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Research Article

Synthesis and Characterization of Novel Series of 1,2,4-Triazolo[3,4-b]-1,3,4-Thiadiazole Derivatives of Anilinoacetic Acids as Promising Antioxidant Agents

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Abstract

The preparation of a novel series of 6-arylaminomethyl-3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (5) by the cyclocondensation of 5-substituted-4-amino-3-mercapto-1,2,4-triazoles (2) with appropriately substituted anilinoacetic acids (4) employing phosphorous oxychloride is reported. The newly synthesized compounds (5) were screened for their antioxidant activity by DPPH radical scavenging assay and their structures were elucidated on the basis of their ^{1}H-NMR, IR, Mass spectral and elemental analysis. Some of the tested compounds showed good DPPH radical scavenger activities comparable to that of standard BHA.

Keywords: Anilinoacetic acids; 1,2,4-Triazoles; Triazolo-thiadiazoles; Antioxidant activity

Introduction

The 1,2,4-triazole nucleus constitutes an integral component in drug discovery. It has been incorporated into both non-bridged drugs such as anastrozole (anticancer) [1,2], ribavirin (antiviral) [1,3], fluconazole, voriconazole (antifungal agents) [4] and in biologically active N-bridged drugs like triazolam (sedative agent) [1,5], estazolam and alprazolam (anxiolytic agents) [1,6,7]. The 1,3,4-thiadiazoles have attracted more interest to the researchers due to their prominent biological properties including anticonvulsant, anti-tubercular, anti-inflammatory, anti-leishmanial, antioxidant [8], antimicrobial and antidepressant activities [8,9]. There are also many drugs containing the 1,3,4-thiadiazole moiety such as acetazolamide, megazol and methazolamide [10]. Interestingly, some current reports showed that the fusion of the biolabile 1,2,4-triazole with 1,3,4-thiadiazole rings affords fused bicyclic compounds with improved biological activities than their corresponding non-bridged precursors. These include some ibuprofen-based 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles with enhanced anti-inflammatory and analgesic properties than precursor ibuprofen [11-13], and some naproxen-based 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles with enhanced analgesic, ulcerogenic, anti-inflammatory, and lipid peroxidation activities than starting naproxen [14]. Furthermore, N-(heteroarylmethyl) aniline derivatives with varied potent activities such as antimicrobial [15,16], antifungal, anticancer [17,18], herbicidal [19] and analgesic [20] were also reported. Prompted by these observations and in continuation of our research for new bioactive fused heterocycles [21,22], we herein describe the synthesis of a new series of 6-arylaminomethyl-3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles as promising antioxidant agents.

Materials and Methods

Chemistry

The Innovative DTC-967A apparatus was used to determine the melting points of the newly synthesized compounds and the results are uncorrected. The IR-spectra were recorded on Shimadzu FT-IR Prestige-21 spectrophotometer in KBr pellets and are expressed in cm^{-1}. The mass spectra were recorded on a Shimadzu LC-MS-8030 mass spectrometer operating at 70 eV. The ^{1}H-NMR spectra were recorded on a Bruker Avance II 400 MHz instrument in DMSO-d_6 solvent and TMS as an internal standard. All chemical shift values were reported as δ (ppm), downfield from TMS. The Systronics spectrophotometer 106 was used to record the absorbance of DPPH radical scavenging antioxidant assay. The C, H, N analysis was carried out on Vario EL III Elemental Analyzer. The completion of the reaction and the purity of the compounds were monitored by

TLC using Merck silica gel 60 F_{256} coated aluminum with hexane: ethylacetate (2:8) as the mobile phase.

General Procedure for the Synthesis of 6-arylaminomethyl-3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (5a-s)

The equimolar amounts of 1,2,4-triazoles (2) (0.01 mol) and anilinoacetic acids (4) in phosphorous oxychloride (20 ml) were heated under reflux for 16 hours. After cooling, the resulting reaction mass was poured into crushed ice with stirring. Finally, powdered sodium bicarbonate was added portion wise till the pH of the reaction mixture was raised to 8. The solid separated was filtered, washed thoroughly with cold water, dried and recrystallized from ethanol to give pure compounds 5a-s. The spectral data of some selected illustrative compounds prepared according to this procedure are given below:

6-(p-Chloroanilinomethyl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole (5a)

