



CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Convenient and efficient synthesis of some thiazole linked hydrazones and *in vitro* antimicrobial evaluation thereof

Satbir Mor* and Savita Nagoria

Department of Chemistry, Guru Jambheshwar University of Science & Technology, Hisar-125001, Haryana, India.

Phone No. +91-1662-263397; Fax No. +91-1662-276240

E-mail: satbir_mor@yahoo.co.in

Received 9 September 2015; Accepted 13 December 2015

Abstract: A convenient and efficient synthesis of a series of twelve new thiazole linked hydrazones (**3a–3l**) is described starting from 2-acyl-(1*H*)-indene-1,3(2*H*)-diones (**1**) *via* the formation of hydrazinecarbothioamides (**2a–2c**). The *in vitro* antimicrobial evaluation of the newly synthesized thiazole linked hydrazones was performed against four bacterial strains *i.e.* two Gram-positive bacteria *viz.* *Bacillus subtilis* (MTCC 441) & *Staphylococcus epidermidis* (MTCC 6880), two Gram-negative bacteria *viz.* *Escherichia coli* (MTCC 1652) & *Pseudomonas aeruginosa* (MTCC 424) and two fungal strains *viz.* *Candida albicans* (MTCC 227) & *Aspergillus niger* (MTCC 8189) by serial dilution technique. The derivatives **3b** and **3c** were found to exhibit better antibacterial activity than other tested compounds against *B. subtilis* and *S. epidermidis*. Investigation of antimicrobial data revealed that antibacterial activities were more prolific than antifungal activities.

Keywords: 2-Acyl-(1*H*)-indene-1,3(2*H*)-diones, Hydrazinecarbothioamides, Thiazole linked hydrazones, Antifungal, Antibacterial

1. Introduction

In the present scenario, pervasiveness of microbial infection is the major concern to public health worldwide. The probable reason for this problem is the rapid development of drug resistance and tolerance towards existing marketed drugs. Therefore, the discovery of more efficacious, safer and new antimicrobial therapeutic drugs having drug-resistant profiles

is one of the most challenging areas in medicinal chemistry research. In order to develop potential antimicrobial agents, enormous attempts have been centered on preparing libraries of small heterocyclic molecules owing to their high degree of structural variety and widespread efficacy as therapeutic agents. In particular, the pharmacoactive agents containing thiazole scaffolds have received considerable attention owing to their

occurrence in essential biologically active natural products such as thiamine, bacitracin, penicillin, and in various synthetic drugs, dyes, and manufacturing chemicals. Thiazole is a versatile bioactive motif incorporated in several synthetic drugs such as riluzole, fanetizole, sulfathiazole, ethoxzolamide, nizatidine, ritonavir, nitazoxanide, niridazole, meloxicam, cefdinir, tiazofurin, abafungin with trade name abasol cream and bleomycin, *etc.* Various thiazole derivatives have proved their efficacy in possessing anticonvulsant [1,2], analgesic [3], antimicrobial [4,5], psychotropic [5], anti-inflammatory [5–7], antitumor [8], antipyretic [9], anti-tubercular [10], anti-HIV [11], antioxidant [12], diuretic [13], anti-allergic [14], antihypertensive [15], anti-diabetic [16,17], FLT3 inhibitory [18], anaplastic lymphoma kinase (ALK) inhibitory [19] activities, *etc.* It was observed that thiazole motif coupled with other pharmacophores has resulted in increased biological activity. Therefore, coupling of thiazole nucleus with hydrazone moiety has turned out to be potential bioactive agents. For instance, thiazole linked hydrazones have been recognized as selective mitochondrial monoamine oxidase inhibitors (MAOI) [20–22]. They are also known to act as acetylcholinesterase inhibitors [23], antimicrobial [24–28], anticancer [29], antioxidant [30], anti-inflammatory [31] agents. Thiazole linked hydrazones are highly active against *Trypanosoma cruzi*, and have turned out to be a core structure for designing trypanocidal agents *via* the inhibition of *T. cruzi* cruzain (TCC) enzyme [32,33]. In addition, thiazole linked hydrazones are endowed with antiglycation [34], HIV-1 reverse transcriptase inhibitory [35] and histone acetyltransferase inhibitory [36] activities. As a consequence, various approaches have been developed for the synthesis of thiazole linked hydrazones [26,37–42].

Inspired by above facts and in continuation of our interest in the synthesis of bioactive

nitrogen and sulfur containing heterocyclic compounds [43–45], we report herein, convenient and efficient synthesis of twelve new thiazole linked hydrazones (**3a–3l**). All the newly synthesized thiazole linked hydrazones were well characterized and screened for their *in vitro* antimicrobial evaluation.

2. Materials and methods

2.1. Chemistry

All reagents were used as obtained from commercial suppliers without additional purification. Melting points (mp, °C) of all the synthesized compounds were determined on an electrothermal apparatus in open capillaries and are uncorrected. The purity of synthesized compounds was checked using precoated TLC plates (Merck Keisegel F₂₅₄) and visualization was attained *via* UV light. The FTIR spectra were recorded on IR affinity-1 FTIR (Shimadzu) spectrometer in KBr and wave numbers ($\nu_{\max}$) are reported in cm⁻¹. ¹H NMR and ¹³C NMR spectra were scanned on Bruker AVANCE II NMR spectrometer operating at 300/400 MHz using CDCl₃ as solvent and tetramethylsilane (TMS) as internal standard. Chemical shift (δ) values are expressed in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded on Waters Quadrupole Detector (TDQ) and elemental analyses were performed on Thermo Scientific FLASH-2000 CHN analyser. Analytical results for C, H, N and S were found to be within ± 0.4 % of the theoretical values.

2.2. General procedure for the synthesis of hydrazinecarbothioamides (2)

The 2-acyl-(1*H*)-indene-1,3(2*H*)-diones (**1**) needed for the purpose were prepared by the Claisen condensation of diethylphthlate and appropriate ketone under the influence of sodium methoxide according to the procedure as described in literature [46,47]. The hydrazinecarbothioamides (**2**) were obtained

by condensation of equimolar quantities of 2-acyl-(1*H*)-indene-1,3(2*H*)-diones (**1**) and thiosemicabazide in dry methanol [48]. The physical and spectral data of **2a–2c** are given as follows:

*2-(1-(1,3-Dioxo-2,3-dihydro-1*H*-inden-2-yl)-3-methylbutylidene)hydrazinecarbothioamide (2a)*

Yellow solid, yield 94%, mp 194–196°C; IR (KBr, cm⁻¹): $\nu_{\max}$ 1639 (C=N), 1690 (C=O), 3319 (N–H); ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.30 (d, 6H, *J* = 7.20 Hz, –CH(CH₃)₂), 2.68–2.72 (m, 1H, –CH(CH₃)₂), 7.63–7.74 (m, 4H, H-4, H-5, H-6, H-7), 11.96 (brs, 1H, OH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 18.62, 26.99, 102.55, 121.44, 121.84, 134.09, 134.27, 139.88, 140.29, 168.16, 184.27, 189.38, 193.40. ESI-MS *m/z*: (M + 1)⁺ 304.21. *Anal.* Calcd. for C₂₂H₁₉N₃O₂S (303.10): C, 59.38; H, 5.65; N, 13.85. Found: C, 59.15; H, 5.77; N, 13.92.

