J. Chem. Sci. Vol. 124, No. 2, March 2012, pp. 469–481.

Synthesis, antioxidant and antimicrobial evaluation of thiazolidinone, azetidinone encompassing indolylthienopyrimidines

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MS received 26 March 2011; revised 22 July 2011; accepted 8 August 2011

Abstract. Various 2-amino-N′-{3-(2′,5′-disubstituted-1H-indol-3′-yl)methylene}-4,5-dimethylthieno-3-carbohydrazides (**3**) synthesized by condensation of 2-amino-4,5-dimethyl thiophene-3-carbohydrazide (**2**) with 2,5- disubstituded indole-3-carboxaldehyde (**1**). The Schiff's base (**3**) on cyclocondensation with acetic anhydride and triethyl orthoformate afforded thienopyrimidine analogues (**4**) and (**7**), respectively. Compounds 4 or 7 on cyclization with thioglycolic acid and chloroacetyl chloride gave thiazolidin-4-ones (**5**) or (**8**) and azitidin-2-ones (**6**) or (**9**) respectively. The structures of these newly synthesized compounds have been established on the basis of their spectral data and elemental analysis. Some of the compounds exhibited promising antioxidant and antimicrobial activities.

Keywords. Indole; thienopyrimidine; thiazolidin-4-one; azetidin-2-one; antioxidant; antimicrobial activities.

1. Introduction

The complex sequence of cellular and molecular changes that take place during cancer formation are mediated by the different endogenous and exogenous stimuli.[1] Among endogenous stimuli are intermediates of oxygen reduction, i.e., *oxygen free radicals* (OFR), or more generally, *reactive oxygen species* (ROS), which interact with DNA, forming various aducts. OFRs are important in the pathogenesis of many different diseases.[2–5] ROS are also involved in the processes of aging. In food, rancidity is one of the major concerns and is mainly related to oxidative degradation of polyunsaturated fatty acids. For years, antioxidants have been used to prevent the degradation of food.[6] Phenolic derivatives are one of the most effective and commonly used antioxidants. These derivatives slow down the degradation of food ingredients by inhibiting their oxidation.[7,8] Among this family of compounds, both synthetic antioxidants for example BHT, BHA, TBHQ and natural ones such as tocopherols, phenolic acids, and herbal extracts are used to protect against oxidative degradation. Although synthetic antioxidants have shown good efficiency, their use has been limited because of their possible detrimental effect on human health.[6] As a consequence, there is a growing interest in the development of new antioxidants that are based on natural components and with low toxicity.

Heterocyclic compounds are highly ranked among pharmaceutically important natural and synthetic materials. The remarkable ability of heterocyclic nuclei to serve as both biomimetics and active pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. It is well known that, indole derivative extensively present in natural products, are very important substances for their medicinal and biological aspects. Malatonin (MLT)[9] is a highly conserved molecule that it acts as a free radical scavenger and a broad spectrum antioxidant.[10] It is known to be a potent *in vitro* antioxidant as well as powerful *in vivo* radical scavenger. Indole nucleus is frequently found in medicinal chemistry and is considered as privileged scaffolds. Indole analogues constitute an important class of therapeutic agents in medicinal chemistry including anticancer,[11] antioxidant,[12] anti-rheumatoidal,[13] anti-HIV,[14] and also play a vital role in the immune system.[15,16] Many indole derivatives considered as the most potent scavengers of free radicals.[17]

The thiophene ring is bioisosteric replacement for the phenyl group broadly present in active drugs, the thiophene core exists in many natural and synthetic

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pharmaceuticals,[18,19] tuberculosis[20] and antimicrobial drugs.[21]

The molecular manipulation of promising lead compounds is still a major line of approach to develop new drugs. It involves an effort to combine the separate pharmacophoric groups of similar activity into one compound, thus making structural changes in the biological activity. As reported earlier the thiazolidinone ring present in a large number of biologically active molecules of different pharmacological classes exhibited different activities. The historical importance of thiazolidine derivative, i.e., the development of penicillin which shows the presence of thiazoline ring. There has been substantial interest in the chemistry of thiazolidin-4-one ring systems, which is the core structure in a variety of synthetic pharmaceuticals with a broad spectrum of biological activity,[22] such as anti-mycobacterial,[23] antifungal,[24] anti-cancer,[25] anti-tuberculosis,[26] anti-convulsant,[27] anti-edematous,[28] anti-diarrhea,[29] anti-HIV,[30,31] anti-platelet-activating factor,[32] antidiabetic,[33] antihistaminic,[34] cyclooxygenase inhibitors, lipoxygenase inhibitors,[35] anti-inflammatory and analgesic[36] activity. In addition, a large number of antibiotics contain the 2-azetidinone (commonly known as β-lactam) moiety[37] such as penicillin, cephalosporin and carbapenem. It is also associated with a variety of therapeutic activities.[38–42]

Due to the diversified nature of indole, thienopyrimidine, thiazolidin-4-one and 2-azetidinones which render them useful substance in drug research. In continuation of our search for novel biologically active indole derivatives,[43,44] in this paper we report the synthesis, antioxidant and antibacterial activities of the title compounds and its derivatives.

2. Experimental

All the reagents were obtained commercially and used by further purification. Melting points were determined by an open capillary method and are uncorrected. The IR (KBr) spectra were recorded with a Perkin-Elmer spectrum one FT-IR spectrometer. The ^{1}HNMR (500 MHz) and ^{13}C NMR (125 MHz) (DMSO-d_6) spectra recorded with an Bruker NMR (500 Mz) and the chemical shifts were expressed in ppm (δ scale) downfield from TMS. Mass spectra were recorded with a JEOL GCMATE II GC-MS mass spectrometer. Elemental analysis carried out using Flash EA1112 series elemental analyzer.

2.1 *2-Amino-4,5-dimethyl-thiophene-3-carbohydrazide (**2**)*

2-Amino-4,5-dimethyl-thiophene-3-carbohydrazide (**2**) was prepared by following reported method.[45]

2.2 *2-Amino-4,5-dimethyl-3-{N^1-[(2′-phenyl-5′-substituted 1H-indol-3′-yl)methylene]}thieno-3-carbohydrazides (**3a–c**)*

A mixture of hydrazide **(2)** (0.001 mol) and the respective 2,-phenyl-5-substituted indole-3-caroxaldehydes[46] (**1 a–c**) (0.001 mol) in ethanol (30 ml) was refluxed for 3 h and then left to cool. The solid formed was collected by filtration and recrystallized from ethanol to give compounds **3a–c**.

2.2a *2-Amino-4,5-dimethyl-3-{N^1-[(2′-phenyl-5′-chloro-1H-indol-3′-yl)methylene]}thieno-3-carbohydrazide (**3a**)*: Yellow powder, Yield 0.31 g (72%), m. p. 125–126°C; IR (KBr) ν cm^{-1} 3404 (NH_2), 3301 (indole NH), 3170 (NH), 1645 (CO), 1598 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (s, 1H, indole NH), 9.9 (s, 1H, NH), 8.9 (s, 1H, CH=N), 7.1–8.0 (m, 10H, 8 ArH and NH_2), 2.7 (s, 3H, 5-CH_3), 2.3 (s, 3H, 4-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.4, 14.1, 114.1, 121.5, 122.5, 125.6, 126.7, 128.5, 129.3, 130.1, 133.2, 134.3, 134.6, 134.9, 138.2, 140.2, 142.6, 142.7, 168.2, 171.2; EI-MS; m/z 422, 424; Anal. calcd. for $C_{22}H_{19}N_4OSCl$: C 62.56; H, 4.50; N, 13.27. Found: C,62.77; H4.33; N, 13.51.

2.2b *2-Amino-4,5-dimethyl-3-{N^1-[(2′-phenyl-5′-methy3–1H-indol-3′-yl)methylene]}thieno-3-carbohydrazide (**3b**)*: Yellow powder, Yield 0.281 g (70%), m. p. 144–145°C; IR (KBr) ν cm^{-1} 3406 (NH_2), 3309 (indole NH), 3176 (NH), 1645 (CO) 1599 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.4 (s, 1H, indole NH), 9.8 (s, 1H, NH), 8.9 (s, 1H, CH=N), 7.0–8.0 (m, 10H, 8 ArH and NH_2), 2.8 (s, 3H, 5-CH_3), 2.5 (s, 3H, 5′-CH_3), 2.2 (s, 3H, 4-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 13.5, 14.3, 24.2, 114.5, 122.0, 123.1, 125.1, 126.9, 128.8, 129.7, 130.4, 133.6, 134.3, 134.6, 134.9, 140.0, 140.7, 142.0, 143.1, 168.6, 171.6; Anal. calcd. for $C_{23}H_{22}N_4OS$: C 68.66; H, 5.47; N, 13.93. Found: C, 68.47; H, 5.29; N, 14.05.

