Medicinal Chemistry Research
https://doi.org/10.1007/s00044-020-02540-5

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial evaluation of new thiazolyl-1,2,3-triazolyl-alcohol derivatives

Shivaji Jagadale[1,2] · Abhijit Chavan[1] · Abhijit Shinde[1] · Vilas Sisode[3] · Vivek D. Bobade[4] · Pravin C. Mhaske[1]

Received: 20 January 2020 / Accepted: 30 March 2020
© Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

A new series of 1-(4-methyl-2-aryl-1,3-thiazol-5-yl)-2-(4-aryl-1,2,3-triazol-1-yl)ethanol (6a-t) have been synthesized by a click reaction of 2-azido-1-(4-methyl-2-phenylthiazol-5-yl)ethanone (3a-e) with substituted ethynylbenzene (4a-c) followed by reduction with sodiumboro hydride. The newly synthesized 1-(4-methyl-2-aryl-1,3-thiazol-5-yl)-2-(4-aryl-1,2,3-triazol-1-yl)ethanol derivatives were screened for in vitro antibacterial activityagainst a Gram negative strains, *Escherichia coli* (National Collection of Industrial Microorganisms, NCIM 2574), a Gram positive strain *Staphylococcus albus* (NCIM 2178) and in vitro antifungal activity against *Candida albicans* (NCIM 3100), *Aspergillus niger* (American Type Culture Collection, ATCC 504), *Rhodotorula glutinis* (NCIM 3168), *and Penicillium chrysogenum* (NCIM 737). Eight thiazolyl-1,2,3-triazolyl-alcohol derivatives 6a, 6i, 6j, 6k, 6m, 6n, 6o, and 6p, reported promissing antifungal activity against *A. niger* with minimum inhibitory concentration (MIC) 31.25–62.5 µg/mL. Compounds 6d, 6m, and 6p showed good antibacterial activity against *S. albus*. It was revealed that, 4-chlorophenyl and 4-fluorophenyl group at position-2 of thiazole ring reported good activity against *A. niger*. The substantial antimicrobial activity of 1-(4-methyl-2-aryl-1,3-thiazol-5-yl)-2-(4-aryl-1,2,3-triazol-1-yl)ethanol derivatives suggested that, these compounds could assist in the development of lead compounds as a treatment against microbial infection.

Keywords Thiazole · 1,2,3-Triazole · Click reaction · Antibacterial activity · Antifungal activity

Introduction

Combating infection has become one of the major challenges to global health, food security and development. The resistance to antimicrobial drugs threatens the effective prevention and treatment of an increasing range of bacterial and fungal infections. Future health management such as surgery, organ transplantation, cancer chemotherapy and diabetes treatments will become a high risk issue without efficient antibiotics (WHO report 2018, Aslam et al. 2018, Fisher et al. 2018)

Azoles are an important class of heterocyclic compounds which exhibit a large spectrum of biological activities (Sheehan et al. 1999, Allen et al. 2015, Choi et al. 2014) against infectious diseases. 1,3-Thiazole containing compounds exhibit a broad spectrum of biological activities (Mark et al. 2005) such as antifungal (Gaikwad et al. 2012, Patil et al. 2015) antibacterial (Tomasic et al. 2015, Brvar et al. 2012, Mhaske et al. 2017, Shelke et al. 2012) antimycobacterial (Abhale et al 2015, 2016, 2017), antimalarial (Bueno et al. 2016), antioxidant (Jaishree et al. 2012), anti-inflammatory (Rostomet al. 2009), and antiviral (Liet al.

Supplementary information The online version of this article (https://doi.org/10.1007/s00044-020-02540-5) contains supplementary material, which is available to authorized users.

✉ Pravin C. Mhaske
mhaskepc18@gmail.com

[1] Department of Chemistry—Postgraduation, S. P. Mandali's Sir Parashurambhau College (affiliated to Savitribai Phule Pune University), Tilak Road, Pune 411 030, India

[2] Department of Chemistry, S. K. Gandhi Arts, Amolak Science and P. H. Gandhi Commerce College (affiliated to Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Kada, Tal. Ashti, District Beed 414202, India

[3] Department of Chemistry, Abasaheb Garware College (affiliated to Savitribai Phule Pune University), Pune, India

[4] Department of Chemistry—Postgraduation, H. P. T. Arts and R. Y. K. Science College (affiliated to Savitribai Phule Pune University), Nashik 422005, India

Published online: 20 April 2020

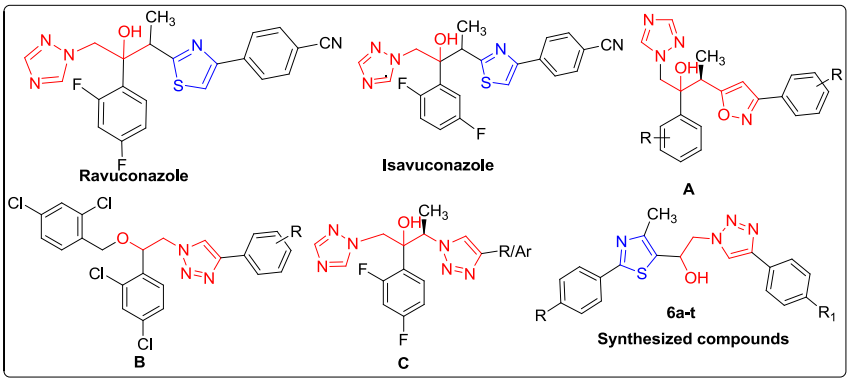


Fig. 1 Triazolyl-alcohol, thiazolyl-triazolyl-alcohol antifungal drugs and lead compounds, and our new proposed analogs (**6a–t**)

2008). 1,2,3-Triazole derivatives are therapeutically important in medicinal chemistry and drug discovery (Dheer et al. 2017, Bonandi et al. 2017), as they exhibit significant biological activities such as antifungal (Bonandi et al. 2017, Choi et al. 2014, Kathiravan et al. 2012), antimicrobial (Calderon et al. 2016, Zhang B 2019) antitubercular (Jadhav et al. 2017, Shaikh et al. 2015, Menendez et al. 2013), antimalarial (Chu et al. 2019), anticancer (Battula et al. 2017, Ma et al. 2015), anti-inflammatory (Dmitry et al. 2014), and antiviral (Tian et al. 2018). Triazole alcohols are vital pharmacophore of the azole antifungal drugs (Bozorov et al. 2019, Hashemi et al. 2015, Emamiet al. 2019) (Fig. 1). 1,2,3-Triazole clubbed with antibacterial drugs such as Rifampicin–Tobramycin hybrids showed potential antibacterial activity (Idowu et al. 2019). The biological importance and structural modification of thiazole and 1,2,3-triazole have made them a prominent target for new antimicrobial lead compounds. 1,3-Thiazole clubbed with other azole derivatives showed antibacterial, antifungal, and antitubercular activities (Nalawade et al. 2019, Takate et al. 2019). The 1,3-thiazole and 1,2,3-triazole tethered nucleus has received attention in recent years due to their significant antimicrobial and antitubercular (Shinde et al. 2018, 2019, Pardeshi et al. 2011, Shiradkar 2007) activities.

Owing to the promising biological activities of thiazole and 1,2,3-triazole derivatives and in continuation of our search for new anti-infection agents, we report herein the synthesis and antimicrobial evaluation of 1-(4-methyl-2-aryl-1,3-thiazol-5-yl)-2-(4-aryl-1,2,3-triazol-1-yl)ethanol derivatives.

Materials and methods

Chemistry

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker at either 500 MHz (^{1}H NMR) and 126 MHz (^{13}C NMR), spectrometer instruments. Chemical shifts are reported from internal tetramethylsilane standard and are reported in δ units.

General procedure for synthesis of 2-azido-1-(4-methyl-2-phenylthiazol-5-yl)ethanone (3a)

The mixture of 2-bromo-1-(4-methyl-2-phenylthiazol-5-yl) ethanone (**2a**) (10 mmol) and sodium azide (0.715 g, 11 mmol) in dimethyl sulphoxide (10 mL) was stirred for 30 min. The progress of the reaction was monitored on thin layer chromatography (TLC), after completion, the reaction mixture was quenched in water (50 mL) and stirred for 20 min. The aqueous solution of reaction was extracted with ethyl acetate (20 mL × 3), the organic layer was washed with water, dried over anhydrous Na_2SO_4. Solvent was removed under vacuum to afford 2-azido-1-(4-methyl-2-phenylthiazol-5-yl)ethanone (**3a**), (yield 85%). The crude product was used for further reaction. Derivative **3b–e** was synthesized by similar protocol (yield 80-88%).