*2-(1-(1,3-Dioxo-2,3-dihydro-1*H*-inden-2-yl)butylidene)hydrazinecarbothioamide (2b)*

Yellow solid, yield 90%, mp 204–208°C; IR (KBr, cm⁻¹): $\nu_{\max}$ 1647 (C=N), 1686 (C=O), 3462 (N–H); ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.95 (d, 6H, *J* = 6.64 Hz, –CH₂CH(CH₃)₂), 1.97–2.03 (m, 1H, –CH₂CH(CH₃)₂), 2.89 (d, 2H, *J* = 7.28 Hz, –CH₂CH(CH₃)₂), 7.64–7.73 (m, 4H, H-4, H-5, H-6, H-7), 11.62 (brs, 1H, OH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 22.83, 28.27, 34.05, 103.23, 121.45, 121.74, 134.07, 134.21, 138.60, 140.09, 167.59, 183.15, 189.64, 193.36. ESI-MS *m/z*: (M + 1)⁺ 290.34. *Anal.* Calcd. for C₂₂H₁₉N₃O₂S (289.09): C, 58.11; H, 5.23; N, 14.52. Found: C, 57.98; H, 5.46; N, 14.70.

*2-(1-(1,3-Dioxo-2,3-dihydro-1*H*-inden-2-yl)-2-methylpropylidene)hydrazinecarbothioamide (2c)*

Yellow solid, yield 87%, mp 98–104°C; IR (KBr, cm⁻¹): $\nu_{\max}$ 1639 (C=N), 1676 (C=O), 3321, 3451 (N–H); ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.99 (t, 3H, –CH₂CH₂CH₃), 1.53–1.63 (m,

2H, –CH₂CH₂CH₃), 2.90 (t, 2H, –CH₂CH₂CH₃), 7.64–7.74 (m, 4H, H-4, H-5, H-6, H-7), 11.47 (brs, 1H, OH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 14.60, 21.43, 28.06, 102.03, 121.43, 121.70, 134.01, 134.17, 138.72, 140.09, 167.15, 183.26, 189.52, 193.35. ESI-MS *m/z*: (M + 1)⁺ 290.25. *Anal.* Calcd. for C₂₂H₁₉N₃O₂S (289.09): C, 58.11; H, 5.23; N, 14.52. Found: C, 57.95; H, 5.49; N, 14.75.

2.3. General procedure for the synthesis of thiazole linked hydrazones (**3**)

To a suspension of an appropriate hydrazinecarbothioamide (**2**) (5 mmol) and sodium acetate (0.41 g, 5 mmol) in dry methanol (30 mL) was added appropriate phenacyl bromide (5 mmol) slowly with stirring and the reaction mixture was gently refluxed for 30 min and then allowed to stand at room temperature. The solid thus obtained was filtered, washed and recrystallized from methanol to afford the corresponding thiazole linked hydrazones (**3a–3l**) in high yields. The physical and spectral data of **3a–3l** are given as follows:

*2-(3-Methyl-1-(2-(4-phenylthiazol-2-yl)hydrazono)butyl)-1*H*-indene-1,3(2*H*)-dione (3a)*

Orange solid (methanol), solid, yield 94%; mp 170–174°C; IR (KBr, cm⁻¹): $\nu_{\max}$ 754, 1086, 1331, 1483, 1568, 1632 (C=N), 1686 (C=O), 2872, 2964 (aliphatic C–H stretch), 3017, 3071 (aromatic C–H stretch), 3441 (N–H); ¹H NMR (300 MHz, CDCl₃): δ 1.08 (d, 6H, *J* = 6.60 Hz, –CH₂CH(CH₃)₂), 2.25–2.32 (m, 1H, –CH₂CH(CH₃)₂), 3.35 (d, 2H, *J* = 7.20 Hz, –CH₂CH(CH₃)₂), 4.91 (s, 1H, H-2), 6.81 (s, 1H, H-5'), 7.26–8.25 (m, 9H, H-4, H-5, H-6, H-7, H-5', H-2'', H-3'', H-4'', H-5'', H-6''), 13.16 (brs, 1H, NH, exchangeable with D₂O); ¹³C NMR (75 MHz, CDCl₃): δ 22.41 (–CH₂CH(CH₃)₂), 28.93 (–CH₂CH(CH₃)₂), 34.38 (–CH₂CH(CH₃)₂), 103.17, 105.78, 121.13, 121.57, 125.78, 128.51, 129.12, 131.67, 133.67, 133.27, 139.08, 140.29, 151.23, 167.35, 179.53, 190.15, 194.91; ESI-

MS m/z : $(M + 1)^+$ 404.38. *Anal.* Calcd. for $C_{23}H_{21}N_3O_2S$ (403.14): C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found: C, 68.65; H, 5.48; N, 10.17; S, 7.63.

2-(1-(2-(4-(4-Chlorophenyl)thiazol-2-yl)hydrazono)-3-methylbutyl)-1H-indene-1,3(2H)-dione (3b)

Orange solid (methanol), yield 97%; mp 178–180°C; IR (KBr, cm^{-1}): ν_{max} 744, 1090, 1339, 1489, 1578, 1632 (C=N), 1693 (C=O), 2899, 2955 (aliphatic C–H stretch), 3090 (aromatic C–H stretch), 3445 (N–H); ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, 6H, J = 6.60 Hz, $-CH_2CH(CH_3)_2$), 2.25–2.29 (m, 1H, $-CH_2CH(CH_3)_2$), 3.34 (d, 2H, J = 7.20 Hz, $-CH_2CH(CH_3)_2$), 4.87 (s, 1H, H-2), 6.85 (s, 1H, H-5'), 7.32–8.03 (m, 8H, H-4, H-5, H-6, H-7, H-2'', H-3'', H-5'', H-6''), 13.15 (brs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.43 ($-CH_2CH(CH_3)_2$), 28.96 ($-CH_2CH(CH_3)_2$), 34.41 ($-CH_2CH(CH_3)_2$), 103.21, 104.35, 121.08, 121.52, 127.18, 129.50, 131.98, 133.12, 133.41, 133.68, 139.03, 140.33, 151.36, 167.38, 179.56, 190.17, 194.95; ESI-MS m/z : $(M + 1)^+$ 438.43. *Anal.* Calcd. for $C_{23}H_{20}ClN_3O_2S$ (437.10): C, 63.08; H, 4.60; N, 9.59; S, 7.32. Found: C, 63.32; H, 4.91; N, 9.35; S, 7.06.

2-(3-Methyl-1-(2-(4-p-tolylthiazol-2-yl)hydrazono)butyl)-1H-indene-1,3(2H)-dione (3c)

Orange solid (methanol), yield 88%; mp 157–159°C; IR (KBr, cm^{-1}): ν_{max} 758, 1092, 1335, 1487, 1583, 1634 (C=N), 1676 (C=O), 2870, 2953 (aliphatic C–H stretch), 3036, 3065 (aromatic C–H stretch), 3454 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (d, 6H, J = 6.32 Hz, $-CH_2CH(CH_3)_2$), 2.28–2.32 (m, 1H, $-CH_2CH(CH_3)_2$), 2.45 (s, 3H, CH_3), 3.34 (d, 2H, J = 7.08 Hz, $-CH_2CH(CH_3)_2$), 4.87 (s, 1H, H-2), 6.85 (s, 1H, H-5'), 7.13–7.97 (m, 8H, H-4, H-5, H-6, H-7, H-2'', H-3'', H-5'', H-6''), 13.15 (brs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.83 (CH_3), 22.45 ($-$

$CH_2CH(CH_3)_2$), 28.95 ($-CH_2CH(CH_3)_2$), 34.40 ($-CH_2CH(CH_3)_2$), 103.24, 106.30, 121.10, 121.55, 128.95, 129.91, 131.79, 133.05, 133.34, 138.88, 139.00, 140.31, 151.46, 167.28, 179.58, 190.20, 194.94; ESI-MS m/z : $(M + 1)^+$ 418.35. *Anal.* Calcd. for $C_{24}H_{23}N_3O_2S$ (417.15): C, 69.04; H, 5.55; N, 10.06; S, 7.68. Found: C, 68.82; H, 5.62; N, 10.35; S, 7.45.