IR (KBr, cm^{-1}): 3316 (NH stretch), 2968 (C-H stretch), 1642 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6)*: δ (ppm) 4.64 (s, 2H, CH_2-N), 6.67 (d, J=8.56 Hz, 2H, Ar-H), 7.11 (d, J=8.48 Hz, 2H, Ar-H), 9.36 (s, 1H, =CH-N of triazolothiadiazole ring). LC-MS (m/z): 263.75 (M^+ - 1), 265.90 (M^+ + 1)

6-(Anilinomethyl)-3-methyl-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole (5d)

IR (KBr, cm^{-1}): 3358 (NH stretch), 2968 (C-H stretch), 1632 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 2.64 (s, 3H, CH_3), 4.62 (s, 2H, CH_2-N), 6.65 (m, 3H, Ar-H), 7.11 (m, 2H, Ar-H), 7.47 (s, broad, 1H, -NH). LC-MS (m/z): 246.00 (M^+ + 1).

6-(p-Chloroanilinomethyl)-3-methyl-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazole (5e)

IR (KBr, cm^{-1}): 3312 (NH stretch), 2974 (C-H stretch), 1624 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 2.64 (s, 3H, CH_3), 4.63 (s, 2H, -CH2-N), 6.67 (d, J=8.84 Hz, 2H, Ar-H), 6.88 (s, broad, ^{1}H, -NH), 7.09 (d, J=8.88 Hz, 2H, Ar-H). LC-MS (m/z): 279.90 (M^+ + 1), 281.90 (M^+ + 3).

6-(p-Fluoroanilinomethyl)-3-methyl-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazole (5f)

IR (KBr, cm^{-1}): 3315 (NH stretch), 2922 (C-H stretch), 1614 (C=N). ^{1}H-NMR (400 MHz, DMSO-d6): δ (ppm) 2.66 (s, 3H, CH_3), 4.59 (s, 2H, -CH_2-N), 6.40-6.55 (broad, 1H, NH), 6.65 (m, 2H, Ar-H), 6.88 (t, 2H, Ar-H). LC-MS (m/z): 264.02 (M^+ + 1).

6-(p-Methylanilinomethyl)-3-methyl-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazole (5g)

IR (KBr, cm^{-1}): 3406 (NH stretch), 2984 (C-H stretch), 1633 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6)*: δ (ppm) 2.18 (s, 3H, CH_3), 2.67 (s, 3H, -CH_3), 4.60 (s, 2H, -CH_2-N), 6.58 (d, J=8.44 Hz, 2H, Ar-H), 6.93 (d, J=8.2 Hz, 2H, Ar-H). LC-MS (m/z): 260.00 (M^+ + 1).

6-(Anilinomethyl)-3-ethyl-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole (5j)

IR (KBr, cm^{-1}): 3346 (NH stretch), 2971 (C-H stretch), 1618 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6)*: δ (ppm) 1.38 (t, 3H, CH_3), 3.03 (q, 2H, -CH_2), 4.62 (s, 2H, -CH2-N), 6.66 (m, 3H, Ar-H), 7.11 (m, 2H, Ar-H). LC-MS (m/z): 260.01 (M^+ + 1).

6-(p-Fluoroanilinomethyl)-3-ethyl-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazole (5l)

IR (KBr, cm^{-1}): 3319 (NH stretch), 2931 (C-H stretch), 1614 (C=N). ^{1}H-NMR (400 MHz, DMSO-d6)*: δ (ppm) 1.40 (t, 3H, CH_3), 3.03 (q, 2H, -CH_2), 4.61 (s, 2H, -CH_2-N), 6.66 (m, 2H, Ar-H), 6.89 (t, 2H, Ar-H). LC-MS (m/z): 278.05 (M^+ + 1).

6-(p-Methylanilinomethyl)-3-ethyl-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazole (5m)

IR (KBr, cm^{-1}): 3344 (NH stretch), 2978 (C-H stretch), 1614 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 1.39 (t, 3H, CH_3), 2.17 (s, 3H, -CH_3), 3.04 (q, 2H, -CH_2), 4.58 (s, 2H, -CH2-N), 6.45 (s, broad, ^{1}H, -NH), 6.57 (d, J=8.2 Hz, 2H, Ar-H), 6.92 (d, J=8.04 Hz, 2H, Ar-H). LC-MS (m/z): 274.05 (M^+ + 1).