General procedure for synthesis of 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl) ethanone (5a)

The mixture of 2-azido-1-(4-methyl-2-phenylthiazol-5-yl) ethanone (**3a**) (5 mmol), ethynylbenzene (**4a**), sodium ascorbate (1 mmol) and copper sulfate (1 mmol) in DMF: H_2O (3:1) (4 mL) was stirred for 12–24 h. After completion of reaction (TLC), the reaction was quenched in water and extracted with ethyl acetate (20 mL × 3), the organic layer was washed with water, dried over anhydrous Na_2SO_4, and solvent was removed under vacuum to afford 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanone (**5a**). The crude product was purified by column chromatography using ethyl acetate:hexane (2:8) as eluent (yield 76%). Derivatives **5b–t** was synthesized using similar experimental procedure (yield 70–85%).

General procedure for synthesis of 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl) ethanol, (6a)

To a solution of 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanone (**5a**) in methanol (10 mL), $NaBH_4$ (5 mmol) was added portion wise at 5–10 °C for 15 min. The reaction mixture was stirred for one hour. After completion of the reaction (TLC), solvent was distilled under vacuum; the residue was dissolved in water (20 mL) and extracted with ethyl acetate (20 mL × 3). Organic layer was washed with water and dried over anhydrous sodium sulfate. Solvent was removed under vacuum to obtain 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanol, (**6a**) (yield 84%). Compounds **6b–t** was synthesized by same experimental procedure (yield 70–88%).

1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-2-(4-phenyl-1,2,3-triazol-1-yl)ethanol, (6a)

MF: $C_{20}H_{17}FN_4OS$; yield: 84%; mp: 138–140 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H, Triazole-H), 7.93 (d, J = 7.9 Hz, 2H, Ar-H), 7.89 (d, J = 7.1 Hz, 2H, Ar-H), 7.54–7.47 (m, 5H, Ar-H), 7.38 (t, J = 7.4 Hz, 1H, Ar-H), 6.56 (d, J = 4.3 Hz, 1H, OH), 5.43 (dt, J = 7.2, 5.1 Hz, 1H, CH), 4.68 (qd, J = 13.8, 6.3 Hz, 2H, CH_2), 2.33 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.90 (C, Thiazole-C2), 149.19 (C, Thiazole-C4), 146.63 (C, Triazole-C4), 134.68 (C, C1′), 133.59 (C, Thiazole-C5), 131.25 (C, C1″), 130.54 (C,C4′), 129.68 (2CH, C2′, C6′), 129.40 (2CH, C3″, C5″), 128.30 (CH, Triazole-C5), 126.24 (2CH, C3′, C5′), 125.59 (2CH, C2″, C6″), 122.81 (CH, C4″), 66.17 (CH, Thiazole−CHOH), 56.56 (CH_2,−CH_2−Triazole), 15.60(CH_3, Thiazole-CH_3); HRMS: m/z = 363.1287 (M + H)+.

1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-2-[4-(4-methylphenyl)-1,2,3-triazol-1-yl]ethanol, (6b)

MF: $C_{20}H_{17}BrN_4OS$; yield: 80%; mp: 150–152 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (s, 1H, Triazole-H), 7.88 (dd, J = 7.7, 1.8 Hz, 2H, Ar-H), 7.73 (d, J = 8.1 Hz, 2H, Ar-H), 7.51–7.45 (m, 3H, Ar-H), 7.26 (d, J = 8.0 Hz, 2H, Ar-H), 6.51 (d, J = 4.3 Hz, 1H, OH), 5.38 (dt, J = 7.2, 5.1 Hz, 1H, CH), 4.62 (qd, J = 13.8, 6.3 Hz, 2H, CH_2), 2.33 (s, 3H, Thiazole-CH_3), 2.28 (s, 3H, Ar-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.89 (C, Thiazole-C2), 149.18 (C, Thiazole-C4), 146.69 (C, Triazole-C4), 137.59 (C, C4″), 134.69 (C, C1′), 133.59 (C, Thiazole-C5), 130.53 (C, C4′), 129.94 (2CH, C3″, C5″), 129.68 (2CH, C2′, C6′), 128.48 (CH, Triazole-C5), 126.23 (2CH, C3′, C5′), 125.53 (2CH, C2″, C6″), 122.36 (C, C1″), 66.18 (CH, Thiazole−CHOH), 56.53 (CH_2,−CH_2−Triazole), 21.30 (CH_3, Ar−CH_3), 15.58 (CH_3, Thiazole-CH_3); HRMS: m/z = 377.1441 (M + H)+.

2-[4-(4-methoxyphenyl)-1,2,3-triazol-1-yl]-1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)ethanol, (6c)

MF: $C_{21}H_{20}N_4O_2S$; yield: 78%; mp: 160–162 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (s, 1H, Triazole-H), 7.89 (d, J = 8.0 Hz, 2H, Ar-H), 7.77 (d, J = 8.8 Hz, 2H, Ar-H), 7.50–7.46 (m, 3H, Ar-H), 7.02 (d, J = 8.8 Hz, 2H, Ar-H), 6.50 (d, J = 4.3 Hz, 1H, OH), 5.37 (dt, J = 7.2, 5.1 Hz, 1H, CH), 4.61 (qd, J = 13.8, 6.3 Hz, 2H, CH_2), 3.79 (s, 3H, O-CH_3), 2.27 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.87 (C, Thiazole-C2), 159.44 (C, C4″), 149.17 (C, Thiazole-C4), 146.56 (C, Triazole-C4), 134.71 (C, C1′), 133.60 (C, Thiazole-C5), 130.53 (C, C4′), 129.68 (2CH, C2′, C6′), 126.93 (2CH, C2″, C6″), 126.23 (2CH, C3′, C5′), 123.85 (CH, Triazole-C5), 121.83 (C, C1″), 114.80 (2CH, C3″, C5″), 66.19 (CH, Thiazole−CHOH), 56.52 (CH_2,−CH−Triazole), 55.62 (CH_3, Ar−OCH_3), 15.59 (CH_3, Thiazole-CH_3); HRMS: m/z = 393.1390 (M + H)+.

2-[4-(4-fluorophenyl)-1,2,3-triazol-1-yl]-1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)ethanol, (6d)

MF: $C_{20}H_{17}FN_4OS$; yield: 84%; mp: 168–170 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H, Triazole-H), 7.92–7.87 (m, 4H, Ar-H), 7.48 (dd, J = 7.2, 4.5 Hz, 3H, Ar-H), 7.29 (dd, J = 9.9, 7.9 Hz, 2H, Ar-H), 6.51 (d, J = 4.3 Hz, 1H, OH), 5.40 – 5.36 (m, 1H, -CH), 4.67–4.59 (m, 2H, –CH_2), 2.33 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.90 (C, Thiazole-C2), 163.19 and 161.24 (C, C4″, d, ^1J = 245.7 Hz), 149.18 (C, Thiazole-C4), 145.77 (C, Triazole-C4), 134.64 (C, C1′), 133.58 (C, Thiazole-C5), 130.54 (C, C4′), 129.68 (2CH, C2′, C6′), 127.83 and 127.80 (C, C1″, d, ^4J = 3.8 Hz), 127.63 and 127.56 (2CH, C2″, C6″, d, ^3J = 8.8 Hz), 126.24 (2CH, C3′, C5′), 122.73 (CH, Triazole-C5), 116.42 and 116.24 (2CH, C3″, C5″, d, ^4J = 22.7 Hz), 66.16 (CH, Thiazole−CHOH), 56.58 (CH_2,−CH_2−Triazole), 15.60 (CH_3, Thiazole-CH_3); HRMS: m/z = 381.1192 (M + H)+.

1-[2-(4-bromophenyl)-4-methyl-1,3-thiazol-5-yl]-2-(4-phenyl-1,2,3-triazol-1-yl)ethanol, (6e)

MF: $C_{20}H_{17}BrN_4OS$; yield: 75%; mp: 140–142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (s, 1H, Triazole-H), 7.94 (d, J = 8.6 Hz, 2H, Ar-H), 7.89 (d, J = 7.2 Hz, 2H, Ar-H), 7.59 (d, J = 8.6 Hz, 2H, Ar-H), 7.50 (t, J = 7.7 Hz, 2H, Ar-H), 7.38 (t, J = 7.4 Hz, 1H, Ar-H), 6.59 (d, J = 4.3 Hz, 1H, OH), 5.47–5.40 (m, 1H, -CH), 4.68 (qd, J = 13.8, 6.2 Hz, 2H, –CH_2), 2.32 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.53 (C, Thiazole-C2), 149.34

(C, Thiazole-C4), 146.64 (C, Triazole-C4), 135.31 (C, C1′), 135.03 (C, Thiazole-C5), 132.40 (C, C4′), 131.23 (C, C1″), 129.73 (2CH, C3′, C5′), 129.40 (2CH, C3″, C5″), 128.30 (CH, Triazole-C5), 127.92 (2CH, C2′, C6′), 125.59 (2CH, C2″, C6″), 122.81 (CH, C4″), 66.16 (CH, Thiazole−CHOH), 56.51 (CH_2, –CH−Triazole), 15.56 (CH_3, Thiazole-CH_3); HRMS: m/z = 441.0385 (M + H) + 443.0371 (M + 2 + H)+.