2-(1-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)-3-methylbutyl)-1H-indene-1,3(2H)-dione (3d)

Greenish yellow solid (methanol), yield 95%; mp 185–188°C; IR (KBr, cm^{-1}): ν_{max} 758, 1092, 1333, 1487, 1580, 1634 (C=N), 1686 (C=O), 2843, 2953 (aliphatic C–H stretch), 3011, 3074 (aromatic C–H stretch), 3472 (N–H); ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, 6H, J = 6.60 Hz, $-CH_2CH(CH_3)_2$), 2.23–2.32 (m, 1H, $-CH_2CH(CH_3)_2$), 3.35 (d, 2H, J = 7.50 Hz, $-CH_2CH(CH_3)_2$), 3.91 (s, 3H, OCH_3), 4.86 (s, 1H, H-2), 6.83 (s, 1H, H-5'), 7.00 (d, 2H, J = 9.00 Hz, H-3'', H-5''), 7.55–7.74 (m, 5H, H-4, H-5, H-6, H-7, H-5''), 8.04 (d, 2H, J = 8.70 Hz, H-2'', H-6''), 13.16 (brs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.45 ($-CH_2CH(CH_3)_2$), 28.97 ($-CH_2CH(CH_3)_2$), 34.42 ($-CH_2CH(CH_3)_2$), 55.62 (OCH_3), 103.23, 105.28, 114.55, 121.11, 121.54, 127.23, 131.08, 133.10, 133.38, 139.06, 140.28, 151.62, 159.50, 167.29, 179.48, 190.18, 194.93; ESI-MS m/z : $(M + 1)^+$ 434.22. *Anal.* Calcd. for $C_{24}H_{23}N_3O_3S$ (433.15): C, 66.49; H, 5.35; N, 9.69; S, 7.40. Found: C, 66.52; H, 5.78; N, 9.43; S, 7.68.

2-(1-(2-(4-Phenylthiazol-2-yl)hydrazono)butyl)-1H-indene-1,3(2H)-dione (3e)

Reddish orange solid (methanol), yield 87%; mp 188–192°C; IR (KBr, cm^{-1}): ν_{max} 754, 1092, 1342, 1362, 1493, 1587, 1634 (C=N), 1677 (C=O), 2868, 2963 (aliphatic C–H stretch), 3063, 3096 (aromatic C–H stretch), 3422 (N–H); ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, 3H, $-CH_2CH_2CH_3$), 1.75–1.84 (m, 2H, $-CH_2CH_2CH_3$), 3.40 (t, 2H, $-CH_2CH_2CH_3$), 4.90 (s, 1H, H-2), 6.75 (s, 1H, H-5'), 7.29–8.07 (m,

9H, H-4, H-5, H-6, H-7, H-2'', H-3'', H-4'', H-5'', H-6''), 13.02 (brs, 1H, NH, exchangeable with D₂O); ¹³C NMR (100 MHz, CDCl₃): δ 14.28 (–CH₂CH₂CH₃), 21.82 (–CH₂CH₂CH₃), 28.19 (–CH₂CH₂CH₃), 102.78, 103.91, 121.17, 121.60, 125.96, 128.54, 129.18, 131.79, 133.15, 133.47, 139.05, 140.34, 149.72, 167.83, 179.59, 190.17, 195.05; ESI-MS *m/z*: (M + 1)⁺ 390.21. *Anal.* Calcd. for C₂₂H₁₉N₃O₂S (389.12): C, 67.84; H, 4.92; N, 10.79; S, 8.23. Found: C, 67.98; H, 4.76; N, 10.92; S, 8.47.

2-(1-(2-(4-(4-Chlorophenyl)thiazol-2-yl)hydrazono)butyl)-1H-indene-1,3(2H)-dione (3f)

Yellow solid (methanol), yield 89%; mp 190–196°C; IR (KBr, cm^{–1}): ν_{max} 752, 1090, 1339, 1358, 1491, 1587, 1632 (C=N), 1693 (C=O), 2831, 2968 (aliphatic C–H stretch), 3091, 3180 (aromatic C–H stretch), 3429 (N–H); ¹H NMR (400 MHz, CDCl₃): δ 1.11 (t, 3H, –CH₂CH₂CH₃), 1.75–1.84 (m, 2H, –CH₂CH₂CH₃), 3.40 (t, 2H, –CH₂CH₂CH₃), 4.87 (s, 1H, H-2), 6.90 (s, 1H, H-5'), 7.33–8.03 (m, 8H, H-4, H-5, H-6, H-7, H-2'', H-3'', H-5'', H-6''), 13.02 (brs, 1H, NH, exchangeable with D₂O); ¹³C NMR (100 MHz, CDCl₃): δ 14.18 (–CH₂CH₂CH₃), 21.82 (–CH₂CH₂CH₃), 28.15 (–CH₂CH₂CH₃), 102.89, 104.26, 121.18, 121.65, 127.22, 129.57, 131.96, 133.14, 133.47, 133.64, 140.13, 140.36, 150.04, 167.82, 179.46, 190.14, 195.09; ESI-MS *m/z*: (M + 1)⁺ 424.35. *Anal.* Calcd. for C₂₂H₁₈ClN₃O₂S (423.08): C, 62.33; H, 4.28; N, 9.91; S, 7.56. Found: C, 62.54; H, 4.49; N, 9.78; S, 7.23.

2-(1-(2-(4-p-Tolylthiazol-2-yl)hydrazono)butyl)-1H-indene-1,3(2H)-dione (3g)

Orange solid (methanol), yield 86%; mp 214–218°C; IR (KBr, cm^{–1}): ν_{max} 754, 1088, 1342, 1362, 1493, 1582, 1634 (C=N), 1676 (C=O), 2870–2961 (aliphatic C–H stretch), 3100–3172 (aromatic C–H stretch), 3454 (N–H); ¹H NMR (400 MHz, CDCl₃): δ 1.11 (t, 3H, –CH₂CH₂CH₃), 1.75–1.84 (m, 2H, –CH₂CH₂CH₃), 2.45 (s, 3H, CH₃), 3.40 (t, 2H, –CH₂CH₂CH₃), 4.88 (s, 1H, H-2), 6.86 (s, 1H, H-5'), 7.29–7.98 (m, 8H, H-4,

H-5, H-6, H-7, H-2'', H-3'', H-5'', H-6''), 13.02 (brs, 1H, NH, exchangeable with D₂O); ¹³C NMR (100 MHz, CDCl₃): δ 14.21 (–CH₂CH₂CH₃), 21.80 (CH₃), 21.85 (–CH₂CH₂CH₃), 28.19 (–CH₂CH₂CH₃), 102.68, 103.06, 121.12, 121.57, 128.96, 129.93, 131.71, 133.06, 133.36, 138.71, 139.06, 140.39, 151.00, 167.78, 179.60, 190.19, 195.04; ESI-MS *m/z*: (M + 1)⁺ 404.18. *Anal.* Calcd. for C₂₃H₂₁N₃O₂S (403.14): C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found: C, 68.23; H, 5.58; N, 10.23; S, 8.22.

