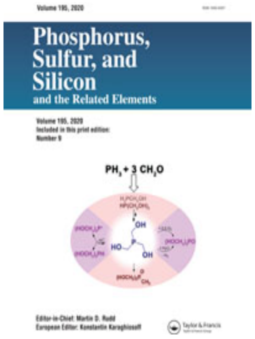

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Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

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To cite this article: Leyla Yurttaş, Aslıhan Kubilay, Asaf Evrim Evren, İpek Kısacık & Hülya Karaca Gençer (2020) Synthesis of some novel 3,4,5-trisubstituted triazole derivatives bearing quinoline ring and evaluation of their antimicrobial activity, Phosphorus, Sulfur, and Silicon and the Related Elements, 195:9, 767-773, DOI: 10.1080/10426507.2020.1756808

To link to this article: https://doi.org/10.1080/10426507.2020.1756808

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
2020, VOL. 195, NO. 9, 767–773
https://doi.org/10.1080/10426507.2020.1756808

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Synthesis of some novel 3,4,5-trisubstituted triazole derivatives bearing quinoline ring and evaluation of their antimicrobial activity

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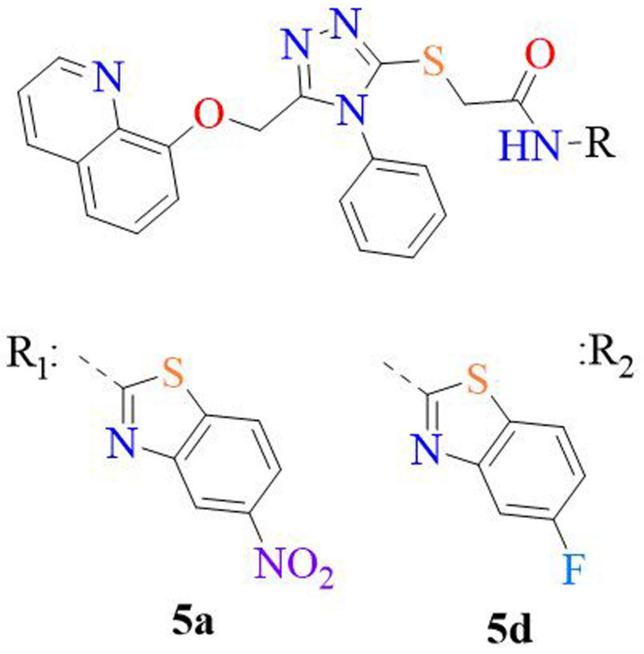
ABSTRACT

Some new 3,4,5-trisubstituted 1,2,4-triazole derivatives were synthesized and studied for their antimicrobial activity. The lead compounds were obtained starting from 8-hydroxyquinoline and ethyl 2-chloroacetate. The obtained ester compound (**1**) first reacted with hydrazine hydrate (**2**) then with phenyl isothiocyanate (**3**). Ring closure by KOH led to 3-mercapto-1,2,4-triazole derivative (**4**). Lastly, it reacted with 2-chloro-*N*-(substituted (benzo)/thiazole)acetamide derivatives to obtain the final compounds (**5a–j**). The structural elucidation of the compounds was performed by ^{1}H NMR and ^{13}C NMR spectroscopy and high resolution mass spectrometry techniques and elemental analysis. The synthesized compounds were investigated for their antimicrobial activities against seven bacteria and four fungi. As a result of the activity studies, it was observed that compounds *N*-(6-nitrobenzothiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl]thio]acetamide (**5a**) and *N*-(6-fluorobenzothiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl]thio]acetamide (**5d**) were the most active molecules. Also, the antifungal activity of the compounds was found to be higher than their antibacterial activity although lower than the standard drug's potential. Additionally, the physicochemical properties of the compounds were calculated which were evaluated to be at a suitable range for oral administration.

ARTICLE HISTORY
Received 5 November 2019
Accepted 14 April 2020

KEYWORDS
Quinoline; triazole; antimicrobial activity

GRAPHICAL ABSTRACT



5a

5d

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Supplemental data for this article is available online at https://doi.org/10.1080/10426507.2020.1756808.

Introduction

Microbial infections are among the most common diseases that cause millions of people to die each year due to insufficient treatment options and/or development of resistance to existing antibiotics. Increased use of antibiotics leads to a rapid increase in resistant bacteria which becomes a serious public health problem.[1,2] If the resistance continues to increase, it is stated that deaths due to antimicrobial infections will exceed the number of cancer-related deaths by 2050.[3] New antimicrobial agents that are more selective, more potent and less toxic than those available in the clinics are needed to prevent microbial resistance and thus to improve the effectiveness of treatment.[4]

Nitrogen-containing heterocyclic compounds have a significant place in medicinal chemistry in terms of both being involved in biological materials and forming the pharmacophoric skeleton for the efficacy of many drugs. Among them, quinoline is a distinguished heterocyclic ring which has C_9H_7N molecular formula and a benzene ring fused with two adjacent carbon atoms of the pyridine ring. The quinoline nucleus exists in many biologically effective natural substances such as quinine, quinidine, berberine, camptothecin. Synthetic derivatives of the ring are also evaluated for a broad spectrum of pharmacological activity profile including their anti-inflammatory,[5] antimalarial,[6] antimicrobial,[7] anticonvulsant,[8] antineoplastic,[9] vasorelaxing,[10] antiproliferative[11] properties. Quinolines which are a separate chemical group involved in many drugs structures used in the clinic. Fluoroquinolones (ciprofloxazine) as antibacterial, 4-aminoquinolines (chlorokine) as antimalarial, isoquinolines (praziquantel) as anthelmintic are prominent groups possessing the ring. Additionally, many molecules derived from 8-hydroxyquinoline are involved in the treatment of amebiasis, malaria and fungal infections.[12,13]

Another five-membered nitrogen heterocycle is triazole which is a useful skeleton for new drug discovery studies due to its applications in many biological fields such as antimicrobial,[14] analgesic,[15] anti-inflammatory,[16] anticancer,[17] antioxidant.[18] Although there are many antimicrobial agents being developed against antimicrobial resistance, triazoles are still the most used molecules in this class.[19] Triazole-containing antifungal drugs (posaconazole, fluconazole, itraconazole and terconazole) are currently being used clinically. Triazole derivatives have been widely studied due to their synthetic convenience and antimicrobial potency.

