+$ and found 414.1234

3. Biological screening

3.1. Antimicrobial screening

Synthesized compounds were screened for *in vitro* antibacterial and antifungal activity by using agar well diffusion method of Pramod S. Phatak et al.[33] For assessing antibacterial activity both Gram positive and Gram negative bacterial pathogens were used. *Staphylococcus aureus* ATCC 6538*, Bacillus megaterium* ATCC 2326, *Bacillus subtilis* ATCC 6633 were Gram positive pathogens used in this study. *Escherichia coli* ATCC 8739*, Salmonella typhi* ATCC 9207*, Shigella boydii* ATCC 12034*, Enterobacter aerogenes* ATCC 13048*, Pseudomonas aerogenosa* ATCC 9027, *Salmonella abony* NCTC 6017 were the Gram negative pathogens used in this study. Antifungal activity of all synthesized compounds was detected against *Aspergillus niger* ATCC 16404*, Saccharomyces cereviseae* ATCC 9763, *Candida albicans* ATCC 10231 fungal pathogens. Fluconozol and ceftazidime were used as antifungal and antibacterial standard reference compounds respectively. Synthesized compounds were dissolved in DMSO at a concentration of 1 mg/ml. Each bacterium and fungi was inoculated into sterile Mueller Hinton medium and kept at 37^{0}C for 24 h for developing inoculums, and thereafter this broth was used for the study. Using sterile saline, the bacterial suspension was diluted to adjust the turbidity to the 0.5 McFarland standards. 200 µL diluted suspension of each pathogen was inoculated on sterile Mueller

each compound solution was put in a separate well. 100 µl of DMSO solution without any compound was also placed in a well to check its activity against the pathogenic culture. All Petri dishes were incubated for 24 h at 37^0C. A clear zone around the well was considered as positive results. After complete incubation, the antimicrobial activity of the synthesized compounds was measured. Zones were measured and recorded in millimeter (mm).

All compounds were tested for antibacterial and antifungal activity but out of fifteen synthesized compounds, four compounds i.e. (**6a-b)**, (**6h)** and (**6i)** showed proficient antimicrobial activities. Compound (**6h**) showed remarkable antibacterial activity. Compound (**6a)** showed powerful inhibitory activity against all bacterial pathogens but it was not that much effective against fungal pathogens on the other hand compound (**6b**) showed satisfactory activity against fungal pathogens as well. Activity of compound (**6h)** and (**6i)** against *S. aureus* was remarkable. Other compounds were found active against few pathogens but activity was good.

Minimal inhibitory concentration (MIC)

It is the lowest concentration of an antimicrobial (compounds) drug that will prevent the visible growth of a microorganism after overnight incubation. The MIC values show the effectiveness of a drug against a pathogen. The MIC values of potent antibacterial and antifungal compound against most sensitive pathogens were determined. The MIC values for the two most potent antimicrobial compounds (**6a-b**) were determined against *S.typhi*, *S.aureus*. For determining MIC values, methods and guidelines of Clinical and Laboratory Standard Institute (CLSI) were followed. The MIC values are shown in Table 2. The compound (**6b)** was found very effective in inhibiting the growth of *S.aureus* ATCC 6538 at low concentration with MIC 190 µg/ml.

Table 1. Synthesis of new chromone linked 1,4-disubstituted 1,2,3-triazole derivatives **(6a-q)**.

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Table 2. Antimicrobial screening data of synthesized compounds against

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Table 3. MIC values of most potent compounds.

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Molecular docking study:

Molecular docking studies were performed using Maestro 11.8.For our studies, X-ray crystal structure of S. aureus KAS III was taken from PDB entry 4XWA, and prepared for docking using a protein preparation wizard. Water molecules in the structure were removed. The bond orders and formal charges were added for hetero groups, and hydrogen was added to all atoms in the structure. Side chains that were not close to the binding cavity and do not participate in salt bridges were neutralized. After preparation, the structures were refined to optimize the hydrogen bond network using OPLS_2005 force field. This helps in reorientation of the side chain hydroxyl group. The minimization was terminated when the energy converged or the RMSD reached a maximum cut off of 0.30 A. Grids were then defined around refined structure by centering on ligand using default box size. The extra precision (XP) docking mode for compounds, optimized by Ligprep, was performed on the generated grid of protein structure.

Molecular docking analysis was utilized to predict the mechanism of action of the synthesized derivatives for antimicrobial potential. All the molecules exhibited binding energies in the range of −33.3 to −65.3 kcal/mol. Compound (**6a)** showed pi-cation interaction with ARG36, hydrophobic interaction with TYR100, GLN10 (Figure 3). Compound (**6b)** showed pi-pi stacking with TYR 100, hydrophobic interaction with LEU 52, VAL51, ARG 48 (Figure 4).

Figure 3. Interaction of compound (**6a**) within the S.Aureus KAS III (4XWA) active site. Binding pose of compound (**6a)** within the S.Aureus KAS III (4XWA) active site.

