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ORIGINAL ARTICLE

Synthesis, antimicrobial and antioxidant activities of 2-oxo-6-phenyl-2-yl-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-1,2-dihydro pyridin-3-carbonitriles and their derivatives

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Abstract 2-Oxo-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-6-phenylpyridin-3-carbnitriles (**2a–c**) and its derivatives containing 1,2,4-triazole (**4a–c**), thiazolo[3,2-b][1,2,4]triazole (**5a–c**), hydrazide (**6a–c**), pyrazolones (**7a–c**) and (**8a–c**) were synthesized. Structures of all these previously unknown compounds were confirmed by their spectral studies and elemental analysis. The compounds were screened for their antioxidant and antimicrobial activities.

1. Introduction

Free radicals are chemical species containing one or more unpaired electrons, most of them being unstable and capable of abstracting electrons from other molecules. The predominant reactive oxygen species generated by cell metabolism or by exogenous factors include hydrogen peroxide (H_2O_2), the hydroxyl radical (HO$^{\bullet}$), the superoxide anion radical (HO—$^{\bullet}$). These free radicals have essential roles in cell signaling, apoptosis and gene expression. On the other hand, excessive free radical attack can damage DNA, proteins and lipids, resulting in diseases like cancer, neurological degeneration and arthritis, as well as the process of aging (Halliwell and Gutteridge, 1990; Halliwell et al., 1992). Therefore, considerable speculation has been directed towards the identification of antioxidants for use in preventive medicine.

It is well known that, indole derivatives extensively present in natural products, are very important substances for their medicinal and biological aspects. Malatonin (MLT) (Tan et al., 1993) is a highly conserved molecule that it acts as a free radical scavenger and a broad spectrum antioxidant (Sreejith et al., 2007). It is known to be a potent *in vitro* antioxidant as well powerful *in vivo* radical scavenger. The 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 (Chen et al., 1996), antioxidant (Suzen and Buyukbingol, 2000), antirheumatoidal (Buyukbingol et al., 1994) and anti-HIV (Buyukbingol et al., 1994; Suzen and

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Buyukbingol, 1998) agents playing a vital role in the immune system (Lieberman et al., 1997; Page et al., 2007). Many indole derivatives considered as the most potent scavengers of free radicals (Chyan et al., 1999). This prompted us to the selection of indole as starting synthon for the present work.

Pyridinoles have attracted considerable attention because of their wide range of pharmacological and biological activities. Pyridinole moieties are used in determination of iron (III) in multivitamins (Hashem and Abudkar, 2000), provide the hepato-protective activity of coffee (Kurakanene and Igarashi, 2006). They are used as drugs for angina pectoris (David, 1968), antioxidant agents (Masashi et al., 2005) and for treatment of ischemic stroke (Zhang et al., 2008). Also thiazolotriazoles have been reported to possess antibacterial, antifungal, anti-inflammatory (Kulkarni et al., 1981), antimycotic, anti HIV-1 (Wujec et al., 2004; Syed and Ali, 2008) and anthelmintic activities (Kamal et al., 2008; Habernickel, 1992).

Over the past two decades, pyrazole containing compounds have received considerable attention owing to their diverse chemotherapeutic potentials including versatile antineoplastic activities. Literature survey revealed that some pyrazoles have been implemented as antileukemic (Daidone et al., 2004; Manett et al., 2008), antitumor (Li et al., 2006; Xia et al., 2007, 2008; Farag et al., 2008) and antiproliferative (Schenone et al., 2004; Daidone et al., 2004) and anticancer activities (Warshakoon et al., 2006; Huang et al., 2007; Zhu et al., 2007).

Hence, in the design of new drugs, the development of hybrid molecules through the combination of different pharmacophores in one frame may lead to compounds with interesting pharmacological profiles. Therefore, combination of indole and pyrazole pharmacophores in the same molecule is an interesting combination for the development of new pharmacologically active antioxidant and antimicrobial agents.

Therefore, in continuation of our interest in functionalization of indoles (Saundane et al., 2009; Saundane and Veeresh Sharma, 2004) and in searching of new biologically active indole analogues, the title compounds were synthesized and screened for their *in vitro* antioxidant activity using DPPH radical scavenging and reducing power assay and antimicrobial assay.

2. Experimental

All the reagents were obtained commercially and used after 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}H NMR (DMSO-d_6) spectra recorded with an Bruker AVANCE III 500 MHz (AV 500) multi nuclei solution NMR 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-Oxo-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-6-phenylpyridin-3-carbonitriles **(2a–c)***

A mixture of (**1a–c**) (0.001 mol) and ethylcyanoacetate (0.001 mol) in glacial acetic acid (30 ml) containing anhydrous ammonium acetate (0.002 mol) was refluxed for 8 h. The reaction mixture was then cooled and poured into ice cold water. The formed product was filtered off, washed with water, dried and recrystallized from ethanol.

*2.2. 2-Oxo-4-(2′-phenyl-5′-chloro-1H-indol-3′-yl)-6-phenylpyridin-3-carbonitrile **2a***

74% yield Yellow crystals. m.p. 245–246 °C. IR (KBr): υ 3300 (indole NH), 3264 (NH), 2206 (CN), 1677 (CO). ^{1}H NMR (DMSO-d_6): δ = 12.1 (s, 1H, indole NH), 9.5 (s, 1H, NH), 7.2–8.2 (m, 14H, ArH) ppm; MS: (m/z) = 421, 423 (M^+, $M^+ + 2$). *Anal.* for $C_{26}H_{16}N_3OCl$: calcd. C, 74.11, H 3.80, N 9.98; Found: C 74.22, H 3.99, N 10.13.

*2.3. 2-Oxo-4-(2′-phenyl-5′-methyl-1H-indol-3′-yl)-6-phenylpyridin-3-carbonitrile **2b***

72% yield Yellow powder. m.p. 239–240 °C. IR (KBr): υ 3303 (indole NH), 3268 (NH), 2201 (CN), 1687 (CO). ^{1}H NMR (DMSO-d_6): δ = 12.0 (s, 1H, indole NH), 9.6 (s, 1H, NH), 7.2–8.3 (m, 14H, ArH), 2.1 (s, 3H, CH_3) ppm; MS: (m/z) = 401. *Anal.* for $C_{27}H_{19}N_3O$: calcd. C, 80.80, H 4.74, N 10.47; Found: C 80.65, H 4.85, N 10.13.

