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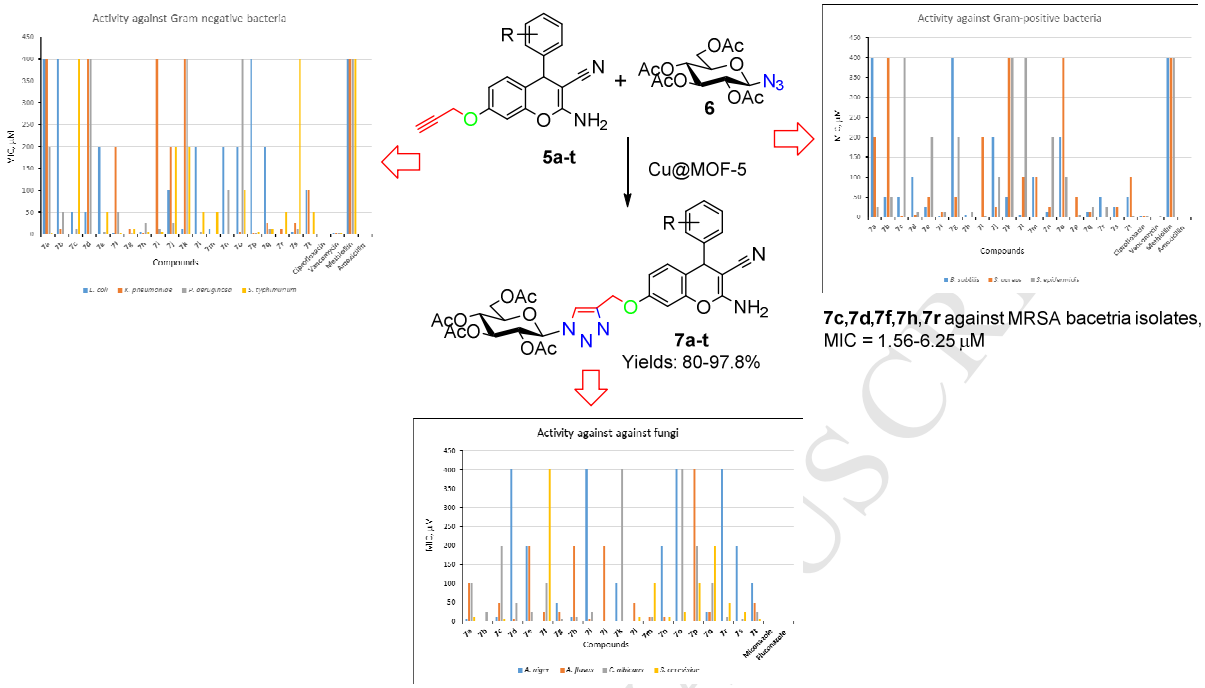
Graphic abstract



7c,7d,7f,7h,7r against MRSA bacetria isolates, MIC = 1.56-6.25 μM

Efficient click chemistry towards novel 1*H*-1,2,3-triazole-tethered 4*H*-chromene−D-glucose conjugates: Design, synthesis and evaluation of *in vitro* antibacterial, MRSA and antifungal activities

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Abstracts. The series of 2-amino-7-propargyloxy-4*H*-chromene-3-carbonitriles **5a-t** were synthesized from corresponding 2-amino-7-phydroxy-4*H*-chromene-3-carbonitriles **4a-t** and propargyl bromide. Two procedures were used in these syntheses: K_2CO_3/acetone and NaH/DMF procedures with yields of 65−89% and 80−96%, respectively. 1*H*-1,2,3-Triazole-tethered 4H-chromene−D-glucose conjugates **7a-t** were synthesized using click chemistry of propargyl ethers

5a-t and tetra-*O*-acetyl-β-D-glucopyranosyl azide. Cu@MOF-5 was the optimal catalyst for this chemistry. The yields of 1*H*-1,2,3-triazoles were 80−97.8%. All triazoles **7a-t** were evaluated *in vitro* for anti-microorganism activities. Among tested compounds with MIC values of 1.56–6.25 μM, there were four compounds against *B. subtilis*, four compounds against *S. aureus*, and four compounds against *S. epidermidis*; five compounds against *E. coli*, four compounds against *K. pneumoniae*, five compounds against *P. aeruginosa*, and six compounds against *S. typhimurium*. Compounds **7c**,**7d**,**7f**,**7h**, and **7r** had MIC values of 1.56−6.25 μM for three clinical MRSA isolates. Some compounds had inhibitory activities against four fungi, including *A. niger*, *A. flavus*, *C. albicans*, and *S. cerevisiae*, with MIC values of 1.56−6.25 μM. Some 1*H*-1,2,3-triazoles had comparatively low toxicity against RAW 264.7 cells.

Keywords. 1*H*-1,2,3-Triazoles; 2-Amino-4*H*-chromene-3-carbonitriles; Propargyl ether; Sugar azide; Cu@MOF-5; Click chemistry; Antibacterial; Antifungal; Cytotoxicity.

1. Introduction

Organic compounds bearing chromene ring exhibit a wide range of biological activities, especially with certain functional groups, such amino, nitrile,… in its molecular skeleton that could be effectively bound to enzyme receptor sites [1-3]. These compounds function as important pharmacophores, which are associated with a broad range of pharmacological activities, including anticancer [3], antimicrobial [4], cytotoxicity [4], anti-proliferative [5], antitumor [6], antibacterial [7, 8], antioxidant [7], antiviral [9] agents, and so on. A large number of synthetic 2-aminochromene derivatives have shown remarkable biological activities that some representative compounds were given in Fig. 1. Kumar *et al.* [10] showed that tetrahydrochromene **A** had antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* with MIC value of 64 μg/mL. Kidwai *et al.* indicated that chromenes **B** bearing benzothiazolyl-2 had antibacterial activity against both Gram-(−), such as *E. coli* and *Pseudomonas aeruginosa*, and Gram-(−), such

as *S. aureus* and *Staphylococcus epidermidis* [11]. Mirjalili *et al.* synthesized benzo[*f*]chromene **C**, which had antifungal activity against *Aspergillus flavus* and *Candida albicans* with MIC < 1 μg/mL [12]. Makawana *et al.* [13] showed that chromene **D** (Fig. 1) was especially active against Gram-negative bacteria *Vibrio cholerate* (MIC = 12.5 μg/mL), whereas chromene **E** was more active against Gram-positive *Streptococcus pneumonia* (MIC = 12.5 μg/mL) as compared to ampillicin (MIC = 100 μg/mL for both strains). Therefore, synthetic procedures of derivatives with chromene moiety have been developed due to their useful biological activities [14, 15].

Figure 1

1*H*-1,2,3-Triazole are an important class of nitrogen-containing heterocycles in the area of organic (chemistry) and medicinal chemistry. Medicinally, they showed a broad range of diverse, interesting pharmacological properties such as antiinfective [9], antituberculosis [16], anticancer [17], antifungal [18], and antibacterial [19], antimicrobial [20], antioxidant [21] activities, and so on. The connection of some heterocycles, such as chromene and 1*H*-1,2,3-triazole rings, even monosaccharide, could bring forth some interesting biological activities. Sangshetti *et al.* [22] showed that triazole **F** (Fig. 2) had inhibitory activities against some fungi, such as *C. albicans* (MIC = 30 μg/mL), *A. niger* (MIC = 15 μg/mL) and *A. flavus* (MIC = 15 μg/mL) in comparison to fluconazole (MIC = 5 μg/mL for all strains). Yadav *et al.* [23] indicated that chalcone-12,3-triazole conjugate **G** exhibited inhibition activity against serial organisms with MIC = 0.0032−0.0063 μg/mL. Chaudhary *et al.* [24] synthesized several novel 1,4-disubstituted-1,2,3-triazolyluridine derivatives (**H**, Fig. 2), which showed significant antifungal activity. One of the compounds **H** showed potent antifungal activity against *C. neoformans* with an MIC value of 8 μg/mL. The other one with 4-methoxy group had antifungal activity against *C. albicans* with MIC value of 24 μg/mL in comparison to MIC = 0.018 μg/mL for fluconazole), whereas the compound having 4-chloro group showed antifungal activity against *F. oxysporum* with MIC = 32 μg/mL.

Figure 2

Saeedi *et al.* [25] showed that compound **I** (Fig. 2) that had chromene and 1*H*-1,2,3-triazole rings exhibited good anti-acetylcholinesterase activity, with IC_{50} = 15.42 μM. Similarly, Shaikh *et al.* [26] synthesized some triazoles **J** (Fig. 2) with remarkable antifungal and antioxidant activities. Some potential pharmaceuticals were based on 1,2,3-triazole ring, including the anticancer agent CAI (carboxyamidotriazole, **K**, Fig. 3) [27], TSAO [2′,5′-bis-*O*-(tert-butyldimethylsilyl)-3′-spiro-5″-(4″-amino- 1″,2″-oxathiole-2″,2″-dioxide)]-β-D-ribofuranose, **L**, Fig. 3), a nucleoside derivative non-nucleoside reverse transcriptase inhibitor [28], and tazobactam (**M**, Fig. 3), one β-lactam antibiotic drug, and so on.

Figure 3

The heterocyclic aromatic ring 1*H*-1,2,3-triazole ring is formed through click chemistry of appropriate alkynes-1 and organic azides, which was often catalyzed by copper [29-32]. Copper-catalyzed azide-alkyne cycloaddition (CuAAC) is a type of Huisgen 1,3-dipolar cycloaddition [30]. Some copper-catalysts in free metal or salt forms (ionic or complex) were employed for most effective promotion of CuAAC processes, such Cu(II) sulfate/sodium ascorbate [32], CuI/DIEA (*N*,*N*-diisopropylethylamine) [33], copper(II) acetate or triflate/sodium ascorbate [34, 35], $CuCl_2$/PMDETA (pentamethyldiethylenetriamine) [36], CuNPs/C (copper nanoparticles on activated carbon) [37], etc… The same catalysts also were employed in click chemistry of carbohydrate [38].

In order to find some hybrid structures between chromene and 1*H*-1,2,3-triazole rings having bacterial and fungal activities, we reported the synthesis of 1*H*-1,2,3-triazole-tethered 4*H*-chromene and D-glucose conjugates and the evaluation of their anti-microorganism activity. These

triazoles were obtained by the click chemistry of 2-amino-4-aryl-7-propargyl-4*H*-chromene-3-carbonitriles to and D-glucose moiety. They were evaluated by their antibacterial and fungal activities against some Gram-positive bacteria, such as *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, some Gram-negative bacteria, such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Salmonella typhimurium*, and some fungi, such as *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans*, and *Saccharomyces cerevisiae*. These compounds were also tested their cytotoxicity against RAW 264.7 cells [39-42].

2. Results and discussion

2.1. Chemistry

2-Amino-4-aryl-7-hydroxyl-4*H*-chromene-3-carbonitriles **4a-t** were prepared by three-component reaction of (un)substituted benzaldehydes **1a-t**, malononitrile **2**, and resorcinol **3** (Scheme 1). The three-component reaction process took place at room temperature (25°C) for 24 h. The basic catalyst for this reaction was sodium carbonate in water (44.7 mol%, i.e. ~0.47% solution). The yields were 62−90% (Table 1S, including their spectral and analytical data, Section 4, Supplementary data in the online version of this article).

Scheme 1

2-Amino-7-propargyloxy-4-aryl-4*H*-chromene-3-carbonitriles **5a-t**, which were the precursors necessary for CuAAC click chemistry, were synthesized by reaction of corresponding 7-hydroxyl-4*H*-chromene **4a-t** with propargyl bromide. We used two synthetic ways in order to accomplish this purpose (Scheme 2). In the first way, anhydrous potassium carbonate was used as a base and dried acetone was used as a solvent (Procedure A). The reaction time was 12 hours at 50°C, and the yields were 65−89%. In the second way, sodium hydride was used as a base in dried DMF solvent (Procedure B). In Procedure B, the formation of ether **5a-t** took place *via* reaction of **4a-t**

with sodium hydride to form sodium phenoxides, named sodium 2-amino-3-cyano-4-phenyl-4*H*-chromene-7-olates **4′a-t**, which were dissolved well in DMF and could not be isolated and allowed to react with propargyl bromide to afford the target ethers **5a-t**. The reaction time was only 2 hours at a temperature of 25°C, and the yields obtained were 80−96%. The synthesized 2-amino-4-aryl-7-propargyloxy-4*H*-chromene-3-carbonitriles **5a-t** were shown in Table 1. Their spectral and analytical data were given in Section 5 (Supplementary data, in the online version of this article).

Scheme 2

Table 1

The spectral data showed that in the reaction with propargyl bromide, the *O*-alkylation of the hydroxyl group on position 7 of benzene moiety of chromene ring occurred instead of the *N*-alkylation of the primary amino group on position 2 of pyran moiety of chromene ring. Crystals for the compound **5i** (2-amino-7-propargyloxy-4-(2′-chlorophenyl)-4*H*-chromene-3-carbonitrile) were grown by slow evaporation technique using a mixture of 96% ethanol and toluene as a solvent system (4:1 by volumes). The X-ray diffraction data showed that the crystal of **5i** had the same empirical formula and formula weight (Table 2). The crystal data of **5i** can be accessed at www.ccdc.cam.ac.uk/data_request/cif under Crystallographic Data Centre number CCDC 1854537 (for crystallographic details, see Section 6.1, Supplementary data in online version of this article). The ORTEP diagram of **5i** was given in Fig. 4.

Table 2

Figure 4

The other precursor for the click chemistry was 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **6**, which was prepared by the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide [43](acetobromo-α-D-glucose) with sodium azide in dried DMF [44] or acetone-water [45]. We have prepared this sugar azide with some modifications of the known procedure (Scheme 3). Dried acetone was used as a solvent, which avoided the decomposition of acetobromo-α-D-glucose by water, and acetone was easily removed from the reaction mixture. This sugar azide derivative was obtained as a crystalline solid on a multi-gram scale.

Scheme 3

The single-crystal X-ray structure of this azide was shown in Table 2 and Fig. 5 with CCDC number is 1855316, www.ccdc.cam.ac.uk/data_request/cif (see Section 6.2, Supplementary data in the online version of this article), which was similar to the azide compound that was synthesized and structurally determined by D. P. Temelkoff *et al.* [46].

Figure 5

From the literature, the click chemistry could be catalyzed by some different catalysts [38]. In order to find the optimal conditions for the click chemistry of propargyl ether of 4H-chromene-3-carbonitriles **5a-t** with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **6**, we have carried out investigations of the CuAAC catalytic conditions in the reaction of the compound **7a** (R = H) with this azide (Scheme 4). The catalysts used included $CuSO_4.5H_2O$/sodium ascorbate, $CuIm_2$ (Im = imidazole), CuI, CuNPs (Cu nano-particles on Montmorillonite K10), and Cu@MOF-5. Some copper catalysts that were utilized in these examinations were prepared in our lab and characterized structurally, except (for the) $CuSO_4$/sodium ascorbate system. The obtained

examination results are shown in Table 3.

Scheme 4

Table 3

The use of the catalytic system of $CuSO_4.5H_2O$ (2 mol%) and sodium ascorbate (5 mol%) in DMSO as solvent (Procedure A, Entry 1, Table 3) made it difficult to handle the reaction, even with the solvent-extraction method being used to isolate the product out of the reaction mixture. On the other hand, reaction time prolonged until 24 hours when the reaction was carried out at room temperature. The yield of **7a** was 60.7% in this case. The increasing of reaction temperature (only to ~40°C) led to the formation of oily or tar substances having indefinite structures possibly due to the decomposition of the reactants and/or products.

The catalysis of $CuIm_2$ (2 mol%) in Entry 2 (Procedure B), which was a complex of copper (II) ion and imidazole, gave an only low yield of **7a** (53.3%) after 1.5-hour heating at 79−80°C in absolute ethanol as solvent. The other CuAAC catalyst systems (Entries 3−5, Table 3) seemed to be preeminent because the treatment of those reactions became easier and produced higher yields since copper did not affect the reaction treatment. Thus, (the) product was easily isolated. The use of nano-structured copper catalyst that supported on montmorillonite K-10 had more advantages in comparison to the catalytic $CuSO_4$/sodium ascorbate system in Entry 1. The reaction time was only 30 min and gave high product yields (up to 94.8%). In this reaction, trimethylamine was often used as an additive. The products were isolated more easily. Usually, water was added to the reaction mixture, and the separated precipitates were filtered simply. These conveniences were also achieved by using the catalyst of copper(I) iodide (2 mol%) in *t*-BuOH as a solvent with a little of water as an additive (Entry 3, Procedure D). However, the reaction time was prolonged (until 1 hour) and a yield of 94.8% was attained. In the last examination, copper was supported on

microporous metal-organic frameworks MOF), and in this case, Cu@MOF-5 (2 mol%) (Procedure E, Entry 5) gave the best results of the catalyst surveyed. The reaction temperature was 79−80°C. On the other hand, the use of absolute ethanol brought in outstanding advantages in this entry. After the end of the reaction, the product was isolated simply by adding toluene (by half a volume), heating and filtering out solid catalyst. The obstructions of the copper salts to isolating products have been avoided. The yield of 97.8% was attained when this procedure was employed. Based on the above results of examinations, we decided to choose Cu@MOF-5 to be a catalyst in the synthesis of remained substituted 1*H*-1,2,3-triazoles **7b-t**. The obtained synthetic results were shown in Table 4. The product yields were 80−97.8%.

Table 4

The assignments proton and carbon-13 signals in ^{1}H NMR and ^{13}C NMR spectra were done based on HSQC and HMBC of compound **7a** (see Section 8.1, Supplementary Data in online version of this article). The spectral data confirmed the formation of 1*H*-1,2,3-triazole ring *via* click chemistry and the presence of 4*H*-chromene and glucopyranose rings.