In this work, some new 3,4,5-trisubstituted triazole derivatives were synthesized and their structures were elucidated. Also, an evaluation of their antimicrobial activities and physicochemical properties is reported.

Result and discussion

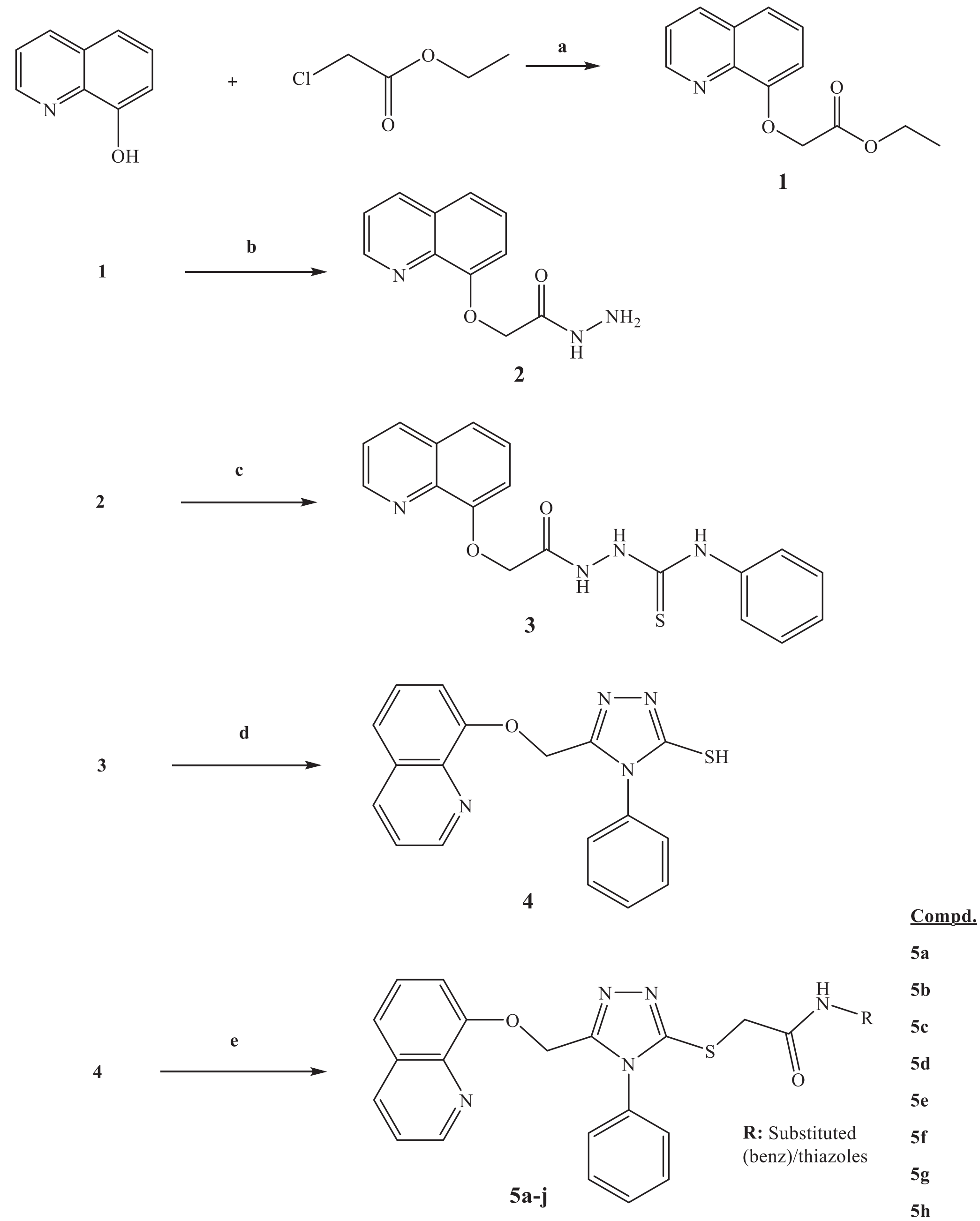
Chemistry

In this study, novel *N*-substituted-2-[(4-phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio]acetamide derivatives (**5a–j**) were synthesized in a five-step synthetic procedure based on our previous work.[20] Initially, 8-hydroxyquinoline and ethyl chloroacetate were refluxed with potassium carbonate. After the reaction was complete, the solvent was evaporated and the material was washed with water to acquire intermediate ether compound. The obtained product, ethyl 2-(quinolin-8-yloxy)acetate (**1**) was reacted with hydrazine hydrate in ethanol. At the end of the reaction, the hydrazinated compound was isolated by filtration. All intermediate compounds were recrystallised from ethanol to gain pure products. The acquired molecule, (quinolin-8-yloxy)acetohydrazide (**2**) was dissolved in ethanol and refluxed with phenylisothiocyanate to synthesize *N*-phenyl-2-(2-(quinolin-8-yloxy)acetyl)hydrazine-1-carbothioamide (**3**) and then in the next step this compound was refluxed with 2 N potassium hydroxide prepared in ethanol. The reaction was terminated by controlling with TLC. The pH was set to 7 to allow the material to settle in a cold environment. The resulting triazole molecule (**4**) was treated with the appropriate 2-chloro-*N*-substituted acetamide derivatives to form ten different final compounds (**5a–j). The target compounds (5a–j**) were obtained purely and the structures of the compounds were elucidated with spectroscopic methods (Scheme 1).