*2.4. 2-Oxo-4-(2′-phenyl-1H-indol-3′-yl)-6-phenylpyridin-3-carbonitrile **2c***

71% yield Yellow powder. m.p. 242–240 °C. IR (KBr): υ 3307 (indole NH), 3259 (NH), 2209 (CN), 1682 (CO). ^{1}H NMR (DMSO-d_6): δ = 12.1 (s, 1H, indole NH), 9.5 (s, 1H, NH), 7.1–8.2 (m, 15H, ArH) ppm; MS: (m/z) = 387. *Anal.* for $C_{26}H_{17}N_3O$: calcd. C, 80.62, H 4.39, N, 10.85; Found: C 80.82, H 4.48, N 11.02.

*2.5. [3-Cyano-6-phenyl-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)pyridin-2-yloxy]-acetic acid ethyl ester **3a–c***

A mixture of compound (**2a–c**) (0.001 mol) and ethyl chloroacetate (0.002 mol) in dry acetone (40 ml) containing sodium acetate (0.001 mol) was refluxed for 7 h. The solvent was removed under vaccum, the residue was poured in cold water to remove inorganic solids, filtered to obtain compound (**3a–c**) and recrystallized from 1,4-dioxane.

*2.6. 3-Cyano-6-phenyl-4-(2′-phenyl-5′-chloro-1H-indol-3′-yl)pyridin-2-yloxy]-acetic acid ethyl ester **3a***

69% yield Pale yellow powder. m.p. 198–199 °C. IR (KBr): υ 3265 (indole NH), 2210 (CN), 1674 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.5 (s, 1H, indole NH), 7.1–8.1 (m, 14H, ArH), 4.9 (s, 2H, CH_2), 4.1 (q, 2H, CH_2), 1.6 (t, 3H, CH_3) ppm; MS: (m/z) = 507, 509 (M^+, $M^+ + 2$). *Anal.* for $C_{30}H_{22}N_3O_3Cl$: calcd. C, 71.00, H 4.34, N 8.28; Found: C 71.21, H 4.25, N 8.41.

*2.7. [3-Cyano-6-phenyl-4-(2′-phenyl-5′-methyl-1H-indol-3′-yl)pyridin-2-yloxy]-acetic acid ethyl ester **3b***

68% yield Pale yellow powder. m.p. 185–186 °C. IR (KBr): υ 3269 (indole NH), 2216 (CN), 1680 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.6 (s, 1H, indole NH), 7.1–8.0 (m, 14H, ArH), 4.89 (s, 2H, CH_2), 4.2 (q, 2H, CH_2), 2.2 (s, 3H, CH_3), 1.7 (t,

3H, CH_3) ppm; MS: (m/z) = 487. *Anal.* for $C_{31}H_{25}N_3O_3$: calcd. C, 76.39, H 5.13, N, 8.62; Found: C 76.52, H, 5.26, N 8.75.

2.8. [3-Cyano-6-phenyl-4-(2′-phenyl-1H-indol-3′-yl)pyridin-2-yloxy]-acetic acid ethyl ester ***3c***

69% yield Pale yellow powder. m.p. 180–181 °C. IR (KBr): υ 3262 (indole NH), 2214 (CN), 1678 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.4 (s, 1H, indole NH), 7.1–8.0 (m, 15H, ArH), 4.89 (s, 2H, CH_2), 4.0 (q, 2H, CH_2), 1.6 (t, 3H, CH_3) ppm; MS: (m/z) = 473 *Anal.* for $C_{30}H_{23}N_3O_3$: calcd. C, 76.10, H 4.86, N, 8.88; Found: C 76.21, H 4.59, N 8.98.

2.9. 5-{[3-Cyano-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-6-phenylpyridin-2-yloxy]methyl}-2H-1,2,4-triazol-3(4H)-thiones ***4a–c***

A mixture of compound (**3a–c**) (0.0001 mol) and thiosemicarbazide (0.0002 mol) in pyridine (20 ml) was refluxed for 5 h. The mixture was then cooled to room temperature and poured into ice cold water and acidified with few drops of acetic acid. The formed solid was filtered, washed with water dried and recrystallized from ethanol.

2.10. 5-{[3-Cyano-4-(2′-phenyl-5′-chloro-1H-indol-3-yl)-6-phenylpyridin-2′-yloxy]methyl}-2H-1,2,4-triazol-3(4H)-thione ***4a***

65% yield Brown solid. m.p. 285–286 °C. IR (KBr): υ 3180 (NH), 3132 (indole NH), 3105 (NH), 2206 (CN). ^{1}H NMR (DMSO-d_6): δ = 11.6 (s, 1H, indole NH), 10.0 (s, 1H, triazole NH), 9.6 (s, 1H, triazole NH), 7.1–7.9 (m, 14H, ArH), 4.0 (s, 2H, CH_2) ppm; MS: (m/z) = 534, 536 (M^+, $M^+ + 2$). *Anal.* for $C_{29}H_{19}N_6OSCl$: calcd. C, 65.17, H 3.56, N 15.73; Found: C 65.31, H 3.71, N 15.92.

2.11. 5-{[3-Cyano-4-(2′-phenyl-5′-methyl-1H-indol-3′-yl)-6-phenylpyridin-2-yloxy]methyl}-2H-1,2,4-triazol-3(4H)-thione ***4b***

68% yield Brown solid. m.p. 276–278 °C. IR (KBr): υ 3182 (NH), 3135 (indole NH), 3110 (NH), 2214 (CN). ^{1}H NMR (DMSO-d_6): δ = 11.5 (s, 1H, indole NH), 10.1 (s, 1H, triazole NH), 9.5 (s, 1H, triazole NH), 7.1–7.8 (m, 14H, ArH), 4.1 (s, 2H, CH_2), 2.2 (s, 3H, CH_3) ppm; MS: (m/z) = 514. *Anal.* for $C_{30}H_{22}N_6OS$: calcd. C, 70.04, H 4.28, N 16.34; Found: C 70.25, H 4.53, N 16.13.

