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# Design, synthesis and biological evaluation of novel N,4-diphenylthiazol-2-amine derivatives

AfraQuasar A. Nadaf[1] · Delicia A. Barretto[2] · Mahesh S. Najare[1] · Shivaraj Mantur[1] · Manjunatha Garbhagudi[1] · Supreet Gaonkar[1] · Shrinivas Joshi[3] · Imtiyaz Ahmed M. Khazi[1]

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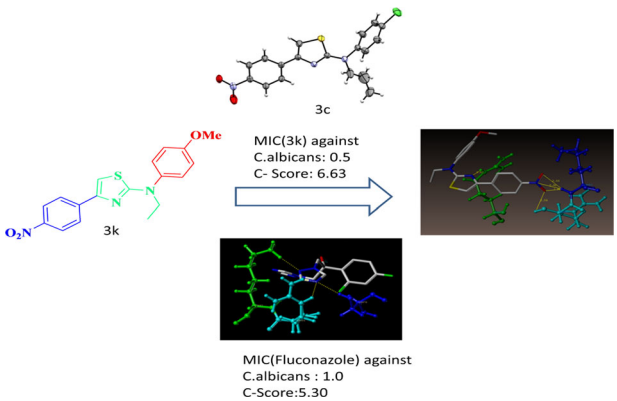
## Abstract

Novel N,4-diphenylthiazol-2-amine derivatives were designed and synthesized employing Hantzsch method. The three-step reaction involved in the synthesis occurred at a faster rate with excellent yields in eco-friendly conditions. The synthesized derivatives were characterized by spectral techniques such as $^{1}$H NMR, $^{13}$C NMR, FT-IR and GCMS. Single-crystal X-ray diffraction studies also confirmed the formation of title compounds. These compounds were evaluated in vitro for their antimicrobial and anti-inflammatory activities. The results demonstrated that most of the tested compounds showed potent antifungal activity. Interestingly, these compounds also exhibited good anti-inflammatory and moderate antibacterial activity towards sensitive as well as resistant bacterial strains. In silico studies depicted their good binding affinity profile against *S. aureus* (PDB ID: 1AD4) and *C. albicans* (PDB ID: 1AI9).

## Graphical Abstract




**Keywords** N,4-diphenylthiazol-2-amine · Antimicrobial · Anti-inflammatory · Ciprofloxacin · Fluconazole · Protein denaturation assay

**Supplementary information** The online version of this article (https://doi.org/10.1007/s00044-019-02495-2) contains supplementary material, which is available to authorized users.

✉ Imtiyaz Ahmed M. Khazi
drimkorgchem@gmail.com

[1] Department of Chemistry, Karnatak University, Dharwad, Karnataka 580003, India

[2] Department of Biotechnology & Microbiology, Karnatak University, Dharwad, Karnataka 580003, India

[3] Novel Drug Design and Discovery Laboratory, Department of Pharmaceutical Chemistry, S.E.T.'s College of Pharmacy, Sangolli Rayanna Nagar, Dharwad, Karnataka 580002, India

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## Introduction

The rapid advancement of research in the field of medical sciences in the past decades has led to a significant improvement in the diagnosis and treatment of infectious diseases, which has resulted in the better health status of human beings. However, the inappropriate use of anti-infectious agents pose one of the major challenges to the scientific community that needs to be resolved effectively (Tenover and McDonald 2005; Pfeltz and Wilkinson 2004; Roberts 2004; Dessen et al. 2001; Muroi et al. 2004; Liaras et al. 2011). The emergence of microbial multidrug resistance against known antibiotics in recent years has created an alarming situation and has attracted great attention for identifying new approaches to design and explore innovative heterocyclic agents with novel mode of actions (Narang et al. 2011, 2012; Perez et al. 2014; Kumar et al. 2009).

Heterocycles are the most appealing chemical structures that offer promising biological activity and have manifested potential in the drug discovery process. The biological activity of heterocycles mainly arises from the heteroatoms such as nitrogen sulfur and oxygen. This has drawn the attention of chemists over the years for the designing and exploration of heterocyclic structures based on structure-activity relationship (Arora et al. 2016). Of particular interest is the thiazole ring, which has demonstrated upsurge interest in drug design and development of novel therapeutic agents. The thiazole ring is integral in the structure of many biologically active compounds; with sulfur and nitrogen respectively at 1, 3 positions, this core moiety has exerted various roles in the lead identification and optimization. It also plays an important role as a pharmacophoric and bioisosteric element; as well as a spacer in molecular frame. In addition, the presence of thiazole ring as a part of drug structure can be determinant for its physicochemical and pharmacokinetic properties (Ayati et al. 2015; Das et al. 2016).

Thiazole core has been featured in many drug molecules (Siddiqui et al. 2009) which include Tiazofurin and dasatinib (antineoplastic agents) (Das et al. 2006), ritonavir (anti-HIV drug) (De Souza and De Almeida 2003), ravuconazole (antifungal agent) (Pasqualotto et al. 2010), nitazoxanide (antiparasitic agent) (Fox and Saravolatz 2005), fanetizole, meloxicam and fentiazac (anti-inflammatory agents) (Knadler et al. 1986) and nizatidine (antiulcer agent) (Nauen et al. 2003). Importantly, thiazole bearing products-Nizatidine, Abafungin and Amiphenazole are among commercially marketed drugs (Fig. 1). Structure-activity relationship study of thiazole based drugs/leads revealed that substituent's on a particular position specifically at position 2 and 4 of the 1, 3- thiazole ring affect the biological outcomes to a great extent. It has so far been shown that 2, 4-disubstituted thiazole moiety seems to be an important pharmacophore in various pharmacologically active agents (Arora et al. 2015).

The main emphasis of our work was to design and develop potent antimicrobial and anti-inflammatory agents. In this regard, we have attempted the synthesis of N-alkyl derivatives of 2,4-disubstituted thiazole by simple and efficient synthetic method. Also, their in silico as well as in vitro antimicrobial and anti-inflammatory properties have been analyzed.

## Materials and Methods

### Chemistry

All the required chemicals and solvents were of reagent grade purchased from Sigma Aldrich and used without further purification. The Melting points were determined and recorded by open capillary method and are uncorrected. The FT-IR spectra were recorded on Perkin Elmer FT-IR spectrometer. $^{1}H$ and $^{13}C$ NMR data were collected by using JEOL 400-MHz FT NMR spectrometer in $CDCl_3$. Chemical shifts (δ) are written in parts per million and are referenced with respect to Tetra Methyl Silane as internal standard. Mass spectra were obtained by using GCMS-QP2010S SHIMADZU instrument.

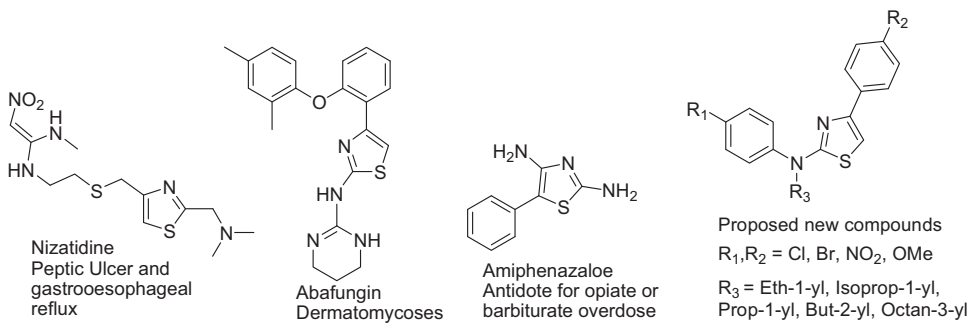



**Fig. 1** Marketed drugs containing thiazole ring

## General procedure for the synthesis of target compounds 1a and 1b

Substituted aniline's (1 g, 0.0107 mmol) and potassium thiocyante (4.17 g, 0.043 mmol) were dissolved in 10 ml of conc.HCl and the mixture was refluxed for overnight at 80 °C. The completion of the reaction was monitored by TLC. The solid formed was filtered, dried and recrystallized using ethanol to obtain the required thiourea with 78–80% yield (Hantzsch and Weber 1887).

## General procedure for the synthesis of target compounds 2a–2d

A mixture of equimolar quantities of the earlier synthesized thiourea (1 g, 0.0059 mmol) and substituted phenacyl bromide (1.17 g, 0.0059 mmol) were taken in ethanol and stirred for 2–5 min. The progress of the reaction was monitored by TLC and the solid separated was filtered, washed with cold ethanol, dried and recrystallized from ethanol to get N,4-diphenylthiazol-2-amine in good yields (Bikobo et al. 2017; Dighe et al. 2011).

## General procedure for the synthesis of target compounds 3a–3t

An equimolar mixture of substituted N,4-diphenylthiazol-2-amine (0.4 g, 0.0014 mmol) and alkyl halide (0.1 mL, 0.0014 mmol) were taken in DMF and stirred overnight at r.t in the presence of $K_2CO_3$. The completion of the reaction was monitored by TLC and quenched with cold water. The solid which separated was filtered, dried and recrystallized using ethanol to give corresponding alkylated product.

### N-(4-chlorophenyl)-N-ethyl-4-(4-nitrophenyl)thiazol-2-amine (3a)

Yellow solid; Yield: 92%; m.p. 122–124 °C; FT-IR ($cm^{-1}$): 1280, 1592, 1530, 1337, 1505, 711; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* 8.9 Hz, 2H), 7.98 (d, *J* 8.9 Hz, 2H), 7.43 (d, *J* 8.7 Hz, 2H), 7.34 (d, *J* 8.7 Hz, 2H), 6.89 (s, 1H), 4.08 (q, *J* 7.1 Hz, 2H), 1.32 (t, *J* 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 169.56, 149.34, 146.81, 143.01, 140.98, 132.98, 130.34, 128.29, 126.48, 124.17, 105.48, 48.33, 13.19; GCMS: m/z calcd for $C_{17}H_{14}ClN_3O_2S$ 359.83, found 359 ($M^+$).

### N-(4-chlorophenyl)-N-isopropyl-4-(4-nitrophenyl)thiazol-2-amine (3b)

Yellow solid; Yield: 90%; m.p. 118–122 °C; FT-IR ($cm^{-1}$): 1282, 1592, 1530, 1337, 1505, 711; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* 8.9 Hz, 2H), 7.96 (d, *J* 8.9 Hz, 2H), 7.42 (d, *J* 8.7 Hz, 2H), 7.32 (d, *J* 8.7 Hz, 2H), 6.86 (s, 1H), 4.08 (m, 1H), 1.32 (d, *J* 7.1 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.79, 143.45, 140.94, 137.83, 135.05, 126.97, 124.45, 122.29, 120.57, 113.72, 99.53, 55.17, 20.39; GCMS: m/z calcd for $C_{18}H_{16}ClN_3O_2S$ 373.86, found 373 ($M^+$).