The structures of the synthesized substances were elucidated by using ^1H NMR and ^{13}C NMR spectroscopy, high resolution mass spectrometry and elemental analysis. The chemical shifts belonging to NH, O-CH_2 and S-CH_2 protons in all materials were seen at about 12.50–13.16 ppm and 5.27 ppm and 3.81–4.36 ppm, respectively. The methoxy proton of compound **5b**, was observed as singlet at 3.81 ppm. For compound **5c**, the signal belonged to substituent CH_3 was determined as singlet at 1.34 ppm, and the signal for O-$\underline{CH_2}$-CH_3 protons at 4.06 ppm as quartet. The signal at 2.40 ppm assigned to CH_3 substituent was an expected value for compound **5f**. The signals attributed to the substituents CH_3, O-CH_2-CH_3 and O-CH_2-CH_3 peaks in the compound **5h** were determined at 1.26 ppm, 2.55 ppm and 4.20–4.25 ppm, respectively. Two singlet signals were detected for compound **5i** indicating CH_3 at 2.48 ppm and CH_3 bound to the carbonyl group was observed at 2.58 ppm. The expected CH_3 peaks for **5j** molecule was seen as a singlet at 2.47 ppm. In addition, multiple peaks were observed in the aromatic region due to the phenyl ring in the substituent. In ^{13}C-NMR spectra of the compounds, signals belong to S-CH_2 and O-CH_2 were detected at 35.84–37.97 ppm and 61.01–61.23 ppm, respectively. The signal of carbonyl carbon was detected at 166.31–170.64 ppm in common with all final compounds. In HRMS analysis, compounds were processed in negative ion mode and peaks were detected in accordance with molecular weights of the compounds. Elemental analysis results also confirmed molecular formula which were found in the range of ±0.4% with molecular weights.

Antimicrobial study

The antimicrobial activity of **5a-j** compounds was screened on seven bacteria and four fungi according to standard procedure of CLSI (Table S1, Supplemental Materials). Their antimicrobial activities were tested against *Escherichia coli*



Compd.	R
5a	6-NO_2bty
5b	6-OCH_3bty
5c	6-OEtbty
5d	6-Fbty
5e	Bty
5f	6-CH_3bty
5g	6-Clbty
5h	4-CH_3-5-COOEtty
5i	4-CH_3-5-$COCH_3$ty
5j	4-Ph-5-CH_3ty

Scheme 1. Synthesis of compounds (**5a–j**) Reactions and conditions: (a) acetone, potassium carbonate, reflux; (b) ethanol, hydrazinium hydroxide, rt; (c) ethanol, phenylisothiocyanate, reflux; (d) ethanol, 2 N potassium hydroxide, reflux; (e) 2-chloro(benzo)/thiazolyl acetamide derivatives, acetone, potassium carbonate, rt.

(ATCC 25922), *Enterococcus faecalis* (ATCC 51299), *Escherichia coli* (ATCC 35218), *Yersinia enterocolitica* (Y53), *Enterococcus faecalis* (ATCC 29212), *Pseudomonas aeruginosa* (ATCC 27853), *Salmonella typhimirium* (NRRL B-4420), *Candida glabrata* (ATCC 90030), *Candida parapsilosis* (ATCC 22019), *Candida albicans* (ATCC 90028), *Candida krusei* (ATCC 6258). Fluconazole and chloramphenicol were used as standard reference drugs. The synthesized chemicals showed no activity against *E. coli* (ATCC 25922) and *E. faecalis* (ATCC 51299). The most active compound against *E. coli* (ATCC 35218) and *Y. enterocolitica* (Y53) were **5d**. The compound derivatized with 6-fluorobenzathiazole had minimum inhibitory concentration (MIC) value of 125 µg/mL against two bacteria *spp*. Compounds **5a** and **5d** had a MIC value of 15.625 µg/mL and were reported as the most active compounds against *E. faecalis* (ATCC 29212). **5d** and **5i** showed a low activity against *P. aeruginosa* (ATCC 27853) and the MIC values was 500 µg/mL. The compounds **5a** and **5i** were the derivatives that showed the best activity against *S. typhimirium* (NRRL B-4420) and their MIC values of were 7.8 µg/ml. Compound **5d** showed lower activity than them. The compounds showed low activity against fungi where MIC values ranged between 31.25 and 1000 µg/mL, while standard drug had a MIC range of 1.95–62.5 µg/mL against four *Candida* species. In general, the antifungal activities were found to be higher than their antibacterial activities. When evaluating the highest potency, antibacterial activity of compounds **5a** and **5d** against *E. faecalis* and antibacterial activity of compounds **5a** and **5i** against *S. typhimurium* show half the efficiency of the standard drug.

To evaluate druglikeness of molecules, several physicochemical and pharmacokinetic properties were predicted for three most active compounds as shown in Table S2. Number of hydrogen bond acceptors, donors and volume, polar surface area, partition coefficient (log P), water solubility (log S), gastrointestinal absorption and log K_p (skin penetration) were identified using SwissADME software.[21–23] All findings were showed in the Table S2 with the violations of Lipinski's rule of five.[24] There is no discrepancy pursuant to the Lipinski's rule for the compounds (**5b–5j**), except compound **5a**. Also, their skin penetration values were found to be in favorable ranges. The final compounds (**5a–5j**) were evaluated as easy regarding synthetic accessibility as the reference drugs (Chloramphenicol and Fluconazole). However, all compounds showed antimicrobial activity, and they could be used orally or topically in the treatment after future tests.

Experimental

All chemicals were purchased from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp., St. Louis, MO, USA) and Merck Chemicals (Merck KGaA, Darmstadt, Germany). All melting points (m.p.) were determined by MP90 digital melting point apparatus (Mettler Toledo, Ohio, USA) and were uncorrected. All reactions were monitored by thin-layer chromatography (TLC) using Silica Gel 60 F254 TLC plates (Merck KGaA, Darmstadt, Germany). Spectroscopic data were recorded with the following instruments: ^{1}H NMR and ^{13}C NMR spectra were recorded by a Bruker 300 MHz and 75 MHz digital FT-NMR spectrometer (Bruker Bioscience, Billerica, MA, USA) in DMSO-d_6, respectively; M-1 peaks were determined by Shimadzu 8040 LC/MS/MS system (Shimadzu, Tokyo, Japan). Elemental analyses were performed on a Leco 932 CHNS analyzer (Leco, Michigan, USA). The Supplemental Materials contains sample ^{1}H and ^{13}C NMR and HRMS of the products 5 (Figures S1–S30).