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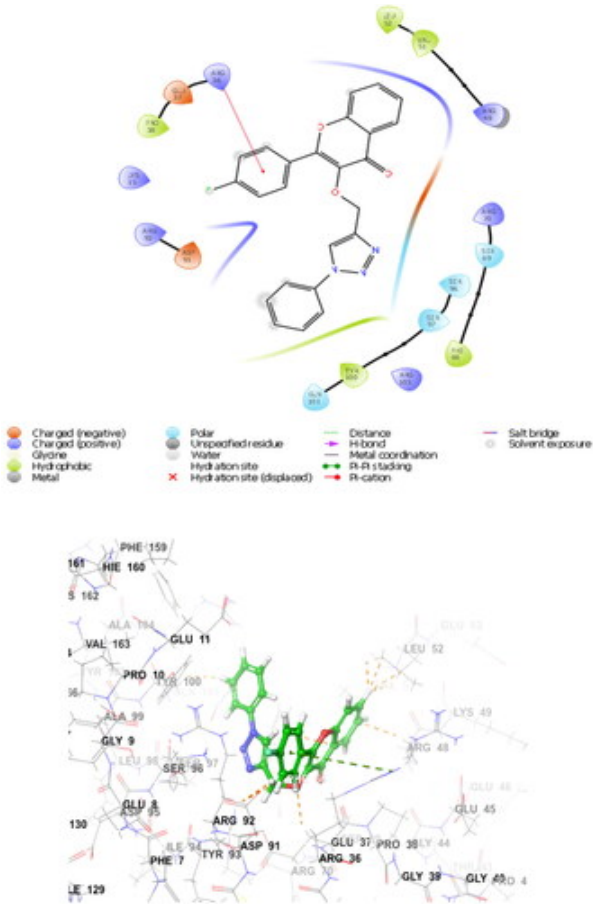

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Figure 4. Interaction of compound (**6b)** within the S.Aureus KAS III (4XWA) active site. Binding pose of compound (**6b)** within the S.Aureus KAS III (4XWA) active site.

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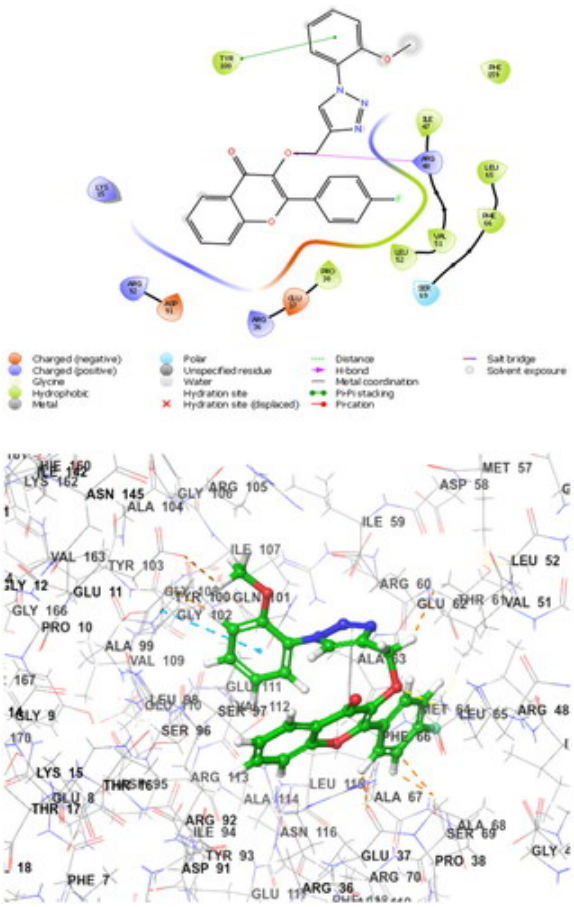

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4. Experimental section

4.1. Material & methods

All the reagents and solvents used for chemical synthesis were purchased from (Spectrochem, Sigma Aldrich, and Alfa Aesar) commercial chemical suppliers and used without further purification. Reaction were monitored by thin-layer chromatography (TLC) with Merck Silica Gel 60 F254 and the spots were visualized using ultraviolet (UV) light with an excitation wavelength of 254 nm. The melting points were determined in open glass capillaries and are uncorrected. The identity of the compounds were confirmed by ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ or DMSO-d_6 solvents by using Bruker Avance II 400 spectrometer. The chemical shifts value (δ) are expressed in ppm (ppm) relative to the standard TMS as an internal reference. The chemical shifts (d) are expressed in parts per million (ppm).

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and doublet of doublets (dd), and coupling constants (J) were given in Hz. The phenyl azides (1,2) were prepared according to the reported procedures in the literature. High resolution mass spectra.

4.1.1. General procedure for the synthesis of chalcone (2)

The (*E*)-3-(4-fluorophenyl)-1-(2-hydroxyphenyl)-prop-2-en-1-one was synthesized by addition of 2-Hydroxyacetophenones (1 mmol) and 4-fluorobenzaldehyde (1 mmol) to a solution of KOH (3 mmol) in ethanol (15 mL) at room temperature. The reaction mixture was stirred for 2–3 h. Then the reaction mixture was quenched with crushed ice and neutralized carefully with acetic acid, and the obtained solid precipitate was filtered, washed with water, and dried. The crude product was crystallized with chloroform-ethanol to afford desired compound.