2.2c *2-Amino-4,5-dimethyl-3-{N^1-[(2′-phenyl-5′-1H-indol-3′-yl)methylene]}thieno-3-carbohydrazide (**3c**)*: Yellow powder, Yield 0.275 g (71%), m. p. 130–131°C; IR (KBr) ν cm^{-1} 3402 (NH_2), 3305 (indole NH), 3172 (NH), 1648 (CO) 1602 (C=N); ^{1}H NMR (500 MHz,

DMSO-d_6) δ 11.3 (s, 1H, indole NH), 9.8 (s, 1H, NH), 8.8 (s, 1H, CH=N), 7.1–7.9 (m, 11H, 9 ArH and NH_2), 2.7 (s, 3H, 5-CH_3), 2.4 (s, 3H, 4-CH_3); Anal. calcd. for $C_{22}H_{20}N_4OS$: C 68.04; H, 5.14; N, 14.43. Found: C, 68.13; H, 5.27; N, 14.29.

2.3 *2,5,6-Trimethyl-3-[(2′-phenyl-5′-substituted 1H-indol-3′-yl)methyleneamino]thieno[2,3-d]pyrimidin-4(3H)-ones (**4a–c**)*

Compound **3** (0.001 mol) in acetic anhydride (18 ml) were heated under reflux for 6 h and cooled to room temperature. The precipitated solid was collected and recrystallized from 1,4-dioxane.

2.3a *2,5,6-Trimethyl-3-[(2′-phenyl-5′-chloro-lH-indol-3′-yl)methyleneamino]-thieno[2,3-d]pyrimidin-4(3H)-one (**4a**)*: Yellow powder, Yield 0.29 g (65%), m. p. 185–186°C; IR (KBr) ν cm^{-1} 3301 (indole NH), 1648 (CO), 1598 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.3 (s, 1H, indole NH), 9.1 (s, 1H, CH=N), 7.1–7.9 (m, 8H, ArH), 3.2 (s, 3H, 2-CH_3), 2.8 (s, 3H, 6-CH_3), 2.4 (s, 3H, 5-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 13.2, 14.3, 16.2, 114.2, 121.4, 122.5, 125.7, 126.6, 128.4, 129.0, 130.4, 130.8, 130.9, 133.2, 134.4, 134.6, 134.9, 142.1, 142.5, 143.8, 150.6, 172.8; EI-MS; m/z 446, 448; Anal. calcd. for $C_{24}H_{19}N_4OSCl$: C 64.57; H, 4.26; N, 12.56. Found: C, 64.71; H, 4.41; N, 12.31.

2.3b *2,5,6-Trimethyl-3-[(2′-phenyl-5′-methyl-lH-indol-3′-yl)methyleneamino]-thieno[2,3-d]pyrimidin-4(3H)-one (**4b**)*: Pale yellow powder, Yield 0.276 g (65%), m. p. 162–163°C; IR (KBr) ν cm^{-1} 3305 (indole NH), 1646 (CO), 1595 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.4 (s, 1H, indole NH), 9.0 (s, 1H, CH=N), 7.0–7.9 (m, 8H, ArH), 3.3 (s, 3H, 2-CH_3), 2.8 (s, 3H, 6-CH_3), 2.5 (s, 3H, 5′-CH_3), 2.3 (s, 3H, 5-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 13.3, 14.2, 16.6, 24.5, 114.3, 121.6, 122.8, 125.9, 126.9, 128.2, 129.1, 130.0, 130.5, 131.1, 133.4, 134.5, 134.9, 135.2, 142.3, 142.5, 143.5, 150.8, 172.3; Anal. calcd. for $C_{25}H_{22}N_4OS$: C 70.42; H, 5.16; N, 13.14. Found: C, 70.55; H, 5.21; N, 13.05.

2.3c *2,5,6-Trimethyl-3-[(2′-phenyl-5′-lH-indol-3′yl)methyleneamino]-thieno[2,3-d]pyrimidin-4(3H)-one (**4c**)*: Pale yellow powder, Yield 0.26 g (63%), m. p. 179–180°C; IR (KBr) ν cm^{-1} 3307 (indole NH), 1652 (CO), 1599 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.3 (s, 1H, indole NH), 9.1 (s, 1H, CH=N), 7.1–8.0 (m, 9H, ArH), 3.3 (s, 3H, 2-CH_3), 2.7 (s, 3H, 6-CH_3), 2.2 (s, 3H, 5-CH_3); EI-MS; Anal. calcd. for $C_{22}H_{20}N_4OS$: C 69.90; H, 4.85; N, 13.59. Found: C, 70.03; H, 4.97; N, 13.45.

2.4 *2,5,6-Trimethyl-3-[2-(2′-phenyl-5′-substituted lH-indol-3′-yl)-4-oxothiazolidin-3-yl]thieno[2,3-d]pyrimidin-4(3H)-ones (**5 a–c**)*

To a solution of compound **4** in methanol containing catalytic amount of anhydrous zinc chloride, thioglycolic acid (0.001 mol) was added drop-wise at room temperature and the reaction mixture was refluxed for 10 h the excess methanol was distilled off, the residue was cooled to room temperature and decomposed in ice cold water. The product that separated was filtered, washed with water, dried and recrystallized from ethanol.

2.4a *2,5,6-Trimethyl-3-[2-(2′-phenyl-5′-chloro-1H-indol-3-yl)-4-oxothiazolidin-3-yl]thieno[2,3-d]pyrimidin-4(3H)-one (**5a**)*: Yellow crystals, Yield 0.374 g (72%), m. p. 201–202°C; IR (KBr) ν cm^{-1} 3313 (indole NH), 1681 (CH_2CO), 1645 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.6 (s, 1H, indole NH), 10.0 (s, 1H, CH-N), 7.0–7.9 (m, 8H, ArH), 4.1 (s, 2H, CH_2CO), 3.2 (s, 3H, 2-CH_3), 2.7 (s, 3H, 6-CH_3), 2.3 (s, 3H, 5-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 12.8, 13.7, 16.7, 35.7, 107.1, 113.8, 121.5, 122.6, 125.4, 126.4, 129.0, 129.3, 130.2, 130.5, 130.8, 133.1, 134.2, 134.5, 134.9, 143.5, 143.8, 149.9,. 168.7, 172.7; EI-MS; m/z 520, 522; Anal. calcd. for $C_{26}H_{21}N_4O_2S_2Cl$: C 60.00; H, 4.04; N, 10.77. Found: C, 60.21; H, 4.32; N, 10.52.

2.4b *2,5,6-Trimethyl-3-[2-(2′-phenyl-5′methyl-1H-indol-3-yl)-4-oxothiazolidin-3-yl]thieno[2,3-d]pyrimidin-4(3H)-one (**5b**)*: Pale yellow crystals, Yield 0.35 g (70%), m. p. 191–192°C; IR (KBr) ν cm^{-1} 3308 (indole NH), 1685 (CH_2CO), 1647 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (s, 1H, indole NH), 10.1 (s, 1H, CH-N), 7.1–8.1 (m, 8H, ArH), 4.0 (s, 2H, CH_2CO), 3.1 (s, 3H, 2-CH_3), 2.6 (s, 3H, 6-CH_3), 2.5 (s, 3H, 5′-CH_3), 2.2 (s, 3H, 5-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 13.1, 14.1, 16.8, 24.3, 35.5, 107.3, 113.7, 121.4, 122.7, 125.4, 126.5, 129.1, 129.4, 130.2, 130.6, 130.7, 133.2, 134.1, 134.5, 134.7, 143.4, 143.7, 149.8, 168.5, 172.8; Anal. calcd. for $C_{27}H_{24}N_4O_2S_2$: C 64.80; H, 4.80; N, 11.12. Found: C, 64.97; H, 4.57; N, 11.37.