### N-(4-chlorophenyl)-4-(4-nitrophenyl)-N-propylthiazol-2-amine (3c)

Orange solid; Yield: 90%; m.p. 96–98 °C; FT-IR ($cm^{-1}$): 1280, 1596, 1530, 1341, 1494, 713; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* 8.0 Hz, 2H), 7.96 (d, *J* 8.8 Hz, 2H), 7.42 (d, *J* 7.1 Hz, 2H), 7.33 (d, *J* 8.6 Hz, 2H), 6.87 (s, 1H), 3.97 (t, *J* 7.5 Hz, 2H), 1.74 (m, 2H), 0.97 (t, *J* 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.04, 149.24, 146.87, 143.27, 140.81, 132.98, 130.29, 128.30, 126.42, 124.08, 105.57, 54.64, 21.28, 11.41; GCMS: m/z calcd for $C_{18}H_{16}ClN_3O_2S$ 373.86, found 373 ($M^+$).

### N-sec-butyl-N-(4-chlorophenyl)-4-(4-nitrophenyl)thiazol-2-amine (3d)

Brown solid; Yield: 94%; m.p. 84–86 °C; FT-IR ($cm^{-1}$): 1197, 1595, 1504, 1339, 1480, 711; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* 8.2 Hz, 2H), 7.99 (d, *J* 8.2 Hz 2H), 7.47 (d, *J* 8.0 Hz, 2H), 7.24 (d, *J* 7.8 Hz, 2H), 6.80 (s, 1H), 2.15 (m, 1H), 1.77 (m, 2H), 1.26 (d, *J* 6.5 Hz, 3H), 1.05 (t, *J* 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.34, 147.13, 141.96, 139.62, 135.02, 131.64, 130.51, 126.93, 124.08, 123.55, 105.25, 58.96, 28.19, 18.87, 11.78; GCMS: m/z calcd for $C_{19}H_{18}ClN_3O_2S$ 387.88, found 387 ($M^+$).

### N-(4-chlorophenyl)-4-(4-nitrophenyl)-N-(octan-3-yl)thiazol-2-amine (3e)

Yellow solid; Yield: 92%; m.p. 76–78 °C; FT-IR ($cm^{-1}$): 1258, 1592, 1536, 1332, 1504, 708; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* 8.9 Hz, 2H), 7.96 (d, *J* 8.9 Hz, 2H), 7.42 (d, *J* 8.7 Hz, 2H), 7.32(d, *J* 8.7 Hz, 2H), 6.86 (s, 1H), 2.16 (m, 1H), 1.34 (m, 10H), 0.87 (t, *J* 7.2 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.71, 149.25, 146.92, 143.82, 141.05, 132.84, 130.29, 128.25, 126.44, 124.10, 105.36, 56.54, 37.83, 30.36, 28.54, 23.93, 23.07, 14.24, 10.58; GCMS: m/z calcd for $C_{23}H_{26}ClN_3O_2S$ 443.99, found 443 ($M^+$).

### 4-(4-bromophenyl)-N-ethyl-N-(4-methoxyphenyl)thiazol-2-amine (3f)

Yellow solid; Yield: 90%; m.p. 126–128 °C; FT-IR ($cm^{-1}$): 1396, 1609, 1593, 729; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* 8.6 Hz, 2H), 7.56 (d, *J* 8.6 Hz, 2H), 7.31 (d, *J* 9.0 Hz,

2H), 6.95 (d, *J* 9.0 Hz, 2H), 6.67 (s, 1H), 3.83 (s, 3H), 2.9 (q, *J* 7.1 Hz, 2H), 0.99 (t, *J* 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 157.24, 150.32, 141.71, 138.54, 134.63, 128.21, 124.73, 114.50, 115.23, 110.54, 102.12, 56.90, 32.11, 14.62; GCMS: m/z calcd for $C_{18}H_{17}BrN_2OS$ 389.31, found 390 ($M^+$).

#### 4-(4-bromophenyl)-N-isopropyl-N-(4-methoxyphenyl) thiazol-2-amine (3g)

Yellow solid; Yield: 90%; m.p. 122–124 °C; FT-IR ($cm^{-1}$): 1395, 1606, 1564, 725; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* 8.6 Hz, 2H), 7.56 (d, *J* 8.6 Hz, 2H), 7.31 (d, *J* 9.0 Hz, 2H), 6.95 (d, *J* 9.0 Hz, 2H), 6.67 (s, 1H), 3.83 (s, 3H), 2.04 (m, 1H), 1.22 (d, *J* 6.7 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 157.24, 150.32, 141.71, 138.54, 134.63, 128.21, 124.73, 114.50, 115.23, 110.54, 102.12, 56.90, 32.11, 14.62; GCMS: m/z calcd for $C_{19}H_{19}BrN_2OS$ 403.34, found 404 ($M^+$).

#### 4-(4-bromophenyl)-N-(4-methoxyphenyl)-N-propylthiazol-2-amine (3h)

Yellow solid; Yield: 94%; m.p. 118–120 °C; FT-IR ($cm^{-1}$): 1395, 1610, 1564, 725; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* 8.5 Hz, 2H), 7.48 (d, *J* 8.5 Hz, 2H), 7.27 (d, *J* 7.2 Hz, 2H), 6.96 (d, *J* 8.8 Hz, 2H), 6.59 (s, 1H), 3.93 (t, *J* 7.5 Hz, 2H), 3.84 (s, 3H), 1.71 (m, 2H), 0.95 (t, *J* 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.41, 158.71, 150.36, 147.07, 137.73, 131.50, 129.38, 127.82, 121.10, 115.37, 101.69, 55.72, 54.66, 20.98, 11.40; GCMS: m/z calcd for $C_{19}H_{19}BrN_2OS$ 403.34, found 404 ($M^+$).

#### N-sec-butyl-4-(4-bromophenyl)-N-(4-methoxyphenyl) thiazol-2-amine (3i)

Yellow solid; Yield: 94%; m.p. 114–116 °C; FT-IR ($cm^{-1}$): 1395, 1608, 1565, 725; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* 8.4 Hz, 2H), 7.50 (d, *J* 8.4 Hz, 2H), 7.29 (d, *J* 7.2 Hz, 2H), 6.91 (d, *J* 8.8 Hz, 2H), 6.69 (s, 1H), 3.81 (s, 3H), 1.69 (m, 1H), 1.20 (m, 2H), 1.01 (d, *J* 6.6 Hz, 3H), 0.86 (t, *J* 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.64, 149.09, 138.38, 131.98, 130.40, 129.55, 128.59, 127.62, 122.31, 119.79, 102.27, 57.93, 28.28, 18.91, 11.70; GCMS: m/z calcd for $C_{20}H_{21}BrN_2OS$ 417.36 found 418 ($M^+$).

#### 4-(4-bromophenyl)-N-(4-methoxyphenyl)-N-(octan-3-yl) thiazol-2-amine (3j)

Yellow solid; Yield: 92%; m.p. 110–112 °C; FT-IR ($cm^{-1}$): 1390, 1610, 1565, 730; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* 8.9 Hz, 2H), 7.49 (d, *J* 8.9 Hz, 2H), 7.32 (d, *J* 8.7 Hz, 2H), 6.93 (d, *J* 8.7 Hz, 2H), 6.48 (s, 1H), 3.86 (s, 3H), 2.92 (m, 1H), 1.48 (m, 2H), 1.52 (m, 2H), 1.33 (m, 2H) 1.09 (t, *J* 7.1 Hz, 3H), 0.96 (t, *J* 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 157.24, 150.32, 141.71, 138.54, 134.63, 128.21, 124.73, 114.50, 115.23, 110.54, 102.12, 62.52, 56.90, 32.11, 25.23, 18.03, 14.62, 9.62; GCMS: m/z calcd for $C_{24}H_{29}BrN_2OS$ 473.47, found 474 ($M^+$).

#### N-ethyl-N-(4-methoxyphenyl)-4-(4-nitrophenyl)thiazol-2-amine (3k)

Orange red solid; Yield: 90%; m.p. 86–88 °C; FT-IR ($cm^{-1}$): 1340, 1592, 1547, 1347, 1505; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* 8.9 Hz, 2H), 7.97 (d, *J* 8.9 Hz, 2H), 7.27 (d, *J* 8.9 Hz, 2H), 6.97 (d, *J* 8.9 Hz, 2H), 6.81 (s,1H), 3.94 (q, 7.1 Hz, 2H), 3.84 (s, 3H), 1.01 (t, *J* 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.40, 159.08, 149.39, 146.74, 141.34, 137.60, 129.13, 126.38, 124.07, 115.34, 105.33, 55.59, 54.68, 11.47; GCMS: m/z calcd for $C_{18}H_{17}N_3O_3S$ 355.41, found 355 ($M^+$).

#### N-isopropyl-N-(4-methoxyphenyl)-4-(4-nitrophenyl)thiazol-2-amine (3l)

Orange red solid; Yield: 88%; m.p. 80–82 °C; FT-IR ($cm^{-1}$): 1335, 1593, 1531, 1331, 1505; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* 8.9 Hz, 2H), 7.97 (d, *J* 8.9 Hz, 2H), 7.27 (d, *J* 8.9 Hz, 2H), 6.97 (d, *J* 8.9 Hz, 2H), 6.81 (s,1H), 3.84 (s, 3H), 3.94 (m, 1H), 1.01 (d, *J* 7.1 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.52, 159.25, 149.46, 146.36, 140.95, 137.46, 129.16, 126.41, 124.14, 115.40, 105.12, 55.74, 50.47, 21.20; GCMS: m/z calcd for $C_{19}H_{19}N_3O_3S$ 369.44, found 369 ($M^+$).

#### N-(4-methoxyphenyl)-4-(4-nitrophenyl)-N-propylthiazol-2-amine (3m)

Orange red solid; Yield: 90%; m.p. 76–78 °C; FT-IR ($cm^{-1}$): 1332, 1593, 1536, 1336, 1504; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* 8.9 Hz, 2H), 7.97 (d, *J* 8.9 Hz, 2H), 7.27 (d, *J* 8.9 Hz, 2H), 6.97 (d, *J* 8.9 Hz, 2H), 6.81 (s,1H), 3.94 (t, *J* 7.1 Hz, 2H), 3.84 (s, 3H), 1.71 (m, 2H), 0.97 (t, *J* 7.4 Hz, 3H); (100 MHz, $CDCl_3$): δ 171.52, 159.25, 149.46, 146.36, 140.95, 137.46, 129.16, 126.41, 124.14, 115.40, 105.12, 55.74, 54.47, 21.19, 11.39; GCMS: m/z calcd for $C_{19}H_{19}N_3O_3S$ 369.44, found 369 ($M^+$).

#### N-sec-butyl-N-(4-methoxyphenyl)-4-(4-nitrophenyl)thiazol-2-amine (3n)

Orange red solid; Yield: 94%; m.p. 72–74 °C; FT-IR ($cm^{-1}$): 1335, 1593, 1531, 1331, 1505; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* 8.9 Hz, 2H), 7.97 (d, *J* 8.9 Hz, 2H), 7.27 (d, *J* 8.9 Hz, 2H), 6.97 (d, *J* 8.9 Hz, 2H), 6.81 (s,1H),

3.84 (s, 3H), 2.95 (m,1H), 1.72 (m, 2H), 1.25 (d, *J* 7.4 Hz 3H), 0.96 (t, *J* 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.51, 159.01, 149.46, 146.73, 141.24, 137.57, 129.10, 126.44, 123.99, 115.34, 105.30, 55.54, 54.67, 31.01, 21.19, 11.47; GCMS: m/z calcd for $C_{20}H_{21}N_3O_3S$ 383.46, found 383 ($M^+$).