2.2. Biological screening

2.2.1. Antibacterial assays

All the synthesized 1*H*-1,2,3-triazoles were screened for their *in vitro* antibacterial activity against three representative Gram-positive bacteria, which were *B. subtilis* (ATCC 11774), *S. aureus* (ATCC 11632), *S. epidermidis* (ATCC 12228), and representative four Gram-negative bacteria, which were *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 25923), *K. pneumoniae* (ATCC 4352), *S. typhimurium* (ATCC 14028). Three methicillin resistant *Staphylococcus aureus* (MRSA) strains isolated from Hospital of Ministry of Public Security (in Ha Noi), numbered MRSA198-1, MRSA198-2 and MRSA198-3, were also included in these tests. Ciprofloxacin, methicillin and

vancomycin were used as positive references for antibacterial activity. It is known that methicillin was used to treat infections caused by certain gram-positive bacteria, including *S. aureus*, *S. epidermidis*, *S. pyogenes*, and *S. pneumoniae*. (However,) methicillin is no longer effective against these mircoorganisms due to resistance. Vancomycin and ciprofloxacin are still used to treat a number of bacterial infections, with the former used to treat serious, life-threatening infections by Gram-positive bacteria (, including *C. difficile*?) that (are) unresponsive to other antibiotics. The latter treated serious infections caused by Gram-negative bacteria, including *P. aeruginosa*. Evaluated results for **7a-t** were given in Table 5.

Table 5

The results in Table 5 showed that almost all novel molecule exhibited antibacterial activity against the tested bacteria at low and high concentrations. In general, it has been observed that almost all tested compounds showed mild to moderate activity against the tested bacteria in comparison with the MIC values of the references compound. MIC values of these reference drugs are as follows: Ciprofloxacin, 3.12 μM (for Gram-positive bacteria), 1.56 μM (for Gram-negative bacteria); vancomycin, 0.78−3.12 μM (for Gram-positive bacteria), 3.12 μM (for Gram-negative bacteria). Methicillin had the least inhibitory activity for all tested bacteria (all MICs = 400 μM). Some 1*H*-1,2,3-triazoles had higher ability to inhibit to Gram-positive bacteria (*B. subtilis*, *S. aureus* and *S. epidermidis*) with MIC values of 1.56–6.25 μM. Amongst these triazoles were compounds **7f** (MIC = 3.12 μM), **7h** (MIC = 6.25 μM), **7i** (MIC = 1.56 μM) against *B. subtilis*. Compounds **7c**,**7h**,**7r** had activity against *S. aureus* with MIC values of 6.25, 3.12 and 3.12 μM, respectively. Compounds **7i**,**7p**,**7s**,**7t** were more active against *S. epidermidis* with MIC values of 3.12, 6.25, 1.56 and 3.12 μM, respectively. In general, the above-mentioned triazoles were more inhibitory active than ciprofloxacin but less than vancomycin, except **7i**,**7h**,**7r**, and **7s** (MICs = 1.56 μM). Some others were less active against these bacteria with MIC values of 12.5−25 μM,

such as **7h**,**7l**,**7n**,**7q** (against *B. subtilis*), **7d**,**7f**,**7q** (against *S. aureus*), **7d**,**7i**,**7p** (against *S. epidermidis*). The remaining triazoles had MIC values of 100−400 μM or higher (not evaluated). Several triazoles had inhibitory activity against each Gram-negative bacterium similar to ciprofloxacin, with MIC value of 1.56 μM, such as **7g**,**7i** (against *E. coli*), **7l** (against *K. pneumoniae*), **7m** (against *P. aeruginosa*), and **7n** (against *S. typhimurium*). The compounds mentioned herein were more active than vancomycin (MIC = 3.12 μM) and methicillin (MIC = 400 μM) for all tested Gram-negative bacteria. The triazoles that had less inhibitory activity against these bacteria (with MICs = 3.12−6.25 μM) included **7f**,**7h**,**7s** (against *E. coli*); **7h**,**7o**,**7p** (against *K. pneumoniae*); **7e**,**7g**,**7l**,**7p** (against *P. aeruginosa*), and **7a**,**7f**,**7h**,**7i**,**7p** (against *S. typhimurium*). Thus, the synthesized 1*H*-1,2,3-triazole-tethered 4*H*-chromene−D-glucose conjugates were more inhibitory active against Gram-negative bacteria than Gram-positive ones. We have evaluated the antibacterial activities of these triazoles against a series of MRSA strains (MRSA198-1, MRSA198-2 and MRSA198-3) from clinical sources. Among the tested compounds, **7c**, **7d**, **7f**, **7h** and **7r** exerted anti-MRSA activities against all the strains tested with MIC values ranging from 1.56 to 6.25 μM. In addition, the inhibitory effects of triazoles **7c**, **7h** and **7r** were obviously observed by treating it against strain MRSA198-1 with MIC values of 1.56, 3.12 and 1.56 μM, respectively. Triazoles **7d**, **7f** and **7r** had the better inhibition activity against strain MRAS198-2 with all MIC values of 1.56 μM. Triazoles **7c**, **7d**, **7f**, and **7h** also had better inhibition activity against strain MRAS198-3 with MIC values of 3.12, 3.12, 3.12 and 1.56 μM, respectively. Compounds **7d**, **7f**, **7j**, **7n** (against MRSA 198-1), **7c**, **7h**, **7j**, **7n** (against MRSA 198-2), and **7j**, **7r**, **7n** (against MRSA 198-3) showed mild anti-MRSA effect with MIC values of 6.25−12.5 μM. Other compounds did not show any significance in anti-MRSA activity (MIC = 25−400 μM or not evaluated) (Table 6). Some triazoles had better activity against Gram-positive, Gram-negative and MRSA bacteria, such as **7f**,**7h**, and **7i**, with MIC values of 1.56−6.25 μM, (respectively.) Amongst these compounds were **7f** and **7h**, which had inhibitory activity against

hospital-isolated MRSA strains (MICs = 1.56−6.25 μM). Triazoles **7c** and **7r** were more inhibitory-active against both *S. aureus* and MRSA (Table 5, Fig. 6).

Figure 6

Some obtained SAR results were as follows:

1. The electron-withdrawing groups on the benzene ring: Gram-positive antibacterial activity against *B. subtilis* increased, with MICs = 1.56−6.25 μM, except compounds with nitro-group, such as **7b**−**7c** (MICs = 50−100 μM), and the ones bearing 4′-chloro and 4′-bromo groups (MICs = 400 and 200 μM, respectively). The compounds with electron-withdrawing groups had also higher activity against *S. aureus* and *S. epidermidis*, except **7b**, **7i** (for *S. aureus*), and **7c**,**7e**,**7g**,**7j** (for *S. epidermidis*). These observations were also true for Gram-negative bacteria, except some cases, such as triazoles **7b**,**7e**,**7j** (for *E. coli*), **7c**−**7f**,**7i**,**7j** (for *K. pneumoniae*), **7d** (for *P. aeruginosa*), (and) **7b**−**7d**,**7j** (for *S. typhimurium*).
2. The electron-donating groups on the benzene ring: Alkyl groups (such as methyl, isopropyl) and dimethylamino group in general decreased the inhibitory activity against Gram-positive bacteria, except compound **7l** (for *B. subtilis*). One methoxy group on the benzene ring increased unnoticeably the inhibitory activity against Gram-positive bacteria, except **7n** (for *B. subtilis*) and **7p** (for *S. epidermidis*), and decreased this activity (against) Gram-negative bacteria, except **7p** (for *K. pneumoniae, P. aeruginosa, S. typhimurium*) (and) **7n** (for *S. typhimurium*).
3. The increasing numbers of methoxy groups on the benzene ring led to increased Gram-positive antibacterial activity, except compounds **7r**,**7s** (for *S. aureus*, MICs = 1.56 μM), and to decreased Gram-negative antibacterial activity, except **7s** (for *E. coli*, MIC = 6.25 μM).

2.2.2. Antifungal assay

We evaluated the antifungal activities of the above 1*H*-1,2,3-triazoles **7a-t** against some fungi, such as *Aspergillus niger* (ATCC 439), *Aspergillus flavus* (ATCC 204304), *Candida albicans* (ATCC 7754), and *Saccharomyces cerevisiae* (SH 20). Miconazole and fluconazole were used as references. Miconazole is mainly used externally for the treatment and prophylactic treatment of *Candida* infection in the oral cavity and the digestive tract. Fluconazole is a first-generation triazole antifungal medication. It has a spectrum of activity, which includes most *Candida* species but not *C. krusei* or *C. glabrata*, *Cryptococcus neoformans*, some dimorphic fungi, and dermatophytes. MIC values of miconazole were 1.56, 1.56, 3.12 and 3.12 μM for each fungus, respectively, and of fluconazole were 1.56, 0.78, 0.78 and 0.78 μM for each fungus, respectively. The obtained results were given in Table 6. Notably, almost all of the tested triazoles **7a-t** were more remarkably active against fungi *A. flavus*, *C. albicans*, and *S. cerevisiae*, but those triazoles were more resistant to *A. niger* than miconazole and fluconazole. In the case of fungi *A. niger*, almost all of the compounds were less active than miconazole and fluconazole, except for triazole **7p** that was as active as these references, with an MIC value of 1.56 μM. Seven compounds 7**b**,**7c**,**7g**,**7h**,**7j**,**7k**,**7t** were active against *S. cerevisiae* with MICs= 1.56−6.25 μM. Some triazoles had more inhibitory activity against these fungi with MIC = 1.56−3.12 μM, such as **7j**,**7p** (*A. niger*), **7b**,**7k**,**7o**,**7s** (*A. flavus*), **7j**,**7l**,**7n** (*C. albicans*), and 7**b**,**7g**,**7h**,**7j**,**7k** (*S. cerevisiae*). Remarkably, compound **7n** was more active against *C. albicans* than miconazole but less active than fluconazole, and compounds **7g** and **7j** were more active against *S. cerevisiae* than miconazole.

Table 6

Triazoles have the remarkable ability to inhibit these fungi with MIC values of 6.25 μM, such as **7a** (*A. niger*), **7d**,**7i** (*A. flavus*), and **7g**,**7s** (*C. albicans*), and **7c**,**7t** (*S. cerevisiae*). Some triazoles displayed mild inhibitory activity with MIC values of 12.5 μM, and other ones exhibited even less

inhibitory activity (with MIC values of 25−50 μM). Triazoles were least active with MIC values of 100−200 μM, such as **7e**,**7k**,**7n**,**7s**,**7t** (*A. niger*), **7a**,**7e**,**7h**,**7j** (*A. flavus*), **7a**,**7c**,**7f**,**7p**,**7q** (*C. albicans*), and **7m**,**7p**,**7q** (*S. cerevisiae*). The remaining compounds had MIC values of 400 μM for each fungus and displayed no activity, such as **7b**, **7f**, **7l**, **7m** (for *A. niger*), **7r** (for *A. flavus*), **7k**, **7o** (for *C. albicans*), and **7d**,**7e**,**7i** (*S. cerevisiae*) (see Table 6, Fig. 7). In general, triazoles that had bulky groups (methoxy, methyl, isopropyl) in their benzene ring were less active. However, there are some exceptional cases. Triazole **7p** with 2′-methoxy group was more active against *A. niger* (MIC = 1.56 μM) but less active against fungus *A. flavus* and *C. albicans*. Triazoles **7b** (with *para*-nitro group) and **7o** (with *meta*-methoxy group) were more active against *A. flavus* (MICs = 1.56 μM) but less active against *S. cerevisiae* and not active against both *A. niger* and *C. albicans*.

Figure 7

The triazoles bearing monomethoxy-substituted phenyl ring, in general, exhibited mild to most activity (with MIC = 1.56 μM and 12.5 μM), except **7n**, **7o** (*A. niger*), **7p** (*A. flavus*), **7o**,**7p** (*C. albicans*). The more introduced methoxy group (compounds **7q-t**) reduced the antifungal inhibitory activity against all tested fungi of these triazoles, except **7s** that was more active against *A. flavus* and *C. albicans*, and **7t** that was more active against *S. cerevisiae*.

2.2.3. Cytotoxicity

All 1*H*-1,2,3-triazoles tethered 4*H*-chromene-D-glucose were also tested for *in vitro* cytotoxicity against mouse macrophage (RAW 264.7) cell lines at 50 μg/mL concentration using (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. All these compounds showed less than 50% inhibition. The percentage inhibitions of cells were given in Table 7. The most promising antitubercular analogs **7c**,**7d**,**7f**,**7h**, and **7r** exhibited 15.56, 15.45, 18.13, 17.20, and 12.45% growth inhibition, at 50 μg/mL, respectively. The results indicated that these potent

1*H*-1,2,3-triazoles were comparatively less toxic than other triazoles and it's suggested that these compounds are suitable subjects for further drug-development studies.

Table 7

3. Conclusions

A series of 2-amino-4-aryl-7-propargyloxy-4*H*-chromene-3-carbonitriles **5a-t** were synthesized by the reaction of corresponding 2-amino-7-hydroxy-4*H*-chromene-3-carbonitriles **4a-t** through Williamson's ether synthesis. Propargyl bromide was used in these syntheses in two procedures: K_2CO_3/acetone and NaH/DMF procedures. Both procedures gave the ethers **5a-t** in high yields. The single-crystal X-ray structure of propargyl ether **5i** has been recorded. This X-ray study helps to confirm the structure of 2-amino-4-aryl-7-propargyloxy-4*H*-chromene-3-carbonitriles. Click chemistry of these propargyl ethers was carried out by reaction with tetra-*O*-acetyl-β-D-glucopyranosyl azide by CuAAC process. The catalysts for this chemistry were examined. The obtained results showed that Cu@MOF-5 was the optimal catalyst for the above chemistry. The yields of 1*H*-1,2,3-triazoles **7a-7t** were 80−97.8%. All synthesized 1*H*-1,2,3-triazole-tethered 4H-chromene−D-glucose conjugates were evaluated for inhibitory activities against some Gram-positive, Gram-negative bacteria, and fungi. Some compounds had remarkable inhibitory activity against the tested microorganisms with MIC values of 1.56−6.25 μM. In particular, triazoles **7c**,**7d**,**7f**,**7h**, and **7r** were active against three clinical MRSA isolates with MIC values of 1.56−6.25 μM. 1*H*-1,2,3-Triazoles **7b**, **7f**, **7i**, **7j**, and **7l** are comparatively less toxic against RAW 264.7 cells than other triazoles.

4. Experimental

Melting points were determined by open capillary method on STUART SMP3 (BIBBY STERILIN, UK). The IR spectra were recorded on FT-IR Affinity-1S Spectrometer (Shimadzu,

Japan) in KBr pellet. The ^{1}H and ^{13}C NMR spectra were recorded on Avance AV500 Spectrometer (Bruker, Germany) at 500 MHz and 125 MHz, respectively, using DMSO-d_6 as solvent and TMS as an internal standard. ESI-mass spectra were recorded on LC-MS LTQ Orbitrap XL, ESI/HR-mass spectra were recorded on Thermo Scientific Exactive Plus Orbitrap spectrometers (ThermoScientific, USA) in methanol using ESI method. The analytical thin-layer chromatography (TLC) was performed on silica gel 60 $WF_{254}S$ aluminum sheets (Merck, Germany) and was visualized with UV light or by iodine vapor. Chemical reagents in high purity were purchased from the Merck Chemical Company (in Viet Nam). All materials were of reagent grade for organic synthesis. The procedures for preparation of the copper catalysts (CuI, $CuIm_2$, CuNPs, Cu@MOF-5), substituted 2-amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitriles (**4a-t**), and also tetra-*O*-acetyl-β-D-glucopyranosyl azide (**6**) were described in Supplemental Data file (in the online version of this article).

4.1 General procedure for the synthesis of substituted 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles

Procedure using potassium carbonate in dried acetone

To a solution of appropriate substituted 2-amino-4-aryl-7-hydroxy-4*H*-chromene-3-carbonitriles **4a-t** (1 mmol) in dried acetone (10 mL) was added anhydrous potassium carbonate (207 mg, 1.5 mmol). Propargyl bromide (1.2 mmol, 143 mg, 0.2 mL of solution 80 wt. % in toluene) then was added dropwise into this suspension mixture. The reaction mixture was heated with stirring at 50°C on water-bath for 12 h. Then the solvent was evaporated completely in vacuum at the ambient temperature. Water was added to the residue to dissolve inorganic salts (K_2CO_3 and KBr). The separated solid product was filtered, washed by water and recrystallized from a mixture of 96% ethanol and toluene (1:1 to 1:2, by volumes) to afford the titled substituted 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles **5a-t**.

Procedure using sodium hydride in dried DMF

The suspension of sodium hydride (24 mg, 1.5 mmol) in dried DMF (2 mL) was cooled to 0°C, then appropriate substituted 2-amino-4-aryl-7-hydroxy-4*H*-chromene-3-carbonitriles **4a-t** (1 mmol) was added to the stirred mixture. The reaction mixture became purple color resulting from the formation of the phenoxide anion of 4*H*-chromene. The reaction mixture was stirred at room temperature until hydrogen ceased (for ~40 min). To this reaction mixture was then added propargyl bromide (1.2 mmol, 143 mg, 0.2 mL of solution 80 wt. % in toluene) in DMF (2 mL) and stirred at room temperature for 2 h. After the completion of the reaction (monitoring by TLC), the reaction mixture was quenched by dropwise addition of water (10 mL) and subsequently extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with a brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the reaction mixture by recrystallized from a mixture of 96% ethanol and toluene (1:1 to 1:2, by volumes) to afford the titled substituted 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles **5a-t** that are the novel compounds. The analytical characteristics for the compound **5a,b** are shown below. The spectral and analytical data of the remained compounds **5c-t** were given in Section 5 (Supplemental Data file in the online version of this article).