2.12. 5-{[3-Cyano-4-(2′-phenyl-1H-indol-3′-yl)-6-phenylpyridin-2-yloxy]methyl}-2H-1,2,4-triazol-3(4H)-thione ***4c***

64% yield Brown solid. m.p. 281–282 °C. IR (KBr): υ 3187 (NH), 3125 (indole NH), 3103 (NH), 2209 (CN). ^{1}H NMR (DMSO-d_6): δ = 11.5 (s, 1H, indole NH), 10.0 (s, 1H, triazole NH), 9.5 (s, 1H, triazole NH), 7.2–7.9 (m, 15H, ArH), 4.1 (s, 2H, CH_2) ppm; MS: (m/z) = 534. *Anal.* for $C_{29}H_{20}N_6OS$: calcd. C, 69.60, H 4.00, N 16.80; Found: C 69.31, H 4.11, N 16.72.

2.13. 2-(6-Oxo-5,6-dihydro-thiazolo[3,2,-b][1,2,4]triazol-2-yl methoxy)-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-6-phenylpyridine-3-carbonitriles ***5a–c***

Compound (**4a–c**) (0.0001 mol) and chloroacetic acid (0.0001 mol) were refluxed in glacial acetic acid (9 ml) and acetic anhydride (3 ml) mixture for 4 h. Then the reaction mixture was cooled to room temperature and poured on to crushed ice. The formed solid was filtered, washed with water, dried and recrystallized from ethanol.

2.14. 2-(6-Oxo-5,6-dihydro-thiazolo[3,2,-b][1,2,4]triazol-2-yl methoxy)-4-(2′-phenyl-5′-chloro-1H-indol-3′-yl)-6-phenylpyridin-3-carbonitrile ***5a***

69% yield Pale yellow crystals. m.p. 165–166 °C. IR (KBr): υ 3265 (indole NH), 2216 (CN), 1713 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.6 (s, 1H, indole NH), 7.1–8.1 (m, 14H, ArH), 5.0 (s, 2H, CH_2), 4.0 (s, 2H, thiazole CH_2) ppm; MS: (m/z) = 574, 576 (M^+, $M^+ + 2$). *Anal.* for $C_{31}H_{19}N_6O_2SCl$: calcd. C, 64.80, H 3.31, N 14.63; Found: C 64.92, H 3.43, N 14.82.

2.15. 2-(6-Oxo-5,6-dihydro-thiazolo[3,2,-b][1,2,4]triazol-2-yl methoxy)-4-(2′-phenyl-5′-methyl-1H-indol-3′-yl)-6-phenylpyridin-3-carbonitrile ***5b***

68% yield. Pale yellow crystals m.p. 169–170 °C. IR (KBr): υ 3260 (indole NH), 2212 (CN), 1715 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.5 (s, 1H, indole NH), 7.1–8.0 (m, 14H, ArH), 5.1 (s, 2H, CH_2), 4.1 (s, 2H, thiazole CH_2), 2.3 (s, 3H, CH_3) ppm; MS: (m/z) = 554. *Anal.* for $C_{32}H_{22}N_6O_2S$: calcd. C, 69.31, H 3.97, N 15.16; Found: C 69.56, H 3.53, N 15.32.

2.16. 2-(6-Oxo-5,6-dihydro-thiazolo[3,2,-b][1,2,4]triazol-2-yl methoxy)-4-(2′-phenyl-1H-indol-3′-yl)-6-phenylpyridin-3-carbonitrile ***5c***

65% yield. Pale yellow powder m.p. 162–163 °C. IR (KBr): υ 3263 (indole NH), 2215 (CN), 1717 (CO). $^{1\,H\,NMR}$ (DMSO-d_6): δ = 11.6 (s, 1H, indole NH), 7.2–8.0 (m, 15H, ArH), 5.0 (s, 2H, CH_2), 4.2 (s, 2H, thiazole CH_2) ppm; MS: (m/z) = 540. *Anal.* for $C_{31}H_{20}N_6O_2S$: calcd. C, 68.89, H 3.70, N 15.56; Found: C 68.76, H 3.63, N 15.39.

2.17. [3-Cyano-6-phenyl-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)pyridin-2-yloxy]-acetic acid hydrazides ***6a–c***

A mixture of compound (**3a–c**) (0.0001 mol) and hydrazine hydrate (99%) (0.0004 mol) was refluxed in 1,4-dioxane (30 ml) for 5 h. The excess of solvent was removed under reduced pressure. After cooling, the formed product was filtered off, washed with cold 1,4-dioxane, dried and recrystallized from methanol.

2.18. [3-Cyano-6-phenyl-4-(2′-phenyl-5′-chloro-1H-indol-3′-yl)pyridin-2-yloxy]-acetic acid hydrazide ***6a***

71% yield. Yellow crystals m.p. 210–211 °C. IR (KBr): υ 3418 (NH_2), 3260 (indole NH), 3141 (NH), 2211 (CN), 1680 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.5 (s, 1H, indole NH), 8.3 (s, 1H, CONH), 7.2–8.0 (m, 14H, ArH), 4.8 (s, 2H, CH_2) ppm;

MS: (m/z) = 493, 495 (M^+, $M^+ + 2$) *Anal.* for $C_{28}H_{20}N_5O_2Cl$: calcd. C, 68.15, H 4.06, N 14.20; Found: C 68.29, H 4.19, N 14.35.

2.19. [3-Cyano-6-phenyl-4-(2′-phenyl-5′-methyl-1H-indol-3′-yl)pyridin-2-yloxy]-acetic acid hydrazide ***6b***

72% yield. Yellow crystals m.p. 215–216 °C. IR (KBr): υ 3419 (NH_2), 3263 (indole NH), 3148 (NH), 2217 (CN), 1685 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.6 (s, 1H, indole NH), 8.4 (CONH), 7.2–8.1 (m, 14H, ArH), 4.7 (s, 2H, CH_2), 2.3 (s, 3H, CH_3) ppm; MS (m/z) = 473. *Anal.* for $C_{29}H_{23}N_5O_2$: calcd. C, 73.57, H 4.86, N 14.80; Found: C 73.35, H 4.59, N 14.65.