1-[2-(4-bromophenyl)-4-methyl-1,3-thiazol-5-yl]-2-[4-(4-methylphenyl)-1,2,3-triazol-1-yl]ethanol, (6f)

MF: $C_{21}H_{19}BrN_4OS$; yield: 84%; mp: 182–184 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (s, 1H, Triazole-H), 7.96–7.92 (m, 2H, Ar-H), 7.77 (d, J = 8.1 Hz, 2H, Ar-H), 7.61–7.57 (m, 2H, Ar-H), 7.30 (d, J = 8.0 Hz, 2H, Ar-H), 6.58 (d, J = 4.3 Hz, 1H, OH), 5.43 (dt, J = 7.1, 5.1 Hz, 1H, -CH), 4.66 (qd, J = 13.8, 6.2 Hz, 2H, –CH_2), 2.38 (s, 3H, Thiazole-CH_3), 2.32 (s, 3H, Ar-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.51 (C, Thiazole-C2), 149.34 (C, Thiazole-C4), 146.70 (C, Triazole-C4), 137.59 C, C4″), 135.33 (C, C1′), 135.03 (C, Thiazole-C5), 132.41 (C, C4′), 129.94 (2CH, C3″, C5″), 129.73 (2CH, C3′, C5′), 128.47 (CH, Triazole-C5), 127.92 (2CH, C2′, C6′), 125.53 (2CH, C2″, C6″), 122.37 (C, C1″), 66.17 (CH, Thiazole−CHOH), 56.49 (CH_2,−CH_2−Triazole), 21.30 (CH_3, Ar−CH_3), 15.56 (CH_3, Thiazole-CH_3); HRMS: m/z = 455.0546 (M + H) + 457.0528 (M + 2 + H)+.

1-[2-(4-bromophenyl)-4-methyl-1,3-thiazol-5-yl]-2-[4-(4-methoxyphenyl)-1,2,3-triazol-1-yl]ethanol, (6g)

MF: $C_{21}H_{19}BrN_4O_2S$; yield: 80%; mp: 160–162 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (s, 1H, Triazole-H), 7.97–7.93 (m, 2H, Ar-H), 7.84–7.79 (m, 2H, Ar-H), 7.61–7.57 (m, 2H, Ar-H), 7.06 (d, J = 8.8 Hz, 2H, Ar-H), 6.58 (d, J = 4.3 Hz, 1H, OH), 5.42 (dt, J = 7.1, 5.0 Hz, 1H, -CH), 4.65 (qd, J = 13.8, 6.3 Hz, 2H, –CH_2), 3.84 (s, 3H, O-CH_3), 2.32 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.50 (C, Thiazole-C2), 159.44 (C, C4″), 149.34 (C, Thiazole-C4), 146.58 (C, Triazole-C4), 135.35 (C, C1′), 135.03 (C, Thiazole-C5), 132.41 (C, C4′), 129.73 (2CH, C3′, C5′), 127.92 (2CH, C2′, C6′), 126.94 (2CH, C2″, C6″), 123.83 (CH, Triazole-C-5), 121.84 (C, C1″), 114.80 (2CH, C3″, C5″), 66.18 (CH, Thiazole−CHOH), 56.48 (CH_2,−CH_2−Triazole), 55.62 (CH_3, Ar−CH_3), 15.56 (CH_3, Thiazole-CH_3); HRMS: m/z = 471.0498 (M + H)+, 473.0478 (M + 2 + H)+.

1-[2-(4-bromophenyl)-4-methyl-1,3-thiazol-5-yl]-2-[4-(4-fluorophenyl)-1,2,3-triazol-1-yl]ethanol, (6h)

MF: $C_{20}H_{16}BrFN_4OS$; yield: 80%; mp: 184–186 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H, Triazole-H), 7.97–7.91 (m, 4H, Ar-H), 7.59 (d, J = 8.6 Hz, 2H, Ar-H), 7.34 (t, J = 8.9 Hz, 2H, Ar-H), 6.59 (d, J = 4.3 Hz, 1H, OH), 5.46–5.40 (m, 1H, -CH), 4.72–4.62 (m, 2H, –CH_2), 2.33 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.53 (C, Thiazole-C2), 163.19 and 161.25 (C,−C4″, d, ^1J = 244.4 Hz), 149.33 (C, Thiazole-C4), 145.78 (C, Triazole-C4), 135.27 (C, C1′), 135.04 (C, Thiazole-C5), 132.40 (C, C4′), 129.74 (2CH, C3′, C5′), 127.92 (2CH, C2′, C6′), 127.81 and 127.79 (C, C1″, d, ^4J = 3.8 Hz), 127.63 and 127.56 (2CH, C2″, C6″, d, ^3J = 8.8 Hz), 122.74 (CH, Triazole-C5), 116.41 and 116.24 (2CH, C3″, C5″, d, ^2J = 21.4 Hz), 66.15 (CH, Thiazole−CHOH), 56.53 (CH_2,−CH −Triazole), 15.57 (CH_3, Thiazole-CH_3); HRMS: m/z = 459.0299 (M + H)+. 461.0280 (M + 2 + H)+.

1-[2-(4-chlorophenyl)-4-methyl-1,3-thiazol-5-yl]-2-(4-phenyl-1,2,3-triazol-1-yl)ethanol, (6i)

MF: $C_{20}H_{17}ClN_4OS$; yield: 88%; mp: 163–165 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H, Triazole-H), 7.83 (dt, J = 4.2, 1.7 Hz, 4H, Ar-H), 7.70–7.66 (m, 2H, Ar-H), 7.45 (t, J = 7.7 Hz, 2H, Ar-H), 7.34 (t, J = 7.4 Hz, 1H, Ar-H), 6.54 (d, J = 4.3 Hz, 1H, OH), 5.39 (dt, J = 7.0, 5.1 Hz, 1H, -CH), 4.63 (qd, J = 13.8, 6.2 Hz, 2H, –CH_2), 2.28 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.61 (C, Thiazole-C2), 149.38 (C, Thiazole-C4), 146.64 (C, Triazole-C4), 135.33 (C, C4′), 132.74 (C, C1′), 132.65 (2CH, C2′, C6′), 131.23 (C, C1″), 129.40 (2CH, C3″, C5″), 128.31 (CH, Triazole-C5), 128.13 (2CH, C3′, C5′), 125.59 (2CH, C2″, C6″), 123.77 (C, Thiazole-C5), 122.81 (CH, C4″), 66.16 (CH, Thiazole−CHOH), 56.50 (CH_2,−CH−Triazole), 15.56 (CH_3, Thiazole-CH_3); HRMS: m/z = 397.0896 (M + H)+, 399.0867 (M + 2 + H)+.

1-[2-(4-chlorophenyl)-4-methyl-1,3-thiazol-5-yl]-2-[4-(4-methylphenyl)-1,2,3-triazol-1-yl]ethanol, (6j)

MF: $C_{21}H_{19}ClN_4OS$; yield: 78%; mp: 198–200 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (s, 1H, Triazole-H), 7.83 (d, J = 8.6 Hz, 2H, Ar-H), 7.73 (d, J = 8.0 Hz, 2H, Ar-H), 7.68 (d, J = 8.6 Hz, 2H, Ar-H), 7.26 (d, J = 7.9 Hz, 2H, Ar-H), 6.53 (d, J = 4.3 Hz, 1H, OH), 5.41 – 5.34 (m, 1H, -CH), 4.62 (qd, J = 13.8, 6.2 Hz, 2H, –CH_2), 2.33 (s, 3H, Ar-CH_3), 2.28 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.59 (C, Thiazole-C2), 149.37 (C, Thiazole-C4), 146.71 64 (C, Triazole-C4), 137.59 (C, C4″), 135.35 (C, C-4′), 132.74 (C, C1′), 132.64 (2CH, C2′, C6′), 129.93 (2CH, C3″, C5″), 128.47 (CH, Triazole-C5), 128.13 (2CH, C3′, C5′), 125.53 (2CH, C2″, C6″), 123.76 (C, Thiazole-C-5), 122.37 (C, C1″), 66.18 (CH, Thiazole−CHOH−), 56.48 (CH_2,−CH_2−Triazole), 21.30 (CH_3, Ar−CH_3), 15.56 (CH_3, Thiazole-CH_3); HRMS: m/z = 411.1052 (M + H) + 0.413.1025 (M + 2 + H)+.