2.4c *2,5,6-Trimethyl-3-[2-(2′-phenyl-1H-indol-3-yl)-4-oxothiazolidin-3-yl]thieno[2,3-d]pyrimidin-4(3H)-one (**5c**)*: Pale yellow powder, Yield 0.315 g (65%),

m. p. 186–187°C; IR (KBr) ν cm^{-1} 3310 (indole NH), 1683 (CH_2CO), 1649 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.4 (s, 1H, indole NH), 10.0 (s, 1H, CH-N), 7.0–8.0 (m, 9H, ArH), 4.1 (s, 2H, CH_2CO), 3.2 (s, 3H, 2-CH_3), 2.6 (s, 3H, 6-CH_3), 2.3 (s, 3H, 5-CH_3); Anal. calcd. for $C_{26}H_{22}N_4O_2S_2$: C 64.20; H, 4.53; N, 11.52. Found: C, 64.37; H, 4.67; N, 11.37.

2.5 *2,5,6-Trimethyl-3-[3-chloro-2-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-4-oxoazetidin-1-yl]-thieno[2,3-d]pyrimidin-4(3H)-ones (**6a–c**)*

A mixture of compound 4 (0.001 mol) and triethyl amine (0.001 mol) was dissolved in methanol (20 ml) and cooled to 0°C. To this well cooled solution, chloroacetylchloride (0.001 mol) was added drop-wise during 30 min with stirring at 0°C. The reaction mixture was further stirred for 1 h and refluxed for 12 h. The triethyl amine hydrochloride salt formed was removed by filtration. The filtrate was concentrated to its half volume, cooled to room temperature and poured on to crushed ice. The product was obtained was filtered, washed with water and recrystallized from ethanol.

2.5a *2,5,6-Trimethyl-3-[3-chloro-2-(2′-phenyl-5′-chloro-1H-indol-3′-yl)-4-o xoazetidin-1-yl]-thieno[2,3-d]pyrimidin-4(3H)-one (**6a**)*: Brown powder, Yield 0.36 g (69%), m. p. 210–211°C; IR (KBr) ν cm^{-1} 3301 (indole NH), 1720 (CHCO), 1645 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (s, 1H, indole NH), 10.0 (d, 1H, CH-N), 6.9–7.8 (m, 8H, ArH), 5.6 (d, 1H, CHCl), 3.2 (s, 3H, 2-CH_3), 2.7 (s, 3H, 6-CH_3), 2.3 (s, 3H, 5-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 13.2, 14.2, 16.7, 82.5, 106.3, 113.1, 113.7, 121.5, 122.5, 125.6, 126.1, 128.1, 129.1, 130.4, 130.5, 130.7, 134.1, 134.6, 134.9, 142.4, 143.8, 150.1, 160.6, 172.7; EI-MS; m/z 522, 524, 526; Anal. calcd. for $C_{26}H_{20}N_4O_2SCl_2$: C, 59.77; H, 3.83; N, 10.73. Found: C, 59.99; H, 3.71; N, 10.95.

2.5b *2,5,6-Trimethyl-3-[3-chloro-2-(2′-phenyl-5′-methyl-1H-indol-3′-yl)-4-oxoazetidin-1-yl]-thieno[2,3-d]pyrimidin-4(3H)-one (**6b**)*: Brown powder, Yield 0.342 g (68%), m. p. 214–215°C; IR (KBr) ν cm^{-1} 3309 (indole NH), 1725 (CHCO), 1653 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.4 (s, 1H, indole NH), 10.1 (d, 1H, CH-N), 7.0–7.9 (m, 8H, ArH), 5.7 (d, 1H, CHCl), 3.3 (s, 3H, 2-CH_3), 2.7 (s, 3H, 6-CH_3), 2.4 (s, 3H, 5′-CH_3), 2.2 (s, 3H, 5-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 13.1, 14.5, 16.8, 24.8, 82.3, 105.2, 106.2, 113.2, 113.8, 121.6, 122.4, 125.5, 126.3, 128.2, 129.1, 130.5, 130.6,130.8, 134.0, 134.5, 134.8, 142.4, 143.5, 160.5, 172.8; Anal. calcd. for $C_{27}H_{23}N_4O_2SCl$: C, 64.54; H, 4.58; N, 11.16. Found: C, 64.71; H, 4.43; N, 11.29.

2.5c *2,5,6-Trimethyl-3-[3-chloro-2-(2′-phenyl-1H-indol-3-yl)-4-oxoazetidin-1-yl]-thieno[2,3-d]pyrimidin-4(3H)-one (**6c**)*: Brown powder, Yield 0.3 g (62%), m. p. 199–200°C; IR (KBr) ν cm^{-1} 3305 (indole NH), 1728 (CHCO), 1649 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (s, 1H, indole NH), 10.0 (d, 1H, CH-N), 6.9–8.0 (m, 9H, ArH), 5.6 (d, 1H, CHCl), 3.3 (s, 3H, 2-CH_3), 2.7 (s, 3H, 6-CH_3), 2.2 (s, 3H, 5-CH_3); Anal. calcd. for $C_{26}H_{21}N_4O_2SCl$: C, 63.93; H, 4.30; N, 11.48. Found: C, 63.87; H, 4.17; N, 11.61.

2.6 *5,6-Dimethyl-3-[(2′-phenyl-5′-substituted 1H-indol-3′-yl)methyleneamino]-thieno[2,3-d]pyrimidin-4(3H)-ones (**7 a–c**)*

A mixture of **3a–c** (0.001) and triethyl orthoformate (5 ml) in acetic anhydride (10 ml) was heated under reflux for 7 h and then allowed to cool. The product separated was collected and recrystallized from ethanol.

2.6a *5,6-Dimethyl-3-[(2′-phenyl-5′-chloro-1H-indol-3′-yl)methyleneamino]-thieno[2,3-d]pyrimidin-4(3H)-one (**7a**)*: Yellow powder, Yield 0.315 g (73%), m. p. 175–176°C; IR (KBr) ν cm^{-1} 3301 (indole NH), 1645 (CO), 1597 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.3 (s, 1H, indole NH), 9.0 (s, 1H, CH=N), 8.5 (s, 1H, pyrimidin-H), 7.0–7.9 (m, 8H, ArH), 2.7 (s, 3H, 6-CH_3), 2.3 (s, 3H, 5-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 13.4, 14.2, 114.0, 121.4, 122.0, 125.6, 126.2, 129.0, 129.2, 130.1, 130.6, 130.9, 133.1, 134.2, 134.6, 134.9, 142.1, 142.9, 143.8, 152.1, 172.9; EI-MS; m/z 432, 434; Anal. calcd. for $C_{23}H_{17}N_4OSCl$: C, 63.89; H, 3.93; N, 12.96. Found: C, 63.71; H, 4.10; N, 12.85.

2.6b *5,6-Dimethyl-3-[(2′-phenyl-5′-methyl-1H-indol-3′-yl)methyleneamino]-thieno[2,3-d]pyrimidin-4(3H)-one (**7b**)*: Yellow powder, Yield 0.288 g (70%), m. p. 169–171°C; IR (KBr) ν cm^{-1} 3305 (indole NH), 1645 (CO), 1594 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.4 (s, 1H, indole NH), 9.1 (s, 1H, CH=N), 8.6 (s, 1H, pyrimidin-H), 7.1–8.0 (m, 8H, ArH), 2.8 (s, 3H, 6-CH_3), 2.4 (s, 3H, 5′-CH_3), 2.2 (s, 3H, 5-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 13.5, 14.1, 24.3, 114.2, 121.3, 122.5, 125.8, 126.3, 129.1, 129.4, 130.3, 130.8, 131.2, 133.5, 134.4, 134.7, 134.8, 142.3, 142.6, 143.6, 152.4, 172.6; Anal. calcd. for $C_{24}H_{20}N_4OS$: C,

69.90; H, 4.85; N, 13.59. Found: C, 69.73; H, 4.98; N, 13.67.