#### N-(4-methoxyphenyl)-4-(4-nitrophenyl)-N-(octan-3-yl) thiazol-2-amine (3o)

Orange red solid; Yield: 90%; m.p. 68–70 °C; FT-IR ($cm^{-1}$): 1335, 1593, 1531, 1331, 1505; $^1$H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* 8.9 Hz, 2H), 7.97 (d, *J* 8.9 Hz, 2H), 7.27 (d, *J* 8.9 Hz, 2H), 6.97 (d, *J* 8.9 Hz, 2H), 6.81 (s,1H), 3.84 (s, 3H), 2.95 (m,1H), 1.52 (m, 2H), 1.48 (m, 2H), 1.34 (m, 2H), 1.28 (m, 2H), 1.29 (m, 2H), 1.03 (t, *J* 7.4 Hz, 3H), 0.96 (t, *J* 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.48, 158.94, 149.43, 146.77, 141.28, 137.60, 129.15, 126.47, 124.07, 115.29, 105.23, 59.64, 55.47, 33.93, 31.03, 25.79, 24.48, 21.08, 17.93, 11.37; GCMS: m/z calcd for $C_{24}H_{29}N_3O_3S$ 439.57, found 439 ($M^+$).

#### 4-(4-bromophenyl)-N-(4-chlorophenyl)-N-ethylthiazol-2-amine (3p)

Yellow solid; Yield: 90%; m.p. 94–96 °C; FT-IR ($cm^{-1}$): 1376, 1530, 1512; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* 8.6 Hz, 2H), 7.49 (d, *J* 8.6 Hz, 2H), 7.41 (d, *J* 8.8 Hz, 2H), 7.32 (d, *J* 8.8 Hz, 2H), 6.64 (s, 1H), 3.93 (q, *J* 7.1 Hz, 2H), 1.07 (t, *J* 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 168.46, 157.71, 132.93, 132.32, 132.04, 127.64, 127.48, 123.47, 115.17, 114.76, 100.18, 45.72, 12.62; GCMS: m/z cacd for $C_{17}H_{14}BrClN_2S$ 393.73, found 394 ($M^+$).

#### 4-(4-bromophenyl)-N-(4-chlorophenyl)-N-isopropylthiazol-2-amine (3q)

Yellow solid; Yield: 94%; m.p. 90–92 °C; FT-IR ($cm^{-1}$): 1376, 1530, 1512; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* 8.6 Hz, 2H), 7.51 (d, *J* 8.6 Hz, 2H), 7.32 (d, *J* 8.8 Hz, 2H), 7.27 (d, *J* 8.8 Hz, 2H), 6.83 (s, 1H), 3.80 (m, 1H), 1.07 (d, *J* 7.4 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.03, 150.37, 138.93, 133.49, 131.95, 130.06, 129.50, 127.82, 121.95, 119.50, 102.63, 43.37, 14.15; GCMS: m/z calcd for $C_{18}H_{16}BrClN_2S$ 407.76, found 408 ($M^+$).

#### 4-(4-bromophenyl)-N-(4-chlorophenyl)-N-propylthiazol-2-amine (3r)

Yellow solid; Yield: 86%; m.p. 86–88 °C; FT-IR ($cm^{-1}$): 1376, 1530, 1512; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* 8.6 Hz, 2H), 7.49 (d, *J* 8.6 Hz, 2H), 7.41 (d, *J* 8.8 Hz, 2H), 7.32 (d, *J* 8.8 Hz, 2H), 6.64 (s, 1H), 4.01 (t, *J* 7.1 Hz, 2H), 1.73 (m, 2H), 0.97 (t, *J* 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 168.46, 157.71, 132.93, 132.32, 132.04, 127.64, 127.48, 123.47, 115.17, 114.76, 100.18, 55.72, 31.08, 21.19; GCMS: m/z calcd for $C_{18}H_{16}BrClN_2S$ 407.76, found 408 ($M^+$).

#### N-sec-butyl-4-(4-bromophenyl)-N-(4-chlorophenyl)thiazol-2-amine (3s)

Yellow solid; Yield: 88%; m.p. 82–84 °C; FT-IR ($cm^{-1}$): 1376, 1530, 1512; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* 8.6 Hz, 2H), 7.50 (d, *J* 8.6 Hz, 2H), 7.35 (d, *J* 8.8 Hz, 2H), 7.30 (d, *J* 8.8 Hz, 2H), 6.79 (s, 1H), 2.91 (m, 1H), 1.69 (m, 2H), 1.23 (d, *J* 7.4 Hz, 3H), 1.01 (t, *J* 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.64, 149.09, 138.38, 131.98, 130.40, 129.55, 128.59, 127.62, 122.31, 119.79, 102.27, 57.93, 28.28, 18.91, 11.70; GCMS: m/z calcd for $C_{19}H_{18}BrClN_2S$ 421.78, found 422 ($M^+$).

#### 4-(4-bromophenyl)-N-(4-chlorophenyl)-N-(octan-3-yl) thiazol-2-amine (3t)

Yellow solid; Yield: 90%; m.p. 76–78 °C; FT-IR ($cm^{-1}$): 1376, 1530, 1512; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* 8.6 Hz, 2H), 7.49 (d, *J* 8.6 Hz, 2H), 7.41 (d, *J* 8.8 Hz, 2H), 7.32 (d, *J* 8.8 Hz, 2H), 6.64 (s, 1H), 3.64 (m, 1H), 1.73 (m, 2H), 1.52(m, 2H), 1.33(m, 2H), 1.30(m, 2H), 1.28(m, 2H), 1.09 (t, *J* 7.4 Hz, 3H), 0.97 (t, *J* 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.68, 156.58, 150.29, 133.72, 132.17, 131.76, 127.70, 122.30, 121.74, 114.74, 101.91, 55.53, 32.02, 31.71, 31.04, 29.79, 22.82, 21.00, 14.13; GCMS: m/z calcd for $C_{23}H_{26}BrClN_2S$ 477.89, found 488 ($M^+$).

## Biological activity

### Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against bacterial strains by macro dilution broth method. Different concentrations (0.125–256 μg/mL) of the synthesized compounds were added to the respectively labeled sterile Mueller Hinton Broth (MHB) medium tubes. The tubes were inoculated with 1 mL lag phase cultures of the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* and that of the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*. The inoculated tubes were incubated at 37 °C for 24 h followed by observing the inhibition of growth of the test bacteria in the tubes. The MIC was determined as the lowest concentration of the synthesized compounds containing tube showing no visible growth of the test bacteria.

### Antibacterial activity against drug-resistant bacteria

The active compounds against the sensitive bacterial strains were screened for antibacterial activity against resistant bacterial strains by macro dilution broth method. Different concentrations (25–500 mg/mL) of the compounds were added to the respectively labeled sterile MHB medium tubes. The tubes were inoculated with 1 mL lag phase cultures of the Methicillin-resistant *S. aureus* and (MDR) Multidrug-resistant *P. aeruginosa* obtained from Kuvempu University, Shimoga. The inoculated tubes were incubated at 37 °C for 24 h followed by observing the inhibition of growth of the test bacteria in the tubes. Ciprofloxacin was taken as the standard drug. The MIC was determined as the lowest concentration of the synthesized compounds containing tube showing no visible growth of the test bacteria.

### Antifungal activity

The prepared compounds were studied by macrodilution broth method for their antifungal activity. Different concentrations (0.125–256 µg/mL) of the synthesized compounds were added to the respectively labeled sterile saboraud dextrose broth tubes. The tubes were inoculated with lag phase cultures of the fungi *A. flavus, Trichoderma harzianum, Penicillium chrysogenum* and yeast *C. albicans*. The inoculated tubes were incubated at 27 °C for 48 h followed by observing the inhibition of growth of the test fungi in the tubes. The MIC was determined as the lowest concentration of the synthesized compounds containing tube showing no visible growth of the test fungi.

### Anti-inflammatory activity by protein denaturation assay

Anti-inflammatory activity was carried out by protein denaturation method. Aspirin was used as the standard drug. The reaction mixture consisted of 50 µL of 1% egg albumin in PBS and different concentrations (0, 100, 200 µg/mL) of either test samples or the standard drug were added and final volume was made upto 2 ml with PBS and incubated for 15 min at room temperature. Denaturation was induced by keeping at 70 °C in hot water bath for 10 min. The absorbance was measured at 660 nm (Labman UV Visible Spectrophotometer). The percent of inhibition of protein denaturation was calculated using the following formula:

$$\%\,\text{inhibition of Protein denaturation activity} = [(A_c - A_t)/Ac] \times 100$$

where, $A_c$ and $A_t$ are the absorbances of control and test sample, respectively.

### Cytotoxicity

To evaluate the effects of active compounds on cell viability, Human Embryonic kidney Cells (HEK293) were used to perform the assay by MTT method. MTT is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The cells were seeded at a density of ~$5 \times 10^3$ cells/well in a 96-well flat-bottom micro plate and maintained at 37 °C in 95% humidity and 5% $CO_2$ for overnight. Different concentrations (600, 300, 150, 75, 37.5, 18.75 µg/mL) of samples were treated and the cells were incubated for 48 h. The cells in well were washed twice with phosphate buffer solution and 20 µL of the MTT staining solution was added to each well and plate was incubated at 37 °C. After 4 h, 100 µL of Dimethyl sulfoxide (DMSO) was added to each well to dissolve the formazan crystals and absorbance was recorded at a 570 nm using micro plate reader.

### Molecular docking studies

Surflex-Dock was used to investigate detailed intermolecular interactions between the ligand and the target protein. Three-dimensional structure information on the target protein was taken from the Protein Data Bank (PDB) entry 4FDO. The proteins were prepared for docking by adding polar hydrogen atom with Gasteiger–Huckel charges and water molecules were removed. The 3D structure of the ligands were generated by the SKETCH module implemented in the SYBYL program Tripos International (2012) and its energy-minimized confirmation was obtained with the help of the Tripos force field using Gasteiger–Huckel charges (Dolomanov et al. 2003) and molecular docking was performed with Surflex-Dock program that is interfaced with Sybyl-X 2.0. (Sheldrick 1997) and other miscellaneous parameters were assigned with the default values given by the software.