1-[2-(4-chlorophenyl)-4-methyl-1,3-thiazol-5-yl]-2-[4-(4-methoxyphenyl)-1,2,3-triazol-1-yl]ethanol, (6k)

MF: $C_{21}H_{19}ClN_4O_2S$; yield: 85%; mp: 178–180 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (s, 1H, Triazole-H), 7.87 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.81 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.74–7.71 (m, 2H, Ar-H), 7.06 (d, $J = 8.8$ Hz, 2H, Ar-H), 6.57 (d, $J = 4.3$ Hz, 1H, OH), 5.42 (dt, $J = 7.1$, 5.1 Hz, 1H, -CH), 4.65 (qd, $J = 13.8$, 6.2 Hz, 2H, –CH_2), 3.84 (s, 3H, Ar-OCH_3), 2.32 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.59 (C, Thiazole-C2), 159.44 (C, C4″), 149.37 (C, Thiazole-C4), 146.58 (C, Triazole-C4), 135.37 (C, C4′), 132.74 (C, C1′), 132.64 (2CH, C2′, C6′), 128.13 (2CH, C3′, C5′), 126.94 (2CH, C2″, C6″), 123.83 (C, C1″), 123.76 (C, Thiazole-C5), 121.84 (CH, Triazole-C5), 114.80 (2CH,C3″, C5″), 66.19 (CH, Thiazole −CHOH), 56.46 (CH_2,−CH−Triazole), 55.62 (CH_3, Ar-OCH_3), 15.55 (CH_3, Thiazole-CH_3); HRMS: $m/z =$ 427.1002 (M + H)+, 429.0974 (M + 2 + H)+.

1-[2-(4-chlorophenyl)-4-methyl-1,3-thiazol-5-yl]-2-[4-(4-fluorophenyl)-1,2,3-triazol-1-yl]ethanol, (6l)

MF: $C_{20}H_{16}ClFN_4OS$; yield: 78%; mp: 162–164 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H, Triazole-H), 7.94–7.92 (m, 2H, Ar-H), 7.88 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.73 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.34 (t, $J = 8.9$ Hz, 2H, Ar-H), 6.56 (d, $J = 4.3$ Hz, 1H, OH), 5.46 – 5.39 (m, 1H, -CH), 4.73–4.63 (m, 2H, –CH_2), 2.33 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.61 (C, Thiazole-C2), 163.19 and 161.25 (C, C4″, d, $^1J = 244.4$ Hz), 149.18 (C, Thiazole-C4), 145.79 (C, Triazole-C4), 135.30 (C, C4′), 133.58 C, C1′), 132.65 (2CH, C2′, C6′), 128.13 (2CH, C3′, C5′), 127.81 and 127.79 (C, C1″, d, $^4J = 3.8$ Hz), 127.63 and 127.57 (2CH, C2″, C6″, d, $^3J = 8.8$ Hz), 126.24 (C, Thiazole-C5), 122.73 (CH, Triazole-C5), 116.41 and 116.24 (2CH, C3″, C5″, d, $^2J = 21.4$ Hz), 66.16 (CH, Thiazole−CHOH), 56.58 (CH_2,−CH_2 − Triazole), 15.60 (CH_3, Thiazole-CH_3); HRMS: $m/z = 415.0802$ (M + H)+, 417.0774 (M + 2 + H)+.

1-[2-(4-fluorophenyl)-4-methyl-1,3-thiazol-5-yl]-2-(4-phenyl-1,2,3-triazol-1-yl)ethanol, (6m)

MF: $C_{20}H_{17}FN_4OS$; yield: 75%; mp: 160-162 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (s, 1H, Triazole-H), 7.97 (dd, $J = 8.7$, 5.4 Hz, 2H, Ar-H), 7.89 (d, $J = 7.3$ Hz, 2H, Ar-H), 7.49 (t, $J = 7.7$ Hz, 2H, Ar-H), 7.37 (dd, $J = 17.7$, 8.8 Hz, 3H, Ar-H), 6.57 (d, $J = 4.3$ Hz, 1H, OH), 5.47 – 5.40 (m, 1H, -CH), 4.67 (qd, $J = 13.8$, 6.3 Hz, 2H, –CH_2), 2.31 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.75 (C, Thiazole-C2), 164.53 and 162.56 (C, C4′, d, $^1J = 244.4$ Hz), 149.17 (C, Thiazole-C4), 146.64 (C, Triazole-C4), 134.81 (C, Thiazole-C5), 131.24 (C, C1″), 130.28 and 130.25 (C, C1′, d, $^4J = 3.8$ Hz), 129.40 (2CH, C3″, C5″), 128.55 and 128.48 (2CH, C2′, C6′, d, $^3J = 8.8$ Hz), 128.30 (CH, Triazole-C5), 125.59 (2CH, C2″, C6″), 122.80 (CH, C4″), 116.78 and 116.60 (2CH, C3′, C5′, d, $^2J = 21.4$ Hz), 66.15 (CH, Thiazole−CHOH), 56.55 (CH_2,−CH_2−Triazole), 15.56 (CH_3, Thiazole-CH_3); HRMS: $m/z = 381.1193$ (M + H)+.

1-[2-(4-fluorophenyl)-4-methyl-1,3-thiazol-5-yl]-2-[4-(4-methylphenyl)-1,2,3-triazol-1-yl]ethanol, (6n)

MF: $C_{21}H_{19}FN_4OS$; yield: 72%; mp: 172–174 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (s, 1H, Triazole-H), 7.97 (dd, $J = 8.8$, 5.4 Hz, 2H, Ar-H), 7.77 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.36 (t, $J = 8.8$ Hz, 2H, Ar-H), 7.30 (d, $J = 7.9$ Hz, 2H, Ar-H), 6.55 (d, $J = 4.3$ Hz, 1H, OH), 5.42 (dt, $J = 7.2$, 5.0 Hz, 1H, -CH), 4.65 (qd, $J = 13.8$, 6.3 Hz, 2H, –CH_2), 2.37 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.73 (C, Thiazole-C2), 164.53 and 162.56 (C, C4′, d, $^1J = 244.4$ Hz), 149.16 (C, Thiazole-C4), 146.70 (C, Triazole-C4), 137.59 (C, C4″), 134.83 (C, Thiazole-C5), 130.28 and 130.26 (C, C1′, d, $^4J = 2.5$ Hz), 129.93 (2CH, C3″, C5″), 128.55 and 128.48 (2CH, C2′, C6′, d, $^3J = 8.8$ Hz), 128 48 (C, C1″), 125.53 (2CH, C2″, C6″), 122.36 (CH, Triazole-C5), 116.77 and 116.60 (2CH, C3′, C5′, d, $^2J = 21.4$ Hz), 66.16 (CH, Thiazole−CHOH), 56.52 (CH_2,−CH_2−Triazole), 21.29 (CH_3, Ar−CH_3), 15.55 (CH_3, Thiazole-CH_3); HRMS: $m/z = 395.1350$ (M + H)+.

1-[2-(4-fluorophenyl)-4-methyl-1,3-thiazol-5-yl]-2-[4-(4-methoxyphenyl)-1,2,3-triazol-1-yl]ethanol, (6o)

MF: $C_{21}H_{19}FN_4O_2S$; yield: 70%; mp: 123–125 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (s, 1H, Triazole-H), 7.93 (dd, $J = 8.8$, 5.4 Hz, 2H, Ar-H), 7.76 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.32 (t, $J = 8.8$ Hz, 2H, Ar-H), 7.02 (d, $J =$ 8.8 Hz, 2H, Ar-H), 6.51 (d, $J = 4.3$ Hz, 1H, OH), 5.37 (dt, J = 7.2, 5.1 Hz, 1H, -CH), 4.60 (qd, $J = 13.8$, 6.3 Hz, 2H, –CH_2), 3.79 (s, 3H, Ar-OCH), 2.26 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.73 (C, Thiazole-C2), 164.53 and 162.56 (C, C4′, d, $^1J = 244.4$ Hz), 159.44 (C, C4″), 149.16 (C, Thiazole-C4), 146.57 (C, Triazole-C4), 134.85 (C, Thiazole-C5), 130.28 and 130.26 (C, C1′, d, $^4J = 2.5$ Hz), 128.55 and 128.48 (2CH, C2′, C6′, d, $^3J =$ 8.8 Hz), 126.94 (2CH, C2″, C6″), 123.84 (C, C1″), 121.83 (CH, Triazole-C5), 116.77 and 116.60 (2CH, C3′, C5′, d, $^2J = 21.4$ Hz), 114.80 (2CH, C3″, C5″), 66.17 (CH, Thiazole−CHOH), 56.51 (CH_2,−CH_2−Triazole), 55.62 (CH_3, Ar−OCH_3), 15.55 (CH_3, Thiazole−CH_3); HRMS: $m/z =$ 411.1294 (M + H)+.