6-(p-Chloroanilinomethyl)-3-propyl-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazole (5p)

IR (KBr, cm^{-1}): 3304 (NH stretch), 2956 (C-H stretch), 1612 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6): δ(ppm) 0.94 (t, 3H, CH_3), 1.81 (m, 2H, -CH2-), 2.98 (t, 2H, -CH_2-), 4.61 (s, 2H, -CH_2-N), 6.64 (d, J=8.84 Hz, 2H, Ar-H), 7.06 (d, J=6.96 Hz, 2H, Ar-H), 7.46 (s, broad, 1H, -NH). LC-MS (m/z): 309.9 (M^+ + 1), 311.9 (M^+ + 3).

6-(p-methylanilinomethyl)-3-propyl-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazole (5r)

IR (KBr, cm^{-1}): 3311 (NH stretch), 2929 (C-H stretch), 1614 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6)*: δ (ppm) 1.00 (t, 3H, CH_3), 1.84 (m, 2H, -CH_2), 2.17 (s, 3H, -CH_3), 2.99 (t, 2H, -CH2), 4.58 (s, 2H, -CH2-N), 6.58 (d, J=8.4 Hz, 2H, Ar-H), 6.92 (d, J=8.2 Hz, 2H, Ar-H). LC-MS (m/z): 288.05 (M^+ + 1).

*NH peak was not seen probably due to the rapid exchange between this NH with D2O that might be present as impurities in the DMSO-d6 solvent used to record these spectra.

Antioxidant activity

The DPPH radical scavenging assay was carried out by the modified method of Mensor et al. [23]. The working test sample solution (1mg/ml) was made in DMSO. 150µl was taken from each test sample solution in a test tube, diluted with ethanol up to 2.5 ml, then freshly prepared DPPH solution (3mM in ethanol) (1ml) was added to each test tube and shaken well. After 30 min of incubation in dark condition at the ambient room temperature, the absorbance of the sample was read at 518 nm against the absorbance of the control (Ac) prepared in the same way as the sample solution,

except that 150µl of test sample was replaced by ethanol solvent. The DPPH radical scavenging activity was calculated as follows: % radical scavenged = [(Ac-As)/Ac]x 100. The experiments were replicated thrice and the results were presented as their mean value ± SD.

Result and Discussion

Chemistry

The synthesis of title compounds (5) is as outlined in the Figure 1. The key starting material thiocarbohydrazide (1) was prepared by reacting hydrazine hydrate with carbon disulfide [24]. The cyclocondensation of thiocarbohydrazide (1) with different carboxylic acids (formic, acetic, propionic and butyric acids) under reflux condition afforded 5-substituted-4-amino-3-mercapto-1,2,4-triazoles (2) [25,26]. The required substituted anilinoacetic acids (4) were synthesized by hydrolyzing their corresponding esters (3) in aqueous NaOH [27]. The latter compounds (3) were prepared by refluxing various anilines, sodium acetate and ethyl chloroacetate in ethanol solvent [28]. The cyclocondensation of 5-substituted-4-amino-3-mercapto-1,2,4-triazoles (2) with anilinoacetic acids (4) using phosphorous oxychloride as a condensing agent afforded new bicyclic compounds 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles carrying N-methyl aniline moiety (5). The ^{1}H-NMR, IR, Mass spectral and elemental analysis confirmed the proposed structure of the newly synthesized compounds. The characterization data of the title compounds (5) is given in Table 1. The detailed description of the spectra data of compound 5h taken as a typical example is given below.

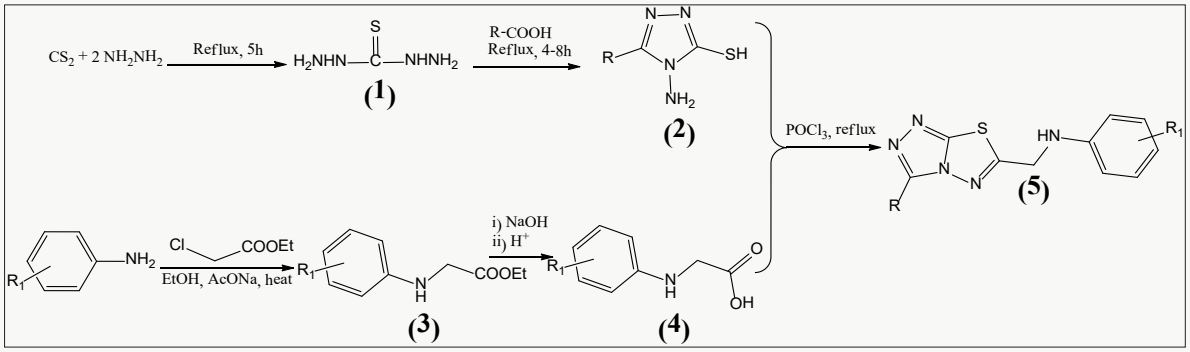

Figure 1: Outline for the synthesis of novel 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (5a-s).