*4.1.1. 2-Amino-4-phenyl-7-propargyloxy-4H-chromene-3-carbonitrile (**5a**)*

Ivory solids. From **4a** (R = H, 1 mmol, 264 mg) and propargyl bromide (1.2 mmol, 143 mg, 0.2 mL of solution 80 wt.% in toluene). M.p. 288–289°C (from 96% ethanol/toluene 1:1); FT-IR (KBr), ν (cm^{-1}): 3437, 3333, 3059, 2200, 2133, 1650, 1612, 1501, 1410; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 7.34−7.31 (m, 2H, H-2′ & H-6′), 7.24−7.20 (m, 3H, H-4′, H-3′ & H-5′), 6.96 (d, *J* = 8.75 Hz, 1H, H-5), 6.95 (s, 2H, 2-NH_2), 6.72 (dd, *J* = 8.75, 2.5 Hz, 1H, H-6), 6.67 (d, *J* = 2.5 Hz, 1H, H-8), 4.81 (d, *J* = 2.5 Hz, 2H, 7-O**CH_2**C≡CH), 4.71 (s, 1H, H-4), 3.59 (t, *J* = 2.5 Hz, 1H, 7-OCH_2C≡**CH**); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 160.7 (C-2), 157.6 (C-7), 149.3 (C-8a), 146.8 (C-1′), 130.5 (C-5), 129.1 (C-3′ & C-5′), 127.9 (C-2′ & C-6′), 127.2 (C-4′), 121.1

(C≡N), 114.2 (C-4a), 112.9 (C-6), 102.7 (C-8), 79.4 (7-OCH$_2$**C**≡CH), 79.0 (7-OCH$_2$C≡**CH**), 56.6 (C-3), 56.2 (7-O**CH$_2$**C≡CH), 40.5 (C-4); ESI/HRMS: calcd. for $C_{19}H_{14}N_2O_2$, M = 302.1055 Da; found: *m/z* 302.1058 (100%) $[M]^+$; Elemental anal., calcd: C, 75.48; H, 4.67; N, 9.27%; found: C, 75.77; H, 4.93; N, 9.07%.

*4.1.2. 2-Amino-4-(4′-nitrophenyl)-7-propargyloxy-4H-chromene-3-carbonitrile (**5b**)*

Pale yellow crystals. From **4b** (R = 4′-NO_2, 1 mmol, 309 mg) and propargyl bromide (1.2 mmol, 143 mg, 0.2 mL of solution 80 wt.% in toluene). M.p. 289−290°C (from 96 % ethanol/toluene 1:1); FT-IR (KBr), ν (cm^{-1}): 3445, 3402, 3342, 3267, 3083, 2971, 2865, 2179, 2117, 1657, 1615, 1523, 1404, 1349; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 8.11 (d, *J* = 7.5 Hz, 2H, H-3′ & H-5′), 7.49 (d, *J* = 7.5 Hz, 2H, H-2′ & H-6′), 7.23 (d, *J* = 7.5 Hz, 1H, H-5), 7.02 (s, 2H, 2-NH_2), 6.73 (dd, *J* = 7.5, 1.5 Hz, 1H, H-6), 6.66 (d, *J* = 1.5 Hz, 1H, H-8), 4.88 (dd, *J* = 9.0, 3.0 Hz, 1H, 7-O**CH$_2$**$^{(a)}$C≡CH), 4.87 (s, 1H, H-4), 4.82 (d, *J* = 9.0, 3.0 Hz, 1H, 7-O**CH$_2$**$^{(b)}$C≡CH), 3.60 (t, *J* = 3.0 Hz, 1H, 7-OCH$_2$C≡**CH**); ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 163.9 (C-2), 159.4 (C-7), 153.7 (C-8a), 146.8 (C-1′), 146.5 (C-4′), 146.5 (C-1′), 129.3 (C-2′ & C-6′), 127.1 (C-5), 123.6 (C-3′ & C-5′), 120.6 (C≡N), 119.4 (C-4a), 111.6 (C-6), 102.2 (C-8), 79.0 (7-OCH$_2$**C**≡CH), 75.9 (7-OCH$_2$C≡**CH**), 60.4 (C-3), 56.3 (7-O**CH$_2$**C≡CH), 44.0 (C-4); ESI/MS: calcd. for $C_{19}H_{13}N_3O_4$, M = 347.09 Da, M−H = 346.08 Da; found: *m/z* 346.07 $[M-H]^-$ (100%).

4.2. General procedures for click chemistry of substituted 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles with tetra-O-acetyl-β-D-glucopyranosyl azide

Procedure A. *Use of $CuSO_4.5H_2O$/sodium ascorbate for synthesis of 1H-1,2,3-triazole **7a** (Entry 1, Table 3)*

Reaction mixture consisted of 2-amino-4-phenyl-7-propargyloxy-4*H*-chromene-3-carbonitrile **5a** (1 mmol, 302 mg) and tetra-*O*-acetyl-β-D-glucopyranosyl azide **6** (1 mmol, 373 mg) in DMSO (5 mL). The mixture was stirred gently in order to dissolve the reactants. To the stirred reaction

mixture distilled water (5 mL) was added dropwise. Then, $CuSO_4.5H_2O$ (0.02 mmol, 5.0 mg) and sodium ascorbate (0.05 mmol, 9,9 mg) were added successively to the reaction mixture at room temperature. After stirring the reaction mixture for about 3−5 minutes at room temperature, some white precipitate appeared. The reaction mixture was stirred overnight at room temperature and poured into water (10 mL). The separated solids were filtered, washed with water and crystallized from solvent mixture of 96% ethanol and toluene (ratio of 2:1 by volumes) to afford the titled compounds **7a** as white solids. Yield: 410 mg (60.7%).

Procedure B. *Use of $CuIm_2$ for synthesis of 1H-1,2,3-triazole* ***7a*** *(Entry 2, Table 3)*

Reaction mixture consisted of 2-amino-4-phenyl-7-propargyloxy-4*H*-chromene-3-carbonitrile **5a** (1 mmol, 302 mg) and azide **6** (1 mmol, 373 mg) in absolute ethanol (2 mL). Amount of used catalyst $CuIm_2$ (0.02 mmol, 3.99 mg) was added. The reaction mixture was heated under reflux at 70−75°C on bath for 90 min. Then, the reaction mixture was cooled to room temperature, toluene (with half a volume) was added, the reaction mixture was heated to boiling, and the solid copper catalysts were filtered out. The filtrate was left to stand overnight, and the product separated was filtered and crystallized from solvent mixture of 96% ethanol and toluene (ratio of 2:1 by volumes) to yield the compound **7a** as white solids. Yield: 360 mg (53.3%).

Procedure C. *Use of CuNPs for synthesis of 1H-1,2,3-triazole* ***7a*** *(Entry 3, Table 3)*

This procedure was performed similarly to Procedure B, but CuNPs was used as a catalyst, and NEt_3 was used as an additive. Reaction mixture consists of 2-amino-4-phenyl-7-propargyloxy-4*H*-chromene-3-carbonitrile **5a** (1 mmol, 302 mg) and azide **6** (1 mmol, 373 mg) and CuNPs (0.02 mmol, 34.8 mg) in *t*-BuOH (2 mL). Then, NEt_3 (0.1 mL) was added in the stirring mixture. The reaction mixture was heated and stirred under reflux at 85−87°C on bath for 30 min. After that, the mixture was poured into water (10 mL), and the separated solids were filtered, washed with water and crystallized from solvent mixture of 96% ethanol and toluene (ratio of 2:1 by volumes) to

afford the compound **7a** as white solids. Yield: 643 mg (95.2%).

Procedure D. *Use of CuI for synthesis of 1H-1,2,3-triazole* ***7a*** *(Entry 4, Table 3)*

This procedure was performed similarly to Procedure B, but CuI was used as a catalyst. The reaction mixture consisted of 2-amino-4-phenyl-7-propargyloxy-4*H*-chromene-3-carbonitrile **5a** (1 mmol, 302 mg) and azide **6** (1 mmol, 373 mg) in a mixture of *t*-BuOH (2 mL) and water (0.1 mL). Amount of catalyst CuI (0.02 mmol, 3.82 mg) was added. The reaction mixture was heated under reflux at 85−87°C on bath for 1 h. Then, the reaction mixture was poured into water (10 mL), and the separated solids were filtered, washed with water and crystallized from solvent mixture of 96% ethanol and toluene (ratio of 2:1 by volumes) to afford compound **7a** as white solids. Yield: 640 mg (94.8%).

Procedure E. *Use of Cu@MOF-5 for synthesis of 1H-1,2,3-triazole* ***7a*** *(Entries 5, Table 3)*

This procedure was performed similarly to Procedure B, using Cu@MOF-5 as a catalyst. Reaction mixture consists of 2-amino-4-phenyl-7-propargyloxy-4*H*-chromene-3-carbonitrile **5a** (1 mmol) and azide **6** (1 mmol) in absolute ethanol (2 mL). Amount of catalyst Cu@MOF-5 (0.02 mmol, 15 mg) was added. The reaction mixture was heated under reflux at 79−80°C on bath for 30 min. Then, toluene (1 mL) was added to the reaction mixture, filtered off the solid catalyst, and the filtrate was slowly cooled to give the product, recrystallized from solvent mixture of 96% ethanol and toluene (ratio of 2:1 by volumes). Compound **7a** was obtained with a yield of 97.8% (660 mg). Because the procedure E gave the best yield, the other 1*H*-1,2,3-triazoles **7b-t** were synthesized using this procedure. The characterizations of these 1*H*-1,2,3-triazoles **7a-t** are as follows.

*4.2.1. 2-Amino-4-phenyl-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7a**)*

Pale orange solids, from **5a** (R = H; 1 mmol, 302 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +90.1 (*c* =

0.22, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3424, 3343, 3219, 3123, 2953, 2193, 1755, 1657, 1581, 1506, 1456, 1375, 1224, 1155, 1101, 1039, 924; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 7.32 (t, *J* = 7.25 Hz, 2H, H-3′ & H-5′), 7.23 (t, *J* = 7.25 Hz, 1H, H-4′), 7.19 (d, *J* = 7.25 Hz, 2H, H-2′ & H-6′), 6.95 (s, 2H, 2-NH_2), 6.94 (d, *J* = 8.25 Hz, 1H, H-5), 6.75 (ddd, *J* = 8.25, 5.25, 2.75 Hz, 1H, H-6), 6.71 (d, *J* = 2.0 Hz, 1H, H-8), 6.38 (d, *J* = 9.25 Hz, 1H, H-1″), 5.68 (t, *J* = 9.25 Hz, 1H, H-2″), 5.57 (t, *J* = 9.25 Hz, 1H, H-3″), 5.20 (t, *J* = 9.25 Hz, 1H, H-4″), 5.17 (s, 2H, CH_2O), 4.70 (s, 1H, H-4), 4.38 (ddd, *J* = 10.0, 5.5, 2.5 Hz, 1H, H-5″), 4.12 (dd, *J* = 12.5, 5.5 Hz, 1H, H-6″a), 4.08 (d, *J* = 5.5 Hz, 1H, H-6″b), 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.76 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-**CO**CH_3), 168.9 (2-CH_3**CO**), 160.7 (C-2), 158.0 (C-7), 149.3 (C-8a), 146.6 (C-1′), 143.7 (C-b), 130.5 (C-5), 129.1 (C-3′ & C-5′), 127.9 (C-2′ & C-6′), 127.2 (C-4′), 124.2 (C-a), 121.0 (C≡N), 116.4 (C-4a), 112.5 (C-6), 102.3 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.6 (C-3), 39.5 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{33}H_{33}N_5O_{11}$, M = 675.22 Da; found: *m/z* 676.13 (98%) $[M+H]^+$, 698.31 (100%) $[M+Na]^+$; Elemental analysis, calcd: C, 58.66; H, 4.92; N, 10.37%; found: C, 58.79; H, 4.77; N, 10.52%.

*4.2.2. 2-Amino-4-(4′-nitrophenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7b**)*

Pale yellow solids, from **5b** (R = 4′-NO_2; 1 mmol, 347 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +86.2 (*c* = 0.20, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3470, 3285, 3143, 2958, 2931, 2192, 1756, 1651, 1614, 1585, 1531, 1502, 1352, 1227, 1165, 1105, 1037, 924; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 8.12 (d, *J* = 7.5 Hz, 2H, H-3′ & H-5′), 7.49 (d, *J* = 7.5 Hz, 2H, H-2′ & H-6′), 7.03 (s, 2H, 2-NH_2), 7.23 (d, *J* = 7.5 Hz, 1H, H-5), 6.73 (dd, *J* = 7.5, 1.5 Hz, 1H, H-6), 6.66 (d, *J* = 1.5 Hz, 1H, H-8), 6.37 (d, *J* = 9.25 Hz, 1H, H-1″), 5.67 (td, *J* = 9.25, 2.5 Hz, 1H, H-2″), 5.56 (t, *J* = 9.5 Hz, 1H, H-3″), 5.19 (s, 2H, CH_2O), 4.97 (s, 1H, H-4), 4.38 (ddd, *J* = 9.75, 5.25, 2.5 Hz, 1H, H-5″), 4.12 (dd, *J* = 5.5,

1.5 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.5 Hz, 1H, H-6″a), 2.04 (s, 3H, 6-**CH$_3$**CO), 2.00 (s, 3H, 4-**CH$_3$**CO), 1.98 (s, 3H, 3-**CH$_3$**CO), 1.75 (s, 3H, 2-**CH$_3$**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH$_3$**CO**), 170.0 (3-CH$_3$**CO**), 169.8 (4-CH$_3$**CO**), 168.9 (2-CH$_3$**CO**), 160.9 (C-2), 157.6 (C-7), 149.3 (C-8a), 148.4 (C-1′), 146.8 (C-4′), 146.5 (C-1′), 143.7 (C-b), 130.5 (C-5), 129.3 (C-2′ & C-6′), 124.2 (C-a), 123.6 (C-3′ & C-5′), 120.6 (C≡N), 115.4 (C-4a), 112.9 (C-6), 102.6 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH$_2$O), 55.7 (C-3), 39.5 (C-4), 21.0 (6″-**CH$_3$**CO), 20.9 (4″-**CH$_3$**CO), 20.7 (3″-**CH$_3$**CO), 20.3 (2″-**CH$_3$**CO); ESI/MS, calcd for $C_{33}H_{32}N_6O_{13}$, M = 720.20 Da; found: *m/z* 721.16 (30%) $[M+H]^+$, 743.25 (100%) $[M+Na]^+$; Elemental analysis, calcd: C, 55.00; H, 4.48; N, 11.66%; found: C, 55.23; H, 4.74; N, 11.82%.

*4.2.3. 2-Amino-4-(3′-nitrophenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7c**)*

Pale yellow solids, from **5c** (R = 3′-NO$_2$; 1 mmol, 347 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +84.3 (*c* = 0.28, CHCl$_3$). FT-IR (KBr), ν (cm^{-1}): 3471, 3288, 3147, 2958, 2931, 2193, 1757, 1651, 1614, 1587, 1531, 1502, 1352, 1227, 1165, 1105, 1037, 924; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 8.11 (dd, *J* = 8.0, 1.5 Hz, 1H, H-4′), 8.07 (s, 1H, H-2′), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H, H-5′), 7.65 (td, *J* = 8.9, 1.5 Hz, 1H, H-6′), 7.13 (s, 2H, 2-NH$_2$), 6.99 (dd, *J* = 8.5, 2.5 Hz, 1H, H-5), 6.78 (dd, *J* = 8.5, 2.5 Hz, 1H, H-6), 6.75 (d, *J* = 2.5 Hz, 1H, H-8), 6.37 (d, *J* = 9.25 Hz, 1H, H-1″), 5.67 (td, *J* = 9.25, 2.5 Hz, 1H, H-2″), 5.56 (t, *J* = 9.5 Hz, 1H, H-3″), 5.19 (s, 2H, CH$_2$O), 5.00 (s, 1H, H-4), 4.38 (ddd, *J* = 9.75, 5.25, 2.5 Hz, 1H, H-5″), 4.12 (dd, *J* = 5.5, 1.5 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.5 Hz, 1H, H-6″a), 2.04 (s, 3H, 6-**CH$_3$**CO), 2.00 (s, 3H, 4-**CH$_3$**CO), 1.98 (s, 3H, 3-**CH$_3$**CO), 1.75 (s, 3H, 2-**CH$_3$**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH$_3$**CO**), 170.0 (3-CH$_3$**CO**), 169.8 (4-CH$_3$**CO**), 168.9 (2-CH$_3$**CO**), 160.9 (C-2), 158.3 (C-7), 149.4 (C-8a), 148.8 (C-3′), 148.5 (C-1′), 143.7 (C-b), 134.8 (C-6′), 130.9 (C-5), 130.5 (C-2′), 124.2 (C-a), 122.4 (C-5′), 122.3 (C-4′), 120.7 (C≡N), 115.2 (C-4a), 112.8 (C-6), 102.5 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH$_2$O), 55.7 (C-3), 39.5 (C-4), 21.0 (6″-**CH$_3$**CO), 20.9 (4″-**CH$_3$**CO), 20.7 (3″-

CH$_3$CO), 20.3 (2″-**CH$_3$**CO); ESI/MS, calcd for $C_{33}H_{32}N_6O_{13}$, M = 720.20 Da; found: *m/z* 721.14 (30%) $[M+H]^+$, 743.27 (100%) $[M+Na]^+$; Elemental analysis, calcd: C, 55.00; H, 4.48; N, 11.66%; found: C, 55.33; H, 4.64; N, 11.86%.