2-[4-(4-fluorophenyl)-1,2,3-triazol-1-yl]-1-[2-(4-fluorophenyl)-4-methyl-1,3-thiazol-5-yl]ethanol, (6p)

MF: $C_{20}H_{16}F_2N_4OS$; yield: 74%; mp: 182–184 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H, Triazole-H), 7.95–7.86 (m, 4H, Ar-H), 7.35–7.27 (m, 4H, Ar-H), 6.53 (d, $J = 4.3$ Hz, 1H, OH), 5.41 – 5.34 (m, 1H, -CH), 4.67 – 4.58 (m, 2H, –CH_2), 2.27 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.75 (C, Thiazole-C2), 164.53 and 162.56 (C, C4′, d, $^1J = 244.4$ Hz), 163.19 and 161.25 (C, C4″ $^1J = 244.4$ Hz), 149.15 (C, Thiazole-C4), 145.78 (C, Triazole-C4), 134.77 (C, Thiazole-C5), 130.27 and 130.25 (C, C1′, d, $^4J = 2.5$ Hz), 128.55 and 128.48 (2CH, C2′, C6′, d,$^3J = 8.8$ Hz), 127.82 and 127.79 (C, C1″ d, $^4J =$ 3.8 Hz), 127.63 and 127.56 (2CH, C2″, C6″, d, $^3J =$ 8.8 Hz), 122.72 (CH, Triazole-C5), 116.77 and 116.60 (2CH, C3′, C5′, d, $^2J = 21.4$ Hz), 116.41 and 116.24 (2CH, C3″, C5″, d,$^2J = 21.4$ Hz), 66.15 (CH, Thiazole−CHOH), 56.56 (CH_2,−CH_2−Triazole), 15.56 (CH_3, Thiazole−CH_3). HRMS: $m/z = 399.1095$ (M + H)+.

1-[4-methyl-2-(4-methylphenyl)-1,3-thiazol-5-yl]-2-(4-phenyl-1,2,3-triazol-1-yl)ethanol, (6q)

MF: $C_{21}H_{20}N_4OS$; yield: 86%; mp: 190–192 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H, Triazole-H), 7.84 (d, J = 7.2 Hz, 2H, Ar-H), 7.77 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.45 (t, $J = 7.7$ Hz, 2H, Ar-H), 7.34 (t, $J = 7.4$ Hz, 1H, Ar-H), 7.29 (d, $J = 8.0$ Hz, 2H, Ar-H), 6.48 (d, $J = 4.3$ Hz, 1H, OH), 5.37 (dt, $J = 7.2$, 5.1 Hz, 1H, -CH), 4.62 (qd, $J = 13.8$, 6.3 Hz, 2H, –CH_2), 2.35 (s, 3H, Ar-CH_3), 2.26 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.05 (C, Thiazole-C2), 149.02 (C, Thiazole-C4), 146.62 (C, Triazole-C4), 140.34 (C, C4′), 134.03 (C, Thiazole-C5), 131.24 (C, C1″), 131.01 (C, C1′), 130.21 (2CH, C2′, C6′), 129.40 (2CH, C3″, C5″), 128.30 (CH, Triazole-C5), 126.19 (2CH, C3′, C5′), 125.59 (2CH, C2″, C6″), 122.79 (CH, C4″), 66.16 (CH, Thiazole−CHOH), 56.57 (CH_2,−H_2 −Triazole), 21.39 (CH_3, Ar−CH_3), 15.57 (CH_3, Thiazole −CH_3); HRMS: $m/z = 377.1440$ (M + H)+.

1-[4-methyl-2-(4-methylphenyl)-1,3-thiazol-5-yl]-2-[4-(4-methylphenyl)-1,2,3-triazol-1-yl]ethanol, (6r)

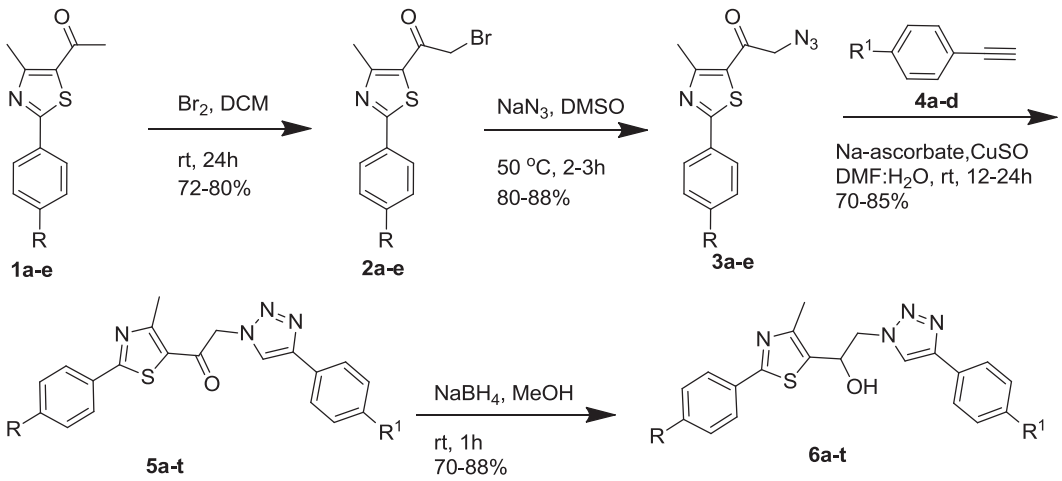
MF: $C_{22}H_{22}N_4OS$; yield: 80%; mp: 190–192 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (s, 1H, Triazole-H), 7.77 (d, J = 8.1 Hz, 2H, Ar-H), 7.73 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.31–7.23 (m, 4H, Ar-H), 6.47 (d, $J = 4.3$ Hz, 1H, OH), 5.37 (dt, $J = 7.2$, 5.1 Hz, 1H, -CH), 4.61 (qd, $J = 13.8$, 6.3 Hz, 2H, –CH_2), 2.35 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3), 2.26 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.02 (C, Thiazole-C2), 149.01 (C, Thiazole-C4), 146.69 (C, Triazole-C4), 140.32 (C, C4′), 137.58 (C, C4″), 134.06 (C, Thiazole-C5), 131.03 (C, C1′), 130.20 (2CH, C2′, C6′), 129.93 (2CH, C3″, C5″), 128.49 (CH, Triazole-C5), 126.18 (2CH, C3′, C5′), 125.53 (2CH, C2″, C6″), 122.35 (C, C1″), 66.17 (CH, Thiazole−CHOH), 56.55 (CH_2,−CH_2−Triazole), 21.39 (CH_3, Ar−CH_3), 21.30 (CH_3, Ar−CH_3), 15.57 (CH_3, Thiazole−CH_3); HRMS: $m/z =$ 391.1597 (M + H)+.

2-[4-(4-methoxyphenyl)-1,2,3-triazol-1-yl]-1-[4-methyl-2-(4-methylphenyl)-1,3-thiazol-5-yl]ethanol, (6s)

MF: $C_{22}H_{22}N_4O_2S$; yield: 86%; mp: 125–127 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (s, 1H, Triazole-H), 7.82 (dd, $J = 8.5$, 3.0 Hz, 4H), 7.33 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.06 (d, $J = 8.8$ Hz, 2H, Ar-H), 6.51 (d, $J =$ 4.3 Hz, 1H, OH), 5.41 (dt, $J = 7.2$, 5.0 Hz, 1H, -CH), 4.64 (qd, $J = 13.8$, 6.3 Hz, 2H, –CH_2), 3.84 (s, 3H, Ar-OCH_3), 2.40 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.02 (C, Thiazole-C2), 159.44 (C, C4″), 149.01 (C, Thiazole-C4), 146.56 (C, Triazole-C4), 140.32 (C, C4′), 134.08 (C, Thiazole-C5), 131.02 (C, C1′), 130.20 (2CH, C2′, C6′), 126.93 (2CH, C2″, C6″), 126.18 (2CH, C3′, C5′), 123.85 (CH, Triazole-C5), 121.82 (C, C1″), 114.79 (2CH, C3″, C5″), 66.18 (CH, Thiazole−CHOH), 56.54 (CH_2,−CH_2−Triazole), 55.61 (CH_3, Ar−OCH_3), 21.39 (CH_3, Ar−CH_3), 15.57 (CH_3, Thiazole−CH_3); HRMS: $m/z = 407.1548$ (M + H)+.