2.20. [3-Cyano-6-phenyl-4-(2′-phenyl-1H-indol-3′-yl)pyridin-2-yloxy]-acetic acid hydrazide ***6c***

71% yield. Yellow crystals m.p. 205–207 °C. IR (KBr): υ 3412 (NH_2), 3262 (indole NH), 3144 (NH), 2218 (CN), 1686 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.4 (s, 1H, indole NH), 8.4 (CONH), 7.2–7.9 (m, 15H, ArH), 4.9 (s, 2H, CH_2) ppm; MS: (m/z) = 459. *Anal.* for $C_{28}H_{21}N_5O_2$: calcd. C, 73.20, H 4.58, N 15.25; Found: C 73.36, H 4.69, N 15.35.

2.21. 1-{2-[4-(2′-Phenyl-5′-substituted 1H-indol-3′-yl)-3-cyano-6-phenylpyridin-2-yloxy]acetyl}-1,2-dihydro-3-methylpyrazol-5-ones ***7a–c***

A mixture of compound (**6a–c**) (0.0001 mol), ethylacetoacetate (0.0001 mol), anhydrous $NaHCO_3$ (0.8 g), and anhydrous Na_2SO_4 (0.8 g) in 1,4-dioxane (35 ml) was refluxed for 10 h. Then excess of solvent was removed under reduced pressure, cooled to room temperature and the residue was poured into ice cold water. The product thus separated was filtered, washed with water and recrystallized from 1,4-dioxane.

2.22. 1-{2-[4-(2′-Phenyl-5′-chloro-1H-indol-3′-yl)-3-cyano-6-phenylpyridin-2-yloxy]acetyl}-1,2-dihydro-3-methylpyrazol-5-one ***7a***

65% yield. Yellow needles m.p. 256–257 °C. IR (KBr): υ 3264 (indole NH), 3100 (NH), 2216 (CN), 1713 (CO), 1702 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.4 (s, 1H, indole NH), 10.0 (s, 1H, NH), 7.1–8.2 (m, 15H, 14ArH, pyrazolone-H), 4.9 (s, 2H, CH_2), 1.6 (s, 3H, CH_3) ppm; MS: (m/z) = 559, 561 (M^+, $M^+ + 2$) *Anal.* for $C_{32}H_{22}N_5O_3Cl$: calcd. C, 68.69, H 3.94, N 12.52; Found: C 68.85, H 4.02, N 12.68.

2.23. 1-{2-[4-(2′-Phenyl-5′-methyl-1H-indol-3′-yl)-3-cyano-6-phenylpyridin-2-yloxy]acetyl}-1,2-dihydro-3-methylpyrazol-5-one ***7b***

64% yield. Yellow needles. m.p. 261–262 °C. IR (KBr) υ: 3268 (indole NH), 3110 (NH), 2220 (CN), 1715 (CO), 1695 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.5 (s, 1H, indole NH), 10.1 (s, 1H, NH), 7.0–8.2 (m, 15H, 14ArH, pyrazolone-H), 4.8 (s, 2H, CH_2), 1.6 (s, 3H, CH_3), 2.2 (s, 3H, CH_3) ppm; MS: (m/z) = 539. *Anal.* for $C_{33}H_{25}N_5O_3$: calcd. C, 73.47, H 4.64, N 12.99; Found: C 73.63, H 4.82, N 12.78.

2.24. 1-{2-[4-(2′-Phenyl-1H-indol-3′-yl)-3-cyano-6-phenylpyridin-2-yloxy]acetyl}-1,2-dihydro-3-methylpyrazol-5-one ***7c***

66% yield. Yellow needles. m.p. 269–270 °C. IR (KBr): υ 3258 (indole NH), 3105 (NH), 2214 (CN), 1712 (CO), 1698 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.4 (s, 1H, indole NH), 10.1 (s, 1H, NH), 7.1–8.0 (m, 16H, 15ArH, pyrazolone-H), 4.9 (s, 2H, CH_2), 1.6 (s, 3H, CH_3) ppm; MS: (m/z) = 525. *Anal.* for $C_{32}H_{23}N_5O_3$: calcd. C, 73.14, H 4.38, N 13.33; Found: C 73.33, H 4.52, N 13.57.

2.25. 1-{2-[3-Cyano-6-phenyl-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)pyridin-2-yloxy]acetyl}-3-amino-1H-pyrazol-5(4H)-ones ***8a-c***

A mixture of compound (**6a–c**) (0.0001 mol) ethylcyanoacetate (0.0001 mol), anhydrous $NaHCO_3$ (0.8 g) and anhydrous Na_2SO_4 (0.8 g) in 1,4-dioxane (30 ml) was refluxed for 9 h. The reaction mixture was cooled to room temperature and poured onto ice cold water, the solid thus separated was filtered off, washed with cold water, dried and recrystallized from ethanol.

2.26. 1-{2-[3-Cyano-6-phenyl-4-(2′-phenyl-5′-chloro-1H-indol-3′-yl)pyridin-2-yloxy]acetyl}-3-amino-1H-pyrazol-5(4H)-one ***8a***

61% yield. Yellow needles. m.p. 221–222 °C. IR (KBr): υ 3400 (NH_2), 3263 (indole NH), 2216 (CN), 1713 (CO), 1690 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.5 (s, 1H, indole NH), 7.0–8.2 (m, 16H, 14ArH and NH_2), 4.9 (s, 2H, OCH_2CO), 4.2 (s, 2H, pyrazole CH_2CO) ppm; MS: (m/z) = 560, 562 (M^+, $M^+ + 2$). *Anal.* for $C_{31}H_{21}N_6O_3Cl$: calcd. C, 66.43, H 3.73, N 15.00; Found: C 64.57, H 3.87, N 15.15.