*4.2.4. 2-Amino-4-(2′-nitrophenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7d**)*

Pale yellow solids, from **5d** (R = 2′-NO_2; 1 mmol, 347 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +90.1 (*c* = 0.22, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3472, 3288, 3147, 2958, 2931, 2194, 1755, 1651, 1614, 1587, 1537, 1502, 1352, 1227, 1165, 1105, 1037, 924; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 8.06 (dd, *J* = 7.5, 1.5 Hz, 1H, H-3′), 7.57 (td, *J* = 7.25, 1.25 Hz, 1H, H-5′), 7.48−7.45 (m, 2H, H-4′ & H-6′), 7.11 (s, 2H, 2-NH_2), 7.01 (d, *J* = 8.0 Hz, 1H, H-5), 6.74 (dd, *J* = 8.5, 2.5 Hz, 1H, H-6), 6.71 (d, *J* = 2.5 Hz, 1H, H-8), 6.37 (d, *J* = 9.25 Hz, 1H, H-1″), 5.67 (td, *J* = 9.25, 2.5 Hz, 1H, H-2″), 5.56 (t, *J* = 9.5 Hz, 1H, H-3″), 5.19 (s, 2H, CH_2O), 4.92 (s, 1H, H-4), 4.38 (ddd, *J* = 9.75, 5.25, 2.5 Hz, 1H, H-5″), 4.12 (dd, *J* = 5.5, 1.5 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.5 Hz, 1H, H-6″a), 2.04 (s, 3H, 6-**CH$_3$**CO), 2.00 (s, 3H, 4-**CH$_3$**CO), 1.98 (s, 3H, 3-**CH$_3$**CO), 1.75 (s, 3H, 2-**CH$_3$**CO); ^{13}C NMR, δ (ppm): 170.49 (6-CH_3**CO**), 170.02 (3-CH_3**CO**), 169.84 (4-CH_3**CO**), 168.90 (2-CH_3**CO**), 160.9 (C-2), 157.6 (C-7), 149.3 (C-8a), 147.9 (C-2′), 143.7 (C-b), 135.5 (C-1′), 132.4 (C-5′), 130.5 (C-5), 129.9 (C-6′), 124.3 (C-3′), 124.2 (C-a), 122.3 (C-6), 120.6 (C≡N), 115.4 (C-4a), 112.9 (C-6), 102.6 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 55.7 (C-3), 39.5 (C-4), 21.0 (6″-**CH$_3$**CO), 20.9 (4″-**CH$_3$**CO), 20.7 (3″-**CH$_3$**CO), 20.3 (2″-**CH$_3$**CO); ESI/MS, calcd for $C_{33}H_{32}N_6O_{13}$, M = 720.20 Da; found: *m/z* 721.18 (30%) $[M+H]^+$, 743.25 (100%) $[M+Na]^+$; Elemental analysis, calcd: C, 55.00; H, 4.48; N, 11.66%; found: C, 55.19; H, 4.75; N, 11.82%.

*4.2.5. 2-Amino-4-(2′,3′-dichlorophenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7e**)*

Dark orange solids, from **5e** (R = 2′,3′-dichloro; 1 mmol, 371 mg), **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +92.5 (*c* = 0.24, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3443, 3352, 3213, 3078, 2953, 2194, 1757, 1729, 1651, 1622, 1585, 1507, 1398, 1250, 1234, 1157, 1041, 928; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 7.38 (dd, *J* = 7.5, 1.5 Hz, 1H, H-4′), 7.25 (t, *J* = 7.5 Hz, 1H, H-5′), 7.20−7.18 (m, 1H, H-6′); 7.06 (s, 2H, 2-NH_2), 6.94 (d, 1H, *J* = 8.5 Hz, H-5), 6.72 (dd, 1H, *J* = 8.5, 2.5 Hz, H-6), 6.66 (d, 1H, *J* = 2.5 Hz, H-8), 6.38 (d, *J* = 9.25 Hz, 1H, H-1″), 5.68 (d, *J* = 9.25 Hz, 1H, H-2″), 5.58 (d, *J* = 9.25 Hz, 1H, H-3″), 5.21−5.17 (m, 3H, H-4″, CH_2O), 5.20 (s, 1H, H=4″), 4.38 (ddd, *J* = 10.0, 5.5, 2.25 Hz, 1H, H-5″), 4.13 (dd, *J* = 12.5, 5.5 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.25 Hz, 1H, H-6″b), 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.98 (s, 3H, 3-**CH_3**CO), 1.77 & 1.76 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.7 (C-2), 157.3 (C-7), 149.2 (C-8a), 143.6 (C-b), 142.4 (C-1′), 132.1 (C-3′), 131.1 (C-2′), 130.5 (C-5), 129.7 (C-6′), 129.4 (C-4′), 127.7 (C-5′), 120.8 (C≡N), 116.1 (C-4a), 112.8 (C-6), 102.4 (C-8), 124.2 (C-a), 120.5 (C≡N), 114.4 (C-4a), 112.7 (C-6), 102.4 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 54.8 (C-3), 37.4 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{33}H_{31}Cl_2N_5O_{11}$, M = 743.14/745.14/747.13 Da; found: *m/z* 742.21 (100%)/744.27 (61%)/746.28 (14%) $[M-H]^+$; Elemental analysis, calcd: C, 53.24; H, 4.20; N, 9.41%; found: C, 53.12; H, 4.47; N, 9.64%.

*4.2.6. 2-Amino-4-(2′,4′-dichlorophenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7f**)*

Dark orange solids, from **5f** (R = 2′,4′-dichloro; 1 mmol, 371 mg), **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +88.2 (*c* = 0.22, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3449, 3356, 3209, 3076, 2951, 2195, 1755, 1651, 1620, 1583, 1506, 1468, 1402, 131, 1230, 1170, 1105, 1041, 926; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 7.61 (d, *J* = 1.5 Hz, 1H, H-3′), 7.42 (dt, *J* = 8.5, 2.75 Hz, 1H, H-6′), 7.26 (d, *J* = 8.5 Hz, 1H, H-5′), 7.06 (s, 2H, 2-NH_2), 6.86 (dd, *J* = 8.75, 2.25 Hz, 1H, H-5), 6.76 (dt, *J* = 8.75, 2.25 Hz, 1H,

H-6), 6.72 (d, *J* = 2.25 Hz, 1H, H-8), 6.38 (d, *J* = 9.25 Hz, 1H, H-1″), 5.68 (d, *J* = 9.25 Hz, 1H, H-2″), 5.58 (d, *J* = 9.25 Hz, 1H, H-3″), 5.21−5.17 (m, 3H, H-4″, CH_2O), 5.20 (s, 1H, H=4″), 4.38 (ddd, *J* = 10.0, 5.5, 2.25 Hz, 1H, H-5″), 4.13 (dd, *J* = 12.5, 5.5 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.25 Hz, 1H, H-6″b), 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.98 (s, 3H, 3-**CH_3**CO), 1.77 & 1.76 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.9 (C-2), 158.3 (C-7), 149.5 (C-8a), 143.6 (C-b), 142.1 (C-1′), 133.3 (C-2′), 132.8 (C-3′ & C-6′), 129.8 (C-5), 129.7 (C-4′), 128.6 (C-5′), 124.2 (C-a), 120.5 (C≡N), 114.4 (C-4a), 112.7 (C-6), 102.4 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 54.8 (C-3), 37.4 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{33}H_{31}Cl_2N_5O_{11}$, M = 743.14/745.14/747.13 Da; found: *m/z* 742.19 (100%)/744.20 (63%)/746.24 (19%) $[M-H]^+$; Elemental analysis, calcd: C, 53.24; H, 4.20; N, 9.41%; found: C, 53.47; H, 4.39; N, 9.57%.

*4.2.7. 2-Amino-4-(4′-chlorophenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7g**)*

White solids, from **5g** (R = 4′-Cl; 1 mmol, 337 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +80.7 (*c* = 0.25, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3441, 3352, 3213, 3078, 2953, 2195, 1757, 1728, 1651, 1620, 1582, 1506, 1398, 1250, 1234, 1157, 1041, 928; ^{1}H NMR δ (ppm): 8.55 (d, *J* = 1.6 Hz, 1H, H-a), 7.38 (d, *J* = 8.5 Hz, 2H, H-2′ & H-6′), 7.22 (d, *J* = 8.5 Hz, 2H, H-3′ & H-5′), 7.00 (s, 2H, 2-NH_2), 6.93 (dd, *J* = 8.5, 2.25 Hz, 1H, H-5), 6.76 (dt, *J* = 8.5, 2.25 Hz, 1H, H-6), 6.72 (s, 1H, H-8), 6.38 (d, *J* = 9.25 Hz, 1H, H-1″), 5.67 (d, *J* = 9.25 Hz, 1H, H-2″), 5.57 (t, *J* = 9.25 Hz, 1H, H-3″), 5.20 (d, *J* = 9.8 Hz, 1H, H-4″), 5.17 (s, 2H, CH_2O), 4.75 (s, 1H, H-4), 4.40–4.36 (m, 1H, H-5″), 4.13 (t, *J* = 8.9 Hz, 1H, H-6″a), 4.08 (d, *J* = 10.9 Hz, 1H, H-6″b), 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.76 & 1.75 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.6 (C-2), 158.1 (C-7), 158.1 (C-1′), 149.3 (C-8a), 145.6 (C-4′), 143.7 (C-b), 131.8 (C-5), 130.5 (C-5), 129.8 (C-2′ & C-

6′), 129.1 (C-3 & C-5′), 124.2 (C-a), 120.9 (C≡N), 115.8 (C-4a), 112.6 (C-6), 102.4 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.2 (C-3), 39.5 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{33}H_{32}ClN_5O_{11}$, M = 709.18/711.18 Da; found: *m/z* 708.36 (100%)/710.39 (38%) $[M-H]^+$; Elemental analysis, calcd: C, 55.82; H, 4.54; N, 9.86%; found: C, 55.66; H, 4.37; N, 9.65%.

*4.2.8. 2-Amino-4-(3′-chlorophenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7h**)*

Pale yellow solids, from **5h** (R = 3′-Cl; 1 mmol, 337 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +76.4 (*c* = 0.18, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3429, 3344, 3215, 3132, 2947, 2895, 2195, 1757, 1730, 1651, 1624, 1582, 1506, 1398, 1371, 1248, 1236, 1157, 1103, 1041, 928; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 7.36 (td, *J* = 7.5, 1.5 Hz, 1H, H-5′), 7.30 (d, *J* = 7.5 Hz, 1H, H-4′), 7.24 (s, 1H, H-2′), 7.17 (d, *J* = 7.5 Hz, 1H, H-6′), 7.04 (s, 2H, 2-NH_2), 6.97 (dd, *J* = 8.75, 3.25 Hz, 1H, H-5), 6.77 (dt, *J* = 8.75, 3.25 Hz, 1H, H-6), 6.72 (dd, *J* = 6.0, 2.5 Hz, 1H, H-8), 6.37 (d, *J* = 9.5 Hz, 1H, H-1″), 5.68 (td, *J* = 9.5, 1.5 Hz, 1H, H-2″), 5.56 (t, *J* = 9.5 Hz, 1H, H-3″), 5.20−5.18 (m, 3H, H-4″ & CH_2O), 4.77 (s, 1H, H-4), 4.38 (ddd, *J* = 10.0, 5.25, 2.25 Hz, 1H, H-5″), 4.13 (dd, *J* = 12.25, 5.25 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.25, 2.25 Hz, 1H, H-6″b), 2.04 (s, 3H, 6-**CH_3**CO), 2.00 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.74 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.8 (C-2), 158.2 (C-7), 149.3 (C-8a), 149.1 (C-1′), 143.7 (C-b), 133.7 (C-3′), 131.1 (C-5′), 130.5 (C-5), 127.6 (C-2′), 127.3 (C-4′), 126.7 (C-6′), 124.2 (C-a), 120.8 (C≡N), 115.6 (C-4a), 112.7 (C-6), 102.4 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.0 (C-3), 39.5 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (2-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{33}H_{32}ClN_5O_{11}$, M = 709.18/711.18 Da; found: *m/z* 708.28 (100%)/ 710.27 (38%) $[M-H]^-$; Elemental analysis, calcd: C, 55.82; H, 4.54; N, 9.86%; found: C, 55.68; H, 4.72; N, 9.57%.

*4.2.9. 2-Amino-4-(2′-chlorophenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7i**)*

White solids, from **5i** (R = 2′-Cl; 1 mmol, 337 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +79.5 (*c* = 0.23, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3426, 3344, 3215, 3132, 2947, 2895, 2192, 1757, 1734, 1651, 1624, 1582, 1506, 1398, 1371, 1248, 1236, 1157, 1103, 1045, 927; ^{1}H NMR δ (ppm): 8.55 (d, *J* = 1.6 Hz, 1H, H-a), 7.44 (dd, 1H, *J* = 1.5, 7.75 Hz, H-3′), 7.32 (td, 1H, *J* = 7.5, 1.5 Hz, H-6′), 7.27 (td, 1H, *J* = 1.5, 7.5 Hz, H-4′), 7.22 (dd, 1H, *J* = 7.5, 1.5 Hz, H-5′), 7.00 (s, 2H, 2-NH_2), 6.87 (d, 1H, *J* = 8.5 Hz, H-5), 6.71 (dd, 1H, *J* = 8.5, 2.5 Hz, H-6), 6.67 (d, 1H, *J* = 2.5 Hz, H-8), 6.38 (d, *J* = 9.25 Hz, 1H, H-1″), 5.67 (d, *J* = 9.25 Hz, 1H, H-2″), 5.57 (t, *J* = 9.25 Hz, 1H, H-3″), 5.20 (d, *J* = 9.8 Hz, 1H, H-4″), 5.17 (s, 2H, CH_2O), 4.77 (s, 1H, H-4), 4.40–4.36 (m, 1H, H-5″), 4.13 (t, *J* = 8.9 Hz, 1H, H-6″a), 4.08 (d, *J* = 10.9 Hz, 1H, H-6″b), 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.76 & 1.75 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.9 (C-2), 157.5 (C-7), 149.4 (C-8a), 143.7 (C-b), 143.0 (C-1′), 132.3 (C-2′), 130.3 (C-5), 129.8 (C-3′), 129.2 (C-4′), 128.4 (C-5′), 124.2 (C-a), 120.6 (C≡N), 115.3 (C-4a), 112.7 (C-6), 102.4 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.2 (C-3), 39.5 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{33}H_{32}ClN_5O_{11}$, M = 709.18/711.18 Da; found: *m/z* 708.25 (100%)/ 710.22 (35%) $[M-H]^-$; Elemental analysis, calcd: C, 55.82; H, 4.54; N, 9.86%; found: C, 55.67; H, 4.74; N, 9.68%.

*4.2.10. 2-Amino-4-(4′-bromophenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7j**)*

White solids, from **5j** (R = 4′-Br; 1 mmol, 381 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +77.5 (*c* = 0.23, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3442, 3353, 3213, 3078, 2953, 2193, 1756, 1728, 1654, 1620, 1582, 1506, 1398, 1251, 1234, 1157, 1041, 928; ^{1}H NMR δ (ppm): 8.55 (d, *J* = 1.6 Hz, 1H, H-a),

7.38 (d, 2H, *J* = 8.5 Hz, H-2′ & H-6′), 7.22 (d, 2H, *J* = 8.5 Hz, H-3′ & H-5′), 6.99 (s, 2H, 2-NH_2), 6.94 (d, 1H, *J* = 8.5 Hz, H-5), 6.72 (dd, 1H, *J* = 8.5, 2.5 Hz, H-6), 6.66 (d, 1H, *J* = 2.5 Hz, H-8), 6.38 (d, *J* = 9.25 Hz, 1H, H-1″), 5.67 (d, *J* = 9.25 Hz, 1H, H-2″), 5.57 (t, *J* = 9.25 Hz, 1H, H-3″), 5.20 (d, *J* = 9.8 Hz, 1H, H-4″), 5.17 (s, 2H, CH_2O), 4.75 (s, 1H, H-4), 4.40–4.36 (m, 1H, H-5″), 4.13 (t, *J* = 8.9 Hz, 1H, H-6″a), 4.08 (d, *J* = 10.9 Hz, 1H, H-6″b), 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.76 & 1.75 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.7 (C-2), 157.3 (C-7), 149.2 (C-8a), 145.5 (C-1′), 143.7 (C-b), 131.9 (C-4′), 130.5 (C-5), 129.8 (C-2′ & C-6′), 129.1 (C-3′ & C-5′), 124.2 (C-a), 120.8 (C≡N), 116.1 (C-4a), 112.8 (C-6), 102.4 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.2 (C-3), 39.5 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{33}H_{32}BrN_5O_{11}$, M = 753.13/755.13 Da; found: *m/z* 752.22 (100%)/754.21 (96%) $[M-H]^-$; Elemental analysis, calcd: C, 52.53; H, 4.27; N, 9.28%; found: C, 52.74; H, 4.51; N, 9.43%.

*4.2.11. 2-Amino-4-(4′-methylphenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7k**)*

White solids, from **5k** (R = 4′-Me; 1 mmol, 316 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +89.3 (*c* = 0.25, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3441, 3352, 3213, 3123, 3003, 2953, 2193, 1757, 1730, 1651, 1622, 1582, 1506, 1398, 1248, 1234, 1157, 1123, 1041, 928; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 7.12 (d, *J* = 7.75 Hz, 2H, H-2′ & H-6′), 7.07 (d, *J* = 7.75 Hz, 2H, H-3′ & H-5′), 6.92 (d, *J* = 3.0 Hz, 1H, H-5), 6.91 (s, 2H, 2-NH_2), 6.76−6.73 (m, 1H, H-6), 6.70 (d, *J* = 2.5 Hz, 1H, H-8), 6.38 (d, *J* = 9.25 Hz, 1H, H-1″), 5.68 (t, *J* = 9.25 Hz, 1H, H-2″), 5.57 (t, *J* = 9.25 Hz, 1H, H-3″), 5.20 (d, *J* = 9.25 Hz, 1H, H-4″), 5.16 (s, 2H, CH_2O), 4.64 (s, 1H, H-4), 4.38 (ddd, *J* = 10.0, 5.25, 2.25 Hz, 2H), 4.12 (dd, *J* = 12.5, 5.25 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.25 Hz, 1H, H-6″b), 2.26 (s, 3H, 4′-CH_3), 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.98 (s, 3H, 3-**CH_3**CO), 1.76 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9

(2-CH_3**CO**), 160.6 (C-2), 157.9 (C-7), 149.3 (C-8a), 143.7 (C-b), 136.3 (C-1′), 130.5 (C-5), 129.6 (C-2′ & C-6′), 127.8 (C-3′ & C-5′), 124.2 (C-a), 124.2 (C-4′), 121.0 (C≡N), 116.5 (C-4a), 112.5 (C-6), 102.2 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.8 (C-3), 39.5 (C-4), 21.1 (4′-CH_3), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{34}H_{35}N_5O_{11}$, M = 689.23 Da; found: *m/z* 690.23 (53%) $[M+H]^+$, 712.26 (100%) $[M+Na]^+$; Elemental analysis, calcd: C, 59.21; H, 5.12; N, 10.15%; found: C, 59.46; H, 5.35; N, 10.42%.