2-[4-(4-fluorophenyl)-1,2,3-triazol-1-yl]-1-[4-methyl-2-(4-methylphenyl)-1,3-thiazol-5-yl]ethanol, (6t)

MF: $C_{21}H_{19}FN_4OS$; yield: 80%; mp: 168–170 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H, Triazole-H), 7.89 (dd, $J = 8.8$, 5.5 Hz, 2H, Ar-H), 7.77 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.29 (dd, $J = 12.3$, 4.7 Hz, 4H, Ar-H), 6.48 (d, $J = 4.3$ Hz, 1H, OH), 5.37 (dt, $J = 7.1$, 5.1 Hz, 1H, -CH), 4.67 – 4.57 (m, 2H, –CH_2), 2.35 (s, 3H, Ar-CH_3), 2.27 (s, 3H, Thiazole-CH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.04 (C, Thiazole-C2), 163.19 and 161.24 (C,−C4″, d, $^1J =$ 245.7 Hz), 149.01 (C, Thiazole-C4), 145.77 (C, Triazole-C4), 140.33 (C, C4′), 134.00 (C, Thiazole-C5), 131.02 (C, C1′), 130.20 (2CH, C2′, C6′), 127.83 and 127.81 (C, C1″, d, $^4J = 2.5$ Hz), 127.62 and 127.56 (2CH, C2″, C6″, d, $^3J =$ 7.6 Hz), 126.18 (2CH, C3′, C5′), 122.71 (CH, Triazole-C5), 116.41 and 116.24 (2CH, C3″, C5″, d, $^2J = 21.4$ Hz), 66.16 (CH, Thiazole−CHOH), 56.60 (CH_2,−CH_2−Triazole), 21.38 (CH_3, Ar−CH_3), 15.58 (CH_3, Thiazole−CH_3); HRMS: $m/z =$ 395.1346 (M + H)+.



Comp.	R	R^1	Comp.	R	R^1	Comp.	R	R^1	Comp.	R	R^1
6a	H	H	**6f**	4-Br	4-CH_3	**6k**	4-Cl	4-OCH_3	**6p**	4-F	4-F
6b	H	4-CH_3	**6g**	4-Br	4-OCH_3	**6l**	4-Cl	4-F	**6q**	4-CH_3	H
6c	H	4-OCH_3	**6h**	4-Br	4-F	**6m**	4-F	H	**6r**	4-CH_3	4-CH_3
6d	H	4-F	**6i**	4-Cl	H	**6n**	4-F	4-CH_3	**6s**	4-CH_3	4-OCH_3
6e	4-Br	H	**6j**	4-Cl	4-CH_3	**6o**	4-F	4-OCH_3	**6t**	4-CH_3	4-F

Scheme 1 : Synthetic route of thiazolyl-1,2,3-triazolyl-ethanol, **6a–t**

Biological activity

Antibacterial activity

The in vitro antibacterial screening of the synthesized thiazolyl-triazole derivatives (**6a–t**) was performed by the well diffusion method (Wayne 2002, NCCLS 2000, Mali et al. 2015). 500 µL of 24–48 h old fresh bacterial culture were spread over the nutrient agar plates and the cultures were inoculated using the sterile cotton swab. Using the well borer, 5 mm diameter wells were punched on the agar plates. The synthesized compounds were dissolved in DMSO. The wells were filled with 80 µL of respective synthesized compounds and a vehicle control, DMSO was added to one agar plate and standard drug Streptomycin used as positive control. The plates were incubated for 24–48 h at 37 °C. After the incubation period, the antimicrobial activity was evaluated by measuring the zone of inhibition in mm using a measuring scale and the average was calculated. The experiments were carried out in five replicates.

Antifungal activity

The in vitro antifungal activity of thiazolyl-triazole derivatives (**6a–t**) was done by well diffusion method (Wayne 2002, NCCLS 2000, Mali et al. 2015). Mueller-Hinton agar plates were prepared by pouring 20 mL in each sterile petriplates for fungal assay and allowed to solidify. During the assay, standard fungal cultures were grown on Potato-Dextrose broth. 500 µL of 48–72 h old fresh fungal spore suspension was spread on the agar plates using a sterile cotton swab to get uniform growth. With the help of well borer, 5 mm diameter wells were punched on the agar plates. The wells were filled with 80 µL of the samples and a vehicle control, DMSO was added to one agar plate. A standard plate with Fluconazole and Ravuconazole was used as a positive control. The plates were incubated for a period of 48–72 h at 30 °C. After the incubation period, the plates were observed for the clear zone of inhibition. The zones of inhibition were measured in mm using a measuring scale and the mean was calculated. The experiments were carried out in five replicates.

The micro-dilution susceptibility test in Sabouraud Liquid Medium (Oxoid) was used for the determination of minimum inhibition concentration (MIC). Stock solution of the test compounds, Streptomycin, Fluconazole and Ravuconazole were prepared in DMSO at concentration of 1000 µg/mL. Two fold serial dilutions of the test compounds solutions were prepared using broth. The final concentration of the solutions was 500, 250, 125, 62.5, 31.25, 15.62, 7.81, and 3.90 µg/mL. The tubes were inoculated with the test organisms and kept for incubation for 48–72 h. at 30 °C. The lowest concentration showing no growth was considered as MIC. Control experiment with DMSO and un-inoculated media were run parallel to the test

compounds under similar conditions. All experiments were carried in triplicates.

Results and discussion

Chemistry

The synthetic route for 1-(4-methyl-2-aryl-1,3-thiazol-5-yl)-2-(4-aryl-1,2,3-triazol-1-yl)ethanol derivatives is presented in Scheme 1. 1-(4-methyl-2-arylthiazol-5-yl)ethanone, **1a–e** on bromination with bromine in dichloromethane gave 2-bromo-1-(4-methyl-2-arylthiazol-5-yl)ethanone **2a–e**. Bromo derivatives **2a–e** on nucleophilic substitution reaction with sodium azide in dimethyl sulphoxide gave 2-azido-1-(4-methyl-2-arylthiazol-5-yl)ethanone, **3a–e**. A click reaction of azide **3a–e** with substituted aryl alkyne **4a–d** in the presence of catalytic sodium ascorbate and copper sulfate in DMF:water (3:1) gave 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanone **5a–t**, which upon reduction with $NaBH_4$ in methanol furnished target compounds 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanol, **6a–t**. The structure of newly synthesized thiazolyl-1,2,3-triazolyl-ethanol, **6a–t** was confirmed by ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

As a representative analysis, of thiazolyl-triazole derivative 1-[2-(4-fluorophenyl)-4-methyl-1,3-thiazol-5-yl]-2-[4-(4-methylphenyl)-1,2,3-triazol-1-yl]ethanol (**6n**), the ^{1}H NMR spectrum revealed the two singlets in the aliphatic region at δ 2.37 and 2.31 integrated for three protons each corresponds to -CH_3 at C-4 of thiazole and C-4 of phenyl ring, respectively. A double doublet at δ 4.70–4.61 integrated for one proton each corresponds to diastereotopic methylene protons. A multiplet appeared at δ 5.44–5.40 and a doublet at δ 6.55 integrated for one proton each was assigned to methine proton and alcohol proton of thiazole–C<u>H</u>O<u>H</u>-CH_2 functional group, respectively. The aromatic protons of fluoro substituted phenyl ring appeared as a triplet at δ 7.97 and a double doublet at δ 7.36 while the protons of 4-methyl substituted in the phenyl ring showed two doublets at δ 7.77 and 7.31. A singlet at δ 8.55, was due to the proton at C-5-position of 1,2,3-triazole ring. The ^{13}C NMR spectrum of compound **6n** displayed four signals in aliphatic region at δ 66.16, 56.52, 21.29, and 15.55 corresponds to CH, CH_2, Ar-CH_3 and thiazole-CH_3, respectively. The carbons of 4-methyl substituted phenyl, 1,2,3-triazole and thiazole resonated between δ 163.73 and 122.36. The carbons of fluoro substituted phenyl ring showed typical C-F coupling, they appeared as four doublets at δ 164.53 and 162.56 (d, $^{1}J = 244.4$ Hz), 116.77, and 116.60 (d, $^{2}J = 21.4$ Hz), 128.55 and 128.48 (d, $^{3}J = 8.8$ Hz), 130.28 and 130.26 (d, $^{4}J = 2.5$ Hz). Structure of compound **6n** was further confirmed by molecular ion peak (HRMS) at *m/z*: 395.1350 $(M + H)^{+}$. Structure of all synthesized compounds was confirmed accordingly.

Compounds 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanol derivatives, **6a–t** were evaluated for antibacterial activity against Gram-negative bacteria *E. coli* and Gram-positive bacteria *S. albus* using well diffusion method (Wayne 2002, NCCLS 2000, Mali et al. 2015). Standard drug Streptomycin and DMSO were used as positive and negative control, respectively. The in vitro antifungal activity was performed against *R. glutinis*, *P. chrysogenum*, *C. albicans* and *A. niger* using the well diffusion method. The antifungal drugs Fluconazole and Ravuconazole were used as reference. All the test solutions were prepared in DMSO at 1000 µg/mL concentrations and the wells were filled with 80 µL (80 µg) of the samples. The result of antimicrobial activity in the zone of inhibition (mm) has been presented in supporting information (Table S1).