## Results and discussion

### Chemistry

The new series of N,4-diphenylthiazol-2-amine derivatives **3a–3t** (Table 1) were synthesized by a three-step synthetic protocol involving eco-friendly conditions. In the initial step, potassium thiocyante and substituted anilines were used to prepare the required thioureas. These thioureas when treated with phenacyl bromide underwent Hantzsch cyclization rapidly without the use of any catalyst in a very short time and at room temperature. The product obtained

**Table 1** Scope of the reaction

| Compounds | R | $R_1$ | $R_2$ |
|---|---|---|---|
| 3a | -Cl | $-NO_2$ | Eth-1-yl |
| 3b | -Cl | $-NO_2$ | Isoprop-1-yl |
| 3c | -Cl | $-NO_2$ | Prop-1-yl |
| 3d | -Cl | $-NO_2$ | But-2-yl |
| 3e | -Cl | $-NO_2$ | Octan-3-yl |
| 3f | -OMe | -Br | Eth-1-yl |
| 3g | -OMe | -Br | Isoprop-1-yl |
| 3h | -OMe | -Br | Prop-1-yl |
| 3i | -OMe | -Br | But-2-yl |
| 3j | -OMe | -Br | Octan-3-yl |
| 3k | -OMe | $-NO_2$ | Eth-1-yl |
| 3l | -OMe | $-NO_2$ | Isoprop-1-yl |
| 3m | -OMe | $-NO_2$ | Prop-1-yl |
| 3n | -OMe | $-NO_2$ | But-2-yl |
| 3o | -OMe | $-NO_2$ | Octan-3-yl |
| 3p | -Cl | -Br | Eth-1-yl |
| 3q | -Cl | -Br | Isoprop-1-yl |
| 3r | -Cl | -Br | Prop-1-yl |
| 3s | -Cl | -Br | But-2-yl |
| 3t | -Cl | -Br | Octan-3-yl |

was 2, 4-disubstituted thiazole with amine functionality at second position of thiazole ring (Hantzsch and Weber 1887; Bikobo et al. 2017; Dighe et al. 2011). The last step involved nucleophilic substitution yielding the alkyl-substituted final products (Scheme 1). The overall synthetic protocol was designed to be carried out in eco-friendly conditions requiring short time with excellent yield which has been achieved.

The structures of the title compounds were confirmed by using $^1$H NMR, $^{13}$C NMR, FT-IR, and GCMS spectral methods. Also, single-crystal X-ray diffraction study of the derivative **3c** confirmed the formation of the designed moiety. The spectral data of newly synthesized compounds **3a**–**3t** are provided in the experimental section and are in agreement with the desired structures of the compounds.

In case of compound **3a** (R = -Cl, $R_1$ = $-NO_2$, $R_2$ = -Ethyl), the $^1$H NMR spectrum showed signal at δ 6.89 ppm as a singlet of thiazole C-5 proton. The characteristic quartet-triplet pattern of the ethyl chain appeared at δ 4.08 and δ 1.32 ppm, respectively. The absence of singlet proton around δ 4.0–4.5 ppm which corresponds to the N-H proton confirmed the formation of **3a**. It was further supported by recording $^{13}$C NMR spectrum and the signals in the spectrum accounted for all the C-atoms present in the compound. The GCMS spectrum of **3a** showed molecular ion peak at 360[$M^+$] which is in agreement with its respective molecular formula $C_{17}H_{14}ClN_3O_2S$.

For **3m** (R = -OMe, $R_1$ = $-NO_2$, $R_2$ = -Propyl), the $^1$H NMR spectrum showed a signal at δ 6.81 ppm as a singlet which can be ascertain to C-5 proton of thiazole ring. The prop-1-yl substituent appeared as a triplet corresponding to the two protons of $CH_2$ linked to nitrogen at δ 3.94 ppm, multiplet corresponding to two protons of $CH_2$ at δ 1.71 ppm and triplet corresponding to three protons of $CH_3$ at δ 0.97 ppm. The three protons of O-$CH_3$ resonated as singlet at δ 3.84 ppm. The GCMS spectrum showed molecular ion peak at 370[$M^+$] further supported for the formation of compound **3m**. The remaining compounds are in good agreement with the expected spectral data.

## X-ray diffraction studies

Single crystal for compound (**3c**) was developed by slow evaporation of ethanol at room temperature. It crystallized under a triclinic system with the space group P-1. The unit cell dimensions are as follows: $a = 9.3433(3)$ Å, $b = 10.3778(3)$ Å, $c = 10.6275(3)$ Å, $\alpha = 109.6690(10)°$, $\beta = 100.147(2)°$, $\gamma = 102.6970(10)°$, $Z = 2$. Data collection and reduction were performed using Bruker SMART X2S benchtop crystallographic system, APEX2 software was used for preliminary determination of the unit cell. Determination of integrated intensities and unit cell refinement were performed using SAINT (Smart and Saint 2001). OLEX2 (version1.2) (Dolomanov et al. 2003) and SHELXS-97(Sheldrick 1997) was used to solve and refine the crystal structures. Bond lengths and angles are within the normal ranges [R]. The X-ray structure parameters and refinement for the compound are presented in Tables 2–4. The ORTEP and packing diagram of compound (**3c**) is portrayed in Fig. 2.

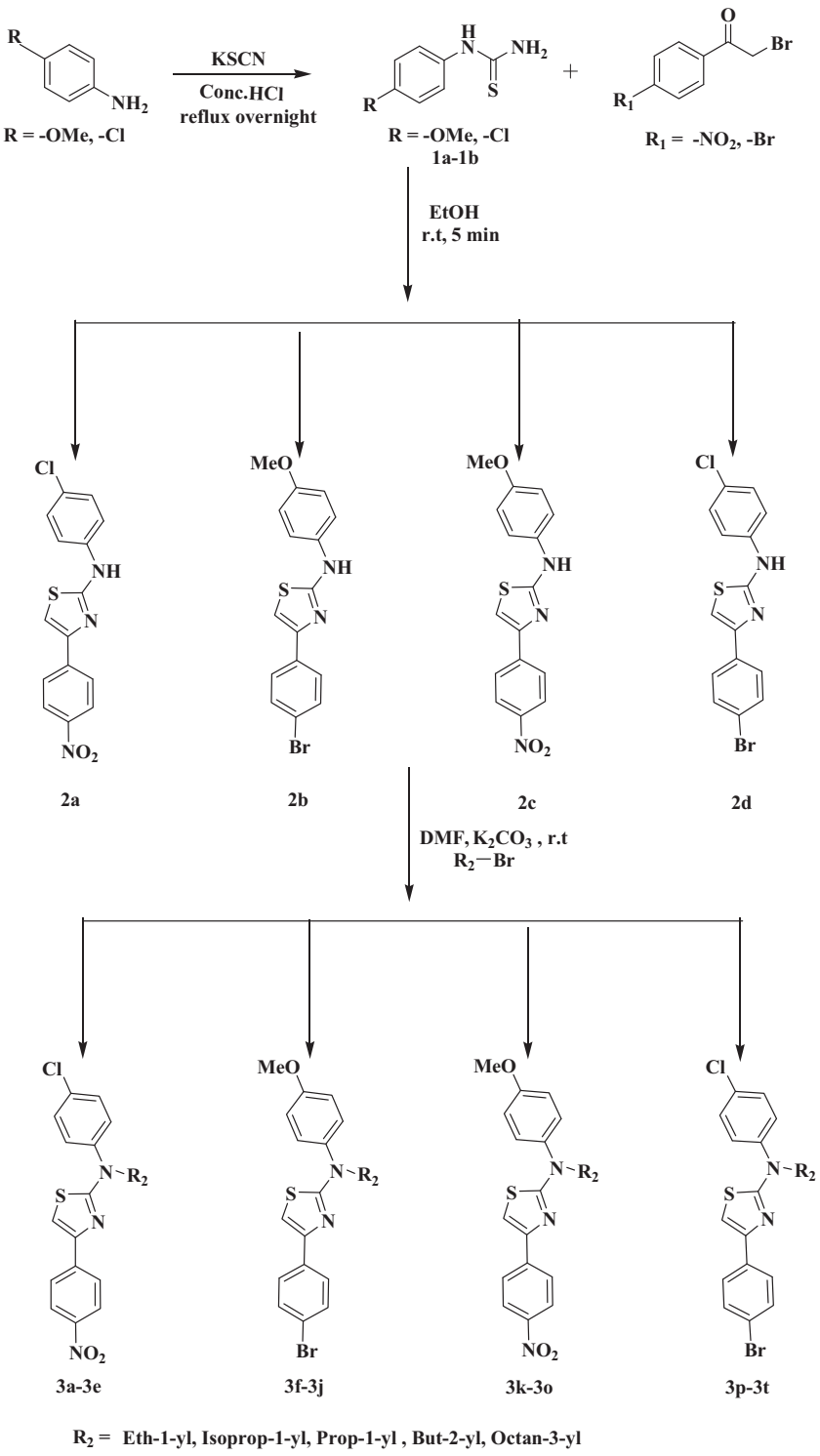
## Biological evaluation

All the compounds prepared herein were screened for their potential in vitro antibacterial activity against Gram-positive bacteria *S. aureus* and *B. subtilis*, Gram-negative bacteria *E. coli* and *P. aeruginosa*, antifungal activity against *A. flavus, T. harzianum, P. chrysogenum and yeast C. albicans* by macrodilution broth method and anti-inflammatory activity by protein denaturation assay (Cockerill et al. 2012; Leelaprakash and Dass 2011). The compounds which showed good activity against the sensitive bacterial strains were further screened against Methicillin-resistant *S. aureus* and (MDR) Multidrug-resistant *P. aeruginosa*.

## Antibacterial studies

The antibacterial screening of all the synthesized compounds against both Gram-positive and Gram-negative

**Scheme 1** Synthetic route for the target compounds **3a–3t**




human pathogenic bacterial strains showed moderate to good activity and was compared with the standard antibiotics Ciprofloxacin and Streptomycin. Screening results are summarized in Table 5. Compounds **3d** and **3o** showed good activity in comparison to the other molecules synthesized and are also similar with both of the standards against all the bacterial strains. Compounds 3e, 3h, 3l, 3m and 3t showed good activity whereas 3b, 3c, 3g, 3i, 3j, 3k and 3r have appeared moderate. The molecules having an electron-donating as well as electron-accepting groups in their framework with branched alkyl chains on the Nitrogen atom exhibited better activity.