*4.2.12. 2-Amino-4-(4′-isopropylphenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7l**)*

White solids, from **5l** (R = 4′-iPr; 1 mmol, 344 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +77.8 (*c* = 0.23, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3456, 3352, 3213, 3121, 2961, 2193, 1755, 1734, 1649, 1620, 1582, 1506, 1462, 1396, 1230, 1101, 1041, 926; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 7.18 (d, *J* = 7.0 Hz, 2H, H-2″ & H-6″), 7.10 (d, *J* = 7.0 Hz, 2H, H-3″ & H-5″), 6.95 (dd, *J* = 8.25, 2.75 Hz, 1H, H-5), 6.92 (s, 2H, 2-NH_2), 6.75 (ddd, *J* = 8.25, 5.5, 2.75 Hz, 1H, H-6), 6.70 (d, *J* = 2.75 Hz, 1H, H-8), 6.37 (d, *J* = 9.25 Hz, 1H, H-1″), 5.68 (t, *J* = 9.25 Hz, 1H, H-2″), 5.56 (t, *J* = 9.25 Hz, 1H, H-3″), 5.18 (t, *J* = 10.0 Hz, 1H, H-4″), 5.16 (s, 2H, CH_2O), 4.65 (s, 1H, H-4), 4.37 (ddd, *J* = 10.0, 5.5, 2.5 Hz, 1H, H-5″), 4.13 (dd, *J* = 12.75, 5.25 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.0 Hz, 1H, H-6″b), 2.84 [septet, *J* = 7.0 Hz, 1H, 4′-**CH**(CH_3)$_2$], 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.74 (s, 3H, 2-**CH_3**CO), 1.18 [d, *J* = 7.0 Hz, 6H, 4′-CH**(CH_3)$_2$**]; ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.7 (C-2), 157.9 (C-7), 149.3 (C-8a), 147.2 (C-4′), 144.1 (C-1′), 143.7 (C-b), 130.5 (C-5), 127.7 (C-2′ & C-6′), 127.0 (C-3′ & C-5′), 124.2 (C-a), 121.1 (C≡N), 116.6 (C-4a), 112.5 (C-6), 102.3 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.7 (C-3), 38.9 (C-4), 33.5 [4′-**CH**(CH_3)$_2$]. 24.3 [4′-CH**(CH_3)$_2$**], 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{36}H_{39}N_5O_{11}$, M = 717.26

Da; found: *m/z* 718.23 (100%) $[M+H]^+$, 740.26 (76%) $[M+Na]^+$; Elemental analysis, calcd: C, 60.24; H, 5.48; N, 9.76%; found: C, 60.52; H, 5.63; N, 9.54%.

*4.2.13. 2-Amino-4-(4′-dimethylaminophenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7m**)*

White solids, from **5m** (R = 4′-dimethylamino; 1 mmol, 345 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +79.3 (*c* = 0.22, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3454, 3352, 3215, 3121, 2961, 2192, 1755, 1737, 1645, 1620, 1582, 1513, 1465, 1396, 1230, 1101, 1041, 926; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 7.14 (d, *J* = 6.5 Hz, 2H, H-2′ & H-6′), 6.96 (d, 1H, *J* = 9.0 Hz, H-5), 6.91 (s, 2H, 2-NH_2), 6.71 (dd, 1H, *J* = 9.0, 2.5 Hz, H-6), 6.64 (d, *J* = 7.5 Hz, 2H, H-3′ & H-5′), 6.70 (d, 1H, *J* = 2.5 Hz, H-8), 6.37 (d, *J* = 9.25 Hz, 1H, H-1″), 5.68 (t, *J* = 9.25 Hz, 1H, H-2″), 5.56 (t, *J* = 9.25 Hz, 1H, H-3″), 5.18 (t, *J* = 10.0 Hz, 1H, H-4″), 5.16 (s, 2H, CH_2O), 4.65 (s, 1H, H-4), 4.37 (ddd, *J* = 10.0, 5.5, 2.5 Hz, 1H, H-5″), 4.13 (dd, *J* = 12.75, 5.25 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.0 Hz, 1H, H-6″b), 2.94 [s, 6H, 4′-N(**CH_3**)**$_2$**], 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.74 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.7 (C-2), 157.2 (C-7), 150.7 (C-4′), 149.2 (C-8a), 143.7 (C-b), 134.5 (C-1′), 130.5 (C-5), 128.8 (C-2′ & C-6′), 124.2 (C-a), 121.1 (C≡N), 116.9 (C-4a), 112.6 (C-6), 112.1 (C-3′ & C-5′); 102.3 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.7 (C-3), 40.3 [4′-N(**CH_3**)**$_2$**], 38.9 (C-4), 33.5 [4′-**CH**(CH_3)$_2$], 24.3 [4′-CH**(CH_3)$_2$**], 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{35}H_{38}N_6O_{11}$. M= 718.26 Da; found: *m/z* 718.22 (100%) $[M+H]^+$, 740.25 (80%) $[M+Na]^+$; Elemental analysis, calcd: C, 58.49; H, 5.33; N, 11.69%; found: C, 58.65; H, 5.43; N, 11.34%.

*4.2.14. 2-Amino-4-(4′-methoxyphenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7n**)*

White solids, from **5n** (R = 4′-OMe; 1 mmol, 332 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +87.1 (*c* = 0.22, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3458, 3354, 3211, 3076, 2956, 2191, 1755, 1649, 1612, 1582, 1508, 1462, 1398, 1371, 1232, 1172, 1105, 1039, 926; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 7.10 (d, *J* = 8.5 Hz, 2H, H-2′ & H-6′), 6.93−6.86 (m, 5H, H-3′, H-5′, H-5 & 2-NH_2), 6.76–6.74 (m, 1H, H-6), 6.70 (d, *J* = 2.5 Hz, 1H, H-8), 6.38 (d, *J* = 9.2 Hz, 1H, H-1″), 5.68 (t, *J* = 9.5 Hz, 1H, 2″), 5.57 (t, *J* = 9.5 Hz, 1H, 3″), 5.19 (t, *J* = 9.5 Hz, 1H, 4″), 5.16 (s, 2H, CH_2O), 4.64 (s, 1H, H-4), 4.38 (ddd, *J* = 10.0, 5.5, 2.5 Hz, 1H, H-5″), 4.14 (dd, *J* = 12.5, 5.5 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.5 Hz, 1H, H-6″b), 3.72 (s, 3H, 4′-OCH_3), 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.98 (s, 3H, 3-**CH_3**CO), 1.76 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.5 (C-2), 158.5 (C-7), 157.9 (C-4′), 149.3 (C-8a), 143.7 (C-b), 138.7 (C-1′), 130.5 (C-5), 129.0 (C-2′ & C-6′), 124.2 (C-a), 121.1 (C≡N), 116.7 (C-4a), 114.4 (C-3′ & C-5′), 112.4 (C-6), 102.2 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 57.0 (C-3), 55.5 (4′-OCH_3), 40.4 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{34}H_{35}N_5O_{12}$. M= 705.23 Da; found: *m/z* 706.15 (100%) $[M+H]^+$, 728.30 (82%) $[M+Na]^+$; Elemental analysis, calcd: C, 57.87; H, 5.00; N, 9.92%; found: C, 57.63; H, 5.33; N, 9.66%.

*4.2.15. 2-Amino-4-(3′-methoxyphenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7o**)*

Pale yellow solids, from **5o** (R = 3′-OMe; 1 mmol, 332 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +79.4 (*c* = 0.23, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3455, 3354, 3213, 3076, 2956, 2194, 1756, 1647, 1612, 1582, 1508, 1462, 1398, 1371, 1232, 1173, 1105, 1039, 926; ^{1}H NMR, δ (ppm): 8.54 (s, 1H, H-a), 7.21 (t, *J* = 7.5 Hz, 1H, H-5′), 7.02−7.00 (m, 1H, H-6′), 6.93 (d, 1H, *J* = 8.75 Hz, H-5), 6.90 (s, 2H, 2-NH_2), 6.88−6.87 (m, 1H, H-2′), 6.86−6.85 (m, 1H, H-4′), 6.71 (dd, 1H, *J* = 8.75, 2.5 Hz, H-6), 6.66 (d, 1H, *J* = 2.5 Hz, H-8), 6.38 (d, *J* = 9.5 Hz, 1H, H-1″), 5.68 (t, *J* = 9.5 Hz, 1H, H-2″), 5.57 (t, *J* = 9.5 Hz, 1H, H-3″), 5.19 (t, *J* = 9.75 Hz, 1H, H-4″), 5.15 (s, 2H, CH_2O), 5.04 (s, 1H, H-4),

4.38 (ddd, *J* = 10.0, 5.25, 2.25 Hz, 1H, H-5″), 4.13 (dd, *J* = 12.75, 5.25 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.75, 2.25 Hz, 1H, H-6″b), 3.87 (s, 3H, 3′-OCH_3), 2.07 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.76 & 1.74 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.5 (C-2), 158.5 (C-7), 159.9 (C-3′), 149.2 (C-8a),143.7 (C-b), 143.3 (C-1′), 130.5 (C-5), 129.2 (C-5′), 125.0 (C-6′), 124.2 (C-a), 121.0 (C≡N), 117.0 (C-4a), 114.2 (C-2′), 113.0 (C-4′), 112.6 (C-6), 102.3 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.1 (C-3), 55.6 (2′-OCH_3), 34.1 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{34}H_{35}N_5O_{12}$. M= 705.23 Da; found: *m/z* 706.27 (86%) $[M+H]^+$, 728.26 (100%) $[M+Na]^+$; Elemental analysis, calcd: C, 57.87; H, 5.00; N, 9.92%; found: C, 57.53; H, 5.15; N, 9.57%.

*4.2.16. 2-Amino-4-(2′-methoxyphenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7p**)*

Pale yellow solids, from **5p** (R = 2′-OMe; 1 mmol, 332 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +98.5 (*c* = 0.27, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3452, 3354, 3215, 3076, 2945, 2189, 1757, 1734, 1649, 1622, 1585, 1506, 1462, 1371, 1236, 1159, 1103, 1041, 928; ^{1}H NMR, δ (ppm): 8.54 (s, 1H, H-a), 7.20 (t, *J* = 7.75 Hz, 1H, H-6′), 7.22−7.19 (m, 2H, H-4′ & H-5′), 6.90 (m, 1H, H-3′), 6.86 (s, 2H, 2-NH_2), 6.73−6.11 (m, 1H, H-6), 6.78−6.74 (m, 1H, H-8), 6.38 (d, *J* = 9.5 Hz, 1H, H-1″), 5.68 (t, *J* = 9.5 Hz, 1H, H-2″), 5.57 (t, *J* = 9.5 Hz, 1H, H-3″), 5.19 (t, *J* = 9.75 Hz, 1H, H-4″), 5.15 (s, 2H, CH_2O), 5.04 (s, 1H, H-4), 4.38 (ddd, *J* = 10.0, 5.25, 2.25 Hz, 1H, H-5″), 4.13 (dd, *J* = 12.75, 5.25 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.75, 2.25 Hz, 1H, H-6″b), 3.79 (s, 3H, 2′-OCH_3), 2.07 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.76 & 1.74 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 161.3 (C-2), 157.8 (C-7), 156.8 (C-2′), 149.7 (C-8a), 143.7 (C-b), 134.2 (C-5′), 129.8 (C-5), 129.1 (C-3′), 128.5 (C-4′), 124.2 (C-a), 121.2 (C-1′), 121.1 (C≡N), 116.6 (C-4a), 112.2 (C-3′), 112.1 (C-6),

102.2 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.1 (C-3), 55.6 (2′-OCH_3), 34.1 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{34}H_{35}N_5O_{12}$. M= 705.23 Da; found: *m/z* 706.28 (85%) $[M+H]^+$, 728.25 (100%) $[M+Na]^+$; Elemental analysis, calcd: C, 57.87; H, 5.00; N, 9.92%; found: C, 57.54; H, 5.24; N, 9.71%.

*4.2.17. 2-Amino-4-(2′,3′-dimethoxyphenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7q**)*

Pale yellow solids, from **5q** (R = 2′,3′-dimethoxy; 1 mmol, 362 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +77.5 (*c* = 0.21, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3452, 3353, 3212, 3073, 2945, 2187, 1755, 1733, 1649, 1624, 1585, 1506, 1462, 1371, 1236, 1159, 1103, 1041, 928; ^{1}H NMR, δ (ppm): 8.54 (s, 1H, H-a), 7.04−7.03 (m, 1H, H-6′), 7.00 (t, *J* = 7.5 Hz, 1H, H-5′), 6.93 (d, 1H, *J* = 8.75 Hz, H-5), 6.90 (s, 2H, 2-NH_2), 6.81 (dd, *J* = 6.5, 1.5 Hz, 1H, H-4′), 6.71 (dd, 1H, *J* = 8.75, 2.5 Hz, H-6), 6.66 (d, 1H, *J* = 2.5 Hz, H-8), 6.38 (d, *J* = 9.5 Hz, 1H, H-1″), 5.68 (t, *J* = 9.5 Hz, 1H, H-2″), 5.57 (t, *J* = 9.5 Hz, 1H, H-3″), 5.19 (t, *J* = 9.75 Hz, 1H, H-4″), 5.15 (s, 2H, CH_2O), 5.04 (s, 1H, H-4), 4.38 (ddd, *J* = 10.0, 5.25, 2.25 Hz, 1H, H-5″), 4.13 (dd, *J* = 12.75, 5.25 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.75, 2.25 Hz, 1H, H-6″b), 3.82 (s, 3H, 3′-OCH_3), 3.79 (s, 3H, 2′-OCH_3), 2.07 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.76 & 1.74 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.5 (C-2), 158.5 (C-7), 150.7 (C-3′), 149.2 (C-8a), 148.4 (C-2′), 143.7 (C-b), 130.5 (C-5), 124.6 (C-6′), 124.2 (C-a), 123.6 (C-5′), 132.0 (C-1′), 121.0 (C≡N), 117.0 (C-4a), 113.0 (C-4′), 112.6 (C-6), 102.3 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 60.4 (3′-OCH_3), 56.1 (C-3), 56.0 (2′-OCH_3), 34.1 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2-**CH_3**CO); ESI/MS, calcd for $C_{35}H_{37}N_5O_{13}$. M= 735.24 Da; found: *m/z* 736.28 (84%) $[M+H]^+$, 758.29 (100%) $[M+Na]^+$; Elemental analysis, calcd: C, 57.14; H, 5.07; N, 9.52%; found: C, 57.31; H, 5.32; N, 9.79%.

*4.2.18. 2-Amino-4-(2′,4′-dimethoxyphenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7r**)*

Pale yellow solids, from **5r** (R = 2′,4′-dimethoxy; 1 mmol, 362 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +78.3 (*c* = 0.22, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3452, 3353, 3212, 3073, 2945, 2190, 1756, 1733, 1649, 1624, 1585, 1516, 1465, 1375, 1236, 1159, 1103, 1041, 928; ^{1}H NMR, δ (ppm): 8.54 (s, 1H, H-a), 7.16 (d, *J* = 7.5 Hz, 1H, H-6′), 6.93 (d, 1H, *J* = 8.75 Hz, H-5), 6.90 (s, 2H, 2-NH_2), 6.81 (dd, *J* = 6.5, 1.5 Hz, 1H, H-4′), 6.71 (dd, 1H, *J* = 8.75, 2.5 Hz, H-6), 6.66 (d, 1H, *J* = 2.5 Hz, H-8), 6.59 (dd, *J* = 7.5, 1.5 Hz, 1H, H-5′), 6.54 (d, *J* = 1.5 Hz, 1H, H-3′), 6.38 (d, *J* = 9.5 Hz, 1H, H-1″), 5.68 (t, *J* = 9.5 Hz, 1H, H-2″), 5.57 (t, *J* = 9.5 Hz, 1H, H-3″), 5.19 (t, *J* = 9.75 Hz, 1H, H-4″), 5.15 (s, 2H, CH_2O), 5.04 (s, 1H, H-4), 4.38 (ddd, *J* = 10.0, 5.25, 2.25 Hz, 1H, H-5″), 4.13 (dd, *J* = 12.75, 5.25 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.75, 2.25 Hz, 1H, H-6″b), 3.83 (s, 3H, 4′-OCH_3), 3.82 (s, 3H, 2′-OCH_3), 2.07 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.97 (s, 3H, 3-**CH_3**CO), 1.76 & 1.74 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.5 (C-2), 158.5 (C-7), 159.8 (C-4′), 158.2 (C-2′), 149.2 (C-8a), 143.7 (C-b), 130.5 (C-6′), 127.4 (C-5), 124.2 (C-a), 123.9 (C-1′), 121.0 (C≡N), 117.0 (C-4a), 112.6 (C-6), 108.0 (C-5′), 102.3 (C-8), 99.2 (C-3′), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 56.3 (C-3), 55.8 (2′-OCH_3), 55.6 (3′-OCH_3), 34.1 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{35}H_{37}N_5O_{13}$. M= 735.24 Da; found: *m/z* 736.27 (84%) $[M+H]^+$, 758.31 (100%) $[M+Na]^+$; Elemental analysis, calcd: C, 57.14; H, 5.07; N, 9.52%; found: C, 57.41; H, 5.31; N, 9.75%.