2-(1-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)butyl)-1H-indene-1,3(2H)-dione (3h)

Greenish yellow solid (methanol), yield 88%; mp 216–220°C; IR (KBr, cm^{–1}): ν_{max} 748, 1088, 1337, 1358, 1491, 1582, 1636 (C=N), 1684 (C=O), 2872, 2964 (aliphatic C–H stretch), 3001, 3069 (aromatic C–H stretch), 3447 (N–H); ¹H NMR (400 MHz, CDCl₃): δ 1.11 (t, 3H, –CH₂CH₂CH₃), 1.73–1.84 (m, 2H, –CH₂CH₂CH₃), 3.40 (t, 2H, –CH₂CH₂CH₃), 3.91 (s, 3H, OCH₃), 4.86 (s, 1H, H-2), 6.59 (s, 1H, H-5'), 7.00 (2H, d, *J* = 8.72 Hz, H-3'', H-5''), 7.55–7.73 (m, 4H, H-4, H-5, H-6, H-7), 8.04 (d, 2H, *J* = 8.72 Hz, H-2'', H-6''), 13.03 (brs, 1H, NH, exchangeable with D₂O); ¹³C NMR (100 MHz, CDCl₃): δ 14.19 (–CH₂CH₂CH₃), 21.76 (–CH₂CH₂CH₃), 28.18 (–CH₂CH₂CH₃), 55.64 (OCH₃), 102.57, 103.24, 114.56, 121.52, 127.17, 131.09, 133.00, 133.29, 139.06, 140.32, 151.54, 159.50, 167.67, 179.80, 190.18, 195.00; ESI-MS *m/z*: (M + 1)⁺ 420.33. *Anal.* Calcd. for C₂₃H₂₁N₃O₃S (419.13): C, 65.85; H, 5.05; N, 10.02; S, 7.64. Found: C, 65.63; H, 5.32; N, 10.34; S, 7.91.

2-(2-Methyl-1-(2-(4-phenylthiazol-2-yl)hydrazono)propyl)-1H-indene-1,3(2H)-dione (3i)

Orange solid (methanol), yield 91%; mp 198–200°C; IR (KBr, cm^{–1}): ν_{max} 748, 1103, 1333, 1491, 1580, 1647 (C=N), 1690 (C=O), 2852, 2914 (aliphatic C–H stretch), 3057, 3109 (aromatic C–H stretch), 3441 (N–H); ¹H NMR

(400 MHz, CDCl_3): δ 1.36 (d, 6H, $J = 7.08$ Hz, $-\text{CH}(\text{CH}_3)_2$), 2.70–2.83 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 4.47 (s, 1H, H-2), 6.81 (s, 1H, H-5'), 7.10–7.90 (m, 9H, H-4, H-5, H-6, H-7, H-2'', H-3'', H-4'', H-5'', H-6''), 13.44 (brs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (100 MHz, CDCl_3): δ 18.74 ($-\text{CH}(\text{CH}_3)_2$), 29.70 ($-\text{CH}(\text{CH}_3)_2$), 98.10, 104.57, 121.16, 121.53, 125.61, 128.52, 129.08, 131.63, 133.12, 133.37, 139.06, 140.17, 151.24, 169.19, 180.06, 193.85, 196.21; ESI-MS m/z : ($M + 1$)⁺ 340.37. *Anal.* Calcd. for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$ (389.12): C, 67.84; H, 4.92; N, 10.79; S, 8.23. Found: C, 67.63; H, 4.89; N, 10.94; S, 8.38.

2-(1-(2-(4-(4-Chlorophenyl)thiazol-2-yl)hydrazono)-2-methylpropyl)-1H-indene-1,3(2H)-dione (3j)

Yellowish orange solid (methanol), yield 94%; mp 176–178°C; IR (KBr, cm^{-1}): ν_{max} 766, 1090, 1325, 1360, 1475, 1585, 1643 (C=N), 1711 (C=O), 2874, 2974 (aliphatic C–H stretch), 3065, 3101 (aromatic C–H stretch), 3456 (N–H); ^1H NMR (400 MHz, CDCl_3): δ 1.36 (d, 6H, $J = 7.08$ Hz, $-\text{CH}(\text{CH}_3)_2$), 2.86–2.96 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 4.38 (s, 1H, H-2), 6.89 (s, 1H, H-5'), 7.29–7.84 (m, 8H, H-4, H-5, H-6, H-7, H-2'', H-3'', H-5'', H-6''), 13.16 (brs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (100 MHz, CDCl_3): δ 18.75 ($-\text{CH}(\text{CH}_3)_2$), 28.69 ($-\text{CH}(\text{CH}_3)_2$), 98.10, 104.30, 121.09, 121.20, 127.06, 128.97, 131.87, 132.90, 133.28, 133.72, 139.01, 140.03, 151.48, 169.39, 179.58, 193.84, 194.79; ESI-MS m/z : ($M + 1$)⁺ 424.26. *Anal.* Calcd. for $\text{C}_{22}\text{H}_{18}\text{ClN}_3\text{O}_2\text{S}$ (423.08): C, 62.33; H, 4.28; N, 9.91; S, 7.56. Found: C, 62.50; H, 4.52; N, 9.72; S, 7.32.

2-(2-Methyl-1-(2-(4-p-tolylthiazol-2-yl)hydrazono)propyl)-1H-indene-1,3(2H)-dione (3k)

Orange solid (methanol), yield 86%; mp 178–182°C; IR (KBr, cm^{-1}): ν_{max} 737, 820, 1080, 1308, 1360, 1466, 1572, 1634 (C=N), 1680 (C=O), 2876, 2974 (aliphatic C–H stretch), 3076 (aromatic C–H stretch), 3449 (N–H); ^1H NMR (400 MHz, CDCl_3): δ 1.52 (d, 6H, $J = 7.08$ Hz,

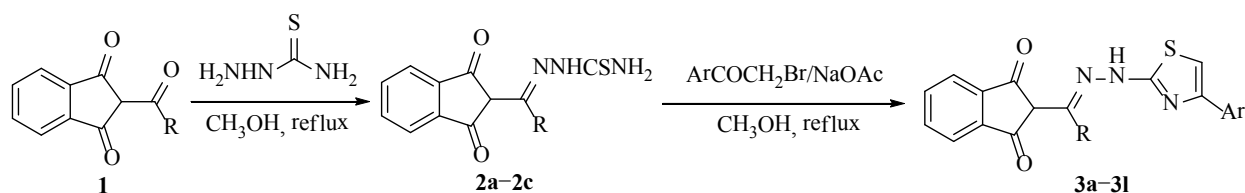
$-\text{CH}(\text{CH}_3)_2$), 2.44 (s, 3H, CH_3), 2.88–2.94 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 4.87 (s, 1H, H-2), 6.86 (s, 1H, H-5'), 7.31 (d, 2H, $J = 8.24$ Hz, H-3'', H-5''), 7.55–7.73 (m, 4H, H-4, H-5, H-6, H-7), 7.96 (d, 2H, $J = 8.04$ Hz, H-2'', H-6''), 13.47 (brs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (100 MHz, CDCl_3): δ 18.66 ($-\text{CH}(\text{CH}_3)_2$), 21.82 (CH_3), 29.70 ($-\text{CH}(\text{CH}_3)_2$), 98.12, 101.97, 121.01, 121.59, 128.93, 129.88, 131.80, 133.01, 133.33, 138.83, 139.12, 140.20, 151.12, 169.08, 179.57, 194.10, 195.59; ESI-MS m/z : ($M + 1$)⁺ 404.31. *Anal.* Calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$ (403.14): C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found: C, 68.17; H, 5.46; N, 10.19; S, 8.28.