**Table 2** Crystal data, data collection and structure refinement of compound **3c**

| Empirical formula | $C_{18}H_{16}ClN_3O_2S$ |
|---|---|
| Formula weight | 373.85 |
| Temperature/K | 293(2) |
| Crystal system | Triclinic |
| Space group | P-1 |
| a/Å | 9.3433(3) |
| b/Å | 10.3778(3) |
| c/Å | 10.6275(3) |
| α/° | 109.6690(10) |
| β/° | 100.147(2) |
| γ/° | 102.6970(10) |
| Volume/Å$^3$ | 910.84(5) |
| Z | 2 |
| $\rho_{calc}$g/cm$^3$ | 1.363 |
| μ/mm$^{-1}$ | 0.341 |
| F(000) | 388.0 |
| Crystal size/mm$^3$ | 0.180 × 0.135 × 0.070 |
| Radiation | MoKα (λ = 0.71073) |
| 2Θ range for data collection/° | 4.22–60.84 |
| Index ranges | −13 ≤ h ≤ 13, −14 ≤ k ≤ 14, −15 ≤ l ≤ 14 |
| Reflections collected | 19465 |
| Independent reflections | 5450 [$R_{int}$ = 0.0232, $R_{sigma}$ = N/A] |
| Data/restraints/parameters | 5450/0/264 |
| Goodness-of-fit on F$^2$ | 1.057 |
| Final R indexes [I >= 2σ (I)] | $R_1$ = 0.0506, $wR_2$ = 0.1345 |
| Final R indexes [all data] | $R_1$ = 0.0669, $wR_2$ = 0.1472 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.55/−0.63 |
| **CCDC No** | **1904641** |

**Table 3** Bond lengths for **3c**

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|---|---|---|---|---|---|
| C(7B) | C(8B) | 1.428(8) | C(5) | C(4) | 1.368(3) |
| C(7B) | N(1) | 1.496(4) | C(5) | C(6) | 1.384(3) |
| C(8B) | C(9B) | 1.590(2) | C(16) | C(15) | 1.371(2) |
| C(8A) | C(7A) | 1.484(9) | C(16) | C(17) | 1.374(2) |
| C(8A) | C(9A) | 1.560(3) | C(16) | N(2) | 1.467(2) |
| C(7A) | N(1) | 1.475(5) | C(13) | C(18) | 1.391(2) |
| O(2B) | N(2) | 1.100(3) | C(10) | N(3) | 1.300(19) |
| O(2A) | N(2) | 1.245(17) | C(10) | N(1) | 1.354(2) |
| C(14) | C(15) | 1.377(2) | C(10) | S(1) | 1.740(16) |
| C(14) | C(13) | 1.391(2) | C(4) | C(3) | 1.367(3) |
| C(1) | C(6) | 1.374(3) | C(4) | Cl(1) | 1.733(18) |
| C(1) | C(2) | 1.377(3) | C(3) | C(2) | 1.384(3) |
| C(1) | N(1) | 1.431(2) | C(11) | S(1) | 1.714(19) |
| C(12) | C(11) | 1.357(2) | C(17) | C(18) | 1.380(2) |
| C(12) | N(3) | 1.385(2) | N(2) | O(1) | 1.215(2) |
| C(12) | C(13) | 1.466(2) | | | |

3b, 3d, 3e, 3h, 3k, 3l, 3m, 3o and 3t were further evaluated for their in vitro activity against Methicillin-resistant *S. aureus* and (MDR) Multidrug-resistant *P. aeruginosa*. **3o** exhibited good activity with MIC same as that of the standard against MRSA whereas **3d** showed 1.5 to 2 fold greater MIC's for both the strains in comparison with the standard. Rest of the molecules have appeared moderate.

## Antifungal studies

Compounds **3a–3t** were screened for their antifungal activity against four strains. Nystatin and Fluconazole were used as a standard for the comparison of antifungal activity. Among the tested compounds **3a**, **3c**, **3k** and **3m** have emerged active against all the tested microorganisms with respect to both the standards. 3b, 3f, 3h, 3p and 3r have exhibited good activity. All the rest compounds are moderate against all the fungal strains. The synthesized molecules with an electron-donating as well as electron-accepting groups in their framework along with straight alkyl chain functionality on Nitrogen atom have shown enhanced results. Screening results are summarized in Table 6.

## Anti-inflammatory activity by protein denaturation assay

The anti-inflammatory activities of the target compounds **3a–3t** were evaluated using protein denaturation assay. Aspirin was used as the standard drug and measured in terms of the percent of inhibition of protein denaturation. Amongst all the tested compounds **3j and 3o** have showed good activity compared with the standard whereas 3f–3i and 3k–3n are moderately active. The presence of electron-donating group and branched alkyl chain might be the reason for the compounds to show enhanced activity. The 3e–3o series also contain the same electron-donating group and hence has showed comparatively good activity whereas rest of them appeared moderate. Screening results are summarized in Table 7.

## Cytotoxicity of the synthesized compounds

The synthesized compounds which exhibited good activity against the bacterial and fungal strains were tested for their toxicity against normal cell lines. Human Embryonic kidney (HEK293) cells have been employed to estimate their toxicity. From Table 8, the tested compounds have exhibited moderate to low levels of cytotoxicity with $IC_{50}$ values

**Table 4** Bond angles for **3c**

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|---|---|---|---|---|---|---|---|
| C(8B) | C(7B) | N(1) | 113.20(5) | C(5) | C(4) | Cl(1) | 119.43(15) |
| C(7B) | C(8B) | C(9B) | 111.80(11) | C(1) | C(6) | C(5) | 120.43(18) |
| C(7A) | C(8A) | C(9A) | 101.80(13) | C(4) | C(3) | C(2) | 119.45(18) |
| N(1) | C(7A) | C(8A) | 109.30(5) | C(12) | C(11) | S(1) | 111.11(13) |
| C(15) | C(14) | C(13) | 121.57(17) | C(16) | C(17) | C(18) | 118.89(16) |
| C(6) | C(1) | C(2) | 119.89(16) | C(1) | C(2) | C(3) | 119.88(17) |
| C(6) | C(1) | N(1) | 120.27(17) | C(16) | C(15) | C(14) | 118.61(16) |
| C(2) | C(1) | N(1) | 119.84(16) | C(17) | C(18) | C(13) | 121.04(15) |
| C(11) | C(12) | N(3) | 114.96(15) | C(10) | N(1) | C(1) | 118.45(14) |
| C(11) | C(12) | C(13) | 125.90(15) | C(10) | N(1) | C(7A) | 122.50(2) |
| N(3) | C(12) | C(13) | 119.14(14) | C(1) | N(1) | C(7A) | 117.10(2) |
| C(4) | C(5) | C(6) | 118.90(18) | C(10) | N(1) | C(7B) | 117.80(2) |
| C(15) | C(16) | C(17) | 121.87(15) | C(1) | N(1) | C(7B) | 120.50(2) |
| C(15) | C(16) | N(2) | 118.36(15) | C(7A) | N(1) | C(7B) | 31.90(2) |
| C(17) | C(16) | N(2) | 119.75(16) | O(2B) | N(2) | O(1) | 120.50(14) |
| C(18) | C(13) | C(14) | 118.00(15) | O(2B) | N(2) | O(2A) | 23.00(2) |
| C(18) | C(13) | C(12) | 120.77(14) | O(1) | N(2) | O(2A) | 122.50(4) |
| C(14) | C(13) | C(12) | 121.21(15) | O(2B) | N(2) | C(16) | 117.00(2) |
| N(3) | C(10) | N(1) | 125.18(15) | O(1) | N(2) | C(16) | 118.99(16) |
| N(3) | C(10) | S(1) | 115.47(12) | O(2A) | N(2) | C(16) | 118.40(4) |
| N(1) | C(10) | S(1) | 119.34(12) | C(10) | N(3) | C(12) | 110.18(13) |
| C(3) | C(4) | C(5) | 121.45(17) | C(11) | S(1) | C(10) | 88.28(8) |
| C(3) | C(4) | Cl(1) | 119.12(16) | | | | |

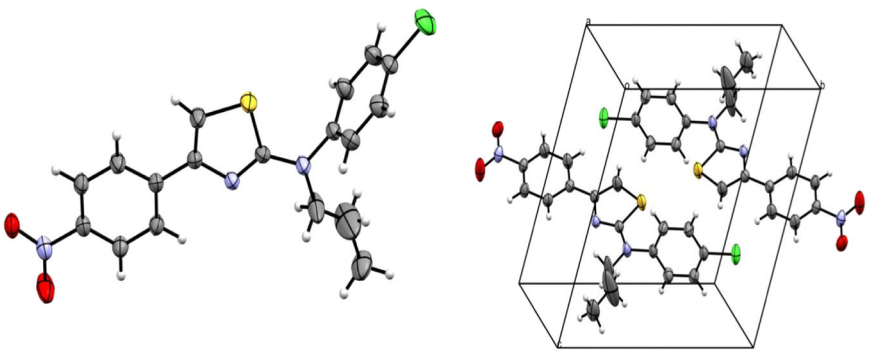


**Fig. 2** ORTEP and packing diagram for compound **3c**

of the human embryonic kidney cells in the range of 360.8–523.8 µg/mL and none of the compounds exhibited any significant cytotoxic effects, suggesting good potential for their in vivo use.

## Structure-activity relationship study

The structure-activity relationship study showed that the substituents on the phenyl rings at 2, 4 positions of thiazole play a decisive role in the activity shown by the compounds. As can be seen, compounds **3d** and **3o** showed better activity with MIC ranging between 2.0–4.0 µg/mL. 3d appeared as a promising candidate against *B. subtilis* and *E. coli* with MIC same as that of streptomycin and Ciprofloxacin whereas 3o was active against *S. aureus and E. coli*. They have also shown good activity against drug-resistant strains of bacteria. Both these compounds possess -$NO_2$ group in one of the phenyl rings and the other having a -Cl and -OMe group, respectively. Rest of the compounds have showed good to moderate activity. Amongst the synthesized compounds containing -OMe and -$NO_2$ groups, eight of them have showed better activity, whereas the compounds containing only -$NO_2$ groups appear good comparatively. The compounds without both the groups exhibited lesser activity than the rest of the compounds. These results suggested

**Table 5** Minimum inhibition concentration (MIC) of compounds **3a–3t** using standard antibiotics for antibacterial activity

| Test organism | *Staphylococcus aureus* | *Bacillus subtilis* | *Escherichia coli* | *Pseudomonas aeruginosa* | *Staphylococcus aureus* (MRSA) | *Pseudomonas aeruginosa* (MDR) |
|---|---|---|---|---|---|---|
| 3a | 64 | 64 | 128 | 64 | nd | nd |
| 3b | 16 | 16 | 16 | 8 | 250 | 300 |
| 3c | 16 | 8 | 16 | 32 | nd | nd |
| **3d** | **4** | **2** | **2** | **4** | **75** | **100** |
| 3e | 4 | 8 | 4 | 8 | 200 | 250 |
| 3f | 32 | 128 | 64 | 64 | nd | nd |
| 3g | 16 | 32 | 16 | 16 | nd | nd |
| 3h | 8 | 8 | 8 | 8 | 200 | 250 |
| 3i | 32 | 16 | 16 | 32 | nd | nd |
| 3j | 32 | 32 | 64 | 32 | nd | nd |
| 3k | 8 | 32 | 16 | 32 | 250 | 400 |
| 3l | 4 | 4 | 8 | 4 | 200 | 150 |
| 3m | 4 | 4 | 8 | 8 | 150 | 200 |
| 3n | 64 | 32 | 32 | 64 | nd | nd |
| **3o** | **2** | **4** | **2** | **4** | **50** | **75** |
| 3p | 64 | 64 | 32 | 64 | nd | nd |
| 3q | 32 | 16 | 32 | 16 | nd | nd |
| 3r | 32 | 16 | 16 | 32 | nd | nd |
| 3s | 64 | 32 | 64 | 128 | nd | nd |
| 3t | 4 | 8 | 8 | 4 | 250 | 200 |
| **Ciprofloxacin** | **2** | **2** | **2** | **2** | **50** | **50** |
| **Streptomycin** | **2** | **2** | **2** | **2** | **–** | **–** |

*nd* not determined

that the compounds containing a strongly electron-donating (-OMe) and electron-withdrawing groups (-$NO_2$) in the scaffold have exhibited better antibacterial activity. The branched longer chains have exhibited better activity compared with the smaller alkyl groups.