The synthesized compounds was confirmed using melting point and is in good agreement with those reported in the literature.[34]

4.1.2. General procedure for the synthesis of chromone (3)

The mixture of (*E*)-3-(4-fluorophenyl)-1-(2-hydroxyphenyl)-prop-2-en-1-one (1 mmol), sodium hydroxide (3 mmol) and hydrogen peroxide (30%) was stirred vigorously (10 mL) for 30 min. Further, reaction mixture was kept for 2-3 h at ice cold condition. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into crushed ice and acidified with 1 M HCl, which yields solid product which then washed with water and crystallized from ethanol to afford pure product. The synthesized compounds was confirmed using melting point and is in good agreement with those reported in the literature.[34]

4.1.3. General procedure for the synthesis of compound chromone alkyne (4)

A mixture of substituted 2-(4-fluorophenyl)-3-hydroxy-4*H*-chromen-4-one (**2**) (1 mmol) and propargyl bromide (**3**) (1 mmol) was dissolved in 4-5 ml DMF and to this solution K_2CO_3 (2 mmol) was added. The reaction mixture was stirred at room temperature for 3-4 h. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured on crushed ice which yields the solid precipitated which then filtered, washed with water and crystallized from ethanol. The synthesized compounds were confirmed using melting point and is in good agreement with those reported in the literature.[34]

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Aniline (0.5 g, 5.4 mmol) was taken in a round bottom flask and placed it in ice bath. Then, conc. HCl was added to it till the precipitation. These precipitate was dissolved in ethanol and the reaction mixture was stirred for 1 -2 min. Further, a solution of $NaNO_2$ (3.87 mmol) in water (4.03 mL) was added dropwise over a period of 10 min with constant stirring. After stirring the reaction mixture was kept for 1 h at 0 °C. Then, a solution of NaN_3 (3.87 mmol) in water (4.03 mL) was added to reaction mixture and allowed to it stir at room temperature for 3 h. The progress of the reaction was monitored with TLC using ethyl acetate: hexane (1:9) as a solvent system. After completion of the reaction, the reaction mixture was poured into water and extracted it with ethyl acetate, dried over anhydrous sodium sulfate, and concentrated under vacuo to give azide, which was used further without purification.[35]

4.1.4. General procedure for synthesis of chromone linked 1,4 disubstituted 1,2,3-triazole derivatives (6a–q)

The title compounds were synthesized using mixture of 2-(4-fluorophenyl)-3-(prop-2-yn-1-oxy)-4*H*-chromen-4-one (**4a**) (1 mmol) and freshly prepared substituted phenyl azide (**5a-q**) (1 mmol) in presence of $CuSO_4.5H_2O$ (20 mol%) and sodium ascorbate (20 mol%) in PEG-400 solvent. The reaction mixture was stirred for 6h at room temperature. The progress of the reaction was monitored by TLC. After stirring for 6h, the reaction mass was poured on crushed ice. The obtained solid product as filtered, washed with water, and crystallized by using ethanol.

2-(4-fluorophenyl)-3-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (6a)

GREEN SOILD, M.P. 166 – 168 YIELD: 85%

IR (ATR μ max cm^{-1}) 1558.48 cm^{-1} (N=N), 1465.90 cm^{-1} (C=C), 2912.42 cm^{-1} C-H).

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) 8.32 (s, 1H, triazoyl-H), 8.12 (dd, *J* = 8.6, 5.4 Hz, 3H, Ar-H), 7.79 − 7.63 (m, 3H, Ar-H), 7.62 − 7.50 (m, 3H, Ar-H), 7.46 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.18 (t, *J* = 8.6 Hz, 2H, Ar-H), 5.41 (s, 2H OCH_2). **^{13}C NMR** (101 MHz, $CDCl_3$ δC ppm) 175.05 (s, C=O), 165.25 (s, C), 155.28 (s, C), 133.69 (s, C), 131.09 (s, CH), 129.75 (s, CH), 128.81 (s, CH), 125.80 (s, CH), 124.94 (s, CH), 120.54 (s, CH), 118.05 (s, CH), 115.54 (s, CH), 65.08 (S, CH_2).

HRMS (ESI)+ Calculated for $C_{24}H_{16}FN_3O_3$ [M + H] +: Calculated 413.1176 and found 414.1234

2-(4-fluorophenyl)-3-((1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one

GREEN SOILD, M.P. 158 – 160 YIELD: 82%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) 8.30 (s, 1H, triazoyl-H), 8.12 (dd, *J* = 20.4, 14.2 Hz, 3H, Ar-H), 7.71 (t, *J* = 8.5 Hz, 2H, Ar-H), 7.53 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.42 (dd, *J* = 15.3, 7.6 Hz, 2H, Ar-H), 7.11 (dt, *J* = 14.7, 8.1 Hz, 4H, Ar-H), 5.46 (s, 2H, OCH_2), 3.77 (s, *J* = 38.0 Hz, 3H, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$ δC ppm) 175.10 (s, C=O), 165.17 (s, C), 162.66 (s, C), 155.55 (s, C), 150.94 (s, C), 133.59 (s, C), 130.06 (s, CH), 127.21 (s, CH), 125.78 (s, CH), 124.83 (s, CH), 121.15 (s, CH), 118.01 (s, CH), 115.40 (s, CH), 112.19 (s, CH), 77.39 (s, CH), 64.91 (s, CH_2), 55.83 (s, OCH_3).