2.6c *5,6-Dimethyl-3-[(2′-phenyl-5′-1H-indol-3′-yl)methyleneamino]-thieno[2,3-d]pyrimidin-4(3H)-one (**7c**)*: Pale yellow powder, Yield 0.286 (72%), m. p. 158–159°C; IR (KBr) ν cm^{-1} 3307 (indole NH), 1653 (CO), 1599 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.3 (s, 1H, indole NH), 9.0 (s, 1H, CH=N), 8.5 (s, 1H, pyrimidin-H), 7.1–8.1 (m, 9H, ArH), 2.7 (s, 3H, 6-CH_3), 2.2 (s, 3H, 5-CH_3); Anal. calcd. for $C_{23}H_{18}N_4OS$: C, 69.35; H, 4.52; N, 14.07. Found: C, 69.60; H, 4.69; N, 14.20.

2.7 *5,6-Dimethyl-3-[2-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-4-oxothiazolidin-3-yl]thieno[2,3-d]pyrimidin-4(3H)-ones (**8 a–c**)*

These compounds were synthesized following the procedure given for compounds **5 a–c**.

2.7a *5,6-Dimethyl-3-[2-(2′-phenyl-5′-chloro-1H-indol-3-yl)-4-oxothiazolidin-3-yl]thieno[2,3-d]pyrimidin-4(3H)-one (**8a**)*: Pale yellow flakes, Yield 0.330 g (72%), m. p. 215–216°C; IR (KBr) ν cm^{-1} 3301 (indole NH), 1701 (CH_2CO), 1645 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (s, 1H, indole NH), 10.0 (s, 1H, CH-N), 8.7 (s, 1H, pyrimidin-H), 7.1–8.0 (m, 8H, ArH), 4.2 (s, 2H, CH_2CO), 2.7 (s, 3H, 6-CH_3), 2.3 (s, 3H, 5-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 13.4, 14.3, 35.8, 107.1, 113.9, 121.6, 122.5, 125.6, 126.3, 129.0, 129.3, 130.2, 130.5, 130.9, 133.0, 134.3, 134.6, 134.8, 142.3, 143.6, 152.3. 168.8, 172.8; EI-MS; m/z 506, 508; Anal. calcd. for $C_{25}H_{19}N_4O_2S_2Cl$: C, 59.29; H, 3.74; N, 11.07. Found: C, 59.42; H, 3.51; N, 11.29.

2.7b *5,6-Dimethyl-3-[2-(2′-phenyl-5′-methyl-1H-indol-3-yl)-4-oxothiazolidin-3-yl]thieno[2,3-d]pyrimidin-4(3H)-one (**8b**)*: Yellow flakes, Yield 0.305 g (65%), m. p. 205–206°C; IR (KBr) ν cm^{-1} 3310 (indole NH), 1705 (CH_2CO), 1649 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.4 (s, 1H, indole NH), 10.1 (s, 1H, CH-N), 8.6 (s, 1H, pyrimidin-H), 7.2–8.1 (m, 8H, ArH), 4.3 (s, 2H, CH_2CO), 2.8 (s, 3H, 6-CH_3), 2.4 (s, 3H, 5′-CH_3), 2.3 (s, 3H, 5-CH_3); ^{13}C NMR (125 M Hz, DMSO-d_6): δ 13.3, 14.2, 24.3, 35.8, 107.1, 113.7, 121.4, 122.7, 125.8, 126.5, 129.1, 129.4, 130.4, 130.7,130.9, 133.2, 134.2, 134.6, 134.8, 142.6, 143.8, 152.5, 168.8, 172.8; Anal. calcd. for $C_{26}H_{22}N_4O_2S_2$: C, 64.20; H, 4.53; N, 11.52. Found: C, 64.35; H, 4.32; N, 11.67.

2.7c *5,6-Dimethyl-3-[2-(2′-phenyl-1H-indol-3-yl)-4-oxothiazolidin-3-yl]thieno[2,3-d]pyrimidin-4(3H)-one (**8c**)*: Pale yellow powder, Yield 0.292 (62%), m. p. 189–190°C; IR (KBr) ν cm^{-1} 3307 (indole NH), 1707 (CH_2CO), 1651 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (s, 1H, indole NH), 10.1 (s, 1H, CH-N), 8.5 (s, 1H, pyrimidin-H), 7.1–8.1 (m, 9H, ArH), 4.2 (s, 2H, CH_2CO), 2.9 (s, 3H, 6-CH_3), 2.3 (s, 3H, 5-CH_3); Anal. calcd. for $C_{25}H_{20}N_4O_2S_2$: C, 63.56; H, 4.24; N, 11.86. Found: C, 63.29; H, 4.37; N, 11.69.

2.8 *5,6-Dimethyl-3-(3-chloro-2-(2′-phenyl-5′-substituted 1H-indol-3-yl)-4-oxoazetidin-1-yl)-thieno[2,3-d]pyrimidin-4(3H)-ones (**9 a–c**)*

These compounds were synthesized by following the procedure reported for compounds **6 a–c**.

2.8a *5,6-Dimethyl-3-[3-chloro-2-(2′-phenyl-5′-chloro-1H-indol-3′-yl)-4-oxoazetidin-1-yl]-thieno[2,3-d]pyrimidin-4(3H)-one (**9a**)*: Yellow flakes, Yield 0.283 g (59%), m. p. 231–232°C; IR (KBr) ν cm^{-1} 3301 (indole NH), 1735 (CHCO), 1645 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.5 (s, 1H, indole NH), 10.0 (d, 1H, CH-N), 8.6 (s, 1H, pyrimidine-H), 6.9–7.8 (m, 8H, ArH), 5.5 (d, 1H, CHCl), 2.7 (s, 3H, 6-CH_3), 2.2 (s, 3H, 5-CH_3); ^{13}C NMR (500 M Hz, DMSO-d_6): δ 12.9, 14.1, 82.4, 106.2, 113.8, 121.4, 122.4, 125.5, 126.2, 128.2, 129.2, 130.2, 130.4, 130.9, 133.2, 134.2, 134.7, 134.9, 142.4, 143.7, 152.4, 160.6, 172.8; EI-MS; m/z 508, 510, 512; Anal. calcd. for $C_{25}H_{18}N_4O_2SCl_2$: C, 59.05; H, 3.54; N, 11.02. Found: C, 59.21; H, 3.69; N, 11.20.

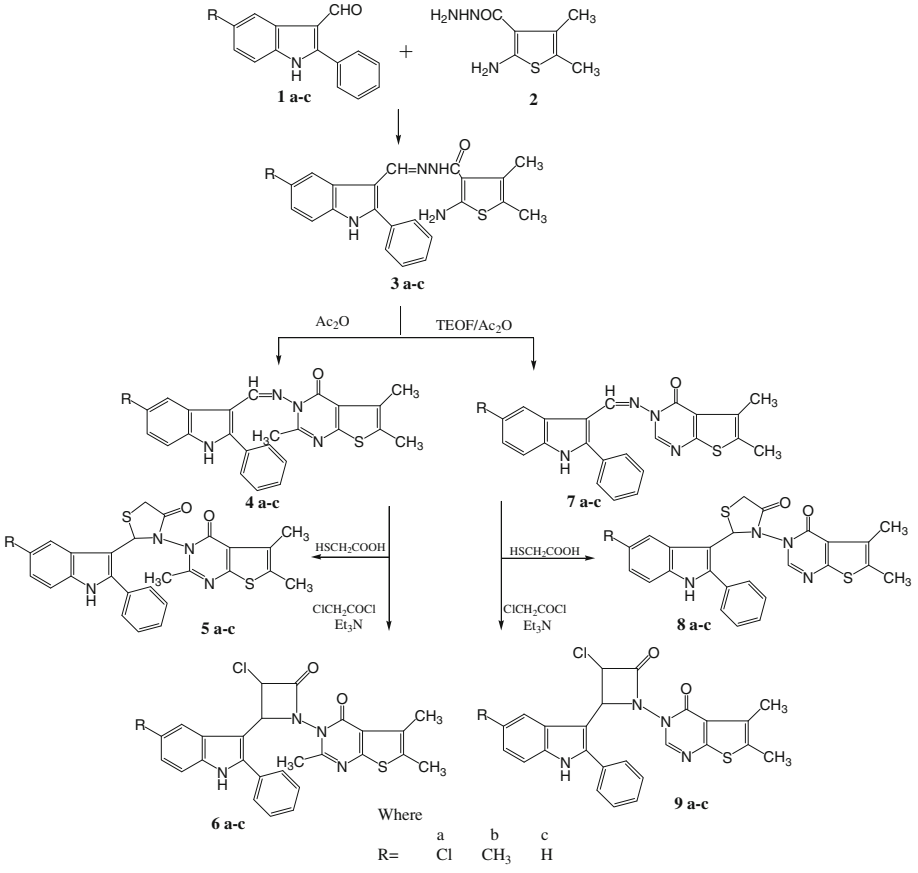
2.8b *5,6-Dimethyl-3-[3-chloro-2-(2′-phenyl-5′-methyl-1H-indol-3′-yl)-4-oxoazetidin-1-yl]-thieno[2,3-d]pyrimidin-4(3H)-one (**9b**)*: Yellow powder, Yield 0.282 (59%), m. p. 223–224°C; IR (KBr) ν cm^{-1} 3315 (indole NH), 1730 (CHCO), 1654 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.4 (s, 1H, indole NH), 10.1 (d, 1H, CH-N), 8.5 (s, 1H, pyrimidine-H), 6.8–7.8 (m, 8H, ArH), 5.6 (d, 1H, CHCl), 2.7 (s, 3H, 6-CH_3), 2.5 (s, 3H, 5′-CH_3), 2.3 (s, 3H, 5-CH_3); ^{13}C NMR (500 M Hz, DMSO-d_6): δ 13.1, 14.2, 24.5, 82.5, 106.2, 113.7, 121.5, 122.5, 125.7, 126.3, 128.3, 129.1, 130.1, 130.6, 130.7, 133.4, 134.3, 134.8, 134.9, 142.5, 143.9, 152.6, 160.7, 172.7; Anal. calcd. for $C_{26}H_{21}N_4O_2SCl$: C, 63.93; H, 4.30; N, 11.48. Found: C, 63.78; H, 4.51; N, 11.29.