2-(1-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)-2-methylpropyl)-1H-indene-1,3(2H)-dione (3l)

Orange solid (methanol), yield 92%; mp 183–186°C; IR (KBr, cm^{-1}): ν_{max} 735, 835, 1076, 1310, 1360, 1462, 1580, 1632 (C=N), 1680 (C=O), 2841, 2937 (aliphatic C–H stretch), 3003, 3074 (aromatic C–H stretch), 3451 (N–H); ^1H NMR (400 MHz, CDCl_3): δ 1.36 (d, 6H, $J = 7.08$ Hz, $-\text{CH}(\text{CH}_3)_2$), 2.87–2.94 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.88 (s, 3H, OCH_3), 4.37 (s, 1H, H-2), 6.77 (s, 1H, H-5'), 7.00 (d, 2H, $J = 8.88$ Hz, H-3'', H-5''), 7.51–7.81 (m, 4H, H-4, H-5, H-6, H-7), 7.84 (d, 2H, $J = 8.88$ Hz, H-2'', H-6''), 13.45 (brs, 1H, NH, exchangeable with D_2O); ^{13}C NMR (100 MHz, CDCl_3): δ 18.64 ($-\text{CH}(\text{CH}_3)_2$), 28.68 ($-\text{CH}(\text{CH}_3)_2$), 55.61 (OCH_3), 98.15, 102.02, 114.51, 120.97, 121.55, 127.41, 131.06, 132.97, 133.28, 138.83, 140.17, 151.71, 159.52, 169.31, 178.97, 194.96, 195.56; ESI-MS m/z : ($M + 1$)⁺ 420.52. *Anal.* Calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$ (419.13): C, 65.85; H, 5.05; N, 10.02; S, 7.64. Found: C, 65.58; H, 5.29; N, 10.27; S, 7.85.

2.4. *In vitro* antimicrobial evaluation

All the newly synthesized twelve thiazole linked hydrazones (**3a–3l**) were assessed for their *in vitro* antimicrobial activity against four bacterial strains *i.e.* two Gram-positive bacteria *viz.* *Bacillus subtilis* (MTCC 441) &



Compounds	R	Ar	Compounds	R	Ar
a	<i>i</i> -Butyl	C ₆ H ₅	g	<i>n</i> -Propyl	4-CH ₃ -C ₆ H ₄
b	<i>i</i> -Butyl	4-Cl-C ₆ H ₄	h	<i>n</i> -Propyl	4-OCH ₃ -C ₆ H ₄
c	<i>i</i> -Butyl	4-CH ₃ -C ₆ H ₄	i	<i>i</i> -Propyl	C ₆ H ₅
d	<i>i</i> -Butyl	4-OCH ₃ -C ₆ H ₄	j	<i>i</i> -Propyl	4-Cl-C ₆ H ₄
e	<i>n</i> -Propyl	C ₆ H ₅	k	<i>i</i> -Propyl	4-CH ₃ -C ₆ H ₄
f	<i>n</i> -Propyl	4-Cl-C ₆ H ₄	l	<i>i</i> -Propyl	4-OCH ₃ -C ₆ H ₄

Scheme 1. Synthetic protocol for thiazole linked hydrazones (**3a–3l**).

Staphylococcus epidermidis (MTCC 6880), two Gram-negative bacteria viz. *Escherichia coli* (MTCC 1652) & *Pseudomonas aeruginosa* (MTCC 424) and two fungal strains viz. *Candida albicans* (MTCC 227) & *Aspergillus niger* (MTCC 8189). The antimicrobial evaluation was performed by employing serial dilution technique [49]. Initially, stock solutions were prepared by dissolving weighed amounts of synthesized compounds in DMSO (1.0 mg of the test compound in 10 mL DMSO) to get a final concentration of 100 µg/mL. Fresh cultures were obtained by inoculation of respective microorganisms in suitable media viz. nutrient broth for bacterial strains and potato dextrose broth for fungal strains, followed by incubation at 37 ± 1 °C for 24 h (all bacteria), 25 ± 1 °C for 7 days (*A. niger*) and 37 ± 1 °C for 48 h (*C. albicans*). The stock solutions of the test compounds were then serially diluted in test tubes containing 1 mL of sterile medium to get the concentrations of 50–0.39 µg/mL. Then 100 µL of the respective microorganism in sterile saline was inoculated to different dilutions of test compounds (each dilution in triplicates). The inoculated test tubes were incubated at 37 ± 1 °C for 24 h (bacteria), 25 ± 1 °C for 7 days (*A. niger*) and 37 ± 1 °C for 48 h (*C. albicans*). Ciprofloxacin and Fluconazole were used as reference antibacterial and antifungal drugs, respectively, which were also assessed

under similar conditions for comparison with the tested compounds. After incubation, microbial growth was monitored visually and spectrophotometrically and the results were recorded in terms of Minimum Inhibitory Concentration (MIC, µmol/mL).

3. Results and discussion

3.1. Chemistry

The synthetic protocol for the preparation of thiazole linked hydrazones (**3**) is presented in **Scheme 1**. The synthesis of twelve new thiazole linked hydrazones (**3**) was carried out starting from 2-acyl-(1*H*)-indene-1,3(2*H*)-diones (**1**), which in turn, were synthesized in accordance with the method described in literature [46,47]. Reaction of appropriate 2-acyl-(1*H*)-indene-1,3(2*H*)-diones (**1**) with thiosemicarbazide resulted in the formation of corresponding hydrazinecarbothioamides (**2**) [48] which upon subsequent treatment with phenacyl bromide or its derivatives in dry ethanol afforded the corresponding target thiazole linked hydrazones (**3**) in high yields.

The structures of all the newly synthesized compounds i.e. hydrazinecarbothioamides (**2**) and thiazole linked hydrazones (**3**) were established by satisfactory spectral (IR, ¹H

NMR, ^{13}C NMR and mass) data. The IR spectra of hydrazinecarbothioamides (**2**) displayed absorption bands in the regions at 1639–1647 cm^{-1} , 1676–1690 cm^{-1} and 3319–3462 cm^{-1} due respectively to $>\text{C}=\text{N}-$, $>\text{C}=\text{O}$ and $\text{N}-\text{H}$ stretching. The ^1H NMR and ^{13}C NMR spectra of hydrazinecarbothioamides (**2**) exhibited signals due to different protons and carbons, respectively in the expected regions (*vide experimental*).