*4.2.19. 2-Amino-4-(3′,4′-dimethoxyphenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7s**)*

White solids, from **5s** (R = 3′,4′-dimethoxy; 1 mmol, 362 mg) and **6** (1 mmol, 373 mg). $[\alpha]_D^{25}$ +79.1 (*c* = 0.22, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3451, 3353, 3212, 3073, 2945, 2188, 1754, 1730,

1650, 1624, 1586, 1506, 1462, 1371, 1236, 1159, 1103, 1041, 928; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 6.84−6.83 (m, 2H, H5′ & H-6′), 6.93 (d, 1H, *J* = 8.75 Hz, H-5), 6.90 (s, 2H, 2-NH_2), 6.78−6.77 (m, 1H, H-2′), 6.71 (dd, 1H, *J* = 8.75, 2.5 Hz, H-6), 6.66 (d, 1H, *J* = 2.5 Hz, H-8), 6.38 (d, *J* = 9.2 Hz, 1H, H-1″), 5.68 (t, *J* = 9.5 Hz, 1H, 2″), 5.57 (t, *J* = 9.5 Hz, 1H, 3″), 5.19 (t, *J* = 9.5 Hz, 1H, 4″), 5.16 (s, 2H, CH_2O), 4.64 (s, 1H, H-4), 4.38 (ddd, *J* = 10.0, 5.5, 2.5 Hz, 1H, H-5″), 4.14 (dd, *J* = 12.5, 5.5 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.5 Hz, 1H, H-6″b), 3.79 (s, 3H, 4′-OCH_3), 3.76 (s, 3H, 3′-OCH_3), 2.04 (s, 3H, 6-**CH_3**CO), 2.01 (s, 3H, 4-**CH_3**CO), 1.98 (s, 3H, 3-**CH_3**CO), 1.76 (s, 3H, 2-**CH_3**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH_3**CO**), 170.0 (3-CH_3**CO**), 169.9 (4-CH_3**CO**), 168.9 (2-CH_3**CO**), 160.5 (C-2), 158.5 (C-7), 149.3 (C-3′), 149.2 (C-8a), 148.5 (C-4′), 143.7 (C-b), 136.4 (C-1′), 127.4 (C-5), 124.2 (C-a), 123.6 (C-6′), 121.0 (C≡N), 117.0 (C-4a), 112.6 (C-6), 112.5 (C-2′), 112.3 (C-5′), 102.3 (C-8), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 57.0 (C-3), 55.9 (3′-OCH_3), 55.8 (4′-OCH_3), 40.4 (C-4), 21.0 (6″-**CH_3**CO), 20.9 (4″-**CH_3**CO), 20.7 (3″-**CH_3**CO), 20.3 (2″-**CH_3**CO); ESI/MS, calcd for $C_{35}H_{37}N_5O_{13}$. M= 735.24 Da; found: *m/z* 736.28 (84%) $[M+H]^+$, 758.30 (100%) $[M+Na]^+$; Elemental analysis, calcd: C, 57.14; H, 5.07; N, 9.52%; found: C, 57.48; H, 5.38; N, 9.81%.

*4.2.20. 2-Amino-4-(3′,5′-dimethoxyphenyl)-7-((1-(2″,3″,4″,6″-tetra-O-acetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (**7t**)*

White solids, from **5t** (R = 3′,5′-dimethoxy; 1 mmol, 362 mg) and **6** (1 mmol, 373 mg). Yield 0.42 g (60%). $[\alpha]_D^{25}$ +79.6 (*c* = 0.21, $CHCl_3$). FT-IR (KBr), ν (cm^{-1}): 3452, 3350, 3212, 3071, 2945, 2187, 1756, 1738, 1645, 1627, 1588, 1514, 1462, 1371, 1236, 1159, 1103, 1041, 928; ^{1}H NMR, δ (ppm): 8.55 (s, 1H, H-a), 6.93 (d, *J* = 8.75 Hz, 1H, H-5), 6.90 (s, 2H, 2-NH_2), 6.66 (d, 1H, *J* = 2.5 Hz, H-8), 6.63−6.62 (m, 2H, H-2′ & H-6′), 12.5 (d, *J* = 8.75 Hz, 1H, H-4′), 6.38 (d, *J* = 9.2 Hz, 1H, H-1″), 5.68 (t, *J* = 9.5 Hz, 1H, 2″), 5.57 (t, *J* = 9.5 Hz, 1H, 3″), 5.19 (t, *J* = 9.5 Hz, 1H, 4″), 5.16 (s, 2H, CH_2O), 4.64 (s, 1H, H-4), 4.38 (ddd, *J* = 10.0, 5.5, 2.5 Hz, 1H, H-5″), 4.14 (dd, *J* = 12.5, 5.5 Hz, 1H, H-6″a), 4.08 (dd, *J* = 12.5, 2.5 Hz, 1H, H-6″b), 3.77 (s, 6H, 3′- & 5′-OCH_3), 2.04 (s, 3H,

6-**CH$_3$**CO), 2.01 (s, 3H, 4-**CH$_3$**CO), 1.98 (s, 3H, 3-**CH$_3$**CO), 1.76 (s, 3H, 2-**CH$_3$**CO); ^{13}C NMR, δ (ppm): 170.5 (6-CH$_3$**CO**), 170.0 (3-CH$_3$**CO**), 169.9 (4-CH$_3$**CO**), 168.9 (2-CH$_3$**CO**), 160.5 (C-2), 159.9 (C-3′ & C-5′), 158.5 (C-7), 149.2 (C-8a), 143.7 (C-b), 142.3 (C-1′), 127.4 (C-5), 124.2 (C-a), 121.0 (C≡N), 117.0 (C-4a), 112.6 (C-6), 108.76 (C-2′ & C-6′), 102.3 (C-8), 100.9 (C-4′), 84.3 (C-1″), 73.7 (C-5″), 72.6 (C-3″), 70.6 (C-2″), 68.0 (C-4″), 62.3 (C-6″), 61.7 (CH_2O), 57.0 (C-3), 55.6 (3′- & 5′-OCH_3), 40.4 (C-4), 21.0 (6″-**CH$_3$**CO), 20.9 (4″-**CH$_3$**CO), 20.7 (3″-**CH$_3$**CO), 20.3 (2″-**CH$_3$**CO); ESI/HRMS, calcd for $C_{35}H_{37}N_5O_{13}$. M= 735.2388 Da, M+H = 736.2461 Da; found: *m/z* 736.2464 (100%) $[M+H]^+$.

4.3. Biological assays

4.3.1. Chemicals

Chrysin, dicyclohexylcarbodiimide (DCC) and diethylphosphoryl cyanide (DEPC), sodium azide, ethylenediamine tetraacetic acid (EDTA), β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), cumene hydroperoxide, glutathione reductase, DL-α-tocopherol acetate, carbon tetrachloride (CCl_4), xanthine, potassium cyanide (KCN), sodium dodecylsulfate, trichloroacetic acid (TCA), cytochrome C, thiobarbituric acid, *n*-butanol, pyridine, HEPES [4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid], L-glutamine, sodium pyruvate, and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide were purchased from Sigma-Aldrich Chemical Co. (Viet Nam). All other chemicals and reagents were analytical grade.

4.3.2. In vitro antimicrobial activity

The all synthesized 1*H*-1,2,3-triazoles **7a-t** were screened the *in vitro* antibacterial and antifungal activities against Gram-positive, Gram-negative bacteria organisms. Gram-positive were chosen were *B. subtilis* (ATCC 11774), *S. aureus* (ATCC 11632), *S. epidermidis* (ATCC 12228); Gram-negative bacteria were *E. coli* (ATCC 25922), *K. pneumoniae* (ATCC 4352), *P. aeruginosa* (ATCC 25923), and *S. typhimurium* (ATCC 1402). Three methicillin resistant *S. aureus*

(MRSA198-1, MRSA198-2 and MRSA198-3 were also chosen. The evaluations were performed by using minimum inhibitory concentration (MIC), as described in our previous article [47]. The microbroth dilutions technique was applied using Mueller-Hinton broth [48]. Each tested compound was dissolved in dimethyl sulfoxide (DMSO) at concentration of 1 mg/mL. The drug references were ciprofloxacin, methicillin and vancomycin (Table 5). The solutions that had the concentrations of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, and 0.78 μM were prepared by further diluting the test compounds and standard drugs prepared above. The inoculum was prepared using a 4–6-h broth adjusted to a turbidity equivalent of an 0.5 McFarland standard, diluted in broth media to give a final concentration of 5×10^5 CFU/mL in the test tray. The plates were incubated at 35°C for 18–20 h. The MIC was defined as the lowest concentration of compound giving complete inhibition of visible growth. All the experiments were performed three times. The MIC values for all tested compounds and reference drug are listed in Table 5.

4.3.3. In vitro antifungal activity

The compounds **7a-t** were evaluated for their *in vitro* antifungal activity against three fungi, including *A. niger* (439), *A. flavus* (ATCC 204304), *S. cerevisiae* (SH 20), and *C. albicans* (ATCC 7754), using agar dilution method with Saburoud's dextrose agar (Hi-Media), as described in our previous article [47]. Miconazole and fluconazole were used as drug references for antifungal activity. The solutions, which had the concentrations of 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, and 0.78 μM of each tested compound and standard drugs, were prepared. Suspensions of each microorganisms were prepared to contain 10 CFU/mL and applied to agar plates, which had been serially diluted with compounds to be tested. The plates were incubated at 35°C. After 72 h, the MICs were determined [48]. Minimal inhibitory concentrations for each compound were investigated against standard fungal strains. All the experiments were performed three times. The MIC values for all tested compounds and reference drug are shown in Table 6.

4.3.4. Cytotoxicity screening

Stock solutions were freshly prepared by dissolving tested compounds in DMSO. Cells were from ATCC and showed no mycoplasma contamination as revealed by Roche ELISA-based test [49, 50]. Cells were cultured in 96-well plates (25,000 cells/well for RAW). Cells were allowed to attach overnight. Drugs were added to wells in 10 mL aliquots of 200-times concentrated drug solutions dissolved in DMSO, in duplicates. DMSO (10 mL) was added to control-wells. Cells were incubated with studied compounds for 120 h at 37°C and 95%/5% CO_2 atmosphere [51]. To all wells 200 mL of solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) in PBS (4 mg/mL) was added and incubated further for 4 h at 37°C. After formazan crystals were solubilized in 1 mL of DMSO, the absorbance was measured using a multi-well plate reader (Victor3, Perkin-Wallac) at λ = 560 nm. Cytotoxicity was determined compared to non-treated cells (% control). The results of cell viability correspond to the mean (±) standard error of at least three independent experiments performed in triplicate and are expressed as the percentage of the untreated control cells.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.....

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Captions to Illustration

Table Captions

Table 1. Synthesis of 2-amino-7-propropargyloxy-4-aryl-4*H*-chromene-3-carbonitriles **5a-t**

Table 2. Crystal data and structure refinements for the compounds **5i** and **6**

Table 3. Investigation of copper catalysts for click chemistry of **5a** with sugar azide **6**

Table 4. Synthesis of substituted 1*H*-1,2,3-triazoles **7a-t** using Cu@MOF-5 as catalyst

Table 5. Antibacterial activity of 1*H*-1,2,3-triazoles **7a-t**

Table 6. Antifungal activity of 1*H*-1,2,3-triazoles **7a-t**

Table 7. Cytotoxicity against RAW 264.7 cells of 1*H*-1,2,3-triazoles **7a-t**

Figure and Scheme Captions

Schema

Scheme 1. Synthetic path for 2-amino-7-hydroxy-4-aryl-4*H*-chromene-3-carbonitriles **4a-t**. Reaction conditions: (*i*) Sodium carbonate, water, 25°C, 24 h.

Scheme 2. Two ways for synthesis of 2-amino-4-aryl-7-propargyloxy-4*H*-chromene-3-carbonitriles **5a-t**. Reaction conditions: (*i*) Anhydrous K_2CO_3, KI, dried acetone, 40−50°C, 12 h; (*ii*) NaH, dried DMF, 0°C; (*iii*) 0°C, 40 min, then to 20−25°C, 2 h.

Scheme 3. Preparation of sugar azide **6**. Reaction conditions: (*a*) 1. Ac_2O, $HClO_4$ 74% (catalyst), 30−40°C; 2. Br_2, red phosphorous, <20°C, then water, <20°C. (*b*) NaN_3, dried acetone, 25°C, 24 h.

Scheme 4. Click chemistry of substituted 2-amino-4-aryl-7-propargyloxy-4*H*-chromene-3-carbonitriles **5a-t** with tetra-*O*-acetyl-β-D-glucopyranosyl azide. Reaction conditions: *see* Table 3.

Figure

Table 1. Synthesis of 2-amino-7-propropargyloxy-4-aryl-4*H*-chromene-3-carbonitriles **5a-t**

Compd.	R	K_2CO_3 as base		NaH as base	
		Reaction Temp. (°C)[a]	Yields (%)[b]	Reaction Temp. (°C)[e]	Yields (%)[f]
5a	H	50	89	25	95
5b	4′-NO_2	40 or 50	– [c]	20	80
5c	3′-NO_2	40	78 [d]	20	82
		50	55		
5d	2′-NO_2	40	70 [d]	20	82
		50	56		
5e	2′,3′-dichloro	40	84 [d]	25	94
		50	78		
5f	2′,4′-dichloro	40	81 [d]	25	92
		50	76		
5g	4′-Cl	40	89 [d]	25	93
		50	70		
5h	3′-Cl	40	86 [d]	25	93
		50	65		
5i	2′-Cl	40	84 [d]	25	94
		50	78		

Compd.	R	K_2CO_3 as base		NaH as base	
		Reaction Temp. (°C)[a]	Yields (%)[b]	Reaction Temp. (°C)[e]	Yields (%)[f]
5j	4′-Br	40	84 [d]	25	94
		50	78		
5k	4′-Me	50	85	25	93
5l	4′-iPr	50	70	25	90
5m	4′-dimethylamino	50	65	25	90
5n	4′-OMe	50	81	25	94
5o	3′-OMe	50	83	25	96
5p	2′-OMe	50	85	25	96
5q	2′,3′-dimethoxy	50	83	25	94
5r	2′,4′-dimethoxy	50	82	25	96
5s	3′,4′-dimethoxy	50	81	25	96
5t	3′,5′-dimethoxy	50	80	25	96

[a] Reaction time: 12 h; [b,f] Isolated yields; [c] N.A; [d] Reaction carried out in 40°C to give the higher yield; [e] Reaction time: 2 h.

Table 2. Crystal data and structure refinements for the compounds **5i** and **6**

Identification code	Compound **5i**	Compound **6**
Molecular formula	$C_{19}H_{13}ClN_2O_2$	$C_{14}H_{19}N_3O_9$
M_r	336.76	373.32
Temperature (K)	100.0	100.0
Crystal system, space group	Triclinic, P-1	Orthorhombic, $P2_12_12_1$
Unit cell dimension	*a* = 8.4787(6) Å; α = 82.480(2)°	*a* = 7.3226(5) Å; α = 90°
	b = 8.5633(6) Å; β = 72.640(2)°	*b* = 14.7489(9) Å; β = 90°
	c = 12.8009(8) Å; γ = 64.001(2)°	*c* = 15.9064(10) Å; γ = 90°
Volume ($Å^3$)	797.31(9)	1717.90(19)
Z	4	4
ρ (g/cm^3, calcd.)	1.279	1.443
μ/mm^{-1}	0.435	0.122
F(000)	308.0	784.0
Crystal size (mm^3)	0.2 × 0.2 × 0.1	0.2 × 0.2 × 0.15
Radiation	Mo *Kα* (λ = 0.71073)	Mo *Kα* (λ = 0.71073)
2Θ range for data collection	5.834−52.998°	5.82−66.844
Index ranges	$-10 \le h \le 10$, $-10 \le k \le 10$, $-16 \le l \le 15$	$-11 \le h \le 11$, $-22 \le k \le 22$, $-24 \le l \le 24$
Reflections collected	7765	78861
Independent reflections	3278 [R_{int} = 0.0243, R_{sigma} =	6686 [R_{int} = 0.0380, R_{sigma} =

	0.0360]	0.0163]
Data/restraints/parameters	3278/0/218	6686/0/239
Goodness-of-fit on F^2	1.040	1.077
Final R indexes [I>=2σ (I)]	R_1 = 0.0417, wR_2 = 0.0982	R_1 = 0.0315, wR_2 = 0.0799
Final R indexes (all data)	R_1 = 0.0591, wR_2 = 0.1077	R_1 = 0.0347, wR_2 = 0.0819
Largest diff. peak and hole (e.Å^{-3})	0.46 and −0.44	0.35 and −0.19
Flack parameter	−	0.06(12)

Table 3. Investigation of copper catalysts for click chemistry of **5a** with sugar azide **6**

Entry	Catalyst	Procedure	Solvents	React. Temp. (°C)	React. Time	Yield (%) [a]
1	$CuSO_4.5H_2O$ (2 mol%)-Sodium ascorbate (5 mol%)	**A**	DMSO/H_2O (1:1 by volume)	25−27	24 h	60.7
2	$CuIm_2$ (2 mol%)	**B**	Abs. ethanol	79−80	90 min	53.3
3	CuNPs (2 mol%)	**C**	*t*-BuOH, NEt_3 [b]	85−87	30 min	95.2
4	CuI (2 mol%)	**D**	*t*-BuOH/H_2O [c]	85−87	1 h	94.8
5	Cu@MOF-5 (2 mol%)	**E**	Abs. ethanol	79−80	30 min	97.8

Reaction conditions: 1 mmol of each reactant.

[a] Isolated yield; [b] *t*-BuH (5 mL), NEt_3 (0.1 mL); [c] *t*-BuOH (5 mL)/H_2O (0.1 mL).

Table 4. Synthesis of substituted 1*H*-1,2,3-triazoles **7a-t** using Cu@MOF-5 as catalyst

Compd.	R	Yields (%)[b]	m.p. (°C)	Compd.	R	Yields (%) [a]	m.p. (°C)
7a	H	97.8	218−220	**7k**	4′-Me	95.7	214−216
7b	4′-NO_2	80.2	205−207	**7l**	4′-iPr	96.8	209−210
7c	3′-NO_2	80.3	197−199	**7m**	4′-dimethylamino	85.3	219−221
7d	2′-NO_2	80.4	185−187	**7n**	4′-OMe	90.1	198−200
7e	2′,3′-dichloro	96.2	188−190	**7o**	3′-OMe	95.2	189−191
7f	2′,4′-dichloro	96.1	168−170	**7p**	2′-OMe	92.3	200−202
7g	4′-Cl	93.3	190−192	**7q**	2′,3′-dimethoxy	92.3	211−213
7h	3′-Cl	85.9	200−202	**7r**	2′,4′-dimethoxy	91.2	212−214
7i	2′-Cl	92.8	190−192	**7s**	3′,4′-dimethoxy	94.8	205−207
7j	4′-Br	92.7	250−252	**7t**	3′,5′-dimethoxy	94.7	213−215

Reaction conditions: 1 mmol for each reactant, 2 mol% of Cu@MOF-5 in 2 mL of abs. ethanol;

[a] Isolated yield.