The antimicrobial activity result analysis of 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl) ethanol derivatives, **6a–t** revealed that, most of the compounds showed moderate activity against *E. coli* and moderate to good activity against *S. albus*. The preliminary antifungal activity against *R. glutinis*, *P. chrysogenum*, *C. albicans* and *A. niger* revealed that, most of the thiazolyl-triazolyl-alcohol derivatives reported moderate to good antifungal activity. The convincing antimicrobial activity against bacterial and fungal strains of compounds **6a–t** leads us to determine that the microbial inhibition in a dose dependent way with the concentrations ranges from 500 to 3.90 µg/mL. The in vitro antimicrobial screening results of minimum inhibitory concentration in µg/mL are presented in Table 1.

The antimicrobial activity analysis revealed that, the thiazolyl-1,2,3-triazolyl-ethanol derivatives were less active against the *E. coli* and *S. albus*. The analysis of antifungal activity presented in Table 1 provided some lead compounds that showed good antifungal activity against *A. niger*.

The structure activity relationship revealed that, amongst the 1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-2-(4-aryl-1,2,3-triazol-1-yl)ethanol (**6a–d**), the compound **6a** (R=H, R^1=H) showed comparable activity against *A. niger* with respect to the standard drug Ravuconazole. Among the compounds **6e-t**, it was observed that compound with R=Cl, exhibited better activity against *A. niger* irrespective of different R' groups. Compounds **6m** (R=F, R^1=H), **6n** (R=F, R^1=CH_3) showed good activity against *A. niger* with MIC 62.5 µg/mL, and were found less active against other strains. Compound **6o** (R=F, R^1=OCH_3) showed good activity against *A. niger* with MIC 31.25 µg/mL comparable to standard antifungal Ravuconazole. The compound **6p**

Table 1 Antimicrobial activity in Minimum Inhibitory Concentration (μg/mL) of compounds **6a–t**

Comp.	R	R^1	*E.coli*	*S.albus*	*R. glutinis*	*P.chrysogenum*	*C. albicans*	*A.niger*
6a	H	H	>250	>250	125	125	125	**31.25**
6b	H	4-CH_3	>250	125	>250	250	250	>250
6c	H	4-OCH_3	>250	250	>250	250	>250	>250
6d	H	4-F	>250	62.5	>250	250	125	125
6e	Br	H	>250	125	125	125	250	>250
6f	Br	4-CH_3	>250	250	>250	>250	250	>250
6g	Br	4-OCH_3	>250	250	250	>250	>250	>250
6h	Br	4-F	>250	250	125	>250	>250	125
6i	Cl	H	>250	>250	250	250	>250	**62.5**
6j	Cl	4-CH_3	>250	>250	>250	125	>250	**62.5**
6k	Cl	4-OCH_3	>250	>250	250	250	>250	**62.5**
6l	Cl	4-F	>250	125	125	>250	>250	125
6m	F	H	>250	62.5	125	250	>250	**62.5**
6n	F	4-CH_3	>250	>250	250	>250	250	**62.5**
6o	F	4-OCH_3	>250	125	>250	>250	250	**31.25**
6p	F	4-F	>250	62.5	62.5	250	>250	**62.5**
6q	CH_3	H	>250	125	250	>250	>250	125
6r	CH_3	4-CH_3	>250	250	250	>250	125	125
6s	CH_3	4-OCH_3	>250	>250	250	>250	250	250
6t	CH_3	4-F	>250	>250	250	>250	250	250
Streptomycin			7.81	7.81	NA	NA	NA	NA
Fluconazole			NA	NA	7.81	7.81	7.81	7.81
Ravuconazole			NA	NA	15.62	7.81	7.81	31.25

NA not applicable

MIC of active compounds are highlighted in bold

(R=F, R^1=F) reported good activity against *A. niger* with MIC 62.5 μg/mL. It is noteworthy that the compounds **6i**, **6j**, **6k**, **6m**, **6n**, and **6p** recorded two fold less activity while compounds **6a** and **6o** were seen to exhibit comparable activity against *A. niger* with Ravuconazole.

It is worth mentioning, among the twenty derivatives of 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanol, **6a–t**, compounds **6a** and **6o** found comparatively active and compounds **6i**, **6j**, **6k**, **6m**, **6n**, and **6p** were found two fold less active against *A. niger* compared with Ravuconazole.

Conclusion

In conclusion, a series of 1-(4-methyl-2-aryl-1,3-thiazol-5-yl)-2-(4-aryl-1,2,3-triazol-1-yl)ethanol **(6a–t)** have been synthesized. The antimicrobial screening studies of compounds **6a–t** was undertaken to evaluate the effects of substituent on the antimicrobial activities. Most of the synthesized compounds exhibited good antifungal activity against *A. niger*. The compounds 1-(4-methyl-2-phenylthiazol-5-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanol, (**6a**) and 1-[2-(4-fluorophenyl)-4-methyl-1,3-thiazol-5-yl]-2-[4-(4-methoxyphenyl)-1,2,3-triazol-1-yl]ethanol, (**6o**) reported comparable antifungal activity against *A. niger* with respect to the standard drug Ravuconazole. It is concluded that, 4-chlorophenyl and 4-fluorophenyl substituted at position-2 of thiazole ring was found to be more active against *A. niger*.

Acknowledgements Authors are thankful to S. P. Mandali's Bhide Foundation, Pune for supporting biological activity facility. Central Instrumentation facility, Savitribai Phule Pune University, Pune is also acknowledged for spectral analysis. A D Shinde is grateful to CSIR-India for award of SRF, Award No 08/319(0004/)17-EMR-1.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Abhale YK, Deshmukh KK, Sasane AV, Chavan AP, Mhaske PC (2016) Fused heterocycles: Synthesis and antitubercular

activity of novel 6-substituted-2-(4-methyl-2-substituted phenylthiazol-5-yl)H-imidazo[1,2-a]pyridine. J Heterocycl Chem 53(1):229–233

Abhale YK, Sasane AV, Chavan AP, Deshmukh KK, Kotapalli SS, Ummanni R, Sayyad SF, Mhaske PC (2015) Synthesis and biological screening of 2'-aryl/benzyl-2-aryl-4-methyl-4',5-bithiazolyls as possible anti-tubercular and antimicrobial agents. Eur J Med Chem 94:340–347

Abhale YK, Sasane AV, Chavan AP, Shekh SH, Deshmukh KK, Bhansali S, Nawale L, Sarkar D, Mhaske PC (2017) Synthesis and antimycobacterial screening of new thiazolyl-oxazole derivatives. Eur J Med Chem 132:333–340

Allen D, Wilson D, Drew R, Perfect J (2015) Azole antifungals: 35 years of invasive fungal infection management. Exp Rev Anti Infect Ther 13(6):787–798

Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU, Salamat MKF, Baloch Z (2018) Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist 11:1645–1658

Battula KS, Narsimha S, Thatipamula RK, Reddy YN, Reddy V (2017) Synthesis and biological evaluation of novel thiomorpholine 1,1-dioxide derived 1,2,3-triazole hybrids as potential anticancer agents. Chem Sel 2(14):4001–1005

Bonandi E, Christodoulou MS, Fumagalli G, Perdicchia D, Rastelli G, Passarella D (2017) The 1,2,3-triazole ring as a bioisostere in medicinal chemistry. Drug Discov Today 22(10):1572–1581

Bozorov K, Zhao J, Aisa HA (2019) 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: a recent overview. Bioorg Med Chem 27(16):3511–3531

Brvar M, Perdih A, Renko M, Anderluh G, Turk D, Solmajer T (2012) Structure-based discovery of substituted 4,5'-bithiazoles as novel DNA gyrase inhibitors. J Med Chem 55(14):6413–6426

Bueno JM, Carda M, Crespo B, Cuñat AC, de Cozar C, León ML, Marco JA, Roda N, Sanz-Cervera JF (2016) Design, synthesis and antimalarial evaluation of novel thiazole derivatives. Bioorg Med Chem Lett 26(16):3938–3944

Calderon D, Mejía-Dionicio M, Morales-Reza MA, Ramírez-Villalva A, Morales-Rodríguez M, Jauregui-Rodríguez B, Díaz-Torres E, Gonzalez-Romero C, Fuentes-Benítes A (2016) Antifungal activity of 1'-homo-N-1,2,3-triazol-bicyclic carbonucleosides: a novel type of compound afforded by azide-enolate (3+2) cycloaddition. Eur J Med Chem 112:60–65

Choi JY, Podust LM, Roush WR (2014) Drug strategies targeting CYP51 in neglected tropical diseases. Chem Rev 114 (22):11242–11271