The IR spectra of thiazole linked hydrazones (**3**) displayed absorption bands of medium intensity in the region at 3422–3456 cm^{-1} ($\text{N}-\text{H}$ stretching) and sharp absorptions in the regions at 1677–1693 cm^{-1} and 1632–1647 cm^{-1} due to $>\text{C}=\text{O}$ and $>\text{C}=\text{N}-$ stretching, respectively. The ^1H NMR spectra of hydrazones (**3**), C_5-H of thiazolyl moiety was observed as singlet in the region at δ 6.59–6.90 in **3e–3l**, however, in **3a–3d**, it got merged with other aromatic protons and was not appeared separately while the signal due to C_2-H was appeared as singlet in the region at δ 4.37–4.91. The signals due to the remaining aliphatic and aromatic protons were found in expected regions. The ^{13}C NMR spectral data of thiazole linked hydrazones (**3**) were obtained in expected regions. Further, the

results obtained from mass spectral analysis and analytical data of thiazole linked hydrazones (**3**) were found in accordance with their molecular formulae (*vide experimental*).

3.2. *In vitro* antimicrobial evaluation

The newly synthesized thiazole linked hydrazone derivatives (**3a–3l**) were assessed for their *in vitro* antimicrobial activity against two Gram-positive bacterial strains *viz.* *Bacillus subtilis* (MTCC 441) and *Staphylococcus epidermidis* (MTCC 6880), two Gram-negative bacterial strains *viz.* *Escherichia coli* (MTCC 1652) and *Pseudomonas aeruginosa* (MTCC 424), and two fungal strains *viz.* *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 8189). Serial dilution technique was employed to carry out *in vitro* antimicrobial evaluation [49]. Ciprofloxacin and Fluconazole were used as reference drugs for antibacterial and antifungal evaluation, respectively. The results were recorded in terms of Minimum Inhibitory Concentration (MIC, $\mu\text{mol/mL}$). The data for the antibacterial activity are presented in **Table 1** and **Figure 1**, and results of antifungal activity are depicted in **Table 1** and **Figure 2**. The results of antibacterial

Table 1. *In vitro* antimicrobial activity of thiazole linked hydrazones (**3a–3l**).

Compounds	Minimum Inhibitory Concentration (MIC) ^a					
	<i>B. subtilis</i> ^b	<i>S. epidermidis</i> ^c	<i>E. coli</i> ^d	<i>P. aeruginosa</i> ^e	<i>C. albicans</i> ^f	<i>A. niger</i> ^g
3a	0.0155	0.0310	0.0155	0.0310	0.0310	0.0620
3b	0.0071	0.0071	0.0285	0.0143	0.0285	0.0285
3c	0.0075	0.0075	0.0299	0.0150	0.0299	0.0599
3d	0.0144	0.0144	0.0288	0.0144	0.0288	0.0577
3e	0.0321	0.0321	0.0160	0.0642	0.0321	0.0321
3f	0.0295	0.0590	0.0295	0.0295	0.0295	0.0590
3g	0.0310	0.0155	0.0310	0.0310	0.0310	0.0310
3h	0.0149	0.0149	0.0149	0.0298	0.0298	0.0298
3i	0.0321	0.0160	0.0321	0.0321	0.0160	0.0321
3j	0.0147	0.0147	0.0295	0.0147	0.0295	0.0295
3k	0.0310	0.0155	0.0620	0.0155	0.0155	0.0310
3l	0.0149	0.0298	0.0149	0.0298	0.0298	0.0298
Ciprofloxacin	0.0047	0.0047	0.0047	0.0047	-	-
Fluconazole	-	-	-	-	0.0051	0.0102

^a Unit: $\mu\text{mol/mL}$

^b *Bacillus subtilis* (MTCC 441)

^c *Staphylococcus epidermidis* (MTCC 6880)

^d *Escherichia coli* (MTCC 1652)

^e *Pseudomonas aeruginosa* (MTCC 424)

^f *Candida albicans* (MTCC 227)

^g *Aspergillus niger* (MTCC 8189)

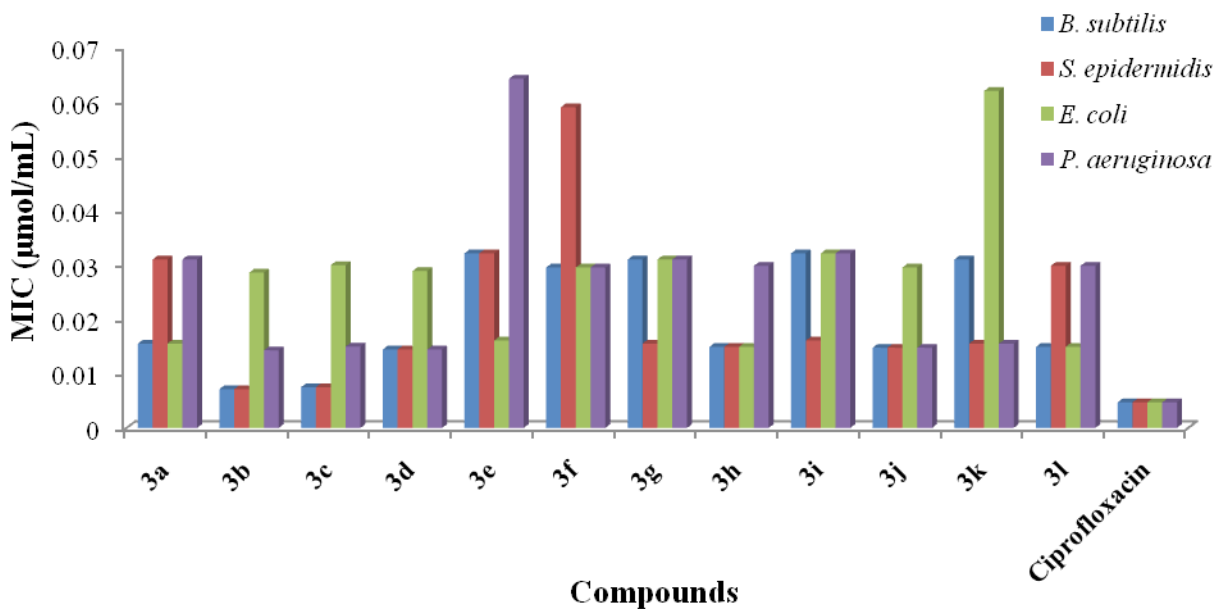


Figure 1. Graphical representation of *in vitro* antibacterial activity of thiazole linked hydrazones (3a–3l).