2.8c *5,6-Dimethyl-3-[3-chloro-2-(2′-phenyl-5′-1H-indol-3-yl)-4-oxoazetidin-1-yl]-thieno[2,3-d]pyrimidin-4(3H)-one (**9c**)*: Yellow powder, Yield 0.26 g (55%), m. p.

198–199°C; IR (KBr) ν cm^{-1} 3313 (indole NH), 1727 (CHCO), 1653 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.3 (s, 1H, indole NH), 10.2 (d, 1H, CH-N), 8.5 (s, 1H, pyrimidine-H), 6.8–7.9 (m, 9H, ArH), 5.7 (d, 1H, CHCl), 2.8 (s, 3H, 6-CH_3), 2.3 (s, 3H, 5-CH_3); Anal. calcd. for $C_{25}H_{19}N_4O_2SCl$: C, 63.29; H, 4.01; N, 11.81. Found: C, 63.52; H, 4.22; N, 11.67.

3. Result and discussion

In the present investigation, we have synthesized fused thienopyrimidines linked to position-3 of indole nucleus. The synthetic route to achieve the target compounds was given in the scheme 1. First, 2-amino-4,5-dimethyl thiophene-3-charbohydrazide (**2**) was prepared by following literature method.[45] This on reaction with hydrazine hydrate gave compound (**2**). Compound (**2**) on condensation with 2.5-disubstituted 1H-indole-3-carboxaldehydes[46] (**1**) afforded 2-amino-N′-{3-(2′-phenyl-5′-substituted 1H-indol-3′-yl)methylene}-4,5-dimethylthieno-3-carbohydrazides (**3**). Formation of compound (**3**) was confirmed by its IR, ^{1}H NMR, ^{13}C NMR and mass spectrum studies. In IR spectrum of compound (**3a**), various bands appeared at 3404, 3301, 3170, 1645 and 1597 cm^{-1} were due to NH_2, indole NH, NH, C=O and C=N functions, respectively. In ^{1}H NMR spectrum of compound (**3a**) exhibited various signals at δ 11.5 (s, 1H, indole NH), 9.9 (s, 1H, NH), 8.9 (s, 1H, CH=N), 7.1–8.0 (m, 10H, 8-ArH and NH_2), 2.7 (s, 3H, 5-CH_3) and 2.3 (s, 3H, 4-CH_3). The two distinctive signals at δ 142.6 and 171.2 due to the CH=N and amide carbonyl in its ^{13}C NMR confirmed the formation of compound **3a**. Where as in mass spectrum, compound **3a** exhibited isotopic molecular ion peaks at 422 and 424 confirms the formation of **3a**. Compound **3** on cyclization with acetic anhydride yielded thienopyrimidine derivatives (**4**). Structural confirmation of compound **4a** was done using IR, ^{1}H NMR, ^{13}C NMR and mass spectra. The IR spectrum showed characteristic absorption bands at 3301, 1648 and 1598 cm^{-1} due to indole NH, C=O and C=N functions respectively and NH_2 and NH functions were disappeared. In ^{1}H NMR spectrum, various signals resonated at δ 11.3 (s, 1H, indole NH), 9.1 (s, 1H,



Scheme 1. Synthesis of compounds **5a-c**, **8a-c** and **5a-c**, **9a-c** from **3a-c**.

CH=N), 7.1–7.9 (m, 8H, ArH), 3.2 (s, 3H, CH_3), 2.8 (s, 3H, 6-CH_3) and 2.4 (s, 3H, 5-CH_3). The new peaks in its ^{13}C NMR at δ16.2 and 150.6 appeared due to the methyl group at 2-position of pyrimidothiophene C_2 of pyrimidine system. In mass spectrum, **4a** exhibited isotopic molecular ion peaks at 446 and 448 confirms the formation of **4a**. Cyclization of compound (**4**) with thioglycolic acid afforded thiazolidin-4-one derivatives (**5**). **5a** Exhibited various absorption bands in its IR spectrum at 3313, 1681 and 1645 cm^{-1} due to indole NH, CH_2CO and C=O functions, respectively. In ^{1}H NMR spectrum, various signals at δ 11.6 (s, 1H, indole NH), 10.0 (s, 1H, CH-N), 7.0–7.9 (m. 8H, ArH), 4.1 (s, 2H, CH_2CO), 3.2 (s, 3H, 2-CH_3), 2.7 (s, 3H, 6-CH_3) and 2.3 (s, 3H, 5-CH_3) were appeared. ^{13}CNMR spectrum, the new signals at δ 35.7 and 107.1 were resonated due to the CH and CH_2 carbon of thiazolidine system. The mass spectrum of compound **5a** exhibited isotopic molecular ion peaks at 520 and 522 confirms the formation of **5a**. Also, compounds (**4**) on treatment with chloroacetylchloride in triethylamine gave azetidin-2-ones (**6**). Compound **6a** in its IR spectrum showed characteristic absorption bands at 3301, 1720 and 1645 due to indole NH, CHCO and C=O functions, respectively. In its ^{1}H NMR spectrum, **6a** showed the absence of NH_2 and NH signals and presence of signals at 11.5 (s, 1H, indole NH), 10.0 (d, 1H, CH-N), 6.9–7.8 (m, 8H, ArH), 3.2 (s, 3H, 2-CH_3), 2.7 (s, 3H, 6-CH_3), 2.3 (s, 3H, 5-CH_3) and appearance of new doublet signal at 5.6 (d, 1H, CH–Cl) confirms the presence of lactum ring. Further, the signals at δ 82.5 and 160.6 corresponding to the CH and CH–Cl of azetidinone moiety. Compound **6a** exhibited isotopic molecular ion peaks at 522, 524 and 526 confirms the formation of lacum ring.

On the other hand, compound **3** ion reaction with triethyhlorthoformate in actic anhydride gave thienopyrimidines (**7**). Compound (**7**) on reaction with thioglycolic acid afforded the indole derivative of thiazolidin-4-ones (**8**). Further, compound (**7**) on cyclocondensation with chloacetylchloride, produced azetidin-2-ones (**9**). Structure of compounds **7, 8** and **9** were confirmed by their spectral studies (see experimental section).

4. Biological activities

4.1 *Reducing power assay*

The reducing power of the synthesized compounds was determined according to the method of Oyaizu.[47] Different concentrations of the samples (25–100 μg/ml) in DMSO (1 ml) were mixed with phosphate buffer (2.5 ml, 0.2 mol, pH=6.6) and potassium ferricyanide (2.5 ml, 1%). The mixture was incubated at 50°C for 20 min. after which a portion (2.5 ml) of trichloroacetic acid (10%) was added to the mixture, which was then centrifuged for 10 min. at 1000 × g. The upper layer of solution (2.5 ml) was mixed with distilled water (2.5 ml) and $FeCl_3$ (0.5 ml, 0.1%), and then the absorbance at 700 nm was measured in a spectrophotometer. BHA, TBHQ and ascorbic acid (A. A) were used as standards.