Table 5. Antibacterial activity of 1*H*-1,2,3-triazoles **7a-t**

Compd.	R	Micro-organisms/ MIC (μM)									
		Gram-positive			Gram-negative				MRSA		
		B.s.[a]	*S.a.*[a]	*S.e.*[a]	*E.c.*[a]	*K.p.*[a]	*P.a.*[a]	*S.t.*[a]	*MRSA198-1*	*MRSA198-2*	*MRSA198-3*
7a	H	400±22.95	200±16.56	25±0.85	400±32.78	400±31.67	200±18.92	3.12±0.87	400±36.12	400±32.22	200±19.23
7b	4′-NO_2	50±2.62	400±35.54	50±2.12	400±33.05	12.5±0.56	50±3.56	NE	400±41.89	400±41.17	200±18.64
7c	3′-NO_2	50±3.45	3.12±0.98	400±32.35	50±2.01	NE	12.5±0.87	400±37.15	1.56±0.54	6.25±0.98	3.12±0.97
7d	2′-NO_2	100±9.13	6.25±1.02	12.5±0.75	50±5.72	400±32.12	400±32.17	NE	6.25±0.81	1.56±0.62	3.12±0.56
7e	2′,3′-dichloro	25±1.84	50±3.23	200±19.33	200±13.54	NE	6.25±0.95	50±3.29	200±17.43	200±20.92	100±15.67
7f	2′,4′-dichloro	3.12±0.75	12.5±0.98	12.5±0.97	3.12±0.56	200±18.52	50±1.54	3.12±0.93	6.25±0.67	1.56±0.94	3.12±0.75
7g	4′-Cl	400±28.95	50±9.12	200±18.43	1.56±0.23	12.5±0.97	3.12±0.82	12.5±0.45	200±19.71	200±21.73	100±12.83
7h	3′-Cl	6.25±0.77	1.56±0.98	12.5±0.81	6.25±0.78	3.12±0.77	25±0.92	6.25±0.25	3.12±0.82	6.25±0.87	1.56±0.82
7i	2′-Cl	1.56±0.27	200±19.45	3.12±0.92	1.56±0.25	400±32.15	12.5±0.87	6.25±0.85	NE	NE	400±29.14
7j	4′-Br	200±19.73	25±1.87	100±9.56	100±12.02	200±19.27	25±1.79	200±17.71	12.5±0.75	12.5±0.83	12.5±0.93
7k	4′-Me	50±3.48	400±32.03	400±32.67	12.5±0.71	400±32.18	400±32.15	200±18.56	NE	NE	400±28.67
7l	4′-iPr	6.25±0.96	100±12.96	400±32.32	200±18.34	1.56±0.77	6.25±0.67	50±2.67	400±35.27	400±42.11	200±19.82
7m	4′-dimethylamino	100±12.72	100±11.75	NE	12.5±0.83	NE	1.56±0.61	50±3.82	400±29.17	400±32.83	200±18.92
7n	4′-OMe	12.5±0.83	25±1.95	200±18.92	200±16.45	NE	100±15.77	1.56±0.47	12.5±0.92	12.5±0.93	12.5±0.98
7o	3′-OMe	200±20.45	400±32.76	100±11.64	200±19.75	6.25±0.94	400±34.61	100±12.23	NE	NE	400±42.21

7p	2′-OMe	NE [b]	50±4.72	6.25±0.91	400±32.67	3.12±0.65	3.12±0.86	6.25±0.78	400±37.82	400±39.56	200±19.71
7q	2′,3′-dimethoxy	12.5±1.13	12.5±0.87	25±1.66	200±17.34	25±1.85	12.5±0.89	12.5±0.82	12.5±0.92	12.5±0.89	12.5±0.93
7r	2′,4′-dimethoxy	50±5.72	1.56±0.34	25±1.98	NE	12.5±1.01	NE	50±3.57	1.56±0.78	1.56±0.46	6.25±0.96
7s	3′,4′-dimethoxy	25±2.24	25±2.32	1.56±0.79	6.25±0.87	25±1.77	12.5±0.93	400±32.82	25±1.72	50±3.67	50±3.07
7t	3′,5′-dimethoxy	50±11.92	100±15.72	3.12±0.92	100±13.36	100±12.67	NE	50±4.51	400±41.17	400±1.89	200±1.54
	Ciprofloxacin	3.12±0.83	3.12±0.87	3.12±0.85	1.56±0.82	1.56±0.83	1.56±0.62	1.56±0.52	400±36.67	400±37.23	400±34.53
	Vancomycin	0.78±0.02	1.56±0.75	3.12±0.13	3.12±0.11	3.12±0.15	3.12±0.17	3.12±0.13	1.55±0.19	1.56±0.14	1.56±0.11
	Methicillin	400±12.35	400±15.57	400±23.25	400±21.01	400±21.77	400±19.56	400±18.36	NE	NE	NE

[a] *B.s.*: *Bacillus subtilis*; *S.a.*: *Staphylococcus aureus*; *S.e.*: *Staphylococcus epidermidis*; *E.c.*: *Escherchia coli*; *K.p.*: *Klebsiella pneumoniae*: *P.a.*: *Pseudomonas aeruginosa*: *S.t.*: *Salmonella typhimurium*.

[b] NE = not evaluated.

Table 6. Antifungal activity of 1*H*-1,2,3-triazoles **7a-t**

Compd.	R	Fungi/ MIC (μM)			
		A.n. [a]	*A.f.* [a]	*C.a.* [a]	*S.c.* [a]
7a	H	6.25±0.82	100±12.01	100±11.67	12.5±1.67
7b	4′-NO_2	NE [b]	1.56±0.14	25±1.05	3.12±0.92
7c	3′-NO_2	12.5±0.33	50±2.43	200±15.13	6.25±1.05
7d	2′-NO_2	400±31.35	6.25±0.73	50±2.79	NE
7e	2′,3′-dichloro	200±14.22	200±17.67	25±1.04	NE
7f	2′,4′-dichloro	NE	25±1.79	100±10.23	400±41.52
7g	4′-Cl	50±3.78	25±1.35	6.25±0.92	1.56±0.02
7h	3′-Cl	12.5±0.93	200±1.53	12.5±1.23	3.12±0.93
7i	2′-Cl	400±41.28	6.25±0.12	25±1.25	NE
7j	4′-Br	3.12±0.93	200±17.01	3.12±0.95	1.56±0.52
7k	4′-Me	100±11.92	3.12±0.94	400±41.02	3.12±0.89
7l	4′-iPr	NE	50±2.96	3.12±0.78	12.5±0.93
7m	4′-dimethylamino	NE	12.5±0.78	12.5±0.75	100±12.16
7n	4′-OMe	200±17.23	12.5±0.83	1.56±0.63	12.5±0.87
7o	3′-OMe	400±32.12	1.56±0.22	400±37.29	25±1.95
7p	2′-OMe	1.56±0.15	400±33.08	200±14.67	100±11.26
7q	2′,3′-dimethoxy	25±1.22	25±1.05	100±11.34	200±17.12
7r	2′,4′-dimethoxy	400±32.03	NE	12.5±0.94	50±3.19
7s	3′,4′-dimethoxy	200±15.49	3.12±0.78	6.25±0.78	25±2.07
7t	3′,5′-dimethoxy	100±10.23	50±3.84	25±1.67	6.25±0.98
	Miconazole	1.56±0.19	1.56±0.21	3.12±0.24	3.12±0.22
	Fluconazole	1.56±0.12	0.78±0.02	0.78±0.03	0.78±0.02

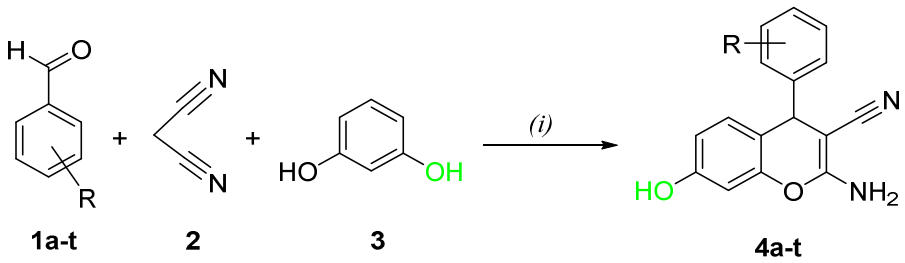
[a] *A.n.*: *Aspergillus niger*; *A.f.*: *Aspergillus niger*; *C.a.*: *Candida albicans*; *S.c.*: *Saccharomyces cerevisiae*.

Table 7. Cytotoxicity against RAW 264.7 cells of 1*H*-1,2,3-triazoles **7a-t**

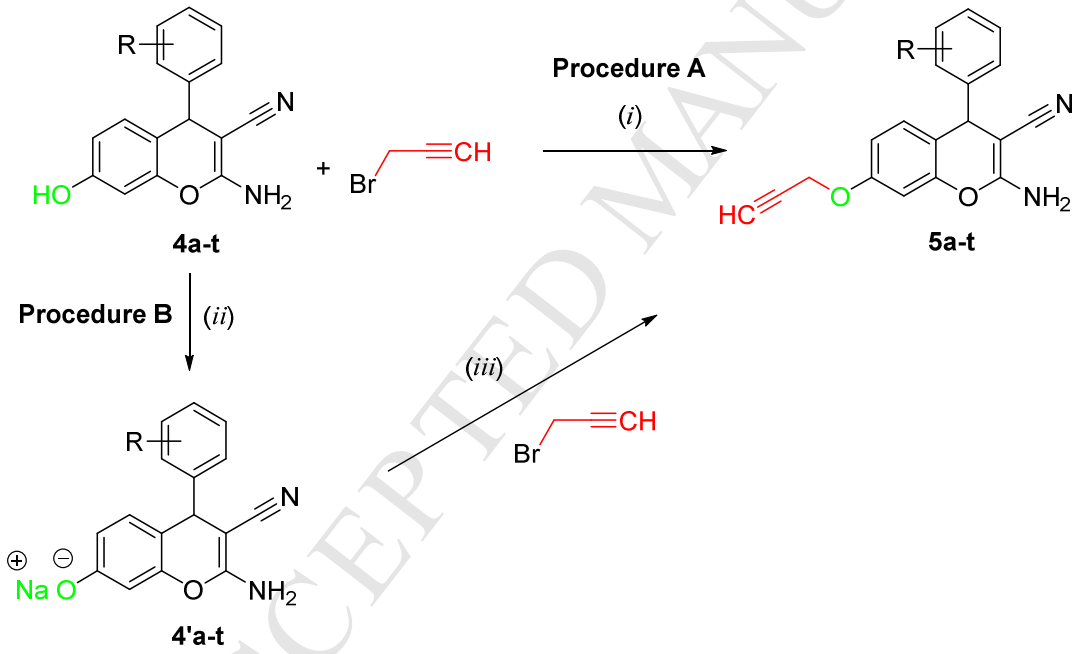
Compd.	Cytotoxicity [a]	Compd.	Cytotoxicity [a]
7a	22.93±2.83	**7k**	19.56±2.12
7b	27.56±2.54	**7l**	17.95±1.55
7c	15.56±1.46	**7m**	19.65±1.79
7d	15.45±1.53	**7n**	29.65±2.93
7e	23.84±2.16	**7o**	25.11±2.71
7f	18.13±1.45	**7p**	22.08±2.78
7g	25.14±2.17	**7q**	31.11±2.88
7h	17.20±1.89	**7r**	12.45±1.15
7i	21.15±2.05	**7s**	21.95±2.78
7j	25.34±2.28	**7t**	19.53±2.56

[a] Cytotoxicity (% inhibition) at 50 μg/mL of RAW 264.7 cells.

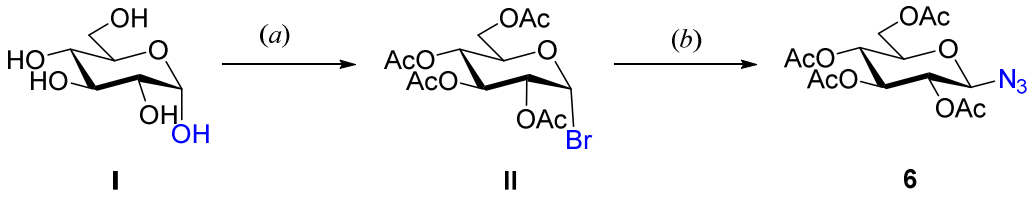
Schema



Scheme 1. Synthetic path for 2-amino-7-hydroxy-4-aryl-4*H*-chromene-3-carbonitriles **4a-t**. Reaction conditions: (*i*) Sodium carbonate, water, 25°C, 24 h.

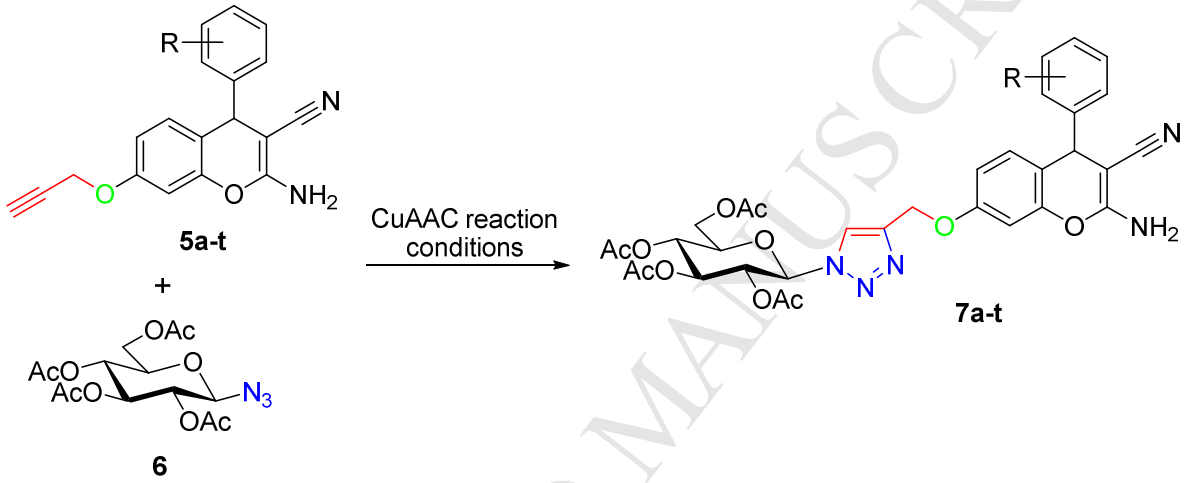


Scheme 2. Two ways for synthesis of 2-amino-4-aryl-7-propargyloxy-4*H*-chromene-3-carbonitriles **5a-t**. Reaction conditions: (*i*) Anhydrous K_2CO_3, KI, dried acetone, 40−50°C, 12 h; (*ii*) NaH, dried DMF, 0°C; (*iii*) 0°C, 40 min, then to 20−25°C, 2 h.



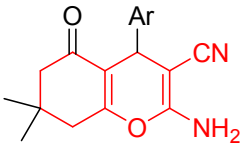
I II 6

Scheme 3. Preparation of sugar azide **6**. Reaction conditions: (*a*) 1. Ac_2O, $HClO_4$ 74% (catalyst), 30−40°C; 2. Br_2, red phosphorous, <20°C, then water, <20°C. (*b*) NaN_3, dried acetone, 25°C, 24 h.

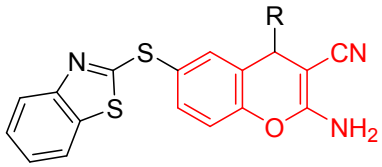


Scheme 4. Click chemistry of substituted 2-amino-4-aryl-7-propargyloxy-4*H*-chromene-3-carbonitriles **5a-t** with tetra-*O*-acetyl-β-D-glucopyranosyl azide. Reaction conditions: *see* Table 3.

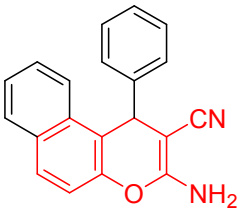
Figures



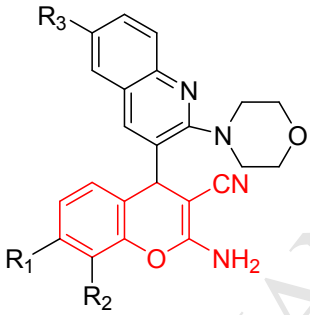
A, Ar = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$
MIC = 64 μg/mL (*E. coli, S. aureus*)



B
R = 4-$MeOC_6H_4$ MIC = 2 μg/mL (*P. aeruginosa*),
3-indolyl MIC = 0.5 μg/mL (*E. coli*),
4-$NO_2C_6H_4$ MIC = 0.5 μg/mL (*S. aureus*),
piperonyl MIC = 0.5 μg/mL (*S. epidermidis*)



C
MIC >1 μg/mL
(*A. flavus*, *C. albicans*)



D, R_1,R_2 = C_6H_4, R_3 = Me:
MIC = 12.5 μg/mL (*V. cholerate*)
E, R_1 = H, R_2 = OH, R_3 = OMe:
MIC = 12.5 μg/mL (*S. pneumonia*)

Figure 1. Some chromene structures having bacterial and fungal activities.