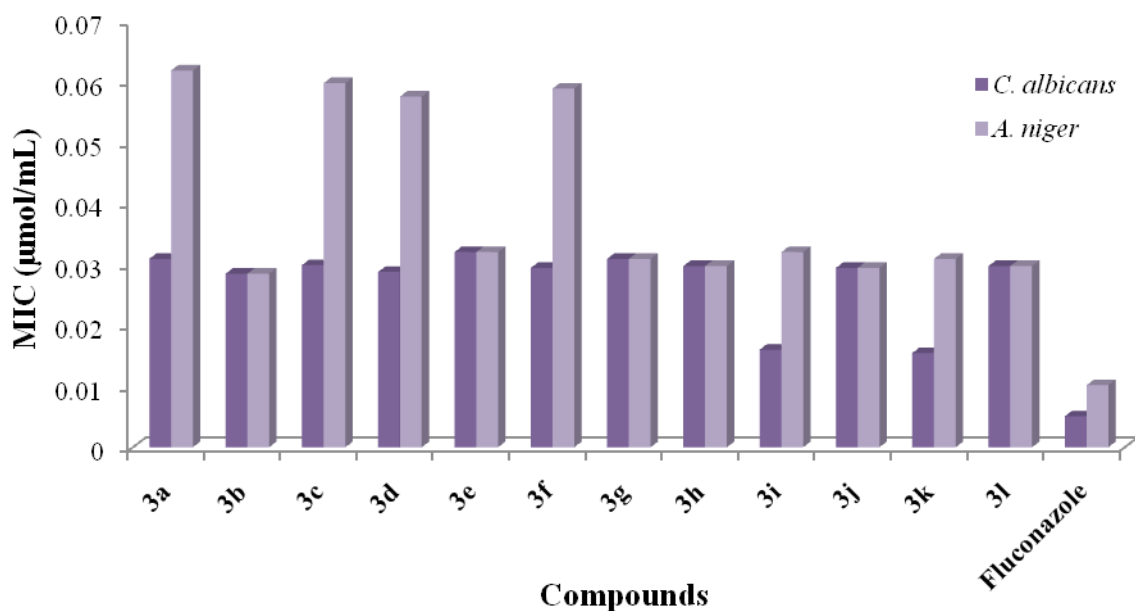


Figure 2. Graphical representation of *in vitro* antifungal activity of thiazole linked hydrazones (3a–3l).

evaluation summarized in **Table 1** and **Figure 1** revealed that the derivatives **3a–3d**, **3h**, **3j** and **3l** against *B. subtilis*; **3b–3d** and **3g–3k** against *S. epidermidis*; **3a**, **3e** and **3l** against *E. coli*, and **3b–3d**, **3j** and **3k** against *P. aeruginosa* were found to be moderately active as compared to the standard drug *i.e.* Ciprofloxacin. The results of antifungal evaluation presented in **Table 1** and **Figure 2** revealed that the derivatives **3i** and **3k** exhibited moderate activity against *C. albicans* as compared to reference drug *i.e.* Fluconazole. Among all the tested derivatives, both **3b** and **3c** exhibited better antibacterial activity against *B. subtilis* and *S. epidermidis*. However, all the tested derivatives were found to exhibit less inhibitory activity as compared to reference drugs *i.e.* Ciprofloxacin and Fluconazole. Moreover, comparison of antibacterial and antifungal evaluation results revealed that the antibacterial activities are more prolific than antifungal activities.

From the above antimicrobial results, following structure activity relationships (SAR) may be inferred-

1. The presence of *i*-butyl moiety improved the antibacterial efficacy against *S. epidermidis*, *E. coli* and *P. aeruginosa*.
2. The presence of 4-methoxyphenyl at thiazole ring enhanced the antibacterial activity against all the tested bacterial strains in most of the cases.
3. In some cases, presence of 4-methylphenyl moiety at thiazole ring improved the antimicrobial activity against *B. subtilis*, *S. epidermidis*, *P. aeruginosa* and *C. albicans*.
4. In most of the cases, presence of 4-chlorophenyl moiety at thiazole ring where R = *i*-butyl and *i*-propyl, increased the antimicrobial potency against all the tested microbial strains.

These results lead to the conclusion that there are different structural requirements for a compound to be effective against different

microbial strains. However, no general trend towards structure activity relationship (SAR) has been established for antimicrobial activity of the tested thiazole linked hydrazones (**3**).

4. Conclusion

In conclusion, twelve new thiazole linked hydrazones (**3**) have been conveniently synthesized in high yields and characterized by using different spectral techniques. The newly synthesized thiazole linked hydrazones (**3**) were evaluated for *in vitro* antimicrobial activity against four bacterial and two fungal strains. Among the synthesized derivatives, both **3b** and **3c** exhibited better activity against *B. subtilis* and *S. epidermidis*. Moreover, antibacterial activities were found to be more prolific than antifungal activities.

Acknowledgements

We gratefully acknowledge the financial support from University Grants Commission, New Delhi, India. Authors are thankful to Dr. Anil Kumar, Assistant Professor, Department of Bio & Nano Technology, Guru Jambheshwar University of Science & Technology, Hisar, for his assistance to carry out antimicrobial evaluation.

References

1. M. F. Arshad, N. Siddiqui, A. Elkerdasy, A. H. Alrohaimi, S. A. Khan, Am. J. Pharmacol. Toxicol., **2014**, 9, 132-138.
2. S. Malik, R. S. Bahare, S. A. Khan, Eur. J. Med. Chem., **2013**, 67, 1-13.
3. S. N. Thore, S. V. Gupta, K. G. Bhahetui, Med. Chem. Res., **2013**, 23, 3802-3811.
4. N. D. Gaikwad, S. V. Patil, V. D. Bobade, J. Hetrocycl. Chem., **2013**, 50, 519-527.
5. A. Zablotskaya, I. Segal, A. Geronikaki, T. Eremkina, S. Belyakov, M. Petrova, I. Shestakova, L. Zvejniece, V. Nikolajeva, Eur. J. Med. Chem., **2013**, 70, 846-856.
6. L. D. Khillare, M. R. Bhosle, A. R. Deshmukh, R. A. Mane, Med. Chem. Res., **2015**, 24, 1380-1386.
7. P. P. Bhosale, R. S. Chavan, A. V. Bhosale, Indian J. Chem. Sect. B., **2012**, 51, 1649-1654.