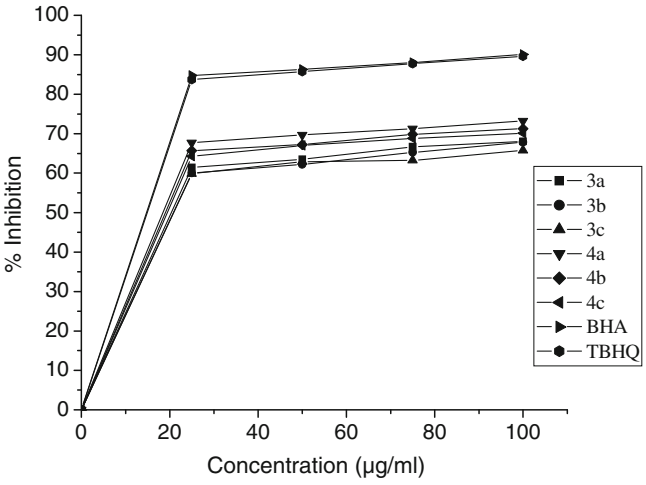


Figure 1. Reducing power of compounds **3** and **4**.

4.2 *Radical scavenging activity (RSA) assay*

The free radical scavenging activity of **3–9** was carried out in the presence of the stable free radical DPPH following Hatano's method[48] using

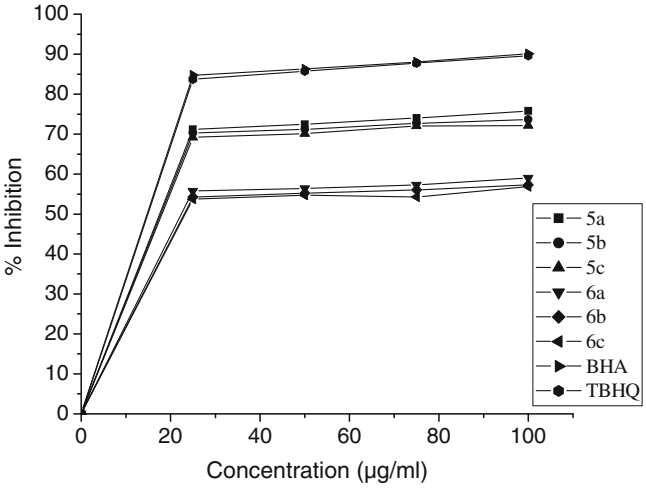


Figure 2. Reducing power of compounds **5** and **6**.

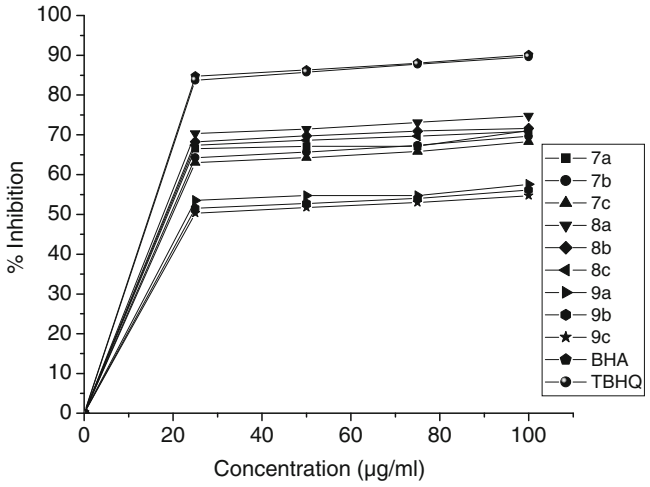


Figure 3. Reducing power of compounds **7, 8** and **9**.

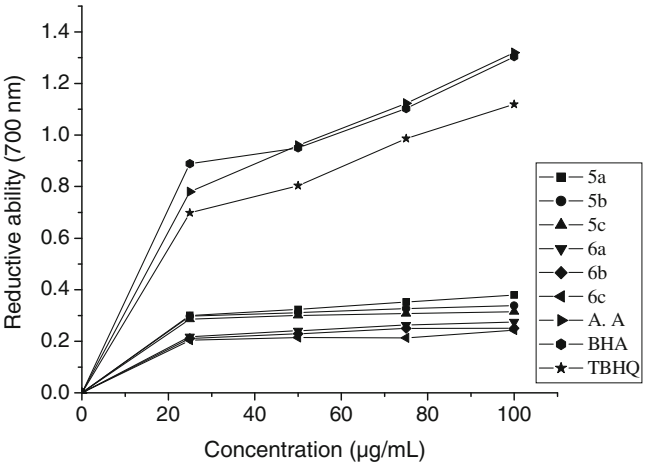


Figure 5. DPPH Radical scavenging activity of compounds **5** and **6**.

2-tert-butyl-4-methoxyphenol (butylated hydroxyl anisole, BHA), 2-(1,1-dimethylethyl)-1,4-benzenediol (2-tert. butyl hydroquinone, TBHQ) and ascorbic acid as standards. The radical scavenging activity (RSA) for methanolic solutions of compounds **3–9** at concentrations 25, 50, 75 and 100 μg/ml containing freshly prepared DPPH solution (0.004% w/v) was carried out and compared with those of standards BHA and TBHQ. All the test analyses were performed on three replicates and results are averaged. The results in percentage are expressed as the ratio of absorption decrease of DPPH in the presence of test compounds and absorption of DPPH in the absence of test compounds at 517 nm using ELICO SL 171 Mini Spec spectrophotometer. The percentage scavenging activity of the DPPH free radical was measured using the following equation

$$\%\text{DPPH radical scavenging} = \frac{\text{Absorbance of control} - \text{Absorbance of test sample}}{\text{Absorbance of control}} \times 100.$$

Antioxidant activity of these compounds was investigated by measuring the reducing power and radical scavenging effect of DPPH radicals. In reducing power assay, the presence of reducer (i.e., antioxidant) causes the reduction of Fe^{+3}/ferricyanide complex to ferrous form. The reducing power of the test

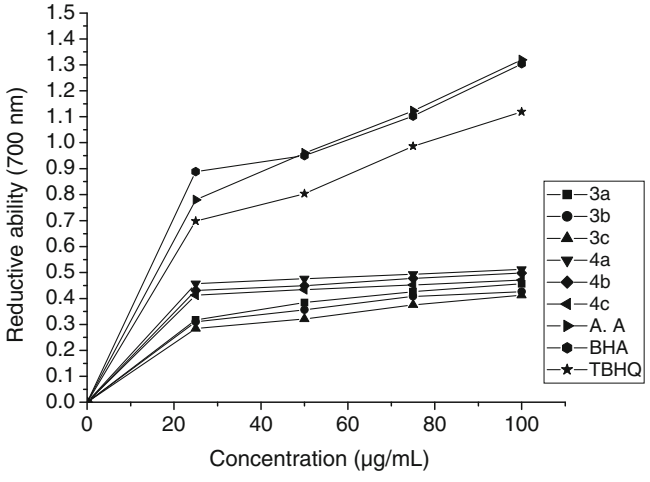


Figure 4. DPPH Radical scavenging activity of compounds **3** and **4**.