Material and methods

Ethyl 2-(quinolin-8-yloxy)acetate (1)

m. p. 58–61 °C, m. p. 60 °C.[25] 8-Hydroxyquinoline (0.034 mol, 5 g), ethyl chloroacetate (0.04 mol, 4.3 mL) and potassium carbonate were mixed and boiled in acetone (200 mL) for 6 h. After TLC analysis, the solvent was evaporated and the material was filtered and washed with water, then recrystallised from ethanol.

2-(Quinolin-8-yloxy)acetohydrazide (2)

m. p. 143–145 °C, m. p. 140 °C.[25] Ethyl 2-(quinolin-8-yloxy)acetate (1) (0.025 mol, 5.7 g) and hydrazine hydrate (0.1 mol of 85% 7.3 mL) were stirred in ethanol (250 mL) at room temperature overnight. After control using TLC, stirring was stopped and the mixture was awaited till two phases solvent and precipitate were formed. The precipitated material was filtered. It was recrystallized from ethanol after drying.

N-phenyl-2-[2-(quinolin-8-yloxy)acetyl)hydrazine-1-carbothioamide (3)

m. p. 187–191 °C, m. p. 195–197 °C.[26] 2-(Quinolin-8-yloxy)acetohydrazide (2) (0.017 mol, 3.8 g) and phenylisothiocyanate (0.02 mol, 2.4 mL) were refluxed in ethanol (150 mL) for 3 h. The reaction was monitored by TLC. The solvent was evaporated and the material scraped off. The raw product was recrystallised from ethanol.

4-Phenyl-5-[(quinolin-8-yloxy)methyl)-4H-1,2,4-triazole-3-thiol (4)

m.p. 221–223 °C, m. p. 224–226 °C.[27] *N*-phenyl-2-(2-(quinolin-8-yloxy)acetyl)hydrazine-1-carbothioamide (3) (0.014 mol, 4.8 g) was refluxed with 2 N potassium hydroxide prepared in ethanol (100 mL). After TLC, the pH was adjusted to 7 in a cold environment to precipitate the material.

General procedure for the synthesis of N-substituted-2-((4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl)thio)acetamide derivatives (5a–j)

4-Phenyl-5-((quinolin-8-yloxy)methyl)-4*H*-1,2,4-triazole-3-thiol (0.001 mol, 3.33 g) and equivalent (0.001 mol) 2-chloro-*N*-substituted acetamide derivatives were reacted in the presence of potassium carbonate (0.001 mol, 0.14 g) in 50 mL acetone. From the reaction mixture, the solvent was evaporated and treated with water to yield the final product. All final compounds were recrystallised from ethanol.

N-(6-nitrobenzothiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl]thio]acetamide (5a)

m. p. 206 °C, yield 78%. ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 4.29 (s, 2H, S-CH$_2$), 5.27 (s, 2H, O-CH$_2$), 7.21 (d, J = 7.69 Hz, 1H, Ar-H), 7.41–7.46 (m, 4H, Ar-H), 7.54 (d, J = 8.22 Hz, 2H, Ar-H), 7.64–7.66 (m, 2H, Ar-H), 7.73 (d, J = 8.94 Hz, 1H, Ar-H), 8.20 (d, J = 8.91 Hz, 1H, Ar-H), 8.31 (d, J = 8.35 Hz, 1H, Ar-H), 8.88 (s, 2H, Ar-H), 13.16 (brs, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 37.97 (S-CH$_2$), 61.20 (O-CH$_2$), 111.86, 118.84, 119.92, 121.52, 121.83, 122.42, 127.02, 127.64, 129.50, 130.09, 130.49, 132.94, 133.05, 136.34, 140.22, 142.28, 149.83, 152.11, 152.51, 153.56, 155.29, 170.64 (C = O). For $C_{27}H_{19}N_7O_4S_2$ calculated: 56.93% C, 3.36% H, 17.21% N, 11.23% O, 11.26% S; found: 56.79% C, 3.35% H, 17.18% N, 11.20% O, 11.29% S.

HRMS (m/z): $[M\text{-}H]^-$ calcd for $C_{27}H_{19}N_7O_4S_2$: 568.0867; found: 568.0871.

N-(6-methoxybenzothiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl]thio]acetamide (5b)

m. p. 248 °C, yield 81%. ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 3.81 (s, 3H, O-CH$_3$), 4.34 (s, 2H, S-CH$_2$), 5.27 (s, 2H, O-CH$_2$), 7.02–7.06 (dd, J = 8.36 and 2.59 Hz, 1H, Ar-H), 7.19–7.21 (m, 1H, Ar-H), 7.44–7.46 (m, 4H, Ar-H), 7.52–7.54 (m, 1H, Ar-H), 7.55–7.57 (m, 1H, Ar-H), 7.58–7.59 (m, 1H, Ar-H), 7.63–7.64 (m, 1H, Ar-H), 7.65–7.68 (m, 2H, Ar-H), 8.29–8.33 (m, 1H, Ar-H), 8.86–8.88 (m, 1H, Ar-H), 12.60 (brs, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 36.02 (S-CH$_2$), 56.08 (O-CH$_3$), 61.22 (O-CH$_2$), 105.16, 111.89, 115.49, 121.55, 121.74, 122.41, 127.00, 127.61, 129.50, 130.10, 130.56, 132.81, 133.24, 136.33, 140.23, 149.83, 151.86, 152.37, 153.56, 156.15, 156.65, 167.11 (C = O). For $C_{28}H_{22}N_6O_3S_2$ calculated: 60.64% C, 4.00% H, 15.15% N, 8.65% O, 11.56% S; found: 60.51% C, 3.99% H, 15.13% N, 8.63% O, 11.59% S. HRMS (m/z): $[M\text{-}H]^-$ calcd for $C_{28}H_{22}N_6O_3S_2$: 553.1122; found: 553.1138.