8. L. Gu, C. Jin, *Org. Biomol. Chem.*, **2012**, 10, 7098-7102.
9. R. Pignatello, S. Mazzone, A. M. Panico, G. Mazzone, G. Penissi, R. Castana, M. Matera, G. Blandino, *Eur. J. Med. Chem.*, **1991**, 26, 929-938.
10. P. Samadhiya, R. Sharma, S. K. Srivastava, *Bull. Chem. Soc. Ethiop.*, **2013**, 27, 249-263.
11. R. K. Rawal, R. Tripathi, S. B. Katti, C. Pannecouque, E. D. Clercq, *Eur. J. Med. Chem.*, **2008**, 43, 2800-2806.
12. M. H. Shih, Y. S. Su, C. L. Wu, *Chem. Pharm. Bull.*, **2007**, 55, 1126-1135.
13. A. Andreani, M. Rambaldi, G. Mascellani, P. Rugarli, *Eur. J. Med. Chem.*, **1987**, 22, 19-22.
14. K. D. Hargrave, F. K. Hess, J. T. Oliver, *J. Med. Chem.*, **1983**, 26, 1158-1163.
15. W. C. Patt, H. W. Hamilton, M. D. Taylor, M. J. Ryan, D. G. Taylor Jr., C. J. C. Connolly, A. M. Doherty, S. R. Klutchko, I. Sircar, B. A. Steinbaugh, B. L. Batley, C. A. Painchaud, S. T. Rapundalo, B. M. Michniewicz, S. C. J. Olson, *J. Med. Chem.*, **1992**, 35, 2562-2572.
16. G. Navarrete-Vazquez, M. G. Morales-Vilchis, S. Estrada-Soto, J. J. Ramirez-Espinosa, S. Hidaigo-Figueroa, C. Nava-Zuazo, H. Tlahuext, I. Leon-Rivera, J. L. Medina-Franco, Fabian Lopez-Vallejo, S. P. Webster, M. Binnie, R. Ortiz-Andrade, H. Moreno-Diaz, *Eur. J. Med. Chem.*, **2014**, 74, 179-186.
17. V. S. Patil, K. P. Nandre, S. Ghosh, V. J. Rao, B. A. Chopade, B. Sridhar, S. V. Bhosale, *Eur. J. Med. Chem.*, **2013**, 59, 304-309.
18. C. T. Chen, J. T. A. Hsu, W. H. Lin, C. T. Lu, S. C. Yen, T. Hsu, Y. L. Huang, J. S. Song, C. H. Chen, L. H. Chou, K. J. Yeh, W. T. Jiaang, *Eur. J. Med. Chem.*, **2015**, 100, 151-161.
19. Z. Liu, X. Yue, Z. Song, X. Peng, J. Guo, Y. Ji, Z. Cheng, J. Ai, M. Geng, A. Zhang, *Eur. J. Med. Chem.*, **2014**, 56, 438-448.
20. S. Distinto, M. Yanez, S. Alcaro, M. C. Cardia, M. Gaspari, M. L. Sanna, R. Meleddu, F. Ortuso, J. Kirchmair, P. Markt, A. Bolasco, G. Wolber, D. Secci, E. Maccioni, *Eur. J. Med. Chem.*, **2012**, 48, 284-295.
21. F. Chimenti, D. Secci, A. Bolasco, P. Chimenti, A. Granese, S. Carradori, E. Maccioni, M. C. Cardia, M. Yanez, F. Orallo, S. Alcaro, F. Ortuso, R. Cirilli, R. Ferretti, S. Distinto, J. Kirchmair, T. Langer, *Bioorg. Med. Chem.*, **2010**, 18, 5063-5070.
22. F. Chimenti, D. Secci, A. Bolasco, P. Chimenti, A. Granese, S. Carradori, M. D'Ascenzio, M. Yanez, F. Orallo, *Med. Chem. Commun.*, **2010**, 1, 61-72.
23. Y. Ozkay, L. Yurttas, U. A. Mohsen, B. Sever, W. Hussein, O. Ozturk, B. N. Saglik, U. Acar, O. N. Erdogan, A. Pekbag Z. A. Kaplancikli, *MUSBED*, **2014**, 4, 38-42.
24. J. Q. Weng, C. X. Tan, X. H. Liu, *J. Pestic. Sci.*, **2012**, 37, 164-168.
25. J. J. F. Xavier, R. Venkateswaramoorthi, A. Kamaraj, K. Krishnasamy, *Med. Chem. Res.*, **2013**, 22, 5105-5111.
26. G. Turan-Zitouni, A. Ozdemir, Z. A. Kaplancikli, J. A. Fehrentz, J. Martinez, P. Chevallet, G. Dusart, *Phosphorus, Sulfur Silicon Relat Elem.*, **2009**, 184, 2613-2623.
27. R. Mohil, D. Kumar, S. Mor, *J. Heterocycl. Chem.*, **2014**, 51, 203-211.
28. R. Anbazhagan, K. R. Sankaran, *Spectrochim. Acta. Mol. Bimol. Spectrosc.*, **2015**, 135, 984-993.
29. M. D. Altıntop, A. Ozdemir, G. Turan-Zitouni, S. Ilgin, O. Atli, F. Demirci, Z. A. Kaplancikli, *Molecules*, **2014**, 19, 14809-14820.
30. C. Nastasa, B. Tiperciuc, M. Duma, D. Benedec, O. Oniga, *Molecules*, **2015**, 20, 17325-17338.
31. C. M. Moldovan, O. Oniga, A. Parvu, B. Tiperciuc, P. Verite, A. Pimau, O. Crisan, M. Bojita, R. Pop, *Eur. J. Med. Chem.*, **2011**, 46, 526-534.
32. M. V. O. Cardoso, L. R. P. de Siqueira, E. B. da Silva, L. B. Costa, M. Z. Hernandez, M. M. Rabello, R. S. Ferreira, L. F. da Cruz, D. R. M. Moreira, V. R. A. Pereira, M. C. A. de Castro, P. V. Bernhardt, A. C. L. Leite, *Eur. J. Med. Chem.*, **2014**, 86, 48-59.
33. M. E. Caputto, A. Ciccarelli, F. Frank, A. G. Moglioni, G. Y. Moltrasio, D. Vega, E. Lombardo, L. M. Finkielstein, *Eur. J. Med. Chem.*, **2012**, 55, 155-163.
34. K. M. Khan, M. Irfan, M. Ashraf, M. Taha, S. M. Saad, S. Perveen, M. I. Choudhary, *Med. Chem. Res.*, **2015**, 24, 3077-3085.
35. R. Meleddu, S. Distinto, A. Corona, G. Bianco, V. Cannas, F. Esposito, A. Artese, S. Alcaro, P. Matyus, D. Bogdan, F. Cottiglia, E. Tramontano, E. Maccioni, *Eur. J. Med. Chem.*, **2015**, 93, 452-460.
36. S. Carradori, D. Rotili, C. D. Monte, A. Lenoci, M. D'Ascenzio, V. Rodriguez, P. Filetici, M. Miceli, A. Nebbioso, L. Altucci, D. Secci, A. Mai, *Eur. J. Med. Chem.*, **2014**, 80, 569-578.
37. F. Chimenti, B. Bizzarri, E. Maccioni, D. Secci, A. Bolasco, R. Fioravanti, P. Chimenti, A. Granese, S. Carradori, D. Rivanera, D. Lilli, A. Zicari, S. Distinto, *Bioorg Med Chem Lett.*, **2007**, 17, 4635-4640.
38. G. Turan-Zitouni, A. Ozdemir, Z. A. Kaplancikli, K. Benkli, P. Chevallet, G. Akalin, *Eur. J. Med. Chem.*, **2008**, 43, 981-985.
39. M. Z. Hernandez, M. M. Rabello, A. C. L. Leite, M. V. O. Cardoso, D. R. M. Moreira, D. J. Brondani, C. A. Simone, L. C. Reis, M. A. Souza, V. R. A. Pereira, R. S. Ferreira, J. H. McKerrow, *Bioorg. Med. Chem.*, **2010**, 18, 7826-7835.
40. D. Castagnolo, M. Pagano, M. Bernardini, M. Botta, *Synlett*, **2009**, 2093-2096.
41. F. Chimenti, B. Bizzarri, A. Bolasco, D. Secci, P. Chimenti, S. Carradori, A. Granese, D. Rivanera, N. Frishberg, C. Bordon, L. J. Brando, *J. Med. Chem.*, **2009**, 52, 4574-4577.
42. E. S. Ramadan, *Chin. J. Chem.*, **2010**, 28, 594-600.
43. S. Mor, R. Mohil, D. Kumar, M. Ahuja, *Med. Chem. Res.*, **2012**, 21, 3541-3548.
44. S. Mor, P. Pahal, B. Narasimhan, *Eur. J. Med. Chem.*, **2012**, 53, 176-189.

45. S. Mor, P. Pahal, B. Narasimhan, Eur. J. Med. Chem., **2012**, 57, 196-210.
46. L. Shapiro, K. Geiger, L. Freedman, J. Org. Chem., **1960**, 25, 1860-1865.
47. S. N. Dhawan, S. Dasgupta, S. Mor, S. C. Gupta, Indian J. Heterocycl. Chem., **1993**, 2, 155-158.
48. K. N. Sawhney, T. L. Lemke, J. Org. Chem., **1983**, 48, 4326-4328.
49. M. A. Mosaddik, M. E. Haque, Phytother. Res., **2003**, 17, 1155-1157.