With regards to the antifungal activity, **3a, 3c, 3k and 3m** have shown excellent activity with MIC value (0.5–1.0 µg/mL) lower than that of the standards used. Rest of the compounds have showed moderate activity. Infact 3k has appeared very potent against *C. albicans* with MIC 0.5 µg/mL. The SAR study depicts that the compounds having -$NO_2$ group have showed better activity than the rest of them. One peculiar thing observed was the compounds having smaller alkyl chains have appeared potent and the activity decreases as the branching in the chain increases.

Structure-activity relationship analysis of anti-inflammatory activity suggests that only those compounds which possessed a -OMe and -$NO_2$ group along with branched longer alkyl chain in the scaffold showed good activity in comparison with the standard Aspirin. **3j** exhibited $IC_{50}$ 285 µg/mL whereas **3o** has an $IC_{50}$ 293 µg/mL. An exception to this is 3f which has an $IC_{50}$ 274 µg/mL with a smaller ethyl group in its scaffold.

## In silico studies

To gain better understanding on the potency of synthesized compounds and guide further SAR studies we proceeded to examine the interaction of these compounds using molecular docking studies. These studies also support the results of the in vitro activity. Docking studies were performed on the X-ray crystal structure of the dihydropteroate synthetase (DHPS) complexed with HO-$CH_2$-pterin-pyrophosphate from *S. aureus* (PDB ID: 1AD4) and *C. albicans* dihydrofolate reductase (PDB ID: 1AI9) from *C. albicans*. Molecular docking was used to explain the binding mode of the compounds and provide information for further structural optimization. The docking study was obtained from the PDB by using Surflex-Dock programme of Sybyl-X software (Gasteiger and Marsili 1980; Tripos International (2012)).

## Docking studies of the title compounds with dihydropteroate synthetase (DHPS) complexed with HO-$CH_2$-pterin-pyrophosphate from *S. aureus* (PDB ID: 1AD4)

All the compounds were docked into the active site of the DHPS (Fig. 3), the predicted binding energies and the

**Table 6** Minimum inhibition concentration (MIC) of compounds **3a–3t** using standard antibiotics for antifungal activity

| Test organism | *Aspergillus flavus* | *Trichoderma harzianum* | *Penicillium chrysogenum* | *Candida albicans* |
|---|---|---|---|---|
| **3a** | **1** | **1** | **2** | **1** |
| 3b | 6 | 8 | 8 | 4 |
| **3c** | **2** | **2** | **2** | **1** |
| 3d | 16 | 16 | 16 | 8 |
| 3e | 64 | 64 | 64 | 32 |
| 3f | 8 | 8 | 4 | 4 |
| 3g | 16 | 8 | 16 | 16 |
| 3h | 8 | 16 | 4 | 8 |
| 3i | 16 | 16 | 32 | 32 |
| 3j | 32 | 64 | 64 | 32 |
| **3k** | **1** | **1** | **1** | **0.5** |
| 3l | 32 | 16 | 8 | 8 |
| **3m** | **2** | **2** | **2** | **1** |
| 3n | 16 | 16 | 16 | 8 |
| 3o | 64 | 64 | 64 | 32 |
| 3p | 8 | 16 | 8 | 4 |
| 3q | 16 | 16 | 16 | 32 |
| 3r | 8 | 4 | 8 | 16 |
| 3s | 16 | 16 | 16 | 8 |
| 3t | 64 | 64 | 64 | 32 |
| **Nystatin** | **2** | **2** | **2** | **4** |
| **Fluconazole** | **4** | **4** | **4** | **1** |

**Table 7** $IC_{50}$ (μg/ml) of compounds **3a–3t** for anti-inflammatory activity by protein denaturation assay

| Sample name | $IC_{50}$ (μg/mL) | Sample name | $IC_{50}$ (μg/mL) |
|---|---|---|---|
| 3a | 120 | 3k | 198 |
| 3b | 104 | 3l | 201 |
| 3c | 98 | 3m | 210 |
| 3d | 95 | 3n | 211 |
| 3e | 100 | **3o** | **293** |
| 3f | 274 | 3p | 98 |
| 3g | 210 | 3q | 94 |
| 3h | 188 | 3r | 80 |
| 3i | 187 | 3s | 100 |
| **3j** | **285** | 3t | 120 |
| **Aspirin** | **315** | | |

**Table 8** Cytotoxicity of the active compounds against human embryonic kidney cells using MTT assay

| Compound name | $IC_{50}$ (μg/mL) | Compound name | $IC_{50}$ (μg/mL) |
|---|---|---|---|
| 3a | 461.4 | 3k | 395.4 |
| 3c | 360.8 | 3l | 410.1 |
| 3d | 396.1 | 3m | 386.6 |
| 3e | 523.8 | 3o | 402.4 |

observed C-score values of all the compounds are ranging from 4.64 to 9.75 which are listed in Table 9. As depicted in Fig. 4, compound **3d** makes three hydrogen bonding interactions at the active site of the enzyme (PDB ID: 1AD4). Among those two interactions were of oxygen atoms of nitro group present on the phenyl ring attached to C-4 of thiazole ring with hydrogen atoms of ASN103 and LYS203 (-O-H-ASN103, 2.44 Å; -O-H-LYS203, 2.15 Å) and the other one raised from the nitrogen atom of nitro group with hydrogen atom of ARG239 (-N-H-ARG239, 2.83 Å).

The binding interaction of standard Ciprofloxacin with dihydropteroate synthetase active sites showed three bonding interactions and the docked view of the same has been depicted in Fig. 5. The comparative molecular docking study of synthesized compounds and standard Ciprofloxacin drug highlighted that the synthesized compounds exhibited **high** C-score values binding to the enzyme in similar a manner as that of Ciprofloxacin. Most of the synthesized compounds have the same H-bonding interaction with same amino acid LYS203 as that of Ciprofloxacin.

Compound **3k** makes five hydrogen bonding interactions at the active site of the enzyme (PDB ID: 1AD4).

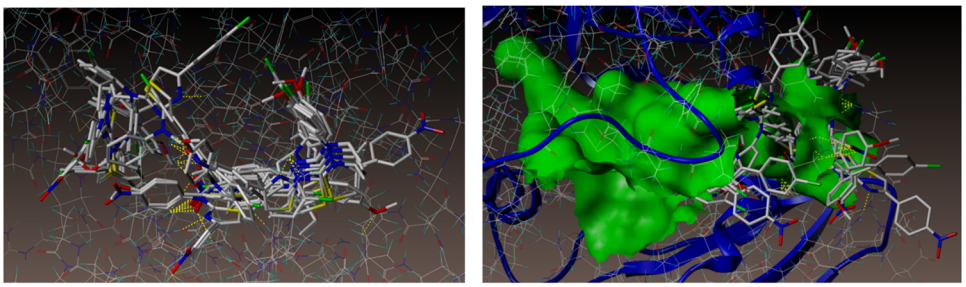


**Fig. 3** Docked view of all the compounds at the active site of the enzyme PDB ID: 1AD4

**Table 9** Surflex docking score (kcal/mol) of the synthesized compounds **3a–3t** docked into the active site of the DHPS

| Compounds | C score[a] | Crash score[b] | Polar score[c] | D score[d] | PMF score[e] | G score[f] | Chem score[g] |
|---|---|---|---|---|---|---|---|
| Ciprofloxacin | 5.01 | −2.26 | 1.91 | −87.704 | −69.857 | −187.231 | −21.485 |
| 3o | 4.88 | −1.59 | 0.00 | −83.725 | −55.646 | −237.662 | −17.549 |
| 3t | 4.74 | −0.92 | 0.36 | −71.419 | −39.276 | −193.342 | −17.451 |
| 3e | 4.68 | −0.88 | 0.85 | −76.068 | −18.796 | −178.984 | −15.004 |
| 3m | 4.22 | −0.81 | 3.80 | −29.921 | −59.095 | −121.251 | −23.035 |
| 3d | 3.60 | −5.44 | 3.91 | −80.116 | −24.097 | −236.632 | −27.179 |
| 3c | 3.58 | −1.12 | 2.43 | −44.296 | −57.889 | −162.298 | −20.108 |
| 3j | 3.55 | −5.82 | 0.04 | −117.809 | −52.495 | −316.910 | −25.819 |
| 3b | 3.51 | −1.00 | 2.08 | −52.028 | −64.975 | −160.653 | −18.511 |
| 3n | 3.45 | −1.50 | 1.72 | −65.475 | −62.187 | −175.167 | −18.872 |
| 3h | 3.42 | −0.79 | 1.22 | −33.483 | −55.977 | −153.647 | −17.968 |
| 3i | 3.40 | −1.93 | 0.00 | −76.750 | −65.701 | −220.590 | −19.750 |
| 3q | 3.17 | −2.06 | 0.37 | −78.507 | −49.014 | −209.947 | −19.422 |
| 3l | 3.14 | −2.91 | 1.14 | −63.176 | −22.324 | −169.093 | −16.548 |
| 3f | 3.06 | −2.61 | 1.18 | −101.281 | −26.399 | −219.142 | −26.866 |
| 3g | 3.05 | −0.92 | 1.25 | −41.051 | −44.343 | −142.739 | −17.231 |
| 3k | 3.01 | −1.71 | 2.70 | −23.425 | −38.172 | −111.663 | −16.781 |
| 3p | 2.49 | −1.47 | 0.01 | −64.801 | −50.998 | −185.705 | −18.432 |
| 3r | 2.37 | −1.71 | 1.20 | −45.526 | −46.867 | −175.813 | −18.285 |
| 3s | 2.29 | −1.60 | 1.05 | −50.204 | −47.179 | −179.185 | −18.273 |
| 3a | 2.18 | −1.02 | 0.88 | −48.823 | −63.740 | −168.492 | −17.967 |

[a]C score (consensus score) integrates a number of popular scoring functions for ranking the affinity of ligand bound to the active site of a receptor and reports the output of total score

[b]Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to 0 are favorable. Negative numbers indicate penetration

[c]Polar indicating the contribution of the polar interactions to the total score. The polar score may be useful for excluding docking results that make no hydrogen bonds

[d]D-score for charge and van der Waals interactions between the protein and the ligand

[e]PMF-score indicating the Helmholtz free energies of interactions for protein-ligand atom pairs (Potential of Mean Force, PMF)

[f]G-score showing hydrogen bonding, complex (ligand-protein) and internal (ligand-ligand) energies

[g]Chem-score points for H-bonding, lipophilic contact and rotational entropy along with an intercept term

Among those two interactions were of oxygen atom of nitro group present on the phenyl ring linked to the C-2 of thiazole ring through nitrogen atom with hydrogen atoms of ARG219 (-O-H-ARG219, 1.91 Å and 2.22 Å) and one hydrogen bonding interaction raised from the nitrogen atom of nitro group present on the phenyl ring with hydrogen atom of ARG219 (-N-H-ARG219, 2.84 Å). Two interactions of the oxygen atom of methoxy group present on the phenyl ring attached to the C-4 of thiazole ring with hydrogen atoms of GLN105 (-O-H-GLN105, 1.87 and 2.72 Å). [Fig. 1 and 2 in Supplementary data].