N-(6-ethoxybenzothiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl]thio]acetamide (5c)

m. p. 240 °C, yield 80%. ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.34 (t, J = 6.92 Hz, 3H, CH$_3$), 4.06 (q, J = 6.88 Hz, J$_2$=6.91 Hz, 2H, O-CH$_2$-CH$_3$), 4.34, (s, 2H, S-CH$_2$), 5.27 (s, 2H, O-CH$_2$), 7.00–7.04 (m, 1H, Ar-H), 7.20 (d, J = 7.44, 1H, Ar-H), 7.44 (m, 4H, Ar-H), 7.52–7.56, (m, 3H, Ar-H), 7.64 (d, J = 8.88 Hz, 3H, Ar-H), 8.29–8.32 (m, 1H, Ar-H), 8.86–8.87 (m, 1H, Ar-H), 12.61 (brs, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 15.17 (CH$_3$), 36.13 (O-CH$_2$-CH$_3$), 61.22 (S-CH$_2$), 64.02 (O-CH$_2$), 105.77, 111.88, 115.76, 121.55, 121.69, 122.41, 127.00, 127.61, 129.50, 130.10, 130.55, 132.82, 133.26, 136.33, 140.23, 142.99, 149.82, 151.91, 152.35, 153.56, 155.85, 156.34, 167.18 (C = O). For $C_{29}H_{24}N_6O_3S_2$ calculated: 61.25% C, 4.25% H, 14.78% N, 8.44% O, 11.28% S; found: 61.14% C, 4.26% H, 14.73% N, 8.42% O, 11.25% S. HRMS (m/z): $[M\text{-}H]^-$ calcd for $C_{29}H_{24}N_6O_3S_2$: 567.1279; found: 567.1264.

N-(6-fluorobenzothiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl]thio]acetamide (5d)

m. p. 231 °C, yield 81%. ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 4.35 (s, 2H, S-CH$_2$), 5.27 (s, 2H, O-CH$_2$), 7.18–7.21 (m, 1H, Ar-H), 7.26–7.33 (m, 1H, Ar-H), 7.41–7.45 (m, 4H, Ar-H), 7.52–7.56 (m, 2H, Ar-H), 7.63–7.66 (m, 2H, Ar-H), 7.75–7.80 (m, 1H, Ar-H), 7.88–7.92 (m, 1H, Ar-H), 8.29–8.32 (m, 1H, Ar-H), 8.85–8.87 (m, 1H, Ar-H), 12.77 (brs, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 36.13 (S-CH$_2$), 61.22 (O-CH$_2$), 108.50, 108.87, 111.89, 114.57, 114.90, 121.55, 122.14, 122.26, 122.41, 127.00, 129.50, 130.10, 132.81, 133.12, 133.27, 136.33, 140.23, 145.73, 149.82, 151.87, 152.37, 153.56, 157.53, 167.66 (C = O). For $C_{27}H_{19}FN_6O_2S_2$ calculated: 59.77% C, 3.53% H, 15.49% N, 5.90% O, 11.82% S; found: 59.65% C, 3.54% H, 15.51% N, 5.88% O, 11.79% S. HRMS (m/z): $[M\text{-}H]^-$ calcd for $C_{27}H_{19}FN_6O_2S_2$: 541.0922; found: 541.0919.

N-(benzothiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)-methyl)-4H-1,2,4-triazol-3-yl]thio]acetamide (5e)

m. p. 283 °C, yield 79%. ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 4.36 (s, 2H, S-CH$_2$), 5.27 (s, 2H, O-CH$_2$), 7.20 (d, J = 7.53 Hz, 1H, Ar-H), 7.30–7.34 (m, 1H, Ar-H), 7.39–7.45 (m, 5H, Ar-H), 7.54 (d, J = 8.21 Hz, 2H, Ar-H), 7.64 (d, J = 7.43 Hz, 2H, Ar-H), 7.77 (d, J = 8.02 Hz, 1H, Ar-H), 7.99 (d, J = 7.82 Hz, 1H, Ar-H), 8.30 (d, J = 8.29 Hz, 1H, Ar-H), 8.85–8.87 (m, 1H, Ar-H), 12.74 (brs, 1H, NH).^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 36.07 (S-CH$_2$), 61.22 (O-CH$_2$), 111.88, 121.15, 121.55, 122.26, 122.41, 124.15, 126.67, 127.00, 127.61, 129.50, 130.10, 130.56, 131.92, 132.81, 136.33, 140.23, 148.99, 149.82, 151.84, 152.38, 153.56, 158.19, 167.42 (C = O). For $C_{27}H_{20}N_6O_2S_2$ calculated: 61.82% C, 3.84% H, 16.02% N, 6.10% O, 12.22% S; found: 61.74% C, 3.83% H, 16.10% N, 6.11% O, 12.27% S. HRMS (m/z): $[M\text{-}H]^-$ calcd for $C_{27}H_{20}N_6O_2S_2$: 523.1016; found: 523.1033.

N-(6-methylbenzothiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl]thio]acetamide (5f)

m. p. 289 °C, yield 79%. ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 2.40 (s, 3H, CH$_3$), 4.34 (s, 2H, S-CH$_2$), 5.27 (s, 2H, O-CH$_2$), 7.20 (d, J = 7.58 Hz, 1H, Ar-H), 7.24–7.27 (m, 1H, Ar-H), 7.41–7.45 (m, 4H, Ar-H), 7.52–7.56 (m, 2H, Ar-H), 7.63–7.67 (m, 3H, Ar-H), 7.77 (s, 1H, Ar-H), 8.29–8.32 (m, 1H, Ar-H), 8.85–8.87 (m, 1H, Ar-H), 12.66 (brs, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 21.46 (CH$_3$), 36.05 (S-CH$_2$), 61.23 (O-CH$_2$), 111.89, 120.79, 121.55, 121.83, 122.41, 127.00, 127.61, 127.99, 129.50, 130.10, 130.55, 132.06, 132.81, 133.61, 136.33, 140.23, 149.82, 151.84, 152.37, 153.56, 157.31, 167.25 (C = O). For $C_{28}H_{22}N_6O_2S_2$ calculated: 62.44% C, 4.12% H, 15.60% N, 5.94% O, 11.90% S; found: 62.31% C, 4.13% H, 15.57% N, 5.92% O, 11.93% S. HRMS (m/z): $[M\text{-}H]^-$ calcd for $C_{28}H_{22}N_6O_2S_2$: 537.1173; found: 537.1179.