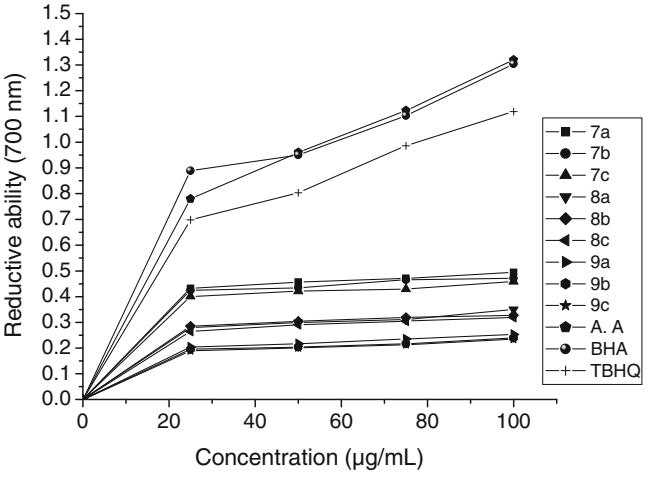
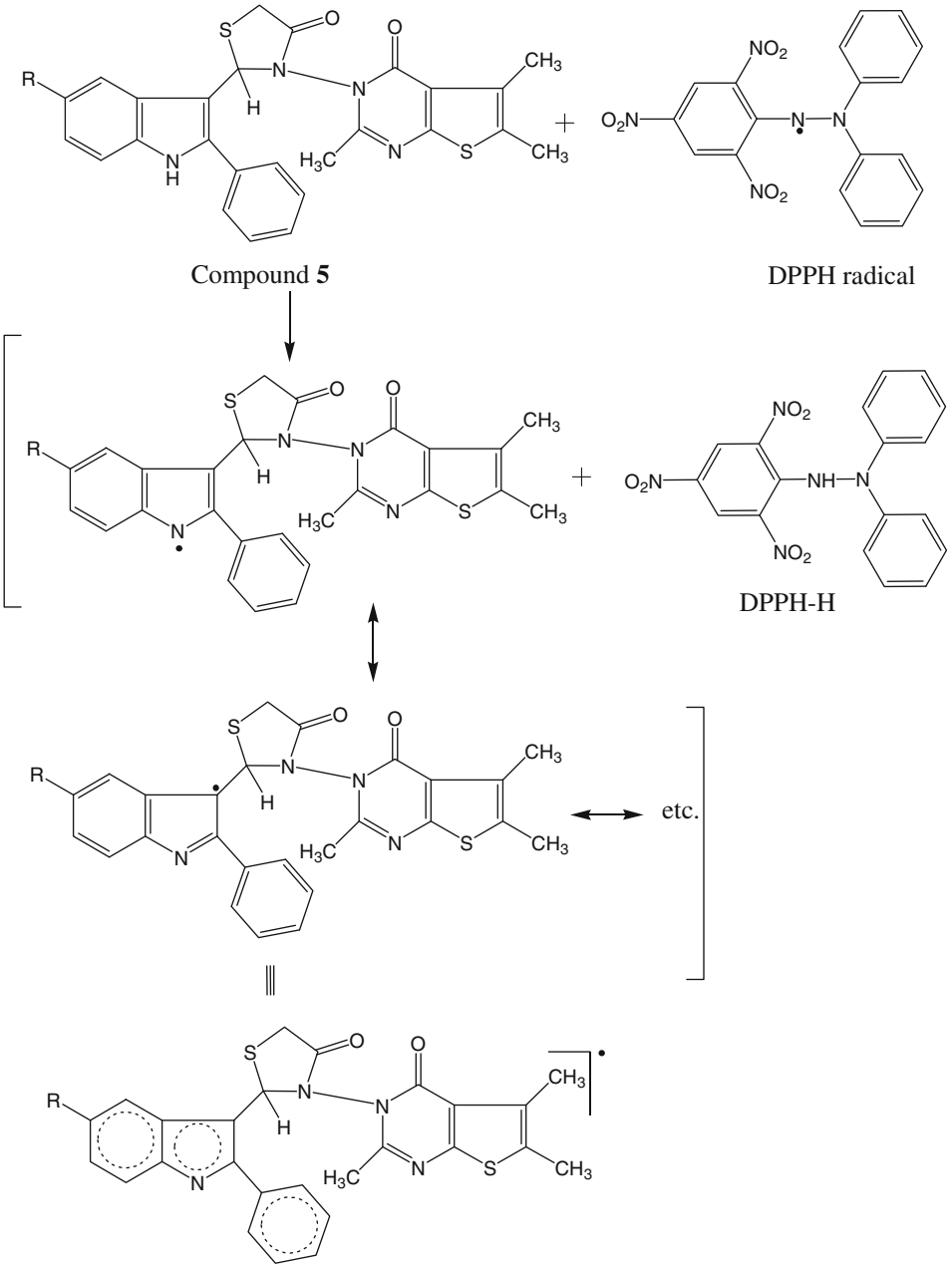


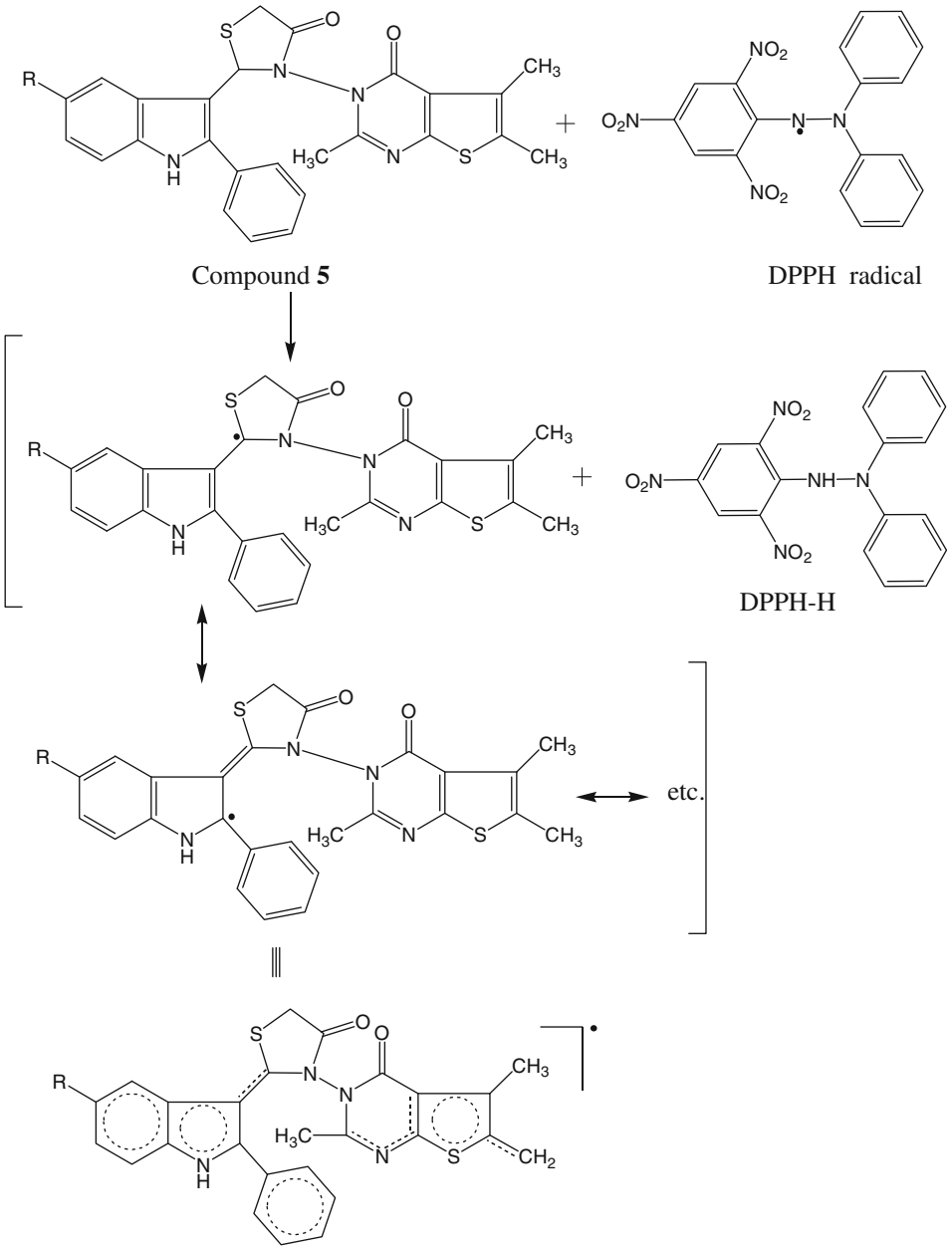
Figure 6. DPPH Radical scavenging activity of compounds **7, 8** and **9**.

compounds increases with increase in concentration. Compounds **3–9** exhibited very low absorption hence, the compounds were less active compared to standards used (figures 1–3). In case of radical scavenging activity, compounds **5** and **7** showed good percentage of inhibition (figures 4–6).