R= H, CH_3, C_2H5, C_3H_7; R1= H, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3,4-Cl_2

Table 1: Characterization data of 6-arylaminomethyl-3-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (5a-s).

Compound	R	R1	M.P (oC) (Yield %)	Molecular Formula (Mol. Wt)	Elemental Analysis Found (Calculated) (%)		
					C	H	N
5a	H	4-Cl	102-104 (48)	$C_{10}H_8ClN_5S$ (265.72)	45.18 (45.20)	3.08 (3.03)	26.24 (26.36)
5b	H	4-F	108-110 (40)	$C_{10}H_8FN5S$ (249.27)	48.16 (48.18)	3.37 (3.23)	28.08 (28.10)
5c	H	4-CH_3	100-102 (32)	$C_{11}H_{11}N_5S$ (245.30)	53.91 (53.86)	4.50 (4.52)	28.62 (28.55)
5d	CH_3	H	158-160 (70)	$C_{11}H_{11}N_5S$ (245.30)	53.88 (53.86)	4.48 (4.52)	28.64 (28.55)
5e	CH_3	4-Cl	102-104 (45)	$C_{11}H_{10}ClN_5S$ (279.75)	47.11 (47.23)	3.62 (3.60)	25.15 (25.03)
5f	CH_3	4-F	108-110 (80)	$C_{11}H_{10}FN_5S$ (263.29)	50.23 (50.18)	3.90 (3.83)	26.52 (26.60)
5g	CH_3	4-CH_3	100-102 (91)	$C_{12}H_{13}N_5S$ (259.33)	55.47 (55.58)	5.09 (5.05)	26.94 (27.01)
5h	CH_3	4-OCH_3	80-82 (82)	$C_{12}H_{13}N_5OS$ (275.33)	52.26 (52.35)	4.87 (4.76)	25.48 (25.44)
5i	CH_3	3,4-Cl_2	101-103 (79)	$C_{11}H_9C_{l2}N_5S$ (314.19)	42.16 (42.05)	3.04 (2.89)	22.12 (22.29)
5j	C_2H_5	H	98-100 (66)	$C_{12}H_{13}N_5S$ (259.33)	55.62 (55.58)	5.18 (5.05)	26.95 (27.01)
5k	C_2H_5	4-Cl	79-81 (71)	$C_{12}H_{12}ClN_5S$ (293.78)	49.18 (49.06)	4.19 (4.12)	23.78 (23.84)
5l	C_2H_5	4-F	118-120 (69)	$C_{12}H_{12}FN_5S$ (277.32)	51.82 (51.97)	4.42 (4.36)	25.19 (25.25)
5m	C_2H_5	4-CH_3	80-82 (82)	$C_{13}H_{15}N_5S$ (273.36)	57.19 (57.12)	5.48 (5.53)	25.69 (25.62)
5n	C_3H_7	H	76-78 (48)	$C_{13}H_{15}N_5S$ (273.36)	57.03 (57.12)	5.44 (5.53)	25.75 (25.62)
5o	C_3H_7	4-Br	82-84 (78)	$C_{13}H_{14}BrN_5S$ (352.25)	44.47 (44.33)	4.08 (4.01)	19.76 (19.88)
5p	C_3H_7	4-Cl	80-82 (92)	$C_{13}H_{14}ClN_5S$ (307.80)	50.61 (50.73)	4.49 (4.58)	22.84 (22.75)
5q	C_3H_7	4-F	81-83 (77)	$C_{13}H_{14}FN_5S$ (291.35)	53.52 (53.59)	4.76 (4.84)	24.12 (24.04)
5r	C_3H_7	4-CH_3	100-102 (97)	$C_{14}H_{17}N_5S$ (287.38)	58.64 (58.51)	5.81 (5.96)	24.43 (24.37)
5s	C_3H_7	4-OCH_3	98-100 (76)	$C_{14}H_{17}N_5OS$ (303.38)	55.38 (55.42)	5.74 (5.65)	23.12 (23.08)