N-(6-chlorobenzothiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl]thio]acetamide (5g)

m. p. 290 °C, yield 80%. ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 4.36 (s, 2H, S-CH$_2$), 5.27 (S, 2H, O-CH$_2$), 7.20 (d, J = 7.57 Hz, 1H, Ar-H), 7.43–7.47 (m, 5H, Ar-H), 7.52–7.56 (m, 2H, Ar-H), 7.63–7.66 (m, 2H, Ar-H), 7.76 (d, J = 8.65, 1H, Ar-H), 8.13 (s, 1H, Ar-H), 8.28–8.32 (m, 1H, Ar-H), 8.85–8.87 (m, 1H, Ar-H), 12.84 (brs, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 36.10 (S-CH$_2$), 61.22 (O-CH$_2$), 111.88, 121.55, 121.96, 122.32, 122.40, 126.99, 127.60, 128.15, 129.50, 130.10, 130.56, 132.80, 133.64, 136.33, 140.23, 147.88, 149.81, 151.84, 152.38, 153.56, 159.19, 167.73 (C = O). For $C_{27}H_{19}ClN_6O_2S_2$ calculated: 58.01% C, 3.43% H, 15.03% N, 5.72% O, 11.47% S; found: 58.17% C, 3.44%

H, 15.08% N, 5.71% O, 11.44% S. HRMS (m/z): $[M\text{-}H]^-$ calcd for $C_{27}H_{19}ClN_6O_2S_2$: 557.0627; found: 557.0621.

Ethyl 4-methyl-2-[2-[(4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl)thio]acetamido]thiazole-5-carboxylate (5h)

m. p. 246 °C, yield 81%. ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.26 (t, J = 7.06 Hz, 3H, CH_3), 2.55 (s, 3H, O-CH_2-CH_3), 4.20–4.25 (q, J_1=7.05 Hz, J_2=14.18 Hz, O-CH_2-CH_3), 4.29 (s, 2H, S-CH_2), 5.27 (S, 2H, O-CH_2), 7.20 (d, J = 7.59 Hz, 1H, Ar-H), 7.41–7.46 (m, 4H, Ar-H), 7.53–7.56 (m, 2H, Ar-H), 7.61–7.65 (m, 2H, Ar-H), 8.29–8.32 (m, 1H, Ar-H), 8.86–8.87 (m, 1H, Ar-H), 12.85 (brs, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 14.65 (CH_3), 17.50 (O-CH_2-CH_3), 35.92 (S-CH_2), 61.01 (O-CH_2-CH_3), 61.22 (O-CH_2), 111.89, 114.60, 121.55, 122.40, 126.99, 127.60, 129.60, 130.09, 130.55, 132.80, 136.32, 140.23, 149.82, 151.75, 152.35, 153.56, 156.73, 160.02, 162.52, 167.47 (C = O). For $C_{27}H_{24}N_6O_4S_2$ calculated: 57.84% C, 4.32% H, 14.99% N, 11.41% O, 11.44% S; found: 57.69% C, 4.33% H, 14.91% N, 11.45% O, 11.48% S. HRMS (m/z): $[M\text{-}H]^-$ calcd for $C_{27}H_{24}N_6O_4S_2$: 559.1228; found: 559.1216.

N-(5-acetyl-4-methylthiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl]thio]acetamide (5i)

m. p. 267 °C, yield 81%. ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 2.48 (s, 3H, CH_3), 2.58 (s, 3H, carbonyl-CH_3), 4.30 (s, 2H, S-CH_2), 5.27 (s, 2H, O-CH_2), 7.20 (d, J = 7.51, 1H, Ar-H), 7.41–7.45 (m, 4H, Ar-H), 7.53–7.56 (m, 2H, Ar-H), 7.62–7.64 (m, 2H, Ar-H), 8.31 (d, J = 7.35 Hz, 1H, Ar-H), 8.86–8.87 (m, 1H, Ar-H), 12.84 (brs, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 18.56 (CH_3), 30.57 (carbonyl-CH_3), 35.86 (S-CH_2), 61.20 (O-CH_2), 111.85, 121.55, 122.41, 126.04, 127.00, 127.59, 129.50, 130.11, 130.56, 132.79, 136.33, 140.22, 149.83, 151.75, 152.36, 153.56, 154.84, 159.81, 167.36 (C = O), 191.17 (thiazole-C = O). For $C_{26}H_{22}N_6O_3S_2$ calculated: 58.85% C, 4.18% H, 15.84% N, 9.05% O, 12.08% S; found: 58.68% C, 4.19% H, 15.82% N, 9.08% O, 12.11% S. HRMS (m/z): $[M\text{-}H]^-$ calcd for $C_{26}H_{22}N_6O_3S_2$: 529.1122; found: 529.1115.