HRMS (ESI)$^{+}$ Calculated for $C_{25}H_{18}FN_3O_4[M^+]^{+}$: 443.1281 and found 444.1360

2-(4-fluorophenyl)-3-((1-(3-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (6c)

GREEN SOILD, M.P. 124 – 126 YIELD: 84%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) 8.31 (s, 1H, triazoyl-H), 8.18 − 8.07 (m, 3H, Ar-H), 7.73 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.64 − 7.34 (m, 2H, Ar-H), 7.25 − 7.09 (m, 4H, Ar-H), 6.99 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.40 (s, 2H, OCH_2), 3.85 (s, *J* = 42.8, Hz, 3H, OCH_3). **^{13}C NMR** (101 MHz, $CDCl_3$ δC ppm) 175.05 (s, C=O), 165.25 (s, C), 162.74 (s, C), 155.55 (s, C), 133.69 (s, C), 131.09 (d, CH), 130.50 (s, CH), 125.79 (s, CH), 124.94 (s, CH), 118.04 (s, CH), 115.76 (s, CH), 112.40 (s, CH), 106.25 (s, CH), 65.04 (s, CH_2), 55.63 (s, OCH_3).

HRMS (ESI)$^{+}$ Calculated for $C_{25}H_{18}FN_3O_4[M^+]^{+}$: 443.1281 and found 444.1360

2-(4-fluorophenyl)-3-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (6d)

YELLOW SOILD, M.P. 190 – 192 YIELD: 80%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) 8.30 (s, 1H, triazoyl-H), 8.11 (s, 2H, Ar-H), 7.72 (s, 1H, Ar-H), 7.61 − 7.37 (m, 4H, Ar-H), 7.23 (d, *J* = 45.2 Hz, 2H, Ar-H), 7.00 (d, 2H, Ar-H), 5.38 (s, 2H, OCH_2), 3.82 (s, 3H, OCH_3).

3-((1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-(4-fluorophenyl)-4*H*-chromen-4-one (6e)

YELLOW SOILD, M.P. 144 – 146 YIELD: 83%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm 8.28 (s, 1H, triazoyl-H), 8.15 (d, *J* = 5.8 Hz, 2H), 8.08 (s, 1H, Ar-

= 8.1 Hz, 2H, Ar-H), 5.48 (s, 2H, OCH_2).

3-((1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-(4-fluorophenyl)-4*H*-chromen-4-one (6f)

YELLOW SOILD, M.P. 134 – 136 YIELD: 77%

HRMS (ESI)$^+$ Calculated for $C_{24}H_{15}ClFN_3O_3[M + H]^+$: 447.0786 and found 448.0868

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm 8.31 (s, 1H, triazoyl-H), 8.12 (dd, *J* = 9.6 Hz, 3H, Ar-H), 7.78 − 7.70 (m, 2H, Ar-H), 7.58 (dd, *J* = 13.0 Hz, 2H, Ar-H), 7.52 − 7.40 (m, 3H, Ar-H), 7.29 (s, 1H, Ar-H), 7.23 − 7.12 (m, 2H, Ar-H), 5.41 (s, 2H, OCH_2).

3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-(4-fluorophenyl)-4*H*-chromen-4-one (6 g)

GREEN SOILD, M.P. 208 – 210 YIELD: 72%

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H, triazoyl-H), 8.13 (s, 3H, Ar-H), 7.73 (s, 1H, Ar-H), 7.65 (d, *J* = 6.3 Hz, 2H Ar-H), 7.52 (t, *J* = 21.4 Hz, 4H Ar-H), 7.19 (s, 2H, Ar-H), 5.39 (s, 2H, OCH_2).

3-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-(4-fluorophenyl)-4*H*-chromen-4-one (6h)

GREEN SOILD, M.P. 152 – 154 YIELD: 89%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) δ 8.30 (s, 1H, triazoyl-H), 8.12 (d, 3H, Ar-H), 7.89 (s, 1H, Ar-H), 7.71 (s, 1H, Ar-H), 7.58 − 7.49 (m, 1H, Ar-H), 7.47 − 7.24 (m, 4H, Ar-H), 7.15 (s, 2H, Ar-H), 5.43 (s, 2H, OCH_2).

HRMS (ESI)$^+$ Calculated for $C_{25}H_{15}F_2N_3O_3$ $[M + H]^+$: 431.1099 and found 432.1154

2-(4-fluorophenyl)-3-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (6i)

GREEN SOILD, M.P. 186 – 188 YIELD: 83%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) δ 8.30 (s, 1H, triazoyl-H), 8.11 (s, 2H, Ar-H), 7.62 (d, *J* = 35.9 Hz, 3H, Ar-H), 7.45 (s, 2H, Ar-H), 7.22 (s, 4H, Ar-H), 5.38 (s, 2H, OCH_2).