2.27. 1-{2-[3-Cyano-6-phenyl-4-(2′-phenyl-5′-methyl-1H-indol-3′-yl)pyridin-2-yloxy]acetyl}-3-amino-1H-pyrazol-5(4H)-one ***8b***

62% yield. Yellow needles. m.p. 225–226 °C. IR (KBr): υ 3405 (NH_2), 3263 (indole NH), 2216 (CN), 1718 (CO), 1695 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.4 (s, 1H, indole NH), 7.1–8.2 (m, 16H, 14ArH and NH_2), 4.8 (s, 2H, OCH_2CO), 4.1 (s, 2H, pyrazole CH_2CO), 2.3 (s, 3H, CH_3) ppm; MS: (m/z) = 540. *Anal.* for $C_{32}H_{24}N_6O_3$: calcd. C, 71.11, H 4.44, N 15.56; Found: C 71.29, H 4.67, N 15.73.

2.28. 1-{2-[3-Cyano-6-phenyl-4-(2′-phenyl-1H-indol-3′-yl)pyridin-2-yloxy]acetyl}-3-amino-1H-pyrazol-5(4H)-one ***8c***

58% yield. Yellow powder. m.p. 216–217 °C. IR (KBr): υ 3409 (NH_2), 3263 (indole NH), 2218 (CN), 1712 (CO), 1696 (CO). ^{1}H NMR (DMSO-d_6): δ = 11.4 (s, 1H, indole NH), 7.0–8.1 (m, 17H, 15ArH and NH_2), 4.8 (s, 2H, OCH_2CO), 4.3 (s, 2H, pyrazole CH_2CO) ppm; MS:(m/z) = 526. *Anal.* for $C_{31}H_{22}N_6O_3$: calcd. C, 70.72, H 4.18, N 15.97; Found: C 70.51, H 4.37, N 16.11.

3. Results and discussion

In the present work, 2-oxo-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-6-phenylpyridin-3-carbnitriles (**2a–c**) were conveniently prepared from the reaction of 3-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-1-phenylprop-2-in-1-ones (**1a–c**) with ethylcyanoacetate in acetic acid containing anhydrous ammonium acetate. Formation of compound **2a** was confirmed by its IR, ^{1}H NMR and mass spectral studies. In its IR spectrum, the band which appeared at 3300, 3264, 2206 and 1677 cm^{-1} were appeared due to NH, indole NH, CN and C═O functions, respectively. Where as in ^{1}H NMR spectrum, the signals resonated at δ 12.1 (s, 1H, indole NH), 9.5 (s, 1H, NH), 7.2–8.2 (m, 14H, ArH) and in mass spectrum isotopic molecular ion peak at m/z 421 and 423 was noticed which confirms the formation of **2a**. Compounds (**2a–c**) on alkylation with ethylchloroacetate in basic conditions afforded acetic acid ethyl esters (**3a–c**). **3a** in its IR spectrum exhibited bands at 3265, 2210 and 1674 cm^{-1} due to indole NH, CN and C═O functions, respectively. In ^{1}H NMR spectrum of compound **3a**, signals were exhibited at δ 11.5 (s, 1H, indole NH), 7.1–8.1 (m, 14H, ArH), 4.9 (s, 2H, CH_2), 4.1 (q, 2H, CH_2) and 1.6 (t, 3H, CH_3). The isotopic molecular ion peaks were observed at m/z 507 and 509 in its mass spectrum. Cyclocondenzation of compounds (**3a–c**) with thiosemicarbazide in boiling pyridine gave 5-{[3-cyano-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-6-phenylpyridin-2-yloxy]methyl}-2H-1,2,4-triazol-3(4H)-thiones (**4a–c**). Compound **4a** in its IR spectrum exhibited bands at 3132, 3180, 3105 and 2206 due to NH, indole NH, NH and CN functions, respectively. In its ^{1}H NMR spectrum, various protons resonated at δ 11.6 (s, 1H, indole NH), 10.0 (s, 1H, triazole NH), 9.6 (s, 1H, triazole NH), 7.1–7.9 (m, 14H, ArH) and 4.0 (s, 2H, CH_2). The mass spectrum of **4a** exhibited isotopic molecular ion peaks at m/z 534 and 536, which confirms the formation of **4a** from **3a**. Further, compounds (**4a–c**) on treatment with chloroacetic acid in acetic acid afforded 2-(6-oxo-5,6-dihydro-thiazolo[3,2-b][1,2,4]triazol-2′-yl)-methoxy-4-(2′-phenyl-5′-substituted 1H-indol-3′-yl)-6-phenylpyridin-3-carbonitriles (**5a–c**). In IR spectrum of **5a**, peaks at 3265, 2216 and 1713 were due to NH, CN and C═O functions, respectively. Where as in its ^{1}H NMR spectrum, the various signals found at δ 11.6 (s, 1H, indole NH), 7.1–8.1 (m, 14H, ArH), 5.0 (s, 2H, CH_2) and 4.0 (s, 2H, thiazole CH_2), and in its mass spectrum, the isotopic molecular ion peaks noticed at m/z 574 and 576 confirms the formation of **5a**.

On the other hand, compounds (**3a–c**) on treatment with hydrazine hydrate gave hydrazide derivatives (**6a–c**). Compound **6a** in its IR spectrum exhibited bands at 3418, 3260, 3141, 2211 and 1680 cm^{-1} due to NH_2, NH, indole NH, CN and C═O functions, respectively. In its ^{1}H NMR spectrum the downfield singlets at δ 11.5 is attributed to indole NH and δ 8.3 due to CONH protons, where as, the multiplet at δ 7.3–8.0 due to 14 aromatic protons and the upfield singlet at δ 4.8 assigned to two methylene protons. Compound **5a** exhibited isotopic molecular ion peak at m/z 493, 495 confirms the formation of **6a** from **3a**. Then, compounds (**6a–c**) on cyclocondenzation with ethylacetoacetate in boiling 1,4-dioxane gave compounds (**7**). In the IR spectrum of compound **7a**, the absorption bands observed at 3264, 3100, 2216, 1713 and 1702 cm^{-1} due to indole NH, NH, CN, pyrazole CO and CO functions, respectively. In its ^{1}H NMR spectrum various protons resonated at δ 11.4 (s, 1H, indole NH), 10.1 (s, 1H, NH), 7.1–8.2 (m, 15H, 14ArH and pyrazole-H), 4.9 (s, 2H, CH_2) and 1.6 (s, 3H, CH_3). In its mass spectrum, the isotopic molecular ion peaks were observed at m/z 559 and 561 confirmed the formation of **7a**. Also, compounds (**6a–c**) on reaction with ethylcyanoacetate in 1,4-dioxane containing anhydrous sodium bicarbonate, gave pyrazole derivatives (**8a–c**). The IR spectrum of compound **8a** showed characteristic bands at 3400, 3263, 2216, 1713 and 1690 cm^{-1} due to NH_2, indole NH, CN, pyrazole CO and CO functions, respectively. In ^{1}H NMR spectrum, the signals at δ 11.5 (s, 1H, indole NH), 7.0–8.2 (m, 16H, 14 ArH and NH_2), 4.9 (s, 2H, O─CH_2─CO) and 4.2 (s, 2H, pyrazole CH_2CO) were noticed. The mass spectrum of compound **8a** showed isotopic molecular ion peaks at m/z 560, 562 confirmed the formation of **8a** (Scheme 1).