N-(5-methyl-4-phenylthiazol-2-yl)-2-[[4-phenyl-5-((quinolin-8-yloxy)methyl)-4H-1,2,4-triazol-3-yl]thio]acetamide (5j)

m. p. 232 °C, yield 79%. ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 2.47 (s, 3H, CH_3), 4.29 (s, 2H, S-CH_2), 5.27 (s, 2H, O-CH_2), 7.19–7.22 (m, 1H, Ar-H), 7.34–7.37 (m, 1H, Ar-H), 7.42–7.43 (m, 2H, Ar-H), 7.44–7.45 (m, 3H, Ar-H), 7.47–7.48 (m, 1H, Ar-H), 7.52–7.53 (m, 1H, Ar-H), 7.55–7.56 (m, 1H, Ar-H), 7.63–7.67 (m, 4H, Ar-H), 8.29–8.32 (m, 1H, Ar-H), 8.86–8.88 (m, 1H, Ar-H), 12.50 (brs, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 12.36 (CH_3), 35.84 (S-CH_2), 61.22 (O-CH_2), 111.86, 121.54, 121.82, 122.41, 127.00, 127.63, 128.44, 128.87, 129.51, 130.08, 130.53, 132.84, 135.27, 136.32, 140.24, 144.69, 149.82, 151.84, 152.33, 153.57, 154.17, 166.31 (C = O). For $C_{30}H_{24}N_6O_2S_2$ calculated: 63.81% C, 4.28% H, 14.88% N, 5.67% O, 11.36% S; found: 63.72% C, 4.27% H, 14.78% N, 5.69% O, 11.33% S. HRMS (m/z): $[M\text{-}H]^-$ calcd for $C_{30}H_{24}N_6O_2S_2$: 563.1329; found: 563.1318.

Conclusion

Spectroscopic data showed that the compounds with the intended 3,4,5-trisubstituted triazole derivatives were synthesized and screened to determine their antimicrobial activity potential against seven bacteria and four fungi species. In general, efficiency exhibited against fungi was better than that against bacteria which means that the synthesized substances have higher antifungal activity than antibacterial activity. However, when evaluating in terms of their potential, compounds **5a** and **5d** exhibited half the potency of chloramphenicol against *E. feacalis*. Likewise, **5a** and **5i** showed half the potency of chloramphenicol against *S. typhimurium*. Additionally, compounds **5a** with 6-nitrobenzothiazole, **5d** with 6-fluorobenzothiazole and **5i** with 4-methyl-5-acetyl-thiazole moieties were found as the most active compounds with antibacterial potential.

Conflict of interest

The author confirms that this article content has no conflict of interest.

References

[1] Thangaraj, M.; Gengan, R. M.; Ranjan, B.; Muthusamy, R. Synthesis, Molecular Docking, Antimicrobial, Antioxidant and Toxicity Assessment of Quinoline Peptides. *J. Photochem. Photobiol. B.* **2018**, *178*, 287–295. DOI: 10.1016/j.jphotobiol.2017.11.019.

[2] Allahverdiyev, A. M.; Abamor, E. S.; Bagirova, M.; Rafailovich, M. Antimicrobial Effects of TiO_2 and Ag_2O Nanoparticles against Drug-Resistant Bacteria and Leishmania Parasites. *Future Microbiol.* **2011**, *6*, 933–940. DOI: 10.2217/fmb.11.78.

[3] Bakka, T. A.; Strøm, M. B.; Andersen, J. H.; Gautun, O. R. Methyl Propiolate and 3-Butynone: Starting Points for Synthesis of Amphiphilic 1,2,3-Triazole Peptidomimetics for Antimicrobial Evaluation. *Bioorg. Med. Chem.* **2017**, *25*, 5380–5395. DOI: 10.1016/j.bmc.2017.07.060.

[4] Rajasekaran, A.; Sivakumar, K. K.; Sureshkumar, K.; Manjushree, M. Design, Synthesis, Characterisation and in-Vitro Antimicrobial Activity of Some Hybridized Triazole Scaffolds. *FJPS* **2017**, *3*, 1–10. DOI: 10.1016/j.fjps.2016.09.003.

[5] Savini, L.; Chiasserini, L.; Pellerano, C.; Filippelli, W.; Falcone, G. Show More Synthesis and Pharmacological Activity of 1,2,4-Triazolo[4,3-a]Quinolines. *Il Farmaco* **2001**, *56*, 939–945. DOI: 10.1016/S0014-827X(01)01166-1.

[6] Teng, P.; Li, C.; Peng, Z.; Vanderschouw, A. M.; Nimmagadda, A.; Su, M.; Li, Y.; Sun, X.; Cai, J. Facilely Accessible Quinoline Derivatives as Potent Antibacterial Agents. *Bioorg. Med. Chem.* **2018**, *26*, 3573–3579. DOI: 10.1016/j.bmc.2018.05.031.

[7] Eswaran, S.; Adhikari, A. V.; Shetty, N. S. Synthesis and Antimicrobial Activities of Novel Quinoline Derivatives Carrying 1,2,4-Triazole Moiety. *Eur. J. Med. Chem.* **2009**, *44*, 4637–4647. DOI: 10.1016/j.ejmech.2009.06.031.

[8] Guo, L.; Wei, C.; Jia, J.; Zhao, L.; Quan, Z. Design and Synthesis of 5-Alkoxy-[1,2,4]Triazolo[4,3-a]Quinoline Derivatives with Anticonvulsant Activity. *Eur. J. Med. Chem.* **2009**, *44*, 954–958. DOI: 10.1016/j.ejmech.2008.07.010.

[9] Afzal, O.; Kumar, S.; Haider, M. R.; Ali, M. R.; Kumar, R.; Jaggi, M.; Bawa, S. A Review on Anticancer Potential of Bioactive Heterocycle Quinoline. *Eur. J. Med. Chem.* **2015**, *97*, 871–910. DOI: 10.1016/j.ejmech.2014.07.044.

[10] Ferlin, M. G.; Chiarelotto, G.; Antonucci, F.; Caparrotta, L.; Froldi, G. Mannich Bases of 3H-Pyrrolo[3,2-f]Quinoline Having Vasorelaxing Activity. *Eur. J. Med. Chem.* **2002**, *37*, 427–434. DOI: 10.1016/S0223-5234(02)01355-7.

[11] Joshi, P. V.; Sayed, A. A.; Ravikumar, A.; Puranik, V. G.; Zinjarde, S. S. 4-Phenyl Quinoline Derivatives as Potential Serotonin Receptor Ligands with Antiproliferative Activity. *Eur. J. Med. Chem.* **2017**, *136*, 246–258. DOI: 10.1016/j.ejmech.2017.05.002.