3-((1-(4-ethylphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-(4-fluorophenyl)-4*H*-chromen-4-one(6j)

GREEN SOILD, M.P. 128 – 130 YIELD: 81%

2-(4-fluorophenyl)-3-((1-(o-tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (6k)

In this article ^

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) δ 8.27 (s, 1H, triazoyl-H), 8.17 (s, 2H, Ar-H), 7.90 (s, 1H, Ar-H), 7.71 (s, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 7.42 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.34 (s, 2H, Ar-H), 7.21 (d, *J* = 24.7 Hz, 3H, Ar-H), 5.44 (s, 2H,OCH_2), 2.11 (s, 3H, OCH_3).

2-(4-fluorophenyl)-3-((1-(m-tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (6 l)

GREEN SOILD, M.P. 126 – 128 YIELD: 80%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) 8.31 (d, 1H, triazoyl-H), 8.10 (s, 3H), 7.72 (s, 1H), 7.51 (dd, *J* = 31.2, 12.6 Hz, 4H), 7.22 (d, *J* = 39.3 Hz, 3H), 5.40 (s, 2H), 2.34(s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$ δC ppm) 175.06 (s, C=O), 165.24 (s, C), 162.72 (s, C), 155.27 (s, C), 139.34 (s, C), 136.82 (s, C), 133.69 (s, C), 131.10 (d, *J* = 8.7 Hz, CH), 125.78 (s, CH), 124.93 (s, CH), 121.18 (s, CH), 118.04 (s, CH), 115.74 (s, CH), 65.08 (s, CH_2), 21.38 (s, CH_3).

2-(4-fluorophenyl)-3-((1-(p-tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (6 m)

BROWN SOILD, M.P. 182 – 184 YIELD: 86%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) 8.31 (s, 1H, triazoyl-H), 8.10 (dd, *J* = 14.9, 9.2 Hz, 3H, Ar-H), 7.55 (d, *J* = 8.1 Hz, 3H, Ar-H), 7.45 (dd, *J* = 7.3 Hz, 2H, Ar-H), 7.29 (s, 2H, Ar-H), 7.17 (s, *J* = 8.3 Hz, 2H, Ar-H), 5.39 (s, 2H, OCH_2), 2.44 (s, 3H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$ δC ppm) 175.05 (s, C=O), 165.23 (s, C), 162.72 (s, C), 155.26 (s, C), 138.94 (s, C), 134.63 (s, C), 131.09 (d, *J* = 8.7 Hz, CH), 130.22 (s, CH), 125.78 (s, CH), 124.92 (s, CH), 120.43 (s, CH), 118.04 (s, CH), 115.74 (s, CH), 65.09 (s, CH_2), 21.09 (s, CH_3).

HRMS (ESI)+ Calculated for: $C_{25}H_{18}FN_3O_3$ [M+] $^+$: 427.1326 and found 428.1358

3-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-(4-fluorophenyl)-4*H*-chromen-4-one (6n)

BROWN SOILD, M.P. 198 – 200 YIELD: 82%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) 8.31 (s, 1H, triazoyl-H), 8.12 (dd, *J* = 8.2, 5.4 Hz, 3H, Ar-H), 7.78 − 7.63 (m, 3H, Ar-H), 7.21 (d, *J* = 20.0 Hz, 2H, Ar-H), 5.38 (s, 2H, OCH_2). **^{13}C NMR** (101 MHz, $CDCl_3$ δC ppm) 175.03 (s, C=O), 155.28 (s, C), 135.87 (s, C), 132.91 (s, C), 131.08 (d, *J* = 8.8 Hz, CH), 125.78 (s, CH), 124.97 (s, CH), 122.19 (d, *J* = 60.9 Hz, CH), 118.06 (s, CH), 115.79 (s, CH), 65.05 (s, CH_2).

HRMS (ESI)+ Calculated for $C_{24}H_{15}BrFN_3O_3$ [M + H] +: 491.0281 and found 493.0494

2-(4-fluorophenyl)-3-((1-(2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (6o)

In this article

GREEN SOILD, M.P. 126 – 128 YIELD: 83%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) 8.27 (s, 1H, triazoyl-H), 8.15 (dd, *J* = 8.4, 5.5 Hz, 2H, Ar-H), 8.06 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.79 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.71 (dd, *J* = 12.5, 7.1 Hz, 2H, Ar-H), 7.59 − 7.52 (m, 2H, Ar-H), 7.43 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.19 (t, *J* = 8.5 Hz, 2H, Ar-H), 5.44 (s, 2H, OCH_2).

2-(4-fluorophenyl)-3-((1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4*H*-chromen-4-one (6p)

GREEN SOILD, M.P. 182 – 184 YIELD: 79%

^{1}H NMR (400 MHz, $CDCl_3$ δH ppm) 8.58 (s, 1H, triazoyl-H), 8.43 − 8.25 (m, 3H, Ar-H), 8.17 − 8.10 (m, 2H, Ar-H), 7.83 − 7.67 (m, 2H, Ar-H), 7.56 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.46 (t, *J* = 7.1 Hz, 1H, Ar-H), 7.30 − 7.11 (m, 2H, Ar-H), 5.40 (s, 2H, OCH_2).