4. Antioxidant activity studies

4.1. Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP)

Figs. 1–3 show the reducing power of synthesized compounds (**2–8**) examined as a function of their concentration. In this as-

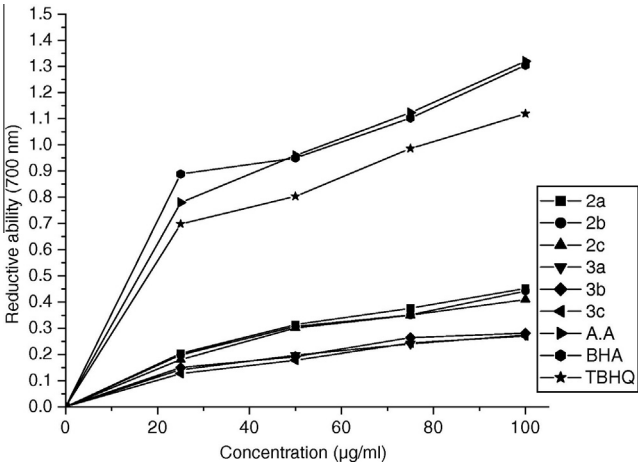


Figure 1 Reducing power of compounds **2–8**.

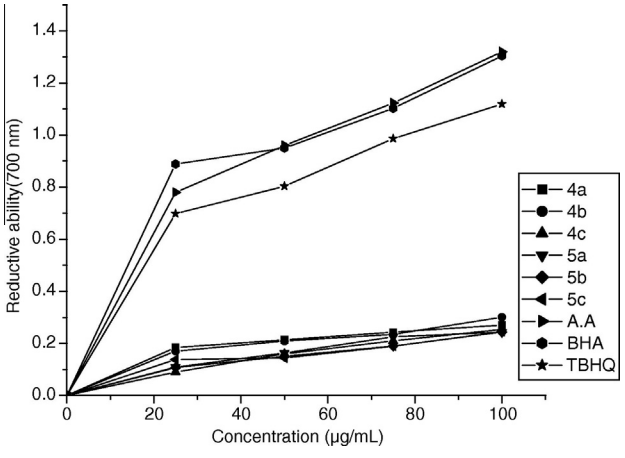


Figure 2 Reducing power of compounds **2–8**.

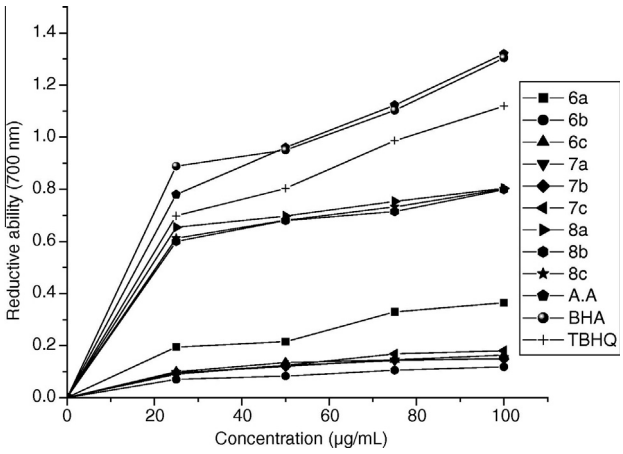


Figure 3 Reducing power of compounds **2–8**.

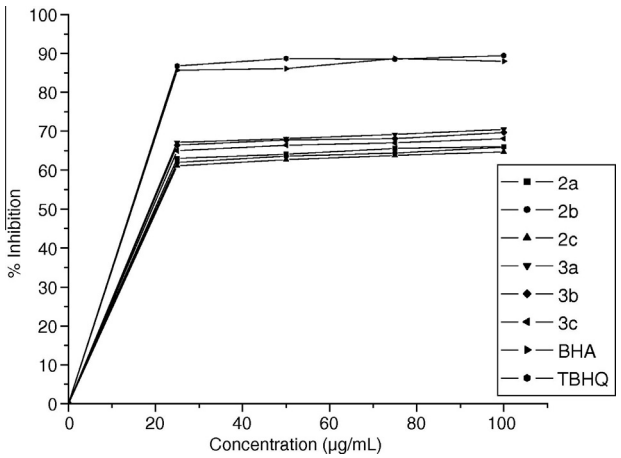


Figure 4 DPPH radical scavenging activity of compounds **2–8**.

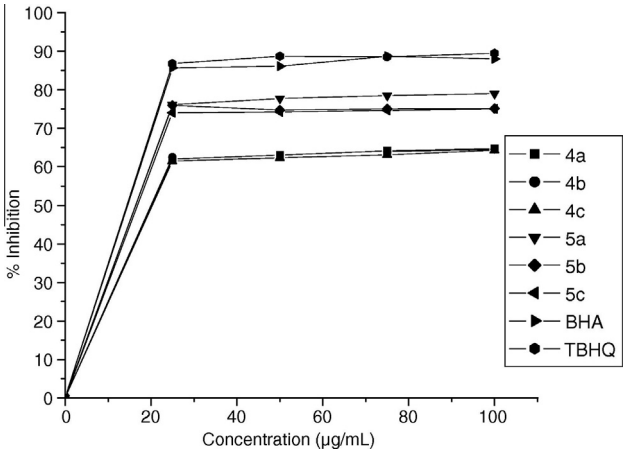


Figure 5 DPPH radical scavenging activity of compounds **2–8**.