[12] Musiol, R.; Jampilek, J.; Buchta, V.; Silva, L.; Niedbala, H.; Podeszwa, B.; Palka, A.; Majerz-Maniecka, K.; Oleksyn, B.; Polanski, J. Antifungal Properties of New Series of Quinoline Derivatives. *Bioorg. Med. Chem.* **2006**, *14*, 3592–3598. DOI: 10.1016/j.bmc.2006.01.016.

[13] Gershon, H.; Gershon, M.; Clarke, D. D. Synergistic Mixtures of Fungitoxic Monochloro and Dichloro-8-Quinolinols against Five Fungi. *Mycopathologia* **2004**, *158*, 131–135. DOI: 10.1023/B:MYCO.0000038427.42852.6a.

[14] Kaya-Çavuşoğlu, B.; Yurttaş, L.; Cantürk, Z. The Synthesis, Antifungal and Apoptotic Effects of Triazole-Oxadiazoles Against Candida Species. *Eur. J. Med. Chem.* **2018**, *144*, 255–261. DOI: 10.1016/j.ejmech.2017.12.020.

[15] Hunashal, R. D.; Ronad, P. M.; Maddi, V. S.; Satyanarayana, D.; Kamadod, M. A. Synthesis, Anti-Inflammatory and Analgesic Activity of 2-[4-(Substituted Benzylideneamino)-5-(Substituted Phenoxymethyl)-4H-1,2,4-Triazol-3-yl Thio] Acetic Acid Derivatives. *ARAB. J. Chem.* **2014**, *7*, 1070–1078. DOI: 10.1016/j.arabjc.2011.01.003.

[16] Tozkoparan, B.; Gökhan, N.; Aktay, G.; Yeşilada, E.; Ertan, M. 6-Benzylidenethiazolo[3,2-b]-1,2,4-Triazole-5(6H)-Onessubstituted with Ibuprofen: Synthesis, Characterizationand Evaluation of Anti-Inflammatory Activity. *Eur. J. Med. Chem.* **2000**, *35*, 743–750. DOI: 10.1016/S0223-5234(00)00157-4.

[17] El Sherief, H. A. M.; Youssif, B. G. M.; Bukhari, S. N. A.; Abdelazeem, A. H.; Abdel-Aziz, M.; Abdel-Rahman, H. M. Synthesis, Anticancer Activity and Molecular Modeling Studies of 1,2,4-Triazole Derivatives as EGFR Inhibitors. *Eur. J. Med. Chem.* **2018**, *156*, 774–789. DOI: 10.1016/j.ejmech.2018.07.024.

[18] Mermer, A.; Demirbaş, N.; Şirin, Y.; Uslu, H.; Özdemir, Z.; Demirbaş, A. Conventional and Microwave Prompted Synthesis, Antioxidant, Anticholinesterase Activity Screening and Molecular Docking Studies of New Quinolone-Triazole Hybrids. *Bioorg. Med. Chem.* **2018**, *78*, 236–248. DOI: 10.1016/j.bioorg.2018.03.017.

[19] Koparır, M.; Orek, C.; Parlak, A. E.; Soylemez, A.; Koparır, P.; Karatepe, M.; Dastan, S. D. Synthesis and Biological Activities of Some Novel Aminomethyl Derivatives of 4-Substituted-5-(2-Thienyl)-2,4-Dihydro-3H-1,2,4-Triazole-3-Thiones. *Eur. J. Med. Chem.* **2013**, *63*, 340–346. DOI: 10.1016/j.ejmech.2013.02.025.

[20] Kaya, B.; Yurttas, L.; Yılmaz Cankılıç, M.; Kaplancıklı, Z. A. Synthesis, Antibacterial, Antifungal, Antimycobacterial Activity Evaluation of Novel 1,2,4-Triazole Derivatives Bearing 4-Aminophenyl Moiety. *Lett. Drug Des. Discov.* **2017**, *14*, 938–948. DOI: 10.2174/1570180814666161130103624.

[21] Daina, A.; Michielin, O.; Zoete, V. iLOGP: A Simple, Robust, and Efficient Description of n-Octanol/Water Partition Coefficient for Drug Design Using the GB/SA Approach. *J. Chem. Inf. Model.* **2014**, *54*, 3284–3301. DOI: 10.1021/ci500467k.

[22] Daina, A.; Zoete, V. A Boiled-Egg to Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *ChemMedChem.* **2016**, *11*, 1117–1121. DOI: 10.1002/cmdc.201600182.

[23] Daina, A.; Michielin, O.; Zoete, V. SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness and Medicinal Chemistry Friendliness of Small Molecules. *Sci. Rep.* **2017**, *7*, 42717. DOI: 10.1038/srep42717.

[24] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3–25. DOI: 10.1016/j.addr.2012.09.019.

[25] Ahmed, M.; Sharma, R.; Nagda, D. P.; Jat, J. L.; Talesara, G. L. Synthesis and Antimicrobial Activity of Succinimido(2-Aryl-4-Oxo-3-[2]-1,3-Thiazolidin-5-yl)Acetates. *Arkivoc* **2006**, *11*, 66–75. DOI: 10.3998/ark.5550190.0007.b06.

[26] Behalo, M. S.; Amine, M. S.; Fouda, I. M. Regioselective Synthesis, Antitumor and Antioxidant Activities of Some 1,2,4-Triazole Derivatives Based on 4-Phenyl-5-(Quinolin-8-Yloxy)Methyl-4H-1,2,4-Triazole-3-Thiol. *Phosphorus Sulfur Silicon Relat. Elem.* **2017**, *192*, 410–417. DOI: 10.1080/10426507.2016.1247087.

[27] Alam, M. M.; Shaharyar, M.; Hamid, H.; Nazreen, S.; Haider, S.; Alam, M. S. Synthesis of Novel 8-Hydroxy Quinolin Based 1,3,4-Oxadiazoles and S-Substituted 1,2,4-Triazole Derivatives and Evaluation of Their anti-Inflammatory, Analgesic, Ulcerogenic and anti-Microbial Activities. *Med. Chem.* **2011**, *7*, 663–673. DOI: 10.2174/157340611797928334.