3-((1-(2,4-dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-(4-fluorophenyl)-4*H*-chromen-4-one (6q)

GREEN SOILD, M.P. 140 – 142 YIELD: 84%

(HRMS) were recorded on a Bruker Micro TOF-QII spectrometer

Conclusion

The novel chromone based 1,4-disubstitued 1,2,3-triazoles hybrid compounds (**6a–q**) which contains two very valuable pharmacophoric groups was synthesized and screened it for the biological activity. All screened compounds show antibacterial and antifungal activities into different extent. Compound (**6a)** showed powerful inhibitory activity against all bacterial pathogens but it was not that much effective against fungal pathogens. On other hand compounds (**6h)** and (**6i**) was shown remarkable activity against *S. aureus.* It can be concluded that incorporation of a 1,2,3-triazole ring into chromone moiety has enhanced the biological effect with the scope of developing chromone-based 1,4-disubstitued 1,2,3-triazole derivatives as promising antibacterial and antifungal derivatives. Molecular docking study of these synthesized chromone-linked triazole derivatives have a high affinity toward the active site of S. Aureus KAS III (4XWA) enzyme which provides a strong platform for new structure-based design efforts. Furthermore, analysis of the ADME parameters for synthesized compounds showed good drug-like properties and can be developed as oral drug candidate. Thus, suggesting that

and developed as a lead molecule

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Disclosure statement

No potential conflict of interest was reported by the author(s).

References

1. R. P. N. Mishra, E. Oviedo-Orta, P. Prachi, R. Rappuoli, and F. Bagnoli, "Vaccines and Antibiotic Resistance," *Current Opinion in Microbiology* 15, no. 5 (2012): 596–602. doi:10.1016/j.mib.2012.08.002
PubMed | Web of Science ® | Google Scholar

2. V. Gandhi, and W. Plunkett, "Cellular and Clinical Pharmacology of Fludarabine," *Clinical Pharmacokinetics* 41, no. 2 (2002): 93–103. doi:10.2165/00003088-200241020-00002
PubMed | Web of Science ® | Google Scholar

3. T. Konno, T. Daitoh, A. Noiri, J. Chae, T. Ishihara, and H. Yamanaka, "A Highly Regio- and Stereoselective Carbocupration of Fluoroalkylated Internal Alkynes: A Short Total Synthesis of the Antiestrogenic Drug Panomifene," *Organic Letters* 6, no. 6 (2004): 933–936. doi:10.1021/

PubMed | Web of Science ® | Google Scholar

4. A. Woollard, and Publishers, S. '' An unusual column effect during the analysis of Cfluorocytosine high-performance liquid chromatography,'' *Journal of chromatography.* 368, (1986):162–163.
Google Scholar

5. J. L. Berk, O. B. Suhr, L. Obici, Y. Sekijima, S. R. Zeldenrust, T. Yamashita, M. A. Heneghan, P. D. Gorevic, W. J. Litchy, J. F. Wiesman, et al. "Repurposing Diflunisal for Familial Amyloid Polyneuropathy: A Randomized Clinical Trial," *Jama* 310, no. 24 (2013): 2658–2667. doi:10.1001/jama.2013.283815
PubMed | Web of Science ® | Google Scholar

6. J. H. Rex, M. A. Pfaller, A. L. Barry, P. W. Nelson, and C. D. Webb, "Resistance of Candida Species to Fluconazole," *Antimicrobial Agents and Chemotherapy* 39, no. 1 (1995): 40–44. doi:10.1128/aac.39.1.1
PubMed | Web of Science ® | Google Scholar

7. S. S. Sutton, "Voriconazole: A New Triazole Antifungal Agent," *P and T* 28, no. 4 (2003): 268–275.
Google Scholar

8. Peter, K. Christopher, Murtaugh, and M. The New England Journal of Medicine Downloaded from Nejm.Org on January 12, 2022. For Personal Use Only. No Other Uses without Permission. Copyright © 1991 Massachusetts Medical Society. All Rights Reserved. 1999.
Google Scholar

9. C. K. Jadhav, A. S. Nipate, A. V. Chate, V. D. Songire, A. P. Patil, and C. H. Gill, "Efficient Rapid Access to Biginelli for the Multicomponent Synthesis of 1,2,3,4-Tetrahydropyrimidines in Room-Temperature Diisopropyl Ethyl Ammonium Acetate," *ACS Omega* 4, no. 27 (2019): 22313–22324. doi:10.1021/acsomega.9b02286
PubMed | Web of Science ® | Google Scholar

In this article ^

10. A. V. Chate, S. P. Kamdi, A. N. Bhagat, C. K. Jadhav, A. Nipte, A. P. Sarkate, S. V. Tiwari, and C. H. Gill, "Design, Synthesis and SAR Study of Novel Spiro [Pyrimido[5,4-b]Quinoline-10,5'-Pyrrolo[2,3-d]Pyrimidine] Derivatives as Promising Anticancer Agents," *Journal of Heterocyclic Chemistry* 55, no. 10 (2018): 2297–2302. doi:10.1002/jhet.3286