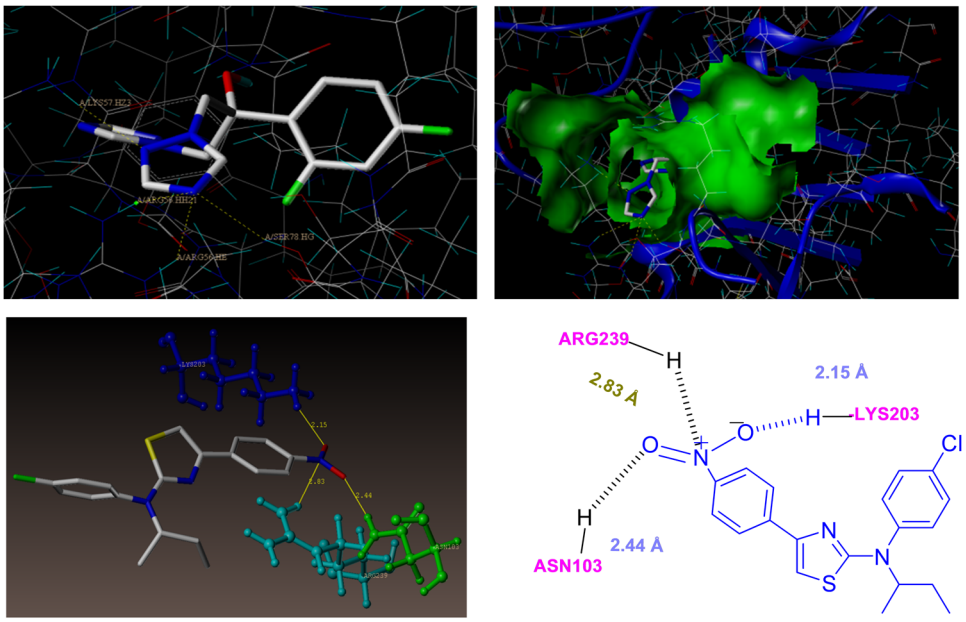



**Fig. 4** Docked view of compound **3d** at the active site of the enzyme PDB: 1AD4

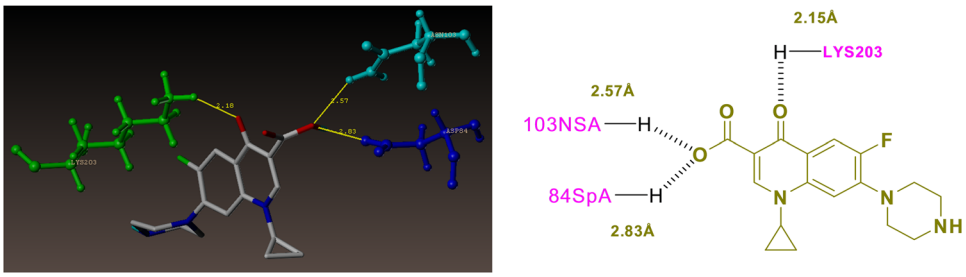



**Fig. 5** Interaction of ciprofloxacin at the binding site of the enzyme (PDB ID: 1AD4)

## Docking studies of the title compounds with *Candida albicans* dihydrofolate reductase (PDB ID: 1AI9)

The docking study revealed that all the compounds have very good docking score against *C. albicans*. Table 10 depicts their predicted binding energies and C-score values. Figure 6 represents the docked view of all the synthesized compounds at the active site of the enzyme PDB ID 1AI9. As depicted in Fig. 7 compound **3k** makes five hydrogen bonding interactions at the active site of the enzyme (PDB ID: 1AI9), among those two interactions were of oxygen atom of nitro group with hydrogen atoms of LYS57 (-O-H-LYS57; 1.98 and 2.50 Å), oxygen atom of nitro group makes an interaction with hydrogen atom of ARG56 (-O-H-ARG56; 2.56 Å), nitrogen atom of nitro group makes an interaction with hydrogen atom of LYS57 (-O-H-LYS57; 2.62 Å) and remaining another hydrogen bonding interaction raised from the nitrogen atom of thiazole ring with hydrogen of ARG79 (O-H-ARG79; 2.01 Å).

As depicted in Fig. 8 Fluconazole makes four hydrogen bonding interaction at the active site of the enzyme (PDB ID: 1AI9) and all the four hydrogen bonding interaction were raised from the nitrogen atom of triazole ring with hydrogen atom of amino acid residues SER78, LYS57, & ARG56 (-N-H-SER78; H-LYS57 & H-ARG56).

Compound **3b** makes three hydrogen bonding interactions at the active site of the enzyme (PDB ID: 1AI9), nitrogen atom of nitro group makes an interaction with hydrogen atom of LYS57 (-O-H-LYS57; 1.91 Å), oxygen atom of nitro group makes an interaction with hydrogen atom of LYS57 (-O-H-LYS57; 2.85 Å) and remaining another hydrogen bonding interaction raised from the nitrogen atom of thiazole ring with hydrogen of ARG79 (O-H-ARG79; 2.08 Å). [Fig. 3 and 4 in Supplementary data].

Also, the studied compounds have shown the same type of interaction with amino acid residue as that of fluconazole standard drug. The comparative molecular docking study of synthesized compounds and standard fluconazole drug highlighted that the synthesized compounds exhibited high C-score value. Fluconazole

**Table 10** Surflex docking score (kcal/mol) of the synthesized compounds **3a–3t** docked into the active site of the Candida albicans dihydrofolate reductase

| Compounds | C score[a] | Crash score[b] | Polar score[c] | D score[d] | PMF score[e] | G score[f] | Chem score[g] |
|---|---|---|---|---|---|---|---|
| Flucanazole | 5.30 | −2.19 | 1.85 | −65.170 | −9.240 | −232.46 | −8.9900 |
| 3k | 6.63 | −1.05 | 2.64 | −98.563 | −35.803 | −190.578 | −23.840 |
| 3c | 6.07 | −1.19 | 0.44 | −78.716 | −45.256 | −253.443 | −22.308 |
| 3a | 5.90 | −0.88 | 2.53 | −96.9080 | −33.218 | −190.098 | −24.194 |
| 3t | 5.90 | −2.97 | 0.14 | −138.236 | −3.0020 | −303.364 | −30.433 |
| 3b | 5.47 | −0.82 | 2.19 | −96.7850 | −36.453 | −190.700 | −24.158 |
| 3m | 5.25 | −2.83 | 1.19 | −112.018 | −25.505 | −250.974 | −25.976 |
| 3p | 5.03 | −1.43 | 0.89 | −73.6420 | −18.556 | −228.257 | −21.117 |
| 3o | 4.97 | −3.06 | 1.11 | −88.2650 | −31.763 | −257.743 | −22.679 |
| 3h | 4.40 | −1.26 | 0.00 | −96.0820 | 22.538 | −209.763 | −20.316 |
| 3i | 4.35 | −2.50 | 2.91 | −108.093 | −48.659 | −209.532 | −26.550 |
| 3l | 4.25 | −2.47 | 3.28 | −100.515 | −43.782 | −189.435 | −26.378 |
| 3e | 4.08 | −4.39 | 0.00 | −125.340 | −18.964 | −281.273 | −25.582 |
| 3i | 4.05 | −2.23 | 0.00 | −116.270 | −1.0150 | −243.366 | −26.488 |
| 3f | 3.70 | −1.39 | 0.03 | −91.3800 | 6.9150 | −201.692 | −20.579 |
| 3r | 3.49 | −1.47 | 0.91 | −101.165 | 25.574 | −195.363 | −21.877 |
| 3j | 3.45 | −4.21 | 0.03 | −112.921 | −45.163 | −300.537 | −24.305 |
| 3d | 3.17 | −1.59 | 0.01 | −91.9240 | 28.452 | −209.565 | −21.637 |
| 3s | 3.07 | −3.21 | 0.69 | −110.655 | 1.9300 | −241.681 | −24.223 |
| 3q | 2.38 | −1.39 | 0.14 | −89.9660 | 15.254 | −171.675 | −22.185 |
| 3g | 2.25 | −1.31 | 0.04 | −90.7530 | 9.2080 | −169.674 | −22.166 |

[a]C score (consensus score) integrates a number of popular scoring functions for ranking the affinity of ligand bound to the active site of a receptor and reports the output of total score

[b]Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to 0 are favorable. Negative numbers indicate penetration

[c]Polar indicating the contribution of the polar interactions to the total score. The polar score may be useful for excluding docking results that make no hydrogen bonds

[d]D-score for charge and van der Waals interactions between the protein and the ligand

[e]PMF-score indicating the Helmholtz free energies of interactions for protein-ligand atom pairs (Potential of Mean Force, PMF)

[f]G-score showing hydrogen bonding, complex (ligand-protein) and internal (ligand-ligand) energies

[g]Chem-score points for H-bonding, lipophilic contact and rotational entropy along with an intercept term

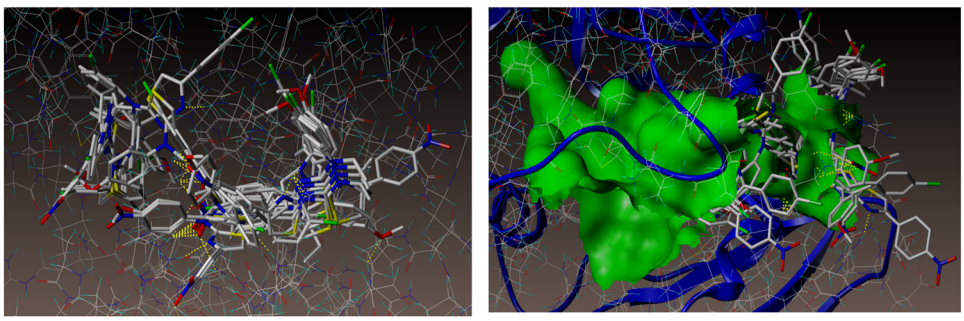


**Fig. 6** Docked view of all the compounds at the active site of the enzyme PDB ID: 1AI9

C-score value 5.30 whereas the five out of twenty compounds synthesized have higher C-score values than the Fluconazole. Thus, from these studies we corroborate the experimental findings, which suggest that N,4-diphenylthiazol-2-amine derivatives may act by inhibiting the dihydrofolate reductase enzyme.