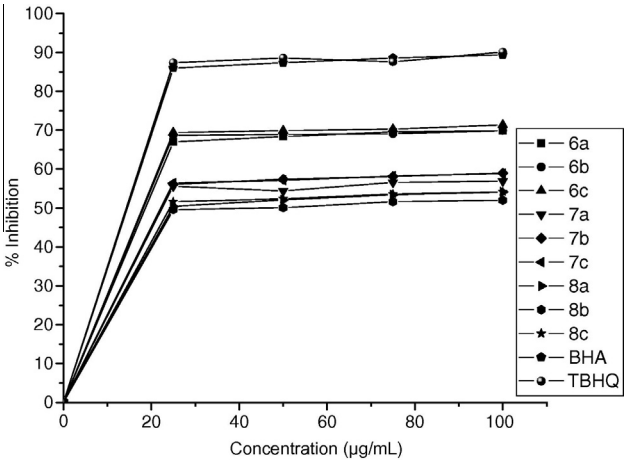


Figure 6 DPPH radical scavenging activity of compounds **2–8**.

say, the yellow color of the test solution changes to various shades of green and blue depending upon the reducing power of each compound. The presence of reducer (i.e. antioxidant) causes the reduction of the Fe^{+3}/Ferricyanide complex to the ferrous form giving after the addition of trichloroacetic acid and ferric chloride, the perls Prussian blue that can be monitored at 700 nm. The reducing power of test compounds increases with increase in concentration. Compounds **2–6** and **8** exhibited very low absorption, whereas compounds **7a–c** were found to have higher absorption but lower than the standards.

The presence of enamine and α,β-unsaturated ketonic functions in the pyrazolone moiety in addition to the alkyl group may play an important role to act as a better electron donor which may enhance reducing power ability of **7.** Where as such systems are not available in the rest of the test compounds. Compound **7a** exhibited the maximum absorption value compare to **7b** and **7c**. This may be due to the chloro-substitution at 5-position of indole, which may be helping for stabilization of the free radical form after donating electron and thus to leading maximum reducing ability compared to **7b** and **7c**.

4.2. Radical scavenging activity (RSA)

Free radical scavenging is one of the best known mechanisms by which antioxidants inhibit lipid oxidation. 1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity evaluation is standard assay in antioxidant activity studies and offers a rapid technique for screening the radical scavenging activity (RSA) of specific compounds. The RSA of synthesized compounds (**2–8**) were tested using methanolic solution of the stable free radical DPPH. The results of the tested compounds were shown in Figs. 4–6. The freshly prepared DPPH solution exhibits a deep purple color with absorption maxima at 517 nm. The purple color generally fades/disappears when an antioxidant is present in the medium. Thus, antioxidant molecule can quench DPPH free radical (i.e. by providing hydrogen atoms or by electron donation, conceivably via a free radical attack on DPPH molecule) and convert them to a colorless/bleached product, resulting in absorbance at 517 nm. Therefore, the more rapidly the absorbance decreases, the more potent the antioxidant activity of the compounds. Hence this method is based on the reduction of alcoholic DPPH solution in the presence of a hydrogen-donating antioxidant due to the formation of the non-radical form DPPH-H by the reaction.

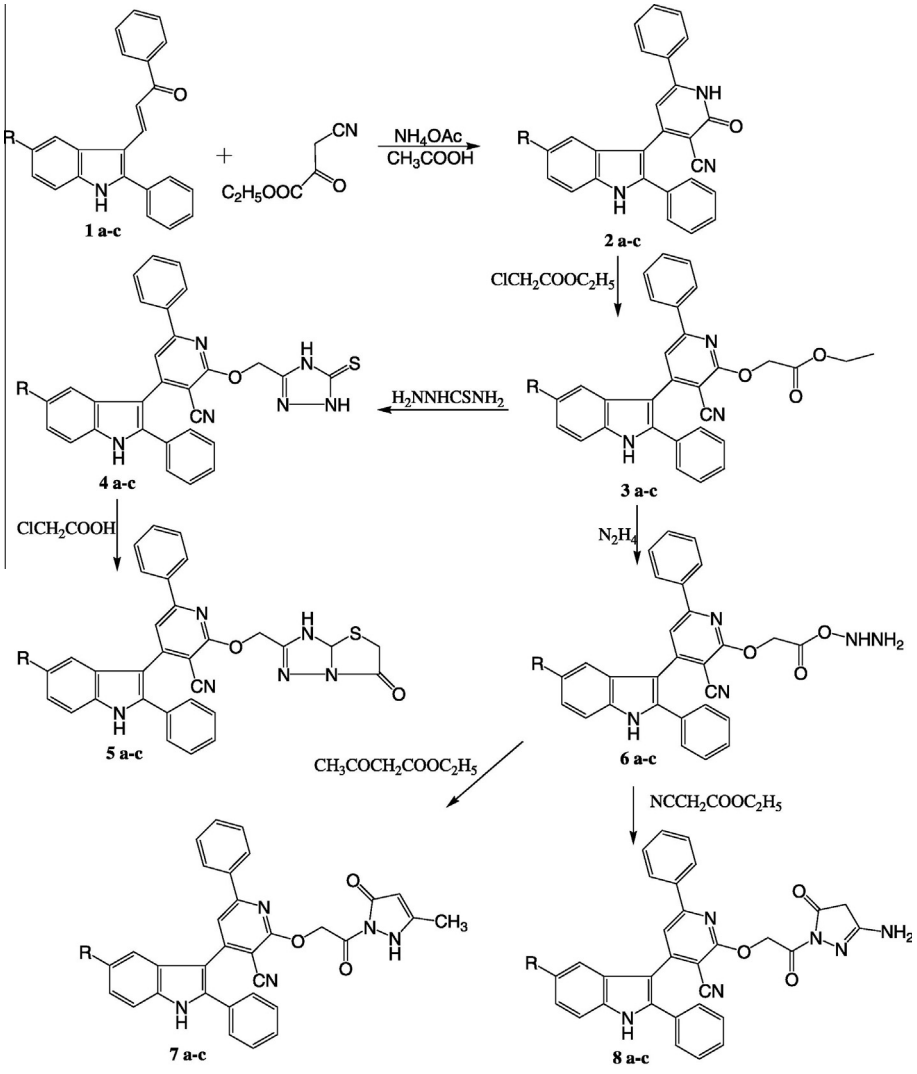
In the case of thiazolo[3,2,-b][1,2,4]triazoles derivative **5a**, this showed highest DPPH scavenging activity with percent