Web of Science ® | Google Scholar

11. A. Gaspar, M. J. Matos, J. Garrido, E. Uriarte, and F. Borges, "Chromone: A Valid Scaffold in Medicinal Chemistry," *Chemical Reviews* 114, no. 9 (2014): 4960–4992. doi:10.1021/cr400265z

PubMed | Web of Science ® | Google Scholar

12. C. Chiruta, D. Schubert, R. Dargusch, and P. Maher, "Chemical Modification of the Multitarget Neuroprotective Compound Fisetin," *Journal of Medicinal Chemistry* 55, no. 1 (2012): 378–389. doi:10.1021/jm2012563

PubMed | Web of Science ® | Google Scholar

13. N. Desideri, P. Mastromarino, and C. Conti, "Synthesis and Evaluation of Antirhinovirus Activity of 3-Hydroxy and 3-Methoxy 2-Styrylchromones," *Antiviral Chemistry & Chemotherapy* 14, no. 4 (2003): 195–203. pp doi:10.1177/095632020301400404

PubMed | Google Scholar

14. S. T. Chung, W. H. Huang, C. K. Huang, F. C. Liu, R. Y. Huang, C. C. Wu, and A. R. Lee, "Synthesis and anti-Inflammatory Activities of 4H-Chromene and Chromeno[2,3-b]Pyridine Derivatives," *Research on Chemical Intermediates* 42, no. 2 (2016): 1195–1215. doi:10.1007/s11164-015-2081-7

Web of Science ® | Google Scholar

15. S. Vogel, M. Barbic, G. Jürgenliemk, and J. Heilmann, "Synthesis, Cytotoxicity, anti-Oxidative and anti-Inflammatory Activity of Chalcones and Influence of A-Ring Modifications on the Pharmacological Effect," *European Journal of Medicinal Chemistry* 45, no. 6 (2010): 2206–2213. doi:10.1016/j.ejmech.2010.01.060

PubMed | Web of Science ® | Google Scholar

In this article

"Searching for New Cytotoxic Agents Based on Chromen-4-One and Chromane-2,4-Dione Scaffolds," *Research in Pharmaceutical Sciences* 14, no. 1 (2019): 74–83. doi:10.4103/1735-5362.251855

PubMed | Web of Science ® | Google Scholar

17. V. S. Dofe, A. P. Sarkate, Z. M. Shaikh, C. K. Jadhav, A. S. Nipte, and C. H. Gill, "Ultrasound-Assisted Synthesis of Novel Pyrazole and Pyrimidine Derivatives as Antimicrobial Agents," *Journal of Heterocyclic Chemistry* 55, no. 3 (2018): 756–762. doi:10.1002/jhet.3105

Web of Science ® | Google Scholar

18. C. K. Jadhav, A. S. Nipate, A. V. Chate, A. P. Patil, and C. H. Gill, "Ionic Liquid Catalyzed One-Pot Multi-Component Synthesis of Fused Pyridine Derivatives: A Strategy for Green and Sustainable Chemistry," *Journal of Heterocyclic Chemistry* 57, no. 12 (2020): 4291–4303. doi:10.1002/jhet.4135

Web of Science ® | Google Scholar

19. H. C. Kolb, M. G. Finn, and K. B. Sharpless, "Click Chemistry: Diverse Chemical Function from a Few Good Reactions," *Angewandte Chemie International Edition* 40, no. 11 (2001): 2004–2021. doi:10.1002/1521-3773(20010601)40:11 < 2004::AID-ANIE2004 > 3.0.CO;2-5

PubMed | Web of Science ® | Google Scholar

20. V. V. Rostovtsev, L. G. Green, V. V. Fokin, and K. B. Sharpless, "A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes - Rostovtsev - 2002 - Angewandte Chemie - Wiley Online Library," *Angewandte Chemie* 114, no. 14 (2002): 2708–2711. doi:10.1002/1521-3757(20020715)114:14<2708::AID-ANGE2708>3.0.CO;2-0

Google Scholar

21. M. Allam, A. K. D. Bhavani, A. Mudiraj, N. Ranjan, M. Thippana, and P. P. Babu, "Synthesis of Pyrazolo[3,4-d]Pyrimidin-4(5H)-Ones Tethered to 1,2,3-Triazoles and Their Evaluation as Potential Anticancer Agents," *European Journal of Medicinal Chemistry* 156 (2018): 43–52. doi:10.1016/j.ejmech.2018.06.055

In this article

22. S. Arroyo, "Rufinamide," *Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics* 4, no. 1 (2007): 155–162. doi:10.1016/j.nurt.2006.11.006
PubMed | Web of Science ® | Google Scholar

23. G. R. Oxnard, J. C.-H. Yang, H. Yu, S.-W. Kim, H. Saka, L. Horn, K. Goto, Y. Ohe, H. Mann, K. S. Thress, et al. "TATTON: A Multi-Arm, Phase Ib Trial of Osimertinib Combined with Selumetinib, Savolitinib, or Durvalumab in EGFR-Mutant Lung Cancer," *Annals of Oncology : Official Journal of the European Society for Medical Oncology* 31, no. 4 (2020): 507–516. ;. doi:10.1016/j.annonc.2020.01.013
PubMed | Web of Science ® | Google Scholar