In the IR spectrum of 6-(p-methoxyanilinomethyl)-3-methyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (5h) the absorption band corresponding to NH stretching was observed at 3317 cm^{-1}, C-H stretching bands were seen at 3047 cm^{-1} and 2924 cm^{-1} while the C=N stretching band appeared at 1614 cm^{-1}. The formation of fused bicyclic compounds (5) was further confirmed by the absence of -OH, -SH and -NH2 peaks of the precursors anilino acetic acids and 4-amino-3-mercapto-1,2,4-triazoles in the condensed products, thereby confirming their involvement in the formation of bicyclic triazolothiadiazole derivatives (5). Furthermore, the appearance of $-CH_2$-NH- peaks in the proton NMR spectra of title compounds (5) was an additional proof for the formation of N-bridged bicyclic compounds (5). In the ^{1}H-NMR spectrum of 6-(p-methoxyanilinomethyl)-3-methyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (5h) (Figure 2a,2b), methyl protons ($-CH_3$) appeared as a singlet at δ 2.65 ppm integrating for three protons, methoxy protons ($-OCH_3$) came into resonance as a singlet at δ 3.67 ppm integrating for three protons, methylene ($-CH_2$-N) protons resonated as a singlet at δ 4.55 ppm integrating for two protons. The peak at δ 6.15 ppm (broad band) integrating for one proton was assigned to NH peak. Two doublets centered at δ 6.62 ppm (J=8.84 Hz) and at δ 6.72 ppm (J=8.76 Hz) integrating for two protons each were attributed to ortho and meta protons of p-methoxyphenyl ring respectively. The mass spectrum of this compound 5h (Figure 3) showed molecular ion peak at m/z 275.80 (M^+ + 1), which is in conformity with its molecular formula $C_{12}H_{13}N_5OS$.

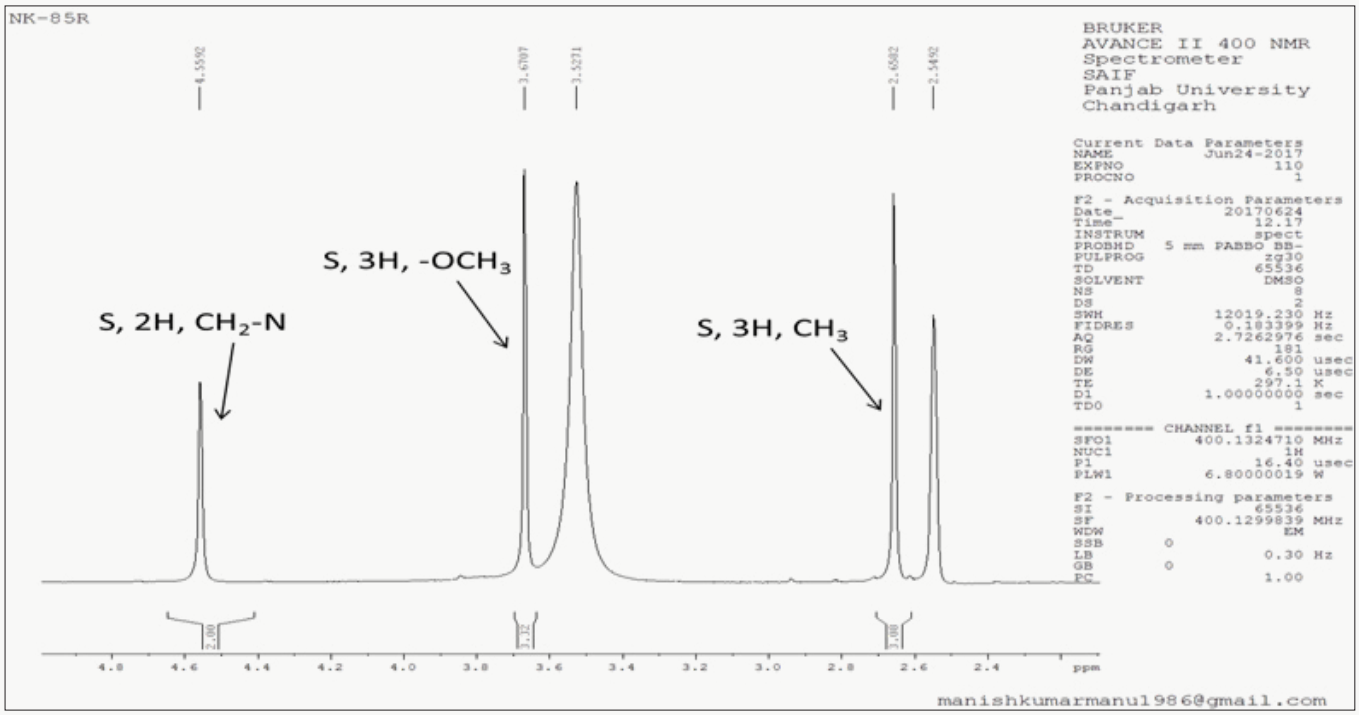

Figure 2b: Aliphatic region of 1H NMR of 6-(p-methoxyanilinomethyl)-3-methyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (5h).

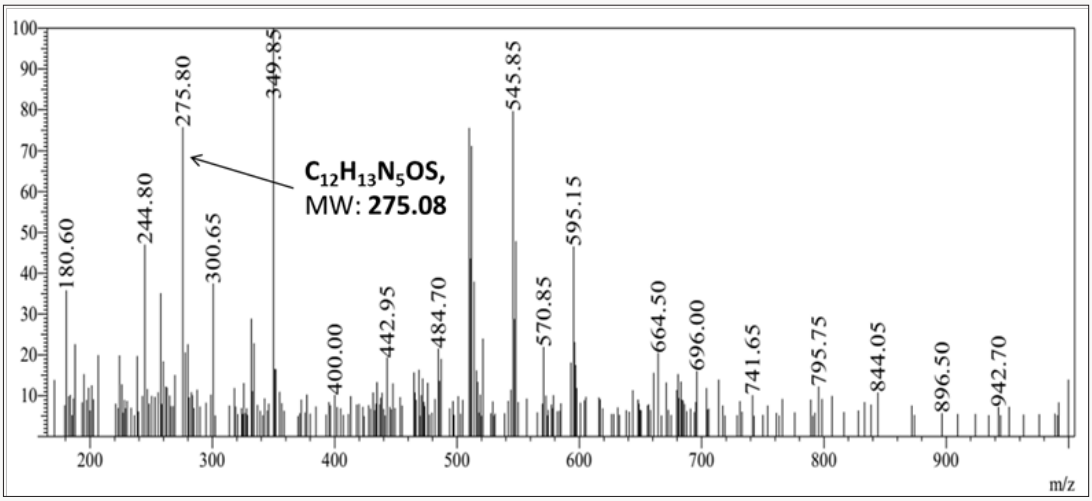

Figure 3: Mass spectrum of 6-(p-methoxyanilinomethyl)-3-methyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (5h).

Antioxidant activity

The DPPH free radical scavenging assay was used to screen for the antioxidant activity of the newly synthesized compounds 5a-s. The extent of discoloration of DPPH stable radical from violet to colorless or pale yellow indicated the scavenging potential of the tested compounds. The results as presented in Table 2 showed that methoxy substituted compounds on phenyl ring (R_1 = 4-OCH3) (5s, 5h), and unsubstituted compounds on 1,2,4-triazole moiety of triazolo-thiadiazole ring (R = H) (5a, 5b, 5c) exhibited very good antioxidant activities in the series with respectively 73.7%, 67.9% and 70.7%, 67.8%, 71.4% DPPH radical scavenger activity comparable to that of standard butylated hydroxyanisole (BHA) (87.1%).

Table 2: DPPH scavenging activity of compounds 5a-s.

Compound	Percentage DPPH Inhibition (%)a
5a	70.7±0.20
5b	67.8±0.30
5c	71.4±0.17
5d	53.5±0.37
5e	25.5±0.10
5f	39.6±0.26
5g	37.5±0.17
5h	67.9±0.20
5i	23.4±0.10
5j	44.5±0.17
5k	29.6±0.10
5l	36.7±0.20
5m	52.6±0.17
5n	49.5±0.10
5o	40.1±0.17
5p	40.3±0.17
5q	37.3±0.10
5r	43.3±0.26
5s	73.7±0.26
BHA	87.1±0.36

Conclusion

In the present study, we achieved the synthesis of a new series of 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles bearing N-methylaniline moiety. These newly synthesized compounds were characterized by analytical and spectroscopic methods. They were also screened for their antioxidant activity by DPPH free radical scavenging assay. Compounds 5a, 5c and 5s were found to be most potent antioxidant agents in the series.

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