Chu X, Wang C, Wang W, Liang L, Liu W, Gong K, Sun K (2019) Triazole derivatives and their antiplasmodial and antimalarial activities. Eur J Med Chem 166:206–223

Dheer D, Singh V, Shankar R (2017) Medicinal attributes of 1,2,3-triazoles: current developments. Bioorg Chem 71:30–54

Dmitry V, Demchuk AV, Samet NB, Chernysheva VI, Ushkarov GA, Stashina LD, Konyushkin MM, Raihstat SI, Firgang AA, Philchenkov MP, Zavelevich LM, Kuiava VF, Chekhun DY, Blokhin AS, Kiselyov MN, Semenova VV (2014) Synthesis and antiproliferative activity of conformationally restricted 1,2,3-triazole analogues of combretastatins in the sea urchin embryo model and against human cancer cell lines. Bioorg Med Chem 22 (2):738–755

Emami S, Ghobadi E, Saednia S, Hashemi SM (2019) Current advances of triazole alcohols derived from fluconazole: design, in vitro and in silico studies. Eur J Med Chem 170:173–194

Fisher MC, Hawkins NJ, Sanglard D, Gurr SJ (2018) Worldwide emergence of resistance to antifungal drugs challenges human health and food security. Science 360:739–742

Gaikwad ND, Patil SV, Bobade VD (2012) Hybrids of ravuconazole: synthesis and biological evaluation. Eur J Med Chem 54:295–302

Hashemi SM, Badali H, Faramarzi MA, Samadi N, Afsarian MH, Irannejad H, Emami S (2015) Novel triazole alcohol antifungals derived from fluconazole: design, synthesis, and biological activity. Mol Divers 19(1):15–27

Idowu T, Arthur G, Zhanel GG, Schweizer F (2019) Heterodimeric Rifampicin-Tobramycin conjugates break intrinsic resistance of *Pseudomonas aeruginosa* to doxycycline and chloramphenicol in vitro and in a Galleria mellonella in vivo model. Eur J Med Chem 174:16–32

Jadhav RP, Raundal HN, Patil AA, Bobade VD (2017) Synthesis and biological evaluation of a series of 1,4-disubstituted 1,2,3-triazole derivatives as possible antimicrobial agents. J Saudi Chem Soc 21 (2):152–159

Jaishree V, Ramdas N, Sachin J, Ramesh B (2012) In vitro antioxidant properties of new thiazole derivatives. J Saudi Chem Soc 16 (4):371–376

Kathiravan MK, Salake AB, Chothe AS, Dudhe PB, Watode RP, Mukta MS, Gadhwe S (2012) The biology and chemistry of antifungal agents: a review. Bioorg Med Chem 20 (19):5678–5698

Li Z, Khaliq M, Zhou Z, Post CB, Kuhn RJ, Cushman M (2008) Design, synthesis, and biological evaluation of antiviral agents targeting flavivirus envelope proteins. J Med Chem 51 (15):4660–4671

Ma L, Wang B, Pang L, Zhang M, Wang S, Zheng Y, Shao K, Xue D, Liu H (2015) Design and synthesis of novel 1,2,3-triazole-pyrimidine-urea hybrids as potential anticancer agents. Bioorg Med Chem Lett 25(5):1124–1128

Mali AB, Joshi M, Kulkarni V (2015) Phytochemical screening and antimicrobial activity of *Stevia rebaudiana* leaves. Int J Curr Microbiol Appl Sci 4(10):678–685

Mark CB, Dale JW, Merritt EA, Xin X (2005) Thiopeptide antibiotics. Chem Rev 105(2):685–714

Menendez C, Rodriguez F, de Jesus Lopes Ribeiro AL, Zara F, Frongia C, Lobjois V, Saffon N, Pasca MR, Lherbet C, Baltas M (2013) Synthesis and evaluation of α-ketotriazoles and α, β-diketotriazoles as inhibitors of *Mycobacterium tuberculosis*. Eur J Med Chem 69:167–173

Mhaske PC, Shelke SH, Bhoye M, Bobade V (2017) Synthesis and antimicrobial screening of 2-aryl-5-((2-arylthiazol-4-yl)methyl)-1,3,4-oxadiazole derivatives. J Heterocycl Chem 54 (2):1590–1597

Nalawade J, Shinde A, Chavan A, Patil S, Suryavanshi M, Modak M, Choudhari P, Bobade VD, Mhaske PC (2019) Synthesis of new thiazolyl-pyrazolyl-1,2,3-triazole derivatives as potential antimicrobial agents. Eur J Med Chem 179:649–659

NCCLS (2000) Approval Standard Document M2-A7. National Committee for Clinical Laboratory Standards, Vilanova, PA, USA

Pardeshi SP, Patil SS, Bobade VD (2011) Synthesis and biological evaluation of some novel triazol-3-ones as antimicrobial agents. Bioorg Med Chem Lett 21(21):6559–6562

Patil A, Jadhav R, Raundal H, Patil S, Bobade V, Sharma L, Badgujar R (2015) Synthesis and antifungal activity of 1, 5-diaryl pyrazole substituted thiazole derivatives. Indian J Chem 54B(7):918–923

Rostom SAF, El-Ashmawy IM, Abd El Razik HA, Badr MH, Ashour HMA (2009) Design and synthesis of some thiazolyl and thiadiazolyl derivatives of antipyrine as potential non-acidic anti-inflammatory, analgesic and antimicrobial agents. Bioorg Med Chem Lett 17(2):882–895

Shaikh MH, Subhedar DD, Nawale L, Sarkar D, Kalam Khan FA, Sangshetti JN, Shingate BB (2015) 1,2,3-Triazole derivatives as antitubercular agents: synthesis, biological evaluation and molecular docking study. Med Chem Comm 6:1104–1116

Sheehan DJ, Hitchcock CA, Sibley CM (1999) Current and emerging azole antifungal agents. Clin Microbiol Rev 12(1):40–79

Shelke SH, Mhaske PC, Nandave M, Narkhade S, Walhekar NM, Bobad VD (2012) Synthesis and pharmacological evaluation of a novel series of 3-aryl-2-(2-substituted-4-methylthiazole-5-yl) thiazolidin-4-one as possible anti-inflammatory and antimicrobial agents. Bioorg Med Chem Lett 22(20):6373–6376

Shinde V, Mahulikar P, Mhaske PC, Chakraborty S, Choudhari P, Sarkar D (2019) Synthesis and antimycobacterial evaluation of new 5-(1-benzyl-1H-1,2,3-triazol-4-yl)-4-methyl-2-arylthiazole derivatives. Med Chem Res 28(6):805–819

Shinde V, Mahulikar P, Mhaske PC, Nawale L, Sarkar D (2018) Synthesis and biological evaluation of new 2-aryl-4-((4-aryl-1H-1,2,3-triazol-1-yl)methyl)thiazole derivatives. Res Chem Intermed 44(2):1247–1260

Shiradkar MR, Murahari KK, Reddy GH, Tatikonda S, Chakravarthy AK, Dolly P, Kaur R, Burange P, Ghogare J, Mokalec V, Rautc M (2007) Synthesis of new S-derivatives of clubbed triazolyl thiazole as anti-Mycobacterium tuberculosis agents. Bioorg Med Chem Lett 15(12):3997–4008

Takate SJ, Shinde AD, Karale BK, Akolkar H, Nawale L, Sarkar D, Mhaske PC (2019) Thiazolyl-pyrazole derivatives as potential antimycobacterial agents. Bioorg Med Chem Let 29 (10):1199–1202

Tian Y, Liu Z, Liu J, Huang B, Kang D, Zhang H, de Clercq E, Daelemans D, Pannecouque C, Lee K, Chen CH, Zhang P, Liu X (2018) Targeting the entrance channel of NNIBP: Discovery of diarylnicotinamide 1,4-disubstituted 1,2,3-triazoles as novel HIV-1 NNRTIs with high potency against wild-type and E138K mutant virus. Eur J Med Chem 151:339–350

Tomasic T, Katsamakas S, Hodnik Z, Ilas J, Brvar M, Solmajer T, Montalvao S, Tammela P, Banjanac M, Ergovic G, Anderluh M, Masic LP, Kikelj D (2015) Discovery of 4,5,6,7-tetrahydrobenzo [1,2-d]thiazoles as novel DNA gyraseinhibitors targeting the ATP-binding site. J Med Chem 58(14):5501–5521

Wayne PA (2002) NCCLS method for dilution antimicrobial susceptibility tests of bacteria that grow aerobically, Approved Standard. M100eS12

WHO report (2018) Antimicrobial resistance

Zhang B (2019) Comprehensive review on the anti-bacterial activity of 1,2,3-triazole hybrids. Eur J Med Chem 168:357–372