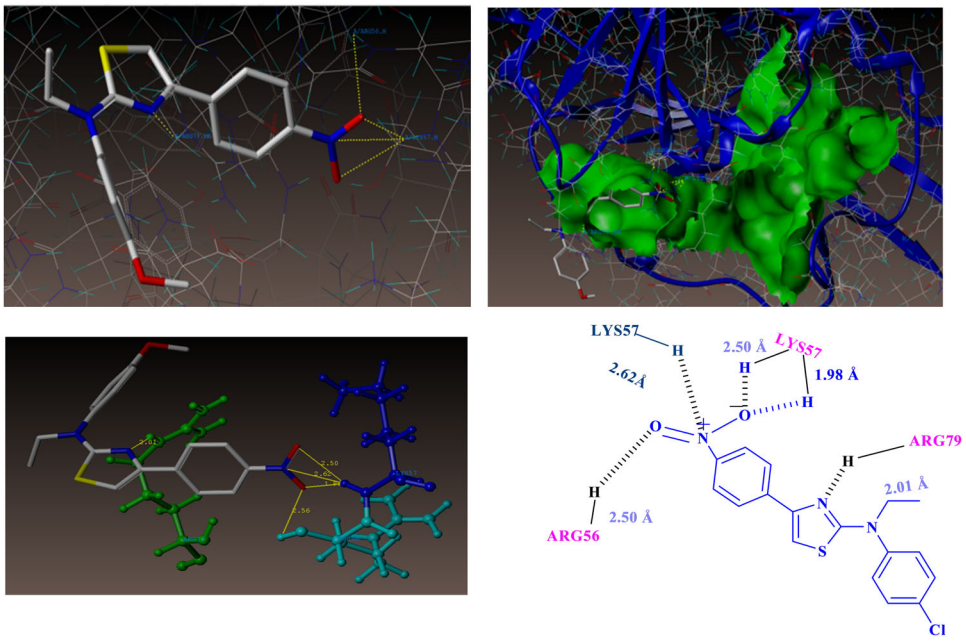



**Fig. 7** Docked view of compound **3k** at the active site of the enzyme PDB: 1AI9

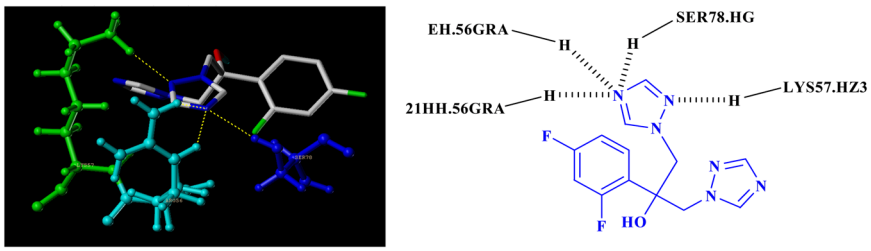



**Fig. 8** Interaction of fluconazole at the binding site of the enzyme (PDB ID: 1AI9)

## Conclusion

An efficient and simple synthetic protocol was employed for the synthesis of novel N,4-diphenylthiazol-2-amine derivatives employing Hantzsch method followed by nucleophilic substitution. The synthesized derivatives were characterized by analytical techniques such as $^{1}$H NMR, $^{13}$C NMR, FT-IR, GCMS and single-crystal X-ray diffraction study.

From the biological screening of N,4 diphenylthiazol-2-amine derivatives, it was found that most of the compounds appeared active against all the bacterial and fungal strains. Amongst the synthesized compounds 3a, 3e, 3k & 3m exhibited potent antifungal activity against all the four strains. The studied compounds showed same type of interaction with amino acid residue as that of standard drug Fluconazole and their comparative molecular docking study highlighted that the synthesized compounds exhibited high C-score value. Thus, from these studies we corroborate the experimental findings which suggest that derivatives may act by inhibiting the dihydrofolate reductase enzyme.

The compounds have shown moderate to good antibacterial activity against Gram-positive and Gram-negative strains. 3d and 3o have shown good activity comparatively than the rest of the compounds towards sensitive as well resistant strains. Docking studies have indicated their good binding profile. Most of the synthesized compounds have same H-bonding interaction with same amino acid LYS203 as that of Ciprofloxacin indicating similar mode of binding. The compounds 3o and 3j have shown good anti-inflammatory activity against aspirin as standard. The toxicity study of the active compounds has manifested them to be nontoxic against normal Human embryonic cell lines. Hence, these compounds can be considered as promising candidates to antimicrobial and anti-inflammatory agents.

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## Compliance with ethical standards

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

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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## References


Arora P, Narang R, Bhatia S, Nayak SK, Singh SK, Narasimhan B (2015) Synthesis, molecular docking and QSAR studies of 2, 4-disubstituted thiazoles as antimicrobial agents. J Appl Pharm Sci 5(02):028–042

Arora P, Narang R, Nayak SK, Singh SK, Judge V (2016) 2,4-Disubstituted thiazoles as multitargated bioactive molecules. Med Chem Res 25:1717–1743

Ayati A, Emami S, Asadipour A, Shafiee A, Foroumadi A (2015) Recent applications of 1,3-thiazole core structure in the identification of new lead compounds and drug discovery. Eur J Med Chem 97:699–718

Bikobo DSN, Vodnar DC, Stana A, Tiperciuc B, Nastasa C, Douchet MP, Oniga O (2017) Synthesis of 2-phenylamino-thiazole derivatives as antimicrobial agents. J Saudi Chem Soc 21:861–868

Cockerill FR, Wikler MA, Alder J, Dudley MN, Eliopoulos GM, Ferraro MJ, Hardy DJ, Hecht DW, Hindler JA, Patel JB, Powell M, Swenson JM, Thomson RB, Traczewski MM, Turnidge JD, Weinstein MP, Zimmer BL (2012) Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard. CLSI document M07-A9.9, 9 ed. C.L.S.I. (Clinical and Laboratory Standard Institute), Pennsylvania, PA, USA

Das D, Sikdar P, Bairagi M (2016) Recent developments of 2-aminothiazoles in medicinal chemistry. Eur J Med Chem 109:89–98

Das J, Chen P, Norris D, Padmanabha R, Lin J, Moquin RV, Shen Z, Cook LS, Doweyko AM, Pitt S, Pang S, Shen DR, Fang Q, de Fex HF, McIntyre KW, Shuster DJ, Gillooly KM, Behnia K, Schieven GL, Wityak J, Barrish JC (2006) 2-Aminothiazole as a novel kinase inhibitor template. Structure-activity relationship studies toward the discovery of N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl)]-2-methyl-4-pyrimidinyl]amino)]-1,3-thiazole-5-carboxamide (dasatinib, BMS-354825) as a potent pan-SRC kinase inhibitor. J Med Chem 49(23):6819–6832

De Souza MVN, De Almeida MV (2003) Drugs anti-HIV: past, present and future perspectives. Quím Nova 26:366–372

Dessen A, Di Guilmi AM, Vernet T, Dideberg O (2001) Molecular mechanisms of antibiotic resistance in gram-positive pathogens. Curr Drug Targets Infect Disord 1:63–77

Dighe SN, Chaskar PK, Jain KS, Phoujdar MS, Srinivasan KV (2011) A remarkably high-speed solution-phase combinatorial synthesis of 2-substituted-amino-4-aryl thiazoles in polar solvents in the absence of a catalyst under ambient conditions and study of their antimicrobial activities. ISRN Org Chem 434613:1–6

Dolomanov OV, Blake AJ, Champness NR, Schroder M (2003) OLEX: new software for visualization and analysis of extended crystal structures. J Appl Cryst 36:1283–1284

Fox LM, Saravolatz LD (2005) Nitazoxanide: a new thiazolide antiparasitic agent. Clin Infect Dis 40(8):1173–1180

Gasteiger J, Marsili M (1980) Iterative partial equalization of orbital electronegativity-a rapid access to atomic charges. Tetrahedron 36:3219–3228

Hantzsch A, Weber JH (1887) For compounds of thiazole (pyridine of the thiophene series). Chem Ber 20:3118–3132

Knadler MP, Bergstrom RF, Callaghan JT, Rubin A (1986) Nizatidine: an H2-blocker its metabolism and disposition in man. Drug Metab Dispos 14:175–182

Kumar P, Narasimhan B, Sharma D, Judge V, Narang R (2009) Hansch analysis of substituted benzoic acid benzylidene/furan-2-yl-methylene hydrazides as antimicrobial agents. Eur J Med Chem 44:1853–1863

Leelaprakash G, Dass SM (2011) Invitro anti-inflammatory activity of methanol extract of Enicostemma axillare. Int J Drug Dev Res 3 (3):189–196

Liaras K, Geronikaki AA, Glamoclija JM, Ciric A, Sokovic M (2011) Novel (E)-1-(4-methyl-2-(alkylamino)thiazol-5-yl)-3-arylprop-2-en-1-ones as potent antimicrobial agents. Bioorg Med Chem 19 (24):7349–7356

Muroi H, Nihei K, Tsujimoto K, Kubo I (2004) Synergistic effects of anacardic acids and methicillin against methicillin resistant Staphylococcus aureus. Bioorg Med Chem 12(3):583–587

Narang R, Narasimhan B, Sharma SK, Shriram D, Perumal Y, De Clercq E, Pannecouque C, Balzarini J (2011) Nicotinic acid benzylidene/phenyl-ethylidene hydrazides: synthesis, antitubercular, antiviral, antimicrobial evaluation and QSAR studies. Lett Drug Des Disco 8(8):733–749

Narang R, Narasimhan B, Sharma SK, Shriram D, Perumal Y, De Clercq E, Pannecouque C, Balzarini J (2012) Synthesis, antimycobacterial, antiviral, antimicrobial activities and QSAR studies of nicotinic acid benzylidene hydrazide derivatives. Med Chem Res 21(8):1–20

Narang R, Narasimhan B, Sharma SK(2012) (Naphthalen-1-yloxy)-acetic acid benzylidene/(1-phenyl-ethylidene)-hydrazide derivatives: synthesis, antimicrobial evaluation and QSAR studies. Med Chem Res 21:2526–2547

Nauen R, Kintscher UE, Salgado VL, Kaussmann M (2003) Thiamethoxam is a neonicotinoid precursor converted to clothianidin in insects and plants. Pest Biochem Physiol 76:55–69

Pasqualotto AC, Thiele KO, Goldani LZ (2010) Novel triazole antifungal drugs: focus on isavuconazole, ravuconazole and albaconazole. Curr Opin Investig Drugs 11(2):165–174

Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Peterson LE, Musser JM (2014) Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic resistant Gram negative bacteremia. J Infect 69(3):216–225

Pfeltz RF, Wilkinson BJ (2004) The escalating challenge of vancomycin resistance in Staphylococcus aureus. Curr Drug Targets Infect Disord 4(4):273–294

Roberts MC (2004) Distribution of macrolide, lincosamide, streptogramin, ketolide and oxazolidinone (MLSKO) resistance genes in Gram-negative bacteria. Curr Drug Targets Infect Disord 4(3):207–215

Sheldrick GM (1997) SHELXS97 and SHELXL97 program for crystal structure solution and refinement. University of Gottingen Germany

Siddiqui N, Arshad FM, Ahsan W, Alam MS (2009) Thiazoles: a valuable insight into the recent advances and biological activities. Int J Pharm Sci Drug Res 1(3):136–143

Smart and Saint Software Reference manuals (2001) Versions 6.28a & 5.625. Bruker Analytical X-ray Systems Inc., USA

Tenover FC, McDonald LC (2005) Vancomycin-resistant staphylococci and enterococci: epidemiology and control. Curr Opin Infect Dis 18(4):300–305

Tripos International (2012) Sybyl-X 2.0. Tripos International, St. Louis, MO, USA