inhibition of 78.85 at concentration of 75 μg/ml, when compared with the other compounds. This increased activity may be due to existence of the CH_2CO group. The presence of cyano group was inadequate for antioxidant activity. All the compounds containing pyridine ring showed low RSA activity. Hence presence of cyano and pyridine substituents may drastically decrease the RSA. None of the compounds showed good RSA activity than standards (see Scheme 1).

4.3. Antimicrobial activities

The results of antimicrobial activity evaluations (Table 1) reveals that substances **4a**, **5a** and **7b** exhibited maximum inhibitory activity against *Pseudomonas aeruginosa*. Compound **4a, 5a** and **8a** exhibited maximum zone of inhibition against gram negative bacteria. In addition, compound **4a**, **5b** and **8a** showed maximum inhibitory growth against *Aspergillus oryzae* and compound **5a** showed maximum inhibitory growth against *Aspergillus niger*. In addition, the results indicate that, rest of the compounds exhibited moderate growth inhibitory activities against all the four tested microbes.

The majority of the compounds containing indole, phenyl, 1,2,4-triazole, thiozolo[3,2,-b][1,2,4]triazole and pyrazolone in the ring system that incorporate the pyridine moiety had growth inhibitory activities. It is worth mentioning that compound (**4a–c**) and (**5a–c**) possessing 1,2,4-triazole ring appended to the pyridine ring system via methyloxy-linker showed a high antibacterial activity. In contrast, attachment of pyrazole nucleus to the pyridine nucleus via acetyloxy-linker exhibited potent antifungal activity against the two organisms used. Compound **5a** exhibited consistent antimicrobial activity towards all the organisms tested. Hence, several synthesized compounds exhibited comparable activity to the gentamycin and fluconazole. However, none of the compounds exhibited zone of inhibition more than the standards.



Scheme 1

Table 1 Antimicrobial activity results of compounds **2–8**.

Comp. no.	Antibacterial activity (in mm)						Antifungal activity (in mm)					
	P. aeruginosa			*P. kneumonia*			*A. oryzae*			*A. niger*		
	250 μg/ml	125 μg/ml	62.5 μg/ml	250 μg/ml	125 μg/ml	62.5 μg/ml	250 μg/ml	125 μg/ml	62.5 μg/ml	250 μg/ml	125 μg/ml	62.5 μg/ml
2a	10	10	09	12	12	12	11	11	10	12	12	11
2b	10	09	09	10	10	09	11	10	10	12	12	12
2c	11	11	10	12	10	10	09	10	10	09	09	08
3a	12	12	11	12	12	12	10	10	09	10	10	10
3b	11	11	10	13	12	12	09	08	08	10	10	08
3c	12	11	11	10	10	09	08	08	07	07	06	06
4a	13	13	13	14	14	13	13	13	13	11	10	10
4b	10	10	10	09	07	06	11	11	11	10	10	09
4c	09	08	06	07	07	07	10	09	09	12	12	11
5a	13	13	12	14	14	13	12	12	12	13	13	12
5b	09	09	07	12	11	12	13	13	12	12	11	11
5c	07	07	06	10	09	09	11	11	10	10	10	09
6a	12	12	12	12	12	12	11	11	11	11	11	10
6b	12	12	12	10	09	08	10	09	09	10	10	09
6c	10	10	09	09	07	07	10	10	10	09	08	08
7a	12	11	11	10	09	09	12	12	12	12	12	12
7b	13	13	13	08	07	07	10	09	09	11	11	10
7c	10	09	09	08	07	07	10	11	11	08	08	07
8a	11	11	09	14	13	13	13	13	12	10	10	10
8b	10	10	10	13	13	13	12	12	12	08	08	08
8c	09	08	08	11	10	10	10	09	09	08	07	07
Std. I	15	14	14	16	16	15	–	–	–	–	–	–
Std. II	–	–	–	–	–	–	14	14	15	14	14	15

Std. I: Gentamycin; Std. II: Flucanozole.

5. Antioxidant activity assays

5.1. Reducing power assay

The reducing power of the synthesized compounds was determined according to the method of Oyaizu (1986). 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.

5.2. Radical scavenging activity (RSA) assay

The free radical scavenging activity of (**2a–c**)–(**8a–c**) was carried out in the presence of the stable free radical DPPH following Hatano's method (Hatano et al., 1988) using 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 (**2a–c**)–(**8a–c**) 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

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

5.3. Antimicrobial assay

The antimicrobial activities (Indian Pharmacopoeia, 1985) of the compounds prepared in this effort were evaluated using *P. aeruginosa* (Gram negative bacteria), *Klebsiella pneumoniae* (gram negative bacteria), *A. oryzae* and *A. 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 DMF, resulting in a final concentration of 250 μg/ml, 125 250 μg/ml and 62.5 250 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.

6. Conclusion

Antioxidants may be classified according to their mode of action as being free radical terminators, chelators of metal ions involved in catalyzing lipid oxidation or radical scavengers that react with oxygen in closed systems. In this study we presented the antioxidant activity of synthesized compounds using two comparable methods, 1,1-diphenyl-2-picrylhydrazyl radical-scavenging activity test and assay for evaluation of reducing power. The synthesized compounds scavenged the DPPH radical reduced Fe^{+3} cations in a concentration dependent manner. These experiments were prompted, first, by the upsurge of interest in the contribution of reactive oxygen species and oxygen-derived free radical to tissue damage and human diseases, and, second, by the increasing awareness antioxidants that counteract oxidative stress may exert valuable protective actions.

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