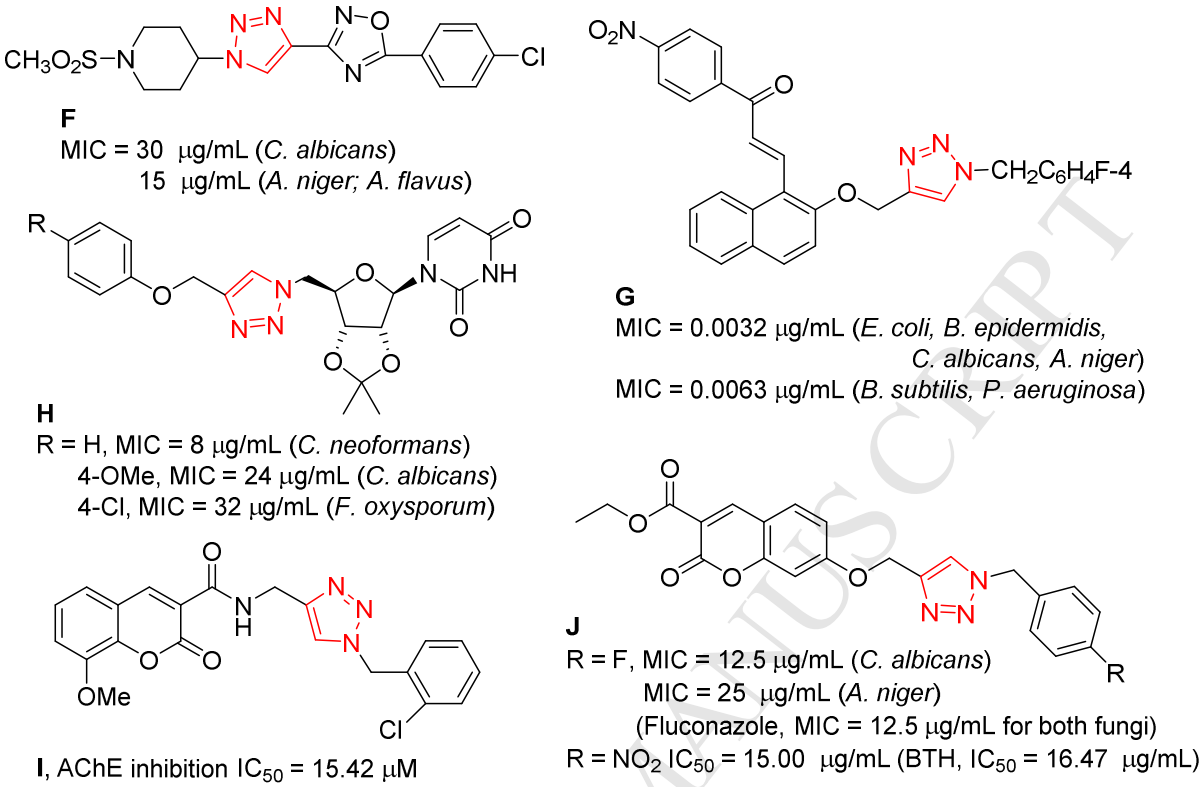


Figure 2. Some 1*H*-1,2,3-triazole structures having bacterial and fungal activities.

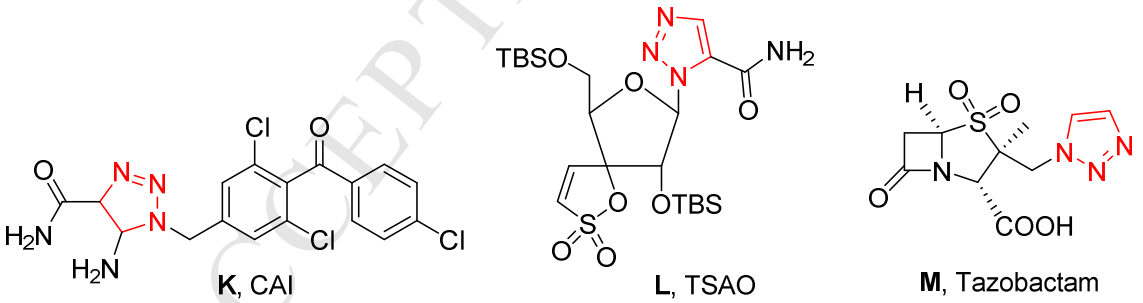


Figure 3. Some drugs having 1*H*-1,2,3-triazole ring.

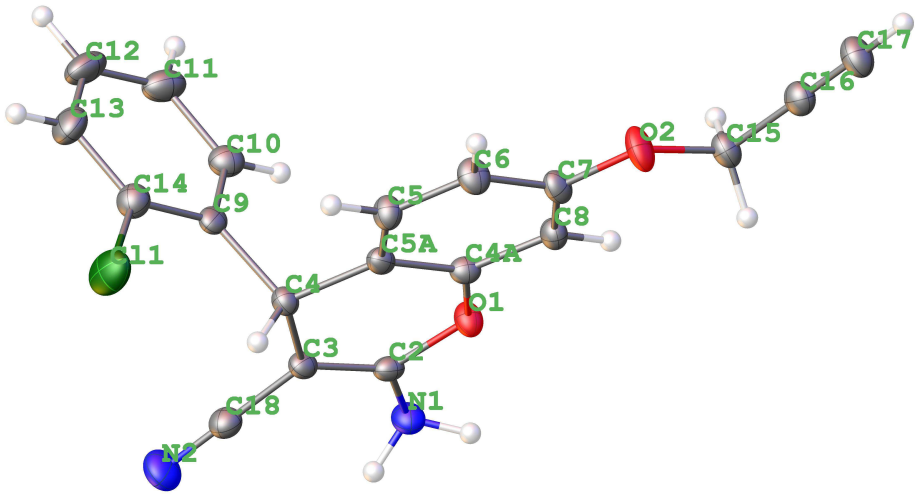


Figure 4. ORTEP diagram of compound **5i**.

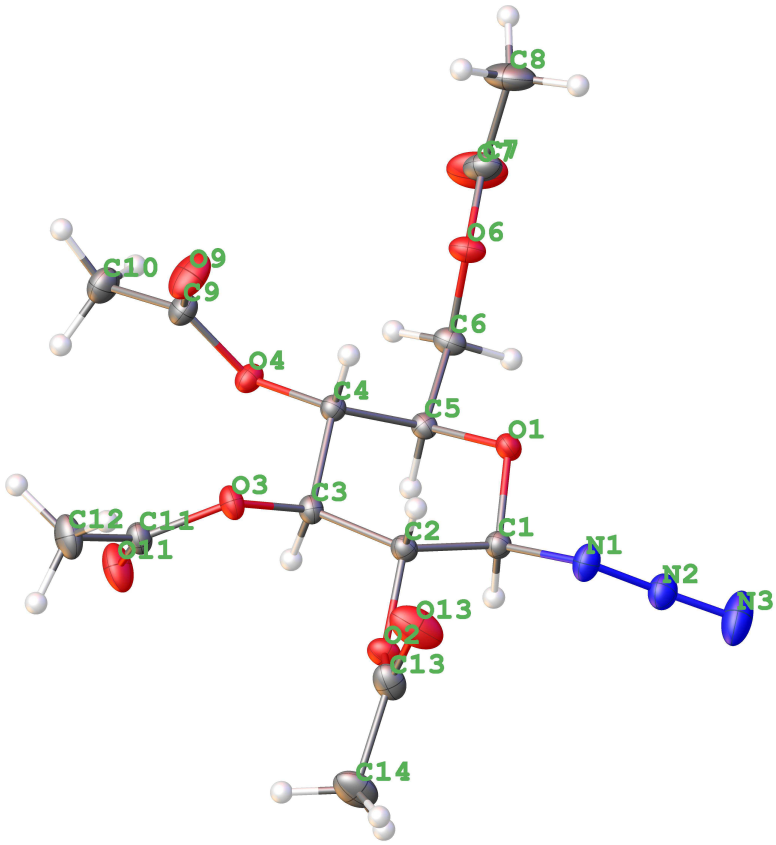


Figure 5. ORTEP diagram of compound **6**.

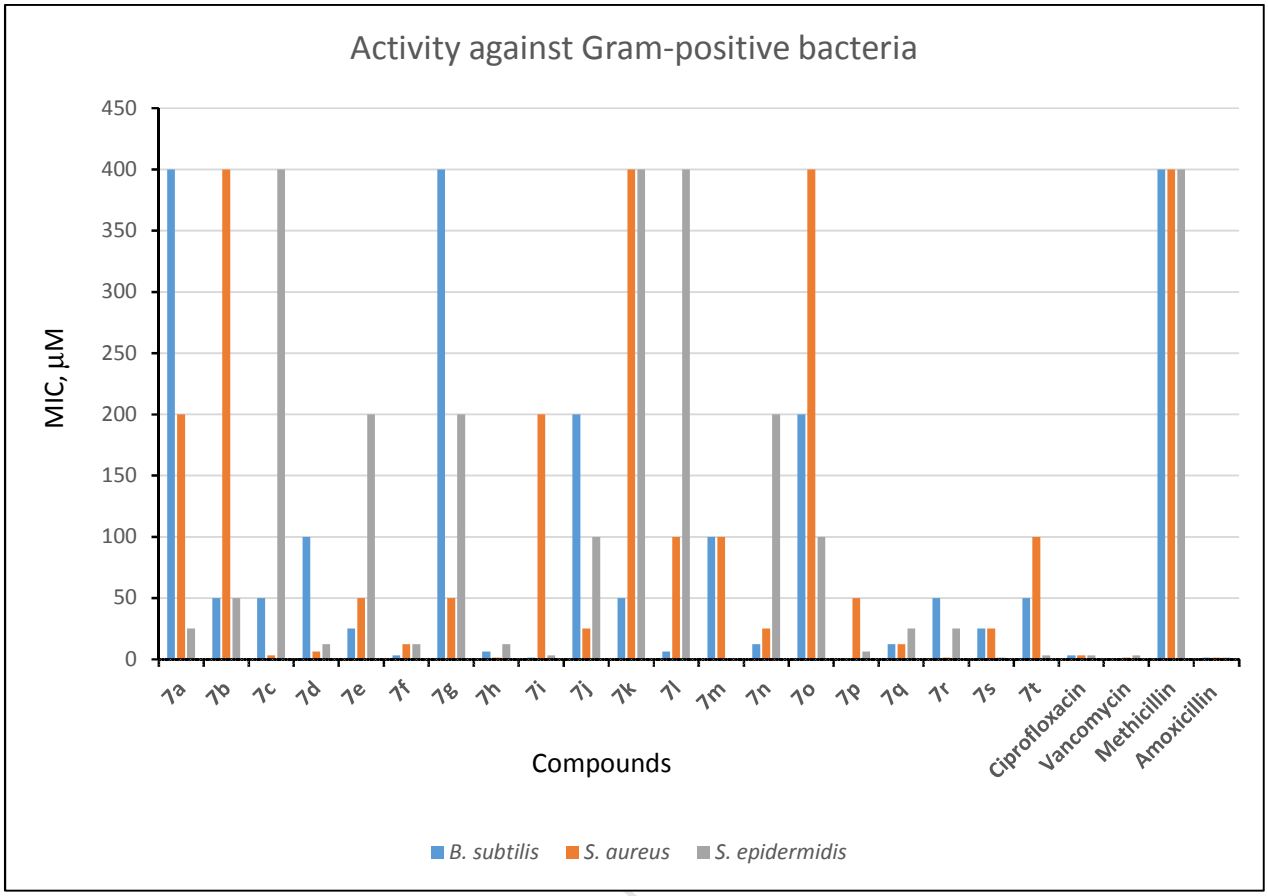


Figure 6. A plot of MIC values (µM) against three Gram-positive bacterial strains for 1*H*-1,2,3-triazoles **7a-t**.

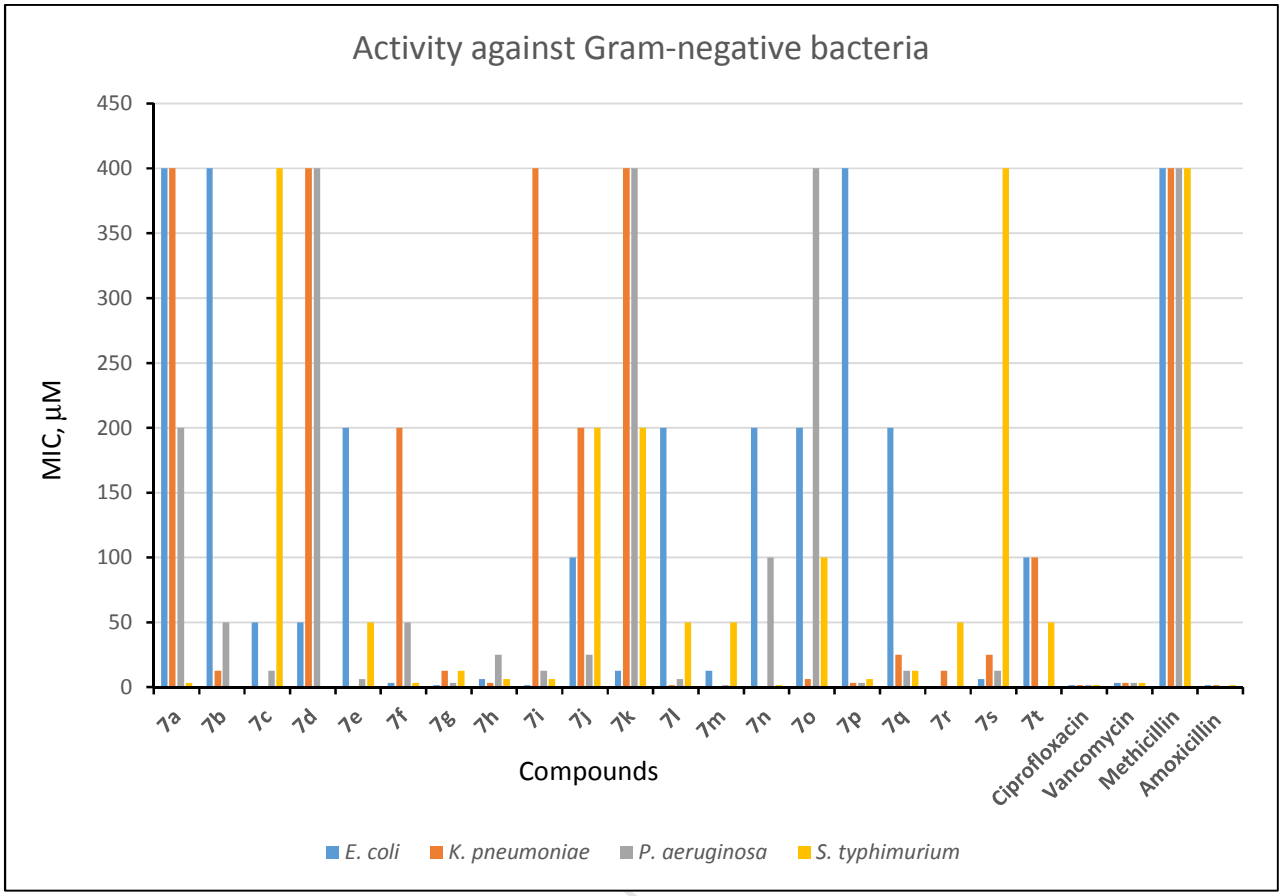


Figure 7. A plot of MIC values (µM) against four Gram-negative bacterial strains for 1*H*-1,2,3-triazoles **7a-t**.

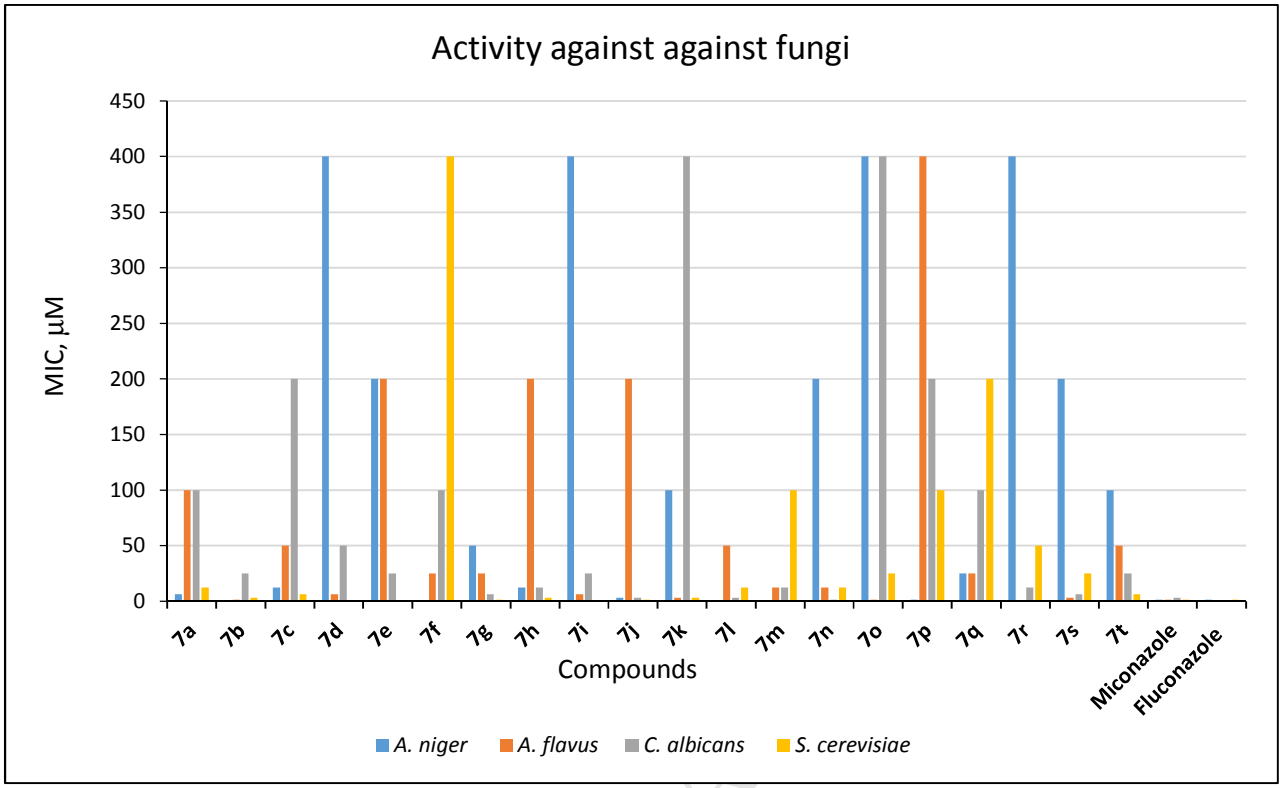


Figure 7. A plot of MIC valus (µM) against four strains of fungi for 1*H*-1,2,3-triazoles **7a-t**.

Highlights

- Novel 1*H*-1,2,3-triazole-tethered 4*H*-chromene−D-glucose conjugates by click chemistry
- Several triazoles were active for three strains of Gram-(+), four strains of Gram-(−) bacteria (MICs=1.56−6.25 μM)
- Some triazoles had activity against four strains of fungi with MICs of 1.56−6.25 μM
- **7c**,**7d**,**7f**,**7h**,**7r** exerted anti-MRSA activities against all strains with MIC of 1.56−6.25 μM
- 1*H*-1,2,3-Triazoles **7c**,**7d**,**7f**,**7h**,**7r** had comparatively low cytotoxicity against RAW 264.7 cells