The probable mode of action of compounds **5** and **7** was illustrated in schemes 2, 3 and 4. In case of compound **5**, two labile hydrogen (hydrogen of indole NH and other at position-2 in 1,3-thiazolidinone system) are available. One of these hydrogens could be donated to the DPPH free radical to form the stable DPPH molecule. The radical formed from compound **5** could be well-stabilized by resonance as shown in schemes 2 and 3. In case of compound **7**, the hydrogen(s) of azomethine and methyl group at position-6 of thienopyrimidine are much more acidic than the hydrogen of the indole NH. Hence, these could be easily donated to DPPH free radical and convert itself into the stable free radical, which could be well-stabilized by



Scheme 2. DPPH radical scavenging activity: Probable mode of action of compound **5** and stabilization of free radical formed after donating hydrogen of indole NH.

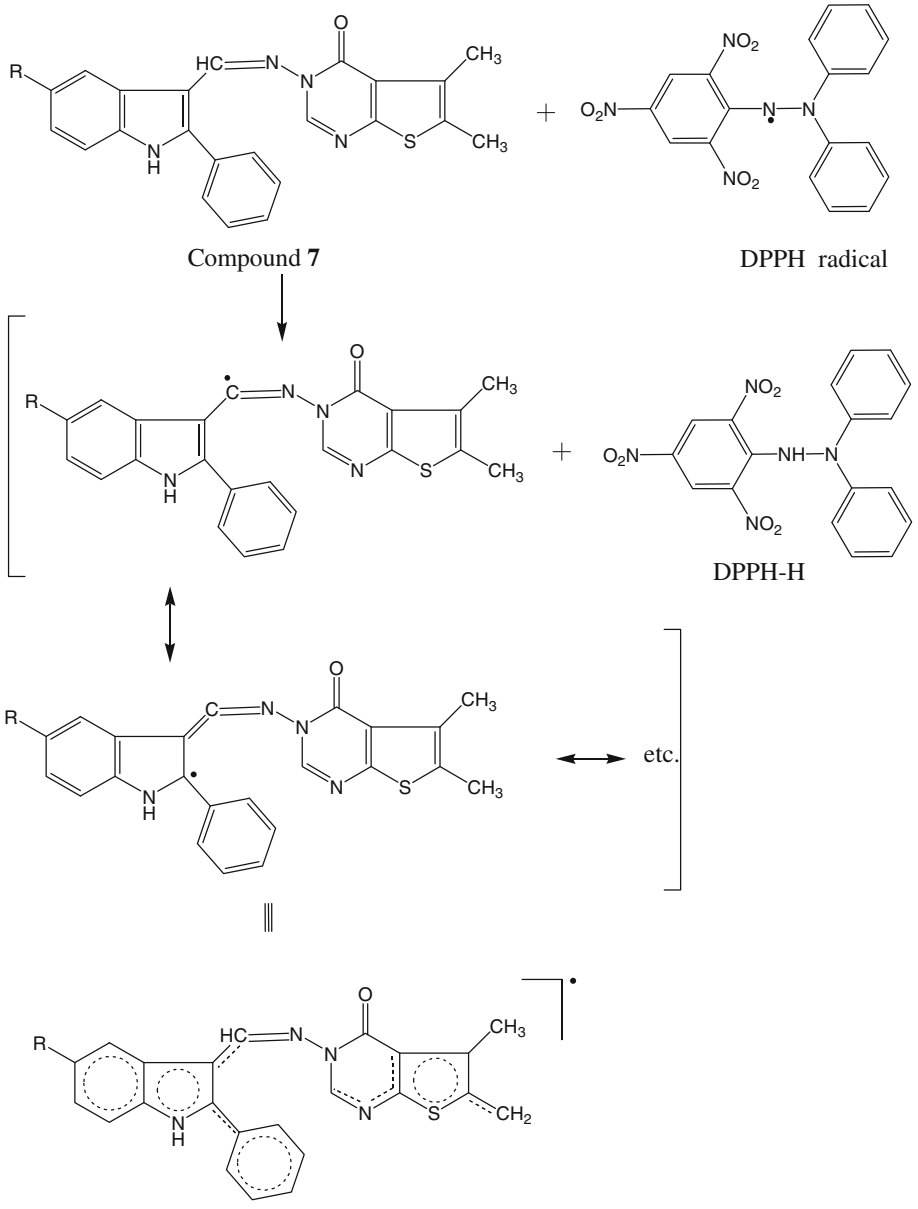


Scheme 3. DPPH radical scavenging activity: Probable mode of action of compound **5** and stabilization of free radical formed after donating hydrogen from thiazolidin-4-one system.

resonance as shown in scheme 4. Thus, compounds **5** and **7** could act as good hydrogen donors and antioxidant as compared to rest of the compounds tested. The same principle holds good for the reducing power assay of compounds **5** and **7**.

4.3 *Antimicrobial assay*

The antimicrobial activities[49] of the compounds prepared in this effort were evaluated using *Pseudomonas aeroginosa* (Gram negative bacteria), *Staphylococcus aureus* and *Klebsiella pneumoniae* (gram negative bacteria), *Aspergillus oryzae*, *Aspergillus terrus* and *Aspergillus niger* (fungi). An aliquot 0.1 ml of each bacterial strain was on nutrient agar while 0.1 ml of the fungal spore suspension was spread on potato dextrose agar (PDA). An agar-well diffusion test was performed in each case. In these tests, 6 mm wells were produced by using a sterile cork borer and each well was then inoculated with 100 μL of each key substance in



Scheme 4. DPPH radical scavenging activity: Probable mode of action of compound **7** and stabilization of free radical formed after donating hydrogen radical.

DMF, resulting in a final concentration of 1000 µg/ml. Nutrient agar plates were incubated at 37°C for 24 h while the PDA plates incubated at 25°C for 72 h. The zone of inhibition around the well was determined. Gentamycin and flucanozole were used as the reference antibacterial and antifungal agents, respectively.

In antimicrobial activity, compounds **3a**, **5a**, **6a** and **9a** showed good zone of inhibition against *S. Aureus*, compounds **3a**, **6a** and **9a** exhibited maximum zone of inhibition against *P. Knemonia.* Where as in case of antifungal activity, compounds **5a**, **6a**, **9a** and **9b** produced maximum zone of inhibition against *A. Oryzae*. Compound **9a** exhibited maximum inhibitory growth against *A. Terrus* and compounds **5a** and **6a** shown maximum zone of inhibition against *A. Nizer* (table 1).

These results suggest that, compounds having chloro substituent were much more capable of inhibiting the growth of organism compared to other compounds. This may be due to the electronegative nature of the chlorine atom in the position-5 of indole nucleus in addition to the different heterocyclic systems present in the individual compounds.

Table 1. Antimicrobial activities of synthesized compounds **(3–9)**.

Comp. No.	Antibacterial activity (zone of inhibition in mm)			Antifungal activity (zone of inhibition in mm)		
	S. aureus	*P. aeruginosa*	*K. pneumonia*	*A. oryzae*	*A. terrus*	*A. nizer*
3a	14	10	14	12	12	10
3b	13	09	10	09	10	11
3c	12	13	09	08	09	12
4a	11	12	12	08	07	10
4b	10	09	10	10	10	10
4c	10	08	09	11	12	09
5a	14	12	13	13	11	13
5b	12	10	11	12	12	10
5c	13	09	10	09	10	11
6a	14	13	14	13	12	13
6b	13	12	13	09	10	10
6c	12	11	11	12	10	12
7a	12	10	09	10	11	13
7b	09	10	08	09	12	09
7c	08	07	08	07	10	10
8a	13	12	12	10	10	10
8b	12	10	13	12	09	11
8c	11	10	11	11	10	11
9a	14	13	14	13	13	12
9b	13	09	10	13	11	12
9c	12	12	10	12	12	10
Gentamycin	15	16	15	–	–	–
Flucanozole	–	–	–	14	15	14

5. Conclusion

In general, it was found that the compounds having chloro substitution along with the thiazolidine and azetidinone systems exhibited good antioxidant and antimicrobial activities.

Acknowledgements

The authors are thankful to the Chairman, Department of Chemistry, Gulbarga University, Gulbarga, for providing laboratory facilities. We are also thankful to the Director, Indian Institute of Technology, Chennai for providing spectral data.

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