24. P. P. Dobesh, and J. H. Oestreich, "Ticagrelor: Pharmacokinetics, Pharmacodynamics, Clinical Efficacy, and Safety," *Pharmacotherapy* 34, no. 10 (2014): 1077–1090. doi:10.1002/phar.1477
PubMed | Web of Science ® | Google Scholar

25. D. R. Giacobbe, M. Bassetti, F. G. De Rosa, V. Del Bono, P. A. Grossi, F. Menichetti, F. Pea, G. M. Rossolini, M. Tumbarello, P. Viale, et al. "Ceftolozane/Tazobactam: Place in Therapy," *Expert Review of anti-Infective Therapy* 16, no. 4 (2018): 307–320. doi:10.1080/14787210.2018.1447381
PubMed | Web of Science ® | Google Scholar

26. C. W. Tornøe, C. Christensen, and M. Meldal, "Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides," *The Journal of Organic Chemistry* 67, no. 9 (2002): 3057–3064. doi:10.1021/jo011148j
PubMed | Web of Science ® | Google Scholar

27. C. Lass-Flörl, "Triazole Antifungal Agents in Invasive Fungal Infections: A Comparative Review," *Drugs* 71, no. 18 (2011): 2405–2419. doi:10.2165/11596540-000000000-00000
PubMed | Web of Science ® | Google Scholar

28. S. Shafi, M. Mahboob Alam, N. Mulakayala, C. Mulakayala, G. Vanaja, A. M. Kalle, R. Pallu, and M. S. Alam, "Synthesis of Novel 2-Mercapto Benzothiazole and 1,2,3-Triazole Based Bis-Heterocycles: Their Anti-Inflammatory and Anti-Nociceptive Activities," *European Journal of*

In this article

PubMed | Web of Science ® | Google Scholar

29. M.H.Shaikh, D. D. Subhedar, L. Nawale, D. Sarkar, F. A. K. Khan, J. N. Sangshetti, and, B. B. Shingate. "1, 2, 3-Triazole derivatives as antitubercular agents: synthesis, biological evaluation and molecular docking study." MedChemComm 6, no. 6 (2015): 1104–1116.
Google Scholar

30. A. K. Jordão, V. F. Ferreira, E. S. Lima, M. C. B. V. de Souza, E. C. L. Carlos, H. C. Castro, R. B. Geraldo, C. R. Rodrigues, M. C. B. Almeida, and A. C. Cunha, "Synthesis, Antiplatelet and in Silico Evaluations of Novel N-Substituted-Phenylamino-5-Methyl-1H-1,2,3-Triazole-4-Carbohydrazides," *Bioorganic & Medicinal Chemistry* 17, no. 10 (2009): 3713–3719. doi:10.1016/j.bmc.2009.03.053
PubMed | Web of Science ® | Google Scholar

31. A. S. Nipate, C. K. Jadhav, A. V. Chate, T. R. Deshmukh, A. P. Sarkate, and C. H. Gill, "Synthesis and in Vitro Anticancer Activities of New 1,4-Disubstituted-1,2,3-Triazoles Derivatives through Click Approach," *ChemistrySelect* 6, no. 21 (2021): 5173–5179. doi:10.1002/slct.202101035
Web of Science ® | Google Scholar

32. Babita Aneja, Rizwan Arif, Ahmad Perwez, John V. Napoleon, Phool Hasan, M. Moshahid A. Rizvi, Amir Azam, and Mohammad Abid, Rahisuddin, "N-Substituted 1,2,3-Triazolyl-Appended Indole-Chalcone Hybrids as Potential DNA Intercalators Endowed with Antioxidant and Anticancer Properties," *ChemistrySelect* 3, no. 9 (2018): 2638–2645. doi:10.1002/slct.201702913
Web of Science ® | Google Scholar

33. M. B. Muluk, S. T. Dhumal, P. S. Phatak, N. N. M. A. Rehman, P. P. Dixit, P. B. Choudhari, R. A. Mane, and K. P. Haval, "Synthesis, Antimicrobial Activity, and Molecular Docking Study of Formylnaphthalenyloxymethyl-Triazolyl-N-Phenylacetamides," *Journal of Heterocyclic Chemistry* 56, no. 9 (2019): 2411–2418. doi:10.1002/jhet.3628
Web of Science ® | Google Scholar

34. V. S. Dofe, A. P. Sarkate, D. K. Lokwani, S. H. Kathwate, and C. H. Gill, "Synthesis, Antimicrobial

Research on Chemical Intermediates 43, no. 1 (2017): 15–28. doi:10.1007/s11164-016-2602-z

Web of Science ® | Google Scholar

35. C. Moberg, and H. Adolfsson, "Aryl Azides'' *Compounds of Groups 15 (as, Sb, Bi) and Silicon Compounds* 45 (2002). doi:10.1055/sos-sd-004-00481

Google Scholar