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Synthesis, Characterization and Pharmacological Activities of 3,6-Disubstituted-1,2,4-triazolo [3,4-*b*]-1,3,4-thiadiazoles and their Dihydro Analogues

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Abstract: 4-Amino-5-aryl/heteroaryl substituted-3-mercapto-1,2,4-triazoles 3(a-d) were prepared from the corresponding aromatic carboxylic acids through a multi-step sequence. Compounds 3(a-d) were made to react with various aromatic/hetero aromatic acids and hetero aromatic aldehydes to give 3,6-disubstituted-1,2,4-triazolo [3,4-*b*]-1,3,4-thiadizoles and 3,6-disubstituted-5,6-dihydro-1,2,4-triazolo [3,4-*b*]-1,3,4-thiadizoles respectively. Elemental analysis, IR, ^{1}H NMR and mass spectral data elucidated the structures of all newly synthesized compounds. Synthesized compounds are studied for their antibacterial, antifungal, anti-inflammatory and analgesic activities. Some of the tested compounds showed significant pharmacological activities.

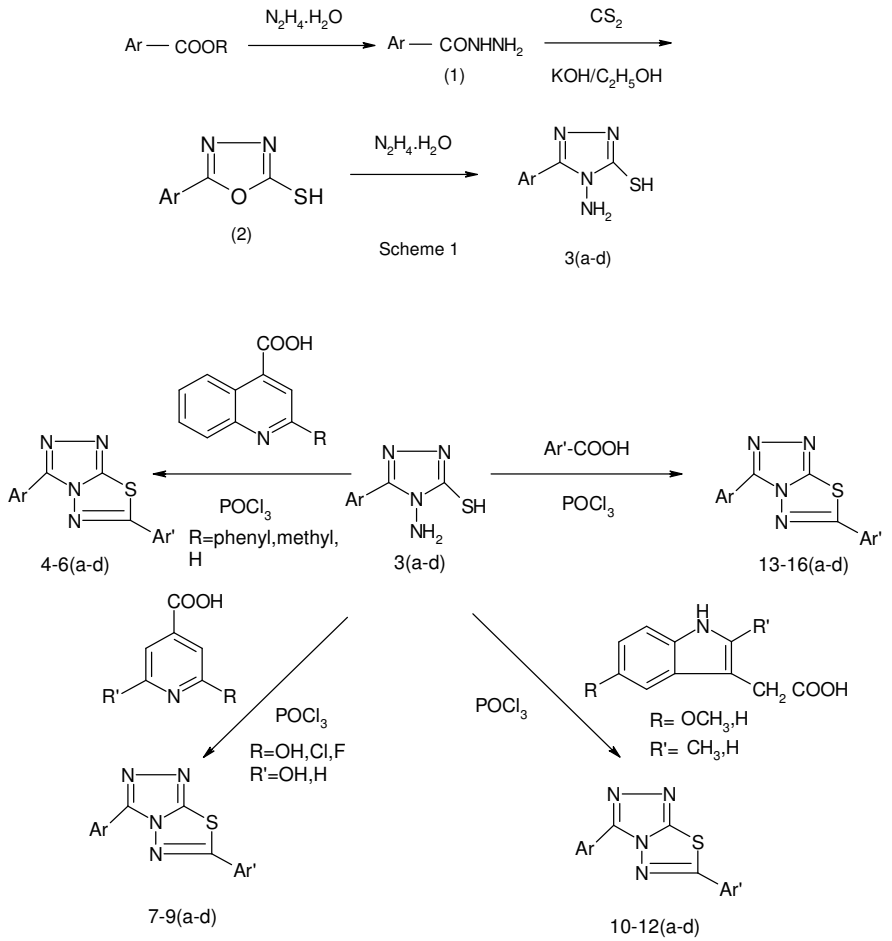
Keywords: Triazoles, Triazolothiadiazoles, Dihydro triazolothiadiazoles, Pharmacological activities.

Introduction

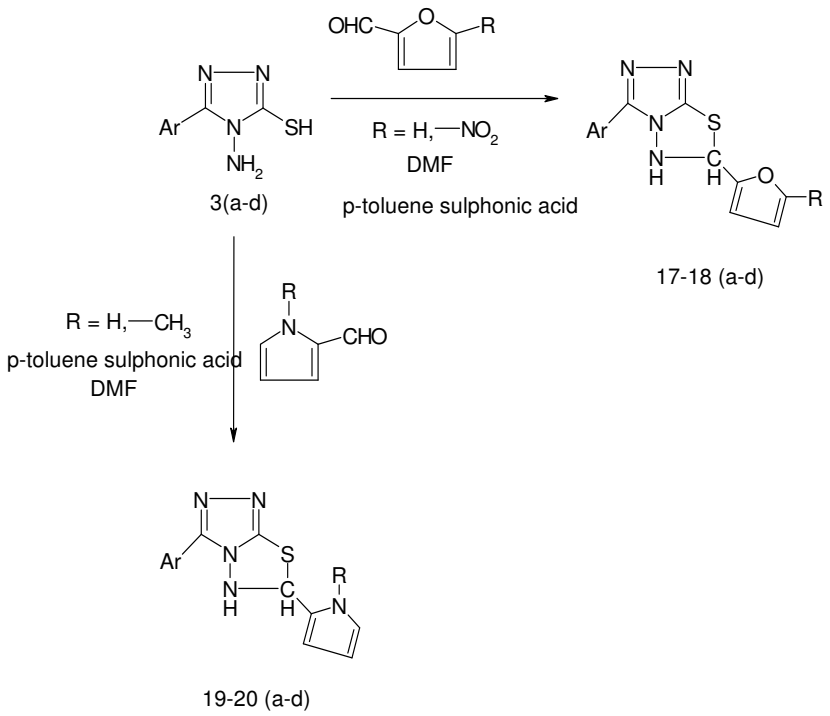
1,2,4-Triazole and 1,3,4-thiadiazoles represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities[1-5]. Various substituted 1,2,4-triazolo [3,4-*b*]-1,3,4-thiadiazoles and their dihydro analogues are associated with diverse pharmacological activities such as antimicrobial[6], antibacterial[7], antitubercular[8], anti-inflammatory[9-10], antifungal[11] *etc*. A triazolo thiadiazole system may be viewed as a cyclic

analogue of two very important components thiosemicarbazide[12] and biguanide[13], which often display diverse biological activities. Prompted by these observations, as part of our research program aimed at developing new biologically active nitrogen and sulphur containing heterocycles, we report the synthesis of some new 3,6-disubstituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles (Scheme 2) and their 5,6-dihydro analogues (Scheme 3). 4-Amino-3-aryl/aralkyl/heteroaryl substituted-5-mercapto-1,2,4-triazole 3(a-d) were prepared using the method[14] (Scheme 1). The structures of the intermediate triazole derivatives were based on their elemental analysis and other spectral data.

Condensation of the triazoles 3 (a-d) with aromatic acids in the presence of phosphorous oxychloride (Scheme 2) produced a series of triazolo thiadiazoles (4-16); while its condensation with hetero aromatic aldehydes (Scheme 3) afforded a series of 5,6-dihydro triazolo thiadiazoles (17-20). The structure assigned to compounds was substantiated by their analytical and other spectral data.



Scheme 2



Scheme 3

Experimental

Thin layer chromatography was used to access the completion of the reaction and purity of the compounds synthesized. Melting points were taken in open glass capillary tubes using thiels tube containing liquid paraffin and are uncorrected. IR spectra in KBr were recorded on a Shimadzu-8400 FTIR spectrophotometer, ^{1}H NMR spectra were recorded on Brucker spectrophotometer (400MHz) in DMSO-d_6/$CDCl_3$ using TMS as an internal standard (chemical shifts are expressed in δ ppm), mass spectra were recorded in Finnigan MAT 8230 mass spectrophotometer and elemental analysis were recorded on Thermo Finnigan FLASH EA 1112 CHNS anlyser. The purity of the compounds were checked on silica gel-G coated plates by using ethyl acetate and petroleum ether (1:1) as the eluent and observed in UV light. All the synthesized compounds gave satisfactory elemental analyses.

General procedure for the preparation of Aryl hydrazide. (1)

To the methyl/ethyl esters of substituted aromatic acids (0.1 mol), hydrazine hydrate (0.1mol) was added and refluxed the solution for 30 min. 20 mL of ethanol was added to the refluxing mixture as a solvent in order to homogenize solution. The resulting mixture was further allowed to reflux for 6 h. Excess ethanol was distilled out and the contents were allowed to cool. The crystals formed was filtered, washed thoroughly with water and dried. The completion of the reaction was monitored on TLC by using silica gel-G coated plates by using ethyl acetate and petroleum ether (1:1) as the eluent and observed under UV light.

General procedure for the preparation of 2-aryl substituted-5-mercapto-1,3,4-oxadiazole (2)

To a solution of **1** (0.1 mol) in ethanol (30 mL), KOH (0.1 mol) in absolute ethanol (50 mL) and CS_2 (0.2 mol) were added and refluxed for about 5 h till evolution of hydrogen sulfide was ceased. The reaction mixture was cooled at room temperature and diluted with water. On acidification with dilute hydrochloric acid, the required oxadiazoles was precipitated. It was filtered, thoroughly washed with cold water and recrystallised from ethanol.

General procedure for the preparation of 3-substituted-4-amino-5-mercapto-1,2, 4-triazole.3 (a-d)

A mixture of **2** (0.1 mol) and hydrazine hydrate (0.1 mol) in dry pyridine (15 mL) was refluxed for about 4 h. The reaction mixture was cooled at room temperature and was neutralized with dilute hydrochloric acid. The solid obtained was filtered, thoroughly washed with cold water and recrystallised from ethanol.

4-Amino-3- (3,4-dimethoxy phenyl) -5- mercapto-1,2,4-triazole.(3a)

Yield: 60%; m.p: 212 ^oC; IR (KBr) ν (cm^{-1}) : 3291 (NH stretching), 1613 (C=N stretching); 3130 (aromatic CH stretching), 2586 (SH), 2934, 2840 (methyl CH stretch), 1269 (asymmetric C-O-C stretching), 1021 (symmetric C-O-C stretching), 1284 (N-N=C), 1582, 1552, 1479 (C=C ring stretching); ^1H NMR δ (ppm): 13.8 (s, 1H, SH), 7.1 (d,1H, C-5 of Ar), 7.56 (s, 1H, C-2 of Ar), 7.7 (d,1H, C-6 of Ar), 5.78 (s, 2H, NH_2), 3.82 (s, 6H, OCH_3); MS *m/z* : 252 M^+; Anal. Calcd. (%) for $C_{10}H_{12}N_4O_2S$: C, 47.61; H, 4.79; N, 22.21; S, 12.71. Found: C, 47.69; H, 4.81; N, 22.16; S, 12.73.

4-Amino-3- (3,5-dimethoxy phenyl) -5 - mercapto-1,2,4-triazole.(3b)

Yield:62%; m.p: 200 ^oC; IR (KBr) ν (cm^{-1}) : 3286 (NH stretching),1610 (C=N stretching); 3090 (aromatic CH stretching), 2580 (SH), 2934, 2847 (methyl CH stretch), 1264 (asymmetric C-O-C stretching), 1018 (symmetric C-O-C stretching), 1280 (N-N=C), 1588, 1548, 1486, 1455 (C=C ring stretching); ^1H NMR δ (ppm): 13.90 (s, 1H, SH), 7.2 (d, 2H, C-2 & C-6 of Ar), 6.7 (d, 1H, C-4 of Ar), 5.84 (s, 2H, NH_2), 3.84 (s, 6H, OCH_3); MS *m/z* : 252 M^+; Anal. Calcd. (%) for $C_{10}H_{12}N_4O_2S$: C, 47.61; H, 4.79; N, 22.21; S, 12.71. Found: C, 47.50; H, 4.84; N, 22.26; S, 12.68.

4-Amino-3- (3,4,5-trimethoxy phenyl) -5 - mercapto -1,2,4-triazole. (3c)

Yield: 60%; m.p: 206 ^oC; IR (KBr) ν (cm^{-1}): 3271 (NH stretching), 1607 (C=N stretching), 3092 (aromatic CH stretching), 1571, 1558, 1480, 1451 (C=C ring stretching), 2585 (SH), 2935, 2838 (methyl CH stretch), 1261 (asymmetric C-O-C stretching), 1037 (symmetric C-O-C stretching), 1287 (N-N=C); ^1H NMR δ (ppm): 13.90 (s, 1H, SH), 7.36 (s, 2H, C-2 & C-6 of Ar), 5.82 (s, 2H, NH_2), 3.76 (s, 9H, OCH_3); MS *m/z*: 282 M+; Anal. Calcd. (%) for $C_{11}H_{14}N_4O_3S$: C, 46.80; H, 5.00; N, 19.85; S, 11.36. Found: C, 46.73; H, 4.97; N, 19.91; S, 11.33.

4-Amino-3- (4-pyridinyl) -5 - mercapto -1,2,4-triazole. (3d)

Yield: 65%; m.p: 262 ^oC; IR (KBr) ν (cm^{-1}): 3271 (NH stretching), 1607 (C=N stretching), 3080 (aromatic CH stretching), 1571, 1558, 1480, 1451 (C=C ring stretching), 2585 (SH), 2935, 2838 (methyl CH stretch), 1261 (asymmetric C-O-C stretching), 1037 (symmetric C-O-C stretching), 1287 (N-N=C); ^1H NMR δ (ppm): 14.10 (s, 1H, SH), 8.0 (d, 2H, C-3 & C-5 of Ar), 8.72 (d, 2H, C-2 & C-6 of Ar), 5.84 (s, 2H, NH_2); MS *m/z*: 193 M^+; Anal. Calcd. (%) for $C_7H_7N_5S$: C, 43.51; H, 3.65; N, 36.24; S, 16.59. Found: C, 43.42; H, 3.68; N, 36.17; S, 16.57.

General method for the synthesis of 3-aryl/heteroaryl- 6- (2-substituted-4-quinolinyl)-1,2,4-triazolo [3,4-b]-1,3,4- thiadiazoles. 4(a-d)

A mixture of respective triazole (0.02mol), 2-phenyl-quinoline-4-carboxylic acid (0.02mol), and phosphorous oxychloride (10mL) was heated under reflux for 4-6 h. The reaction mixture was cooled to room temperature and the mixture was gradually poured onto crushed ice with stirring. Finely powdered potassium carbonate and the required amount of solid potassium hydroxide were added till the pH of the mixture was raised to 8, to remove the excess of phosphorous oxychloride. Allowed the mixture to stand overnight, solid was separated. It was filtered, washed thoroughly with cold water, dried and recrystallized from hot ethanol. Similarly other compounds were prepared.

3-(3,4-dimethoxyphenyl)-6-(2-phenyl-4-quinolinyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (4a)

Yield: 52%, m.p: 222-224 ^{o}C; IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1604 (C=N stretching), 1591, 1572, 1490, 1451 (C=C ring stretch), 2940, 2840 (methyl CH stretch), 1264 (asymmetric C-O-C stretching), 1014 (symmetric C-O-C stretching), 1280 (N-N=C); ^{1}H NMR δ (ppm): 7.14-8.2 (m, Ar-H), 3.80 (s, 6H, OCH_3); MS *m/z*: 465 M^+; Anal. Calcd. (%) for $C_{26}H_{19}N_5O_2S$: C, 67.08; H, 4.11; N, 15.04; S, 6.89. Found: C, 67.19; H, 4.14; N, 15.10; S, 6.86.

3-(3,5-dimethoxyphenyl)-6-(2-phenyl-4-quinolinyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (4b)

Yield: 48%, m.p: 232 ^{o}C; IR (KBr) ν (cm^{-1}): 1611 (C=N stretching), 3085 (aromatic CH stretching), 1585, 1570, 1480 (C=C ring stretching), 2945, 2840 (methyl CH stretch), 1261 (asymmetric C-O-C stretching), 1021 (symmetric C-O-C stretching), 1280 (N-N=C); ^{1}H NMR δ (ppm): 6.7-8.2 (m, Ar-H), 3.82 (s, 6H, OCH_3); MS *m/z*: 465 M^+; Anal. Calcd. (%) for $C_{26}H_{19}N_5O_2S$: C, 67.08; H, 4.11; N, 15.04; S, 6.89. Found: C, 66.94; H, 4.08; N, 15.09; S, 6.85.

3-(3, 4, 5-trimethoxy phenyl)-6- (2-phenyl-4-quinolinyl)-1,2,4-triazolo[3,4-b] - 1,3,4-thiadiazole (4c)

Yield: 46%, m.p: 186 ^{o}C; IR (KBr) ν (cm^{-1}): 3095 (aromatic CH stretching), 1614 (C=N stretching), 1585, 1551, 1479, 1453 (C=C ring stretch), 1254 (asymmetric C-O-C stretching), 1024 (symmetric C-O-C stretching), 2955, 2840 (methyl CH stretch), 1274 (N-N=C); ^{1}H NMR δ (ppm): 7.3-8.2 (m, 12H, Ar-H), 3.86 (s, 9H, OCH_3); MS *m/z*: 495 M^+; Anal. Calcd. (%) for $C_{27}H_{21}N_5O_3S$: C, 65.44; H, 4.27; N, 14.13; S, 6.47. Found: C, 65.57; H, 4.24; N, 14.07; S, 6.43.

3-(4-pyridinyl)-6- (2-phenyl-4-quinolinyl)-1,2,4-triazolo [3,4-b] -1,3,4-thiadiazole (4d)

Yield: 54%, m.p: 212^{o}C; IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1611 (C=N stretching), 1580, 1560 (C=C ring stretch), 1286 (N-N=C); ^{1}H NMR δ (ppm): 7.4-8.2 (m, 13H, Ar-H), 8.70 (d, 2H, C-3 & C-5 of Ar); MS *m/z*: 406 M^+; Anal. Calcd. (%) for $C_{23}H_{14}N_6S$: C, 67.96; H, 3.47; N, 20.68; S, 7.89. Found: C, 68.07; H, 3.45; N, 20.79; S, 7.85.

3-(3,4-dimethoxyphenyl)-6-(2-methyl-4-quinolinyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (5a)

Yield: 56%; m.p: 170°C; IR (KBr) ν (cm^{-1}): 3085 (aromatic CH stretching), 1610 (C=N stretching), 1594, 1480, 1450 (C=C ring stretch), 2960, 2840 (methyl CH stretch), 1260 (asymmetric C-O-C stretching), 1020 (symmetric C-O-C stretching), 1286 (N-N=C); ^{1}H NMRδ: 7.20-8.0 (m, Ar-H), 3.80 (s, 3H, OCH_3), 2.78 (s, 3H, CH_3); MS *m/z*: 404 M^+; Anal. Calcd. (%) for $C_{21}H_{17}N_5O_2S$: C, 62.52; H, 4.25; N, 17.36; S, 7.95. Found: C, 62.61; H, 4.25; N, 17.39; S, 7.92.

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

Yield: 52%; m.p: 186°C; IR (KBr) ν (cm^{-1}): 1608 (C=N stretching), 3080 (aromatic CH stretching), 1580, 1560, 1480(C=C ring stretching), 2942, 2846 (methyl CH stretch), 1266 (asymmetric C-O-C stretching), 1024 (symmetric C-O-C stretching), 1280 (N-N=C); ^{1}H NMR δ (ppm): 6.72-8.02 (m, Ar-H), 3.84 (s, 6H, OCH_3), 2.80 (s, 3H, CH_3); MS *m/z*: 403 M^+; Anal. Calcd. (%) for $C_{21}H_{17}N_5O_2S$: C, 62.52; H, 4.25; N, 17.36; S, 7.95. Found: C, 62.44; H, 4.21; N, 17.32; S, 7.98.

3-(3, 4, 5-trimethoxy phenyl)-6- (2-methyl-4-quinolinyl)-1,2,4-triazolo [3,4-b] - 1,3,4-thiadiazole (5c)

Yield: 53%; m.p: 178°C; IR (KBr) ν (cm^{-1}): 3090 (aromatic CH stretching), 1610 (C=N stretching), 1580, 1561, 1484 (C=C ring stretch), 2965, 2848 (methyl CH stretch), 1262 (asymmetric C-O-C stretching), 1020 (symmetric C-O-C stretching), 1276 (N-N=C); ^{1}H NMR δ (ppm): 7.30-8.02 (m, Ar-H), 3.86 (s, 9H, OCH_3), 2.82 (s, 3H, CH_3 of Ar'); MS *m/z*: 433 M^+; Anal. Calcd. (%) for $C_{22}H_{19}N_5O_3S$: C, 60.96; H, 4.42; N, 16.16; S, 7.40. Found: C, 61.09; H, 4.39; N, 16.21; S, 7.38.

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

Yield: 45%; m.p: 206°C; IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1611 (C=N stretching), 1580, 1560 (C=C ring stretch), 1286 (N-N=C); ^{1}H NMR δ: 7.32-8.1 (m, 5H of Ar'), 8.42 (d, 2H, C-3 & C-5 of Ar); 8.80 (d, 2H, C-2 & C-6 of Ar); 2.8 (s, 3H, CH_3); MS *m/z*: 344 M^+; Anal. Calcd. (%) for $C_{18}H_{12}N_6S$: C, 62.77; H, 3.51; N, 24.40; S, 9.31. Found: C, 62.85; H, 3.49; N, 24.47; S, 9.28.

3-(3,4-dimethoxy phenyl)-6-(4-quinolinyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (6a)

Yield: 46%; m.p: 240 °C;IR (KBr) ν (cm^{-1}): 3073 (aromatic CH stretching), 1607 (C=N stretching), 1592, 1570 (C=C ring stretch), 2945, 2854 (methyl CH stretch), 1267 (asymmetric C-O-C stretching), 1023 (symmetric C-O-C stretching), 1275 (N-N=C); ^{1}H NMR δ (ppm): 7.18-7.7 (m, Ar-H), 8.05 (d, 1H, C-8' of Ar'), 8.88 (d, 1H, C-2' of Ar'), 3.80 (s, 6H, OCH_3); MS *m/z*: 389 M^+; Anal. Calcd. (%) for $C_{20}H_{15}N_5O_2S$: C, 61.68; H, 3.88; N, 17.98; S, 8.23. Found: C, 61.56; H, 3.91; N, 18.05; S, 8.19.

3-(3,5-dimethoxy phenyl)-6-(4-quinolinyl)-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole (6b)

Yield: 49%; m. p: 248°C; IR (KBr) ν (cm^{-1}): 3065 (aromatic CH stretching), 1586, 1566 (C=C ring stretching), 2960, 2854 (methyl CH stretch), 1616 (C=N stretching), 1258 (asymmetric C-O-C stretching), 1020 (symmetric C-O-C stretching), 1281 (N-N=C); ^{1}H NMR δ (ppm): 6.70-7.7 (m, Ar-H), 8.05 (d, 1H, C-8' of Ar'), 8.9 (d, 1H, C-2' of Ar'), 3.84 (s, 6H, OCH_3); MS *m/z*: 389 M^+; Anal. Calcd. (%) for $C_{20}H_{15}N_5O_2S$: C, 61.68; H, 3.88; N, 17.98; S, 8.23. Found: C, 61.79; H, 3.85; N, 18.05; S, 8.20.

3-(3, 4, 5-trimethoxy phenyl)-6- (4-quinolinyl)-1,2,4-triazolo [3,4-b] -1,3,4-thiadiazole (6c)

Yield: 47%; m.p: 234°C; IR (KBr) ν (cm^{-1}): 3078 (aromatic CH stretching), 1614 (C=N stretching), 1590, 1575 (C=C ring stretch), 2970, 2848 (methyl CH stretch), 1263 (asymmetric C-O-C stretching), 1018 (symmetric C-O-C stretching), 1284 (N-N=C); ^{1}H NMR δ (ppm): 7.30-7.74 (m, Ar-H), 8.05 (d, 1H, C-8' of Ar'), 8.9 (d, 1H, C-2' of Ar'), 3.86 (s, 9H, OCH_3); MS *m/z*: 419 M^+; Anal. Calcd. (%) for $C_{21}H_{17}N_5O_3S$: C, 60.13; H, 4.09; N, 16.70; S, 7.64. Found: C, 60.01; H, 4.12; N, 16.65; S, 7.61.

3-(4-pyridinyl)-6- (4-quinolinyl)-1,2,4-triazolo[3,4-b] -1,3,4-thiadiazole (6d)

Yield: 54%; m.p: 284°C; IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1611 (C=N stretching), 1580, 1560 (C=C ring stretch), 1286 (N-N=C); ^{1}H NMRδ: 7.4-7.7 (m, 4H, of Ar'), 7.96 (d, 2H, C-2 & C-6 of Ar), 8.7 (d, 2H, C-2 & C-6 of Ar), 8.05 (d, 1H, C-8' of Ar'), 8.9 (d, 1H, C-2' of Ar'); MS *m/z*: 330 M^+; Anal. Calcd. (%) for $C_{17}H_{10}N_6S$: C, 61.80; H, 3.05; N, 25.44; S, 9.71. Found: C, 61.73; H, 3.07; N, 25.40; S, 9.68.

3-(3, 4-dimethoxy phenyl)-6- (2, 6-dihydroxy-4-pyridinyl)-1, 2, 4-triazolo [3,4-b]-1, 3, 4-thiadiazole (7a)

Yield: 50%; m.p: 280° C(dec.); IR (KBr) ν (cm^{-1}): 3430 (OH stretching), 3074 (aromatic CH stretching), 1612 (C=N stretching), 1590, 1541, 1480, 1455 (C=C ring stretch), 2965, 2931 (methyl CH stretch), 1260 (asymmetric C-O-C stretching), 1026 (symmetric C-O-C stretching), 1290 (N-N=C); ^{1}H NMR δ (ppm): 7.12 (d, 1H, C-5 of Ar), 7.52 (s, 1H, C-2 of Ar), 7.66 (d, 1H, C-6 of Ar), 7.26 (s, 2H, C-3 & C-5 of Ar'), 6.14 (s, 2H, OH), 3.8 (s, 6H, OCH_3); MS *m/z*: 371 M^+; Anal. Calcd. (%) for $C_{16}H_{13}N_5O_4S$: C, 51.75; H, 3.53; N, 18.86; S, 8.63. Found: C, 51.64; H, 3.56; N, 18.81; S, 8.59.

3-(3, 5-dimethoxy phenyl)-6- (2,6-dihydroxy-4-pyridinyl)-1,2,4-triazolo[3,4-b]-1,3,4- thiadiazole (7b)

Yield: 52%; m.p: 294 °C (dec.); IR (KBr) ν (cm^{-1}): 3443 (OH stretching), 3076, 3034 (aromatic CH stretching), 1607(C=N stretching), 1590, 1538, 1478, 1448 (C=C ring stretch), 2970, 2934 (methyl CH stretch), 1262 (asymmetric C-O-C stretching), 1015 (symmetric C-O-C stretching), 1283 (N-N=C); ^{1}H NMR δ (ppm): 6.74 (d, 1H, C-4 of Ar), 7.20 (d, 2H, C-2 & C-6 of Ar), 7.28 (s, 2H, C-3 & C-5 of Ar'), 6.20 (s, 2H, OH), 3.84 (s, 6H, OCH_3); MS *m/z*: 371 M^+; Anal. Calcd. (%) for $C_{16}H_{13}N_5O_4S$: C, 51.75; H, 3.53; N, 18.86; S, 8.63. Found: C, 51.67; H, 3.53; N, 18.91; S, 8.62.

3-(3, 4, 5-trimethoxy phenyl)-6-(2, 6-dihydroxy-4-pyridinyl)-1, 2, 4-triazolo[3,4-b]-1, 3,4-thiadiazole (7c)

Yield: 50%; m.p: 282 °C (dec.); IR (KBr) ν (cm^{-1}): 3450 (OH stretching), 3080 (aromatic CH stretching), 1610 (C=N stretching), 1590, 1564, 1482, 1448 (C=C ring stretch), 2958, 2930 (methyl CH stretch), 1264 (asymmetric C-O-C stretching), 1023 (symmetric C-O-C stretching), 1286 (N-N=C); ^{1}H NMR δ (ppm): 7.36 (s, 2H, C-2 & C-6 of Ar), 7.24 (s, 2H, C-3 & C-5 of Ar'), 3.88 (s, 9H, OCH_3), 6.20 (s, 2H, OH); MS *m/z*: 401 M^+; Calcd. (%) for $C_{17}H_{15}N_5O_5S$: C, 50.87; H, 3.77; N, 17.45; S, 7.99. Found: C, 50.81; H, 3.74; N, 17.51; S, 7.95.

3-(4-pyridinyl)-6-(2, 6-dihydroxy-4-pyridinyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (7d)

Yield: 48%; m.p: 300 ^{o}C (dec.); IR (KBr) ν (cm^{-1}): 3442 (OH stretching), 3087, (aromatic CH stretching), 1612 (C=N stretching), 1585, 1558 (C=C ring stretch), 1283 (N-N=C); ^{1}H NMR δ (ppm): 8.00 (d, 2H, C-3 & C-5 of Ar), 8.72 (d, 2H, C-2 & C-6 of Ar), 7.24 (s, 2H, C-3' & C-5' of Ar'), 6.20 (s, 2H, OH); MS *m/z*: 312 M^{+}; Anal. Calcd. (%) for $C_{13}H_8N_6O_2S$: C, 50.00; H, 2.58; N, 26.91; S, 10.27. Found: C, 49.91; H, 2.60; N, 26.83; S, 10.25.

3-(3, 4-dimethoxy phenyl)-6- (2-chloro-4-pyridinyl)-1, 2, 4-triazolo [3,4-b]-1, 3, 4-thiadiazole (8a)

Yield: 50 %; m.p: 218^{o}C; IR (KBr) ν (cm^{-1}): 3065 (aromatic CH stretching), 1610 (C=N stretching), 1585, 1567, 1484, 1455 (C=C ring stretch), 2970, 2840 (methyl CH stretch), 1254 (asymmetric C-O-C stretching), 1034(symmetric C-O-C stretching), 1275 (N-N=C); ^{1}H NMR δ (ppm): 7.16 (d, 1H, C-5 of Ar), 7.54 (s, 1H, C-2 of Ar), 7.68 (d, 1H, C-6 of Ar), 8.00 (s, 1H, C-3' of Ar'), 7.9 (d, 1H, C-5' of Ar'), 8.9 (d, 1H, C-6' of Ar'), 3.82 (s, 6H, OCH_3); MS *m/z*: 373 M^{+}, 375 M^{+2}; Anal. Calcd. (%) for $C_{16}H_{12}N_5O_2SCl$: C, 51.41; H, 3.24; N, 18.73; S, 8.58. Found: C, 51.52; H, 3.27; N, 18.64; S, 8.54.

3-(3,5-dimethoxy phenyl)-6- (2-chloro-4-pyridinyl)-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole (8b)

Yield: 47%; m.p: 224 ^{o}C; IR (KBr) ν (cm^{-1}): 3084, 3048 (aromatic CH stretching), 1607 (C=N stretching), 1585, 1554, 1464, 1448 (C=C ring stretch), 2984, 2854 (methyl CH stretch), 1260 (asymmetric C-O-C stretching), 1028 (symmetric C-O-C stretching), 1284 (N-N=C); ^{1}H NMR δ (ppm): 7.26 (d, 2H, C-2 & C-6 of Ar), 6.74 (d, 1H, C-4 of Ar), 8.00 (s, 1H, C-3' of Ar'), 7.9 (d, 1H, C-5' of Ar'), 8.88 (d, 1H, C-6' of Ar'), 3.86 (s, 6H, OCH_3); MS *m/z*: 373 M^{+}, 375 M^{+2}; Anal. Calcd. (%) for $C_{16}H_{12}N_5O_2SCl$: C, 51.41; H, 3.24; N, 18.73; S, 8.58. Found: C, 51.37; H, 3.24; N, 18.69; S, 8.56.

3-(3, 4, 5-trimethoxy phenyl)-6-(2-chloro-4-pyridinyl)-1, 2, 4-triazolo[3,4-b]-1, 3,4-thiadiazole (8c)

Yield: 48 %; m.p: 226^{o}C(dec.); IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1614 (C=N stretching), 1587, 1550, 1482 (C=C ring stretch), 1264 (asymmetric C-O-C stretching), 1017 (symmetric C-O-C stretching), 2958, 2854 (methyl CH stretch), 1276 (N-N=C); ^{1}H NMR δ (ppm): 7.34 (s, 2H, C-2 & C-6 of Ar), 8.00 (s, 1H, C-3' of Ar'), 7.9 (d, 1H, C-5' of Ar'), 8.90 (d, 1H, C-6' of Ar'), 3.86 (s, 9H, OCH_3); MS *m/z*: 403 M^{+}, 405 M^{+2}; Anal. Calcd. (%) for $C_{17}H_{14}N_5O_3SCl$: C, 50.56; H, 3.49; N, 17.34; S, 7.94. Found: C, 50.47; H, 3.50; N, 17.29; S, 7.91.

3-(4-pyridinyl)-6-(2-chloro-4-pyridinyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (8d)

Yield: 48 %; m.p: 270^{o}C(dec.); IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1611 (C=N stretching), 1580, 1560 (C=C ring stretch), 1286 (N-N=C); ^{1}H NMR δ (ppm): 8.00 (d, 2H, C-3 & C-5 of Ar), 8.7 (d, 2H, C-2 & C-6 of Ar), 8.02 (s, 1H, C-3' of Ar'), 7.9 (d, 1H, C-5' of Ar'), 8.90 (d, 1H, C-6' of Ar'); MS *m/z*: 314 M^{+}, 316 M^{+2}; Anal. Calcd. (%) for $C_{13}H_7N_6SCl$: C, 49.61; H, 2.24; N, 26.70; S, 10.19. Found: C, 49.52; H, 2.26; N, 26.75; S, 10.14.

3-(3, 4-dimethoxy phenyl)-6- (2-flouro-4-pyridinyl)-1, 2, 4-triazolo [3,4-b]-1, 3, 4-thiadiazole (9a)

Yield: 49 %; m.p: 206°C(dec.); IR (KBr) ν (cm^{-1}): 3082 (aromatic CH stretching), 1618 (C=N stretching), 1580, 1564 (C=C ring stretch), 2964, 2846 (methyl CH stretch), 1258 (asymmetric C-O-C stretching), 1028(symmetric C-O-C stretching), 1280 (N-N=C); ^{1}H NMR δ (ppm): 7.12 (d, 1H, C-5 of Ar), 7.56 (s, 1H, C-2 of Ar), 7.76 (d, 1H, C-6 of Ar), 7.7 (s, 1H, C-3' of Ar'), 7.9 (d, 1H, C-5' of Ar'), 8.60 (d, 1H, C-6' of Ar'), 3.86 (s, 6H, OCH_3); MS *m/z*: 357 M^+; Anal. Calcd. (%) for $C_{16}H_{12}N_5O_2S$ F: C, 53.77; H, 3.38; N, 19.60; S, 8.97. Found: C, 53.68; H, 3.41; N, 19.64; S, 8.93.

3-(3,5-dimethoxyphenyl)-6-(2-flouro-4-pyridinyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole(9b)

Yield: 46 %; m.p: 190°C(dec); IR (KBr) ν (cm^{-1}): 3090 (aromatic CH stretching), 1617 (C=N stretching), 1575, 1560 (C=C ring stretch), 2954, 2837 (methyl CH stretch), 1260 (asymmetric C-O-C stretching), 1024 (symmetric C-O-C stretching), 1284 (N-N=C); ^{1}H NMR δ (ppm): 7.24 (d, 2H, C-2 & C-6 of Ar), 6.72 (d, 1H, C-4 of Ar), 7.68 (s, 1H, C-3' of Ar'), 7.90(d, 1H, C-5' of Ar'), 8.60 (d, 1H, C-6' of Ar'), 3.80 (s, 6H, OCH_3); MS *m/z*: 357 M^+; Anal. Calcd. (%) for $C_{16}H_{12}N_5O_2S$ F: C, 53.77; H, 3.38; N, 19.60; S, 8.97. Found: C, 53.83; H, 3.36; N, 19.55; S, 8.95.

3-(3, 4, 5-trimethoxy phenyl)-6-(2-flouro-4-pyridinyl)-1, 2, 4-triazolo[3,4-b]-1, 3,4-thiadiazole (9c)

Yield: 53 %; m.p: 210°C (dec); IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1614 (C=N stretching), 1587, 1550, 1482 (C=C ring stretch), 1267 (asymmetric C-O-C stretching), 1019 (symmetric C-O-C stretching), 2958, 2854 (methyl CH stretch), 1276 (N-N=C); ^{1}H NMR δ (ppm): ^{1}H NMR δ (ppm): 7.32 (s, 2H of Ar), 7.68 (s, 1H, C-3' of Ar'), 7.88 (d, 1H, C-5' of Ar'), 8.58 (d, 1H, C-6' of Ar'), 3.86 (s, 9H, OCH_3); MS *m/z*: 387 M^+; Anal. Calcd. (%) for $C_{17}H_{14}N_5O_3S$ F: C, 52.71; H, 3.64; N, 18.08; S, 8.28. Found: C, 52.65; H, 3.64; N, 18.15; S, 8.32.

3-(4-pyridinyl)-6-(2-flouro-4-pyridinyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (9d)

Yield: 51 %; m.p: 206°C(dec); IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1611 (C=N stretching), 1580, 1560 (C=C ring stretch), 1286 (N-N=C); ^{1}H NMR δ (ppm): 8.0 (d, 2H, C-3 & C-5 of Ar), 8.8 (d, 2H, C-2 & C-6 of Ar), 7.68 (s, 1H, C-3' of Ar'), 7.88 (d, 1H, C-5' of Ar'), 8.62 (d, 1H, C-6' of Ar'); MS *m/z*: 298 M^+; Anal. Calcd. (%) for $C_{13}H_7N_6S$ F: C, 52.34; H, 2.37; N, 28.17; S, 10.75. Found: C, 52.25; H, 2.39; N, 28.24; S, 10.71.

3-(3, 4-dimethoxy phenyl)-6-(5-methoxy-3-indolyl methyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (10a)

Yield: 48 %; m.p: 160°C; IR (KBr) ν (cm^{-1}): 3084 (aromatic CH stretching), 1614 (C=N stretching), 1587, 1565 (C=C ring stretch), 2980, 2849 (methyl CH stretch), 1265 (asymmetric C-O-C stretching), 1018 (symmetric C-O-C stretching), 1282 (N-N=C); ^{1}H NMR δ (ppm): 7.16 (d,1H of Ar), 7.52 (s, 1H, C-2 of Ar), 7.68 (d, 1H, C-6 of Ar), 7.4 (m, 2H, C-4' & C-6' of Ar'), 7.78 (d, 1H, C-7' of Ar'), 6.86 (s, 1H, C-2' of Ar'), 3.82 (s, 6H, OCH_3 in Ar), 3.74 (s, 3H, OCH_3 in Ar'), 4.10 (s, 2H, CH_2), 10.10 (s, 1H, NH of Ar); MS *m/z*: 421 M^+; Anal. Calcd. (%) for $C_{21}H_{19}N_5O_3S$: C, 59.84; H, 4.54; N, 16.62; S, 7.61. Found: C, 59.75; H, 4.54; N, 16.67; S, 7.58.

3-(3, 5-dimethoxy phenyl)-6-(5-methoxy-3-indolyl methyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (10b)

Yield: 50 %; m.p: 176° C; IR (KBr) ν (cm^{-1}): 3070 (aromatic CH stretching), 1624 (C=N stretching), 1588, 1546 (C=C ring stretch), 2956, 2864 (methyl CH stretch), 1260 (asymmetric C-O-C stretching), 1021 (symmetric C-O-C stretching), 1285 (N-N=C); ^{1}H NMR δ (ppm): 7.20 (d, 2H, C-2 & C-6 of Ar), 6.76 (d, 1H, C-4 of Ar), 7.40 (m, 2H, C-4' & C-6' of Ar'), 7.80 (d, 1H, C-7' of Ar'), 6.84 (s, 1H, C-2' of Ar'), 4.10 (s, 2H, CH_2 of methylene), 3.84 (s, 6H, OCH_3 in Ar), 3.76 (s, 3H, OCH_3 in Ar'), 10.10 (s, 1H, NH of Ar'); MS *m/z*: 421 M^+; Anal. Calcd. (%) for $C_{21}H_{19}N_5O_3S$: C, 59.84; H, 4.54; N, 16.62; S, 7.61. Found: C, 59.72; H, 4.56; N, 16.56; S, 7.64.

3-(3, 4, 5-trimethoxy phenyl)-6-(5-methoxy-3-indolyl methyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (10c)

Yield: 54 %; m.p: 168°C; IR (KBr) ν (cm^{-1}): 3063 (aromatic CH stretching), 1616 (C=N stretching), 1587, 1549, 1479, 1452 (C=C ring stretch), 2964, 2838 (methyl CH stretch), 1267 (asymmetric C-O-C stretching), 1029 (symmetric C-O-C stretching), 1280 (N-N=C); ^{1}H NMR δ (ppm): 7.32 (s, 2H, C-2 & C-6 of Ar), 7.46 (m, 2H, C-4' & C-6' of Ar'), 7.78 (d, 1H, C-7' of Ar'), 6.80 (s, 1H, C-2' of Ar'), 4.10 (s, 2H, CH_2 of methylene), 3.86 (s, 9H, OCH_3 in Ar), 3.76 (s, 3H, OCH_3 in Ar'), 10.10 (s, 1H, NH of Ar'); MS *m/z*: 451 M^+; Anal. Calcd. (%) for $C_{22}H_{21}N_5O_4S$: C, 58.52; H, 4.69; N, 15.51; S, 7.10. Found: C, 58.41; H, 4.71; N, 15.46; S, 7.06.

3-(4-pyridinyl)-6-(5-methoxy-3-indolylmethyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole(10d)

Yield: 46 %; m.p: 224°C; IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1611 (C=N stretching), 1580, 1560 (C=C ring stretch), 1286 (N-N=C); ^{1}H NMR δ (ppm): 8.0 (d, 2H, C-3 & C-5 of Ar), 8.72 (d, 2H, C-2 & C-6 of Ar), 7.42 (m, 2H, C-4' & C-6' of Ar'), 7.78 (d, 1H, C-7' of Ar'), 6.80 (s, 1H, C-2 of pyrrole), 4.12 (s, 2H, CH_2 of methylene), 3.76 (s, 3H, OCH_3), 10.08 (s, 1H, NH of Ar'); MS *m/z*: 362 M^+; Anal. Calcd. (%) for $C_{18}H_{14}N_6OS$: C, 59.66; H, 3.89; N, 23.19; S, 8.85. Found: C, 59.54; H, 3.90; N, 23.16; S, 8.81.

3-(3, 4-dimethoxy phenyl)-6-(5-methoxy-2-methyl-3-indolyl methyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (11a)

Yield: 50 %; m.p: 190°C; IR (KBr) ν (cm^{-1}): 3075 (aromatic CH stretching), 1610 (C=N stretching), 1587, 1565 (C=C ring stretch), 2980, 2849 (methyl CH stretch), 1265 (asymmetric C-O-C stretching), 1018 (symmetric C-O-C stretching), 1282 (N-N=C); ^{1}H NMR δ (ppm): 7.18 (d, 1H, C-5 of Ar), 7.56 (s, 1H, C-2 of Ar), 7.72 (d, 1H, C-6 of Ar), 7.44 (d, 1H, C-7' of Ar'), 7.00 (s, 1H, C-4' of Ar'), 7.32 (d, 1H, C-6' of Ar'), 3.80 (s, 3H, OCH_3 of Ar), 3.76 (s, 6H, OCH_3 of Ar'), 4.10 (s, 2H, CH_2), 10.10 (s, 1H, NH of Ar'), 2.84 (s, 3H, CH_3); MS *m/z*: 435 M^+; Anal. Calcd. (%) for $C_{22}H_{21}N_5O_3S$: C, 60.67; H, 4.86; N, 16.08; S, 7.36. Found: C, 60.79; H, 4.83; N, 16.14; S, 7.31.

3-(3, 5-dimethoxy phenyl)-6-(5-methoxy-2-methyl-3-indolyl methyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (11b)

Yield: 47 %; m.p: 182°C; IR (KBr) ν (cm^{-1}): 3082 (aromatic CH stretching), 1610 (C=N stretching), 1588, 1561 (C=C ring stretch), 2956, 2856 (methyl CH stretch), 1268 (asymmetric C-O-C stretching), 1024 (symmetric C-O-C stretching), 1286 (N-N=C); ^{1}H NMR δ (ppm): 7.20 (d, 2H, C-2 & C-6 of Ar), 6.74 (d, 1H, C-4 of Ar), 7.48 (d, 1H, C-7' of Ar'), 7.00 (s, 1H, C-4' of Ar'), 7.34 (d, 1H, C-6' of Ar'), 4.10 (s, 2H, CH_2 of methylene), 3.82 (s, 6H, OCH_3 in Ar), 3.76 (s, 3H, OCH_3 in Ar'), 10.10 (s, 1H, NH of Ar'), 2.84 (s, 3H, CH_3); MS *m/z*: 435 M^+; Anal. Calcd. (%) for $C_{22}H_{21}N_5O_3S$: C, 60.67; H, 4.86; N, 16.08; S, 7.36. Found: C, 60.72; H, 4.84; N, 16.12; S, 7.33.

3-(3, 4, 5-trimethoxy phenyl)-6-(5-methoxy-2-methyl-3-indolyl methyl)-1,2,4-triazolo [3,4-b] -1,3,4-thiadiazole (11c)

Yield: 50 %; m.p: 186°C; IR (KBr) ν (cm^{-1}): 3068 (aromatic CH stretching), 1616 (C=N stretching), 1587, 1554 (C=C ring stretch), 2943, 2860 (methyl CH stretch), 1258 (asymmetric C-O-C stretching), 1023 (symmetric C-O-C stretching), 1288 (N-N=C); ^{1}H NMR δ (ppm): 7.20 (s, 2H C-2 & C-6 of Ar), 7.58 (d, 1H, C-7' of Ar'), 6.96 (s, 1H, C-4' of Ar'), 7.36 (d, 1H, C-6' of Ar'), 4.24 (s, 2H, CH_2 of methylene), 3.8 (s, 9H, OCH_3 in Ar), 3.76 (s, 3H, OCH_3 in Ar'), 10.08 (s, 1H, NH of Ar'), 2.84 (s, 3H, CH_3); MS *m/z*: 465 M^+; Anal. Calcd. (%) for $C_{23}H_{23}N_5O_4S$: C, 59.34; H, 4.98; N, 15.04; S, 6.89. Found: C, 59.46; H, 4.97; N, 15.09; S, 6.85.

3-(4-pyridinyl)-6-(5-methoxy-2-methyl-3-indolyl methyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (11d)

Yield: 53 %; m.p: 240°C; IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1611 (C=N stretching), 1580, 1560 (C=C ring stretch), 1286 (N-N=C); ^{1}H NMR δ (ppm): 8.0 (d, 2H, C-3 & C-5 of Ar), 8.72 (d, 2H, C-2 & C-6 of Ar), 7.00 (s, 1H, C-4' of Ar'), 7.28 (d, 1H, C-6' of Ar'), 7.56 (d, 1H, C-7' of Ar'), 4.10 (s, 2H, CH_2 of methylene), 3.76 (s, 3H, OCH_3 in Ar'), 10.06 (s, 1H, NH of Ar'), 2.84 (s, 3H, CH_3); MS *m/z*: 376 M^+; Anal. Calcd. (%) for $C_{19}H_{16}N_6OS$: C, 60.62; H, 4.28; N, 22.33; S, 8.52. Found: C, 60.56; H, 4.30; N, 22.27; S, 8.49.

3-(3, 4-dimethoxy phenyl)-6-(3-indolyl methyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (12a)

Yield: 58 %; m.p: 184°C; IR (KBr) ν (cm^{-1}): 3092 (aromatic CH stretching), 1623 (C=N stretching), 1583, 1545 (C=C ring stretch), 2980, 2855 (methyl CH stretch), 1267 (asymmetric C-O-C stretching), 1018 (symmetric C-O-C stretching), 1282 (N-N=C);^{1}H NMR δ (ppm): 7.1 (d, 1H C-5 of Ar), 7.54 (s, 1H, C-2 of Ar), 7.70 (d, 1H, C-6 of Ar), 7.20 (s, 4H, C-4, C-5, C-6 & C-7 of Ar'), 6.8 (s, 1H of C-2 of Ar'), 3.80 (s, 6H, OCH_3 in Ar), 4.20 (s, 2H, CH_2), 10.08 (s, 1H, NH of Ar'); MS *m/z*: 391 M^+; Anal. Calcd. (%) for $C_{20}H_{17}N_5O_2S$: C, 61.37; H, 4.38; N, 17.89; S, 8.19. Found: C, 61.26; H, 4.41; N, 17.82; S, 8.15.

3-(3, 5-dimethoxy phenyl)-6-(3-indolyl methyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (12b)

Yield: 58 %; m.p: 174°C; IR (KBr) ν (cm^{-1}): 3071 (aromatic CH stretching), 1608 (C=N stretching), 1574, 1540 (C=C ring stretch), 2956, 2834 (methyl CH stretch), 1261 (asymmetric C-O-C stretching), 1019 (symmetric C-O-C stretching), 1280 (N-N=C); ^{1}H NMR δ (ppm): 7.28 (d, 2H, C-2 & C-6 of Ar), 6.64 (d, 1H, C-4 of Ar), 7.20 (s, 4H, C-4, C-5, C-6 & C-7 of Ar'), 6.8 (s, 1H of C-2 of Ar'), 4.10 (s, 2H, CH_2), 10.08 (s, 1H, NH of Ar'), 3.84 (s, 6H, OCH_3 in Ar); MS *m/z*: 391 M^+; Anal. Calcd. (%) for $C_{20}H_{17}N_5O_2S$: C, 61.37; H, 4.38; N, 17.89; S, 8.19. Found: C, 61.33; H, 4.38; N, 17.86; S, 8.16.

3-(3, 4, 5-trimethoxy phenyl)-6-(3-indolyl methyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (12c)

Yield: 50 %; m.p: 180°C;IR (KBr) ν (cm^{-1}): 3060 (aromatic CH stretching), 1616 (C=N stretching), 1571, 1549 (C=C ring stretch), 2952, 2839 (methyl CH stretch), 1259 (asymmetric C-O-C stretching), 1022 (symmetric C-O-C stretching), 1271 (N-N=C); ^{1}H NMR δ (ppm): 7.36 (s, 2H, C-2 & C-6 of Ar), 7.20 (s, 4H, C-4, C-5, C-6 & C-7 of Ar'), 6.8 (s, 1H of C-2 of Ar'), 4.10 (s, 2H, CH_2), 10.08 (s, 1H, NH of Ar'), 3.86 (s, 9H, OCH_3 of Ar); MS *m/z*: 421 M^+; Anal. Calcd. (%) for $C_{21}H_{19}N_5O_3S$: C, 59.84; H, 4.54; N, 16.62; S, 7.61. Found: C, 59.73; H, 4.57; N, 16.65; S, 7.58.

3-(4-pyridinyl)-6-(3-indolyl methyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (12d)

Yield: 55 %; m.p: 232°C;IR (KBr) ν (cm^{-1}): 3080 (aromatic CH stretching), 1611 (C=N stretching), 1580, 1560 (C=C ring stretch), 1286 (N-N=C); ^{1}H NMR δ (ppm): 8.0 (d, 1H, C-3 & C-5 of Ar), 8.7 (d, 1H, C-2 & C-6 of Ar), 7.20 (s, 4H, C-4, C-5, C-6 & C-7 of Ar'), 6.8 (s, 1H of C-2 of Ar'), 4.10 (s, 2H, CH_2), 10.18 (s, 1H, NH of Ar'); MS *m/z*: 332 M^+; Anal. Calcd. (%) for $C_{17}H_{12}N_6S$: C, 61.43; H, 3.64; N, 25.28; S, 9.65. Found: C, 61.34; H, 3.66; N, 25.22; S, 9.61.

3-(3,4-dimethoxy phenyl)-6-(4-hydroxy-3-methoxy cinnamyl)-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole (13a)

Yield: 62%; m.p: 194 °C; IR (KBr) ν (cm^{-1}): 3435 (OH stretching), 3036 (aromatic CH stretching), 1614 (C=N stretching), 1590, 1549, 1477, 1453 (C=C ring stretch), 2977, 2840 (methyl CH stretch), 1265 (asymmetric C-O-C stretching), 1023 (symmetric C-O-C stretching), 1280 (N-N=C), 1636 (vinyl group); 1H NMR δ (ppm): 7.16 (d, 1H C-5 of Ar), 7.56 (s, 1H, C-2 of Ar), 7.68 (d, 1H, C-6 of Ar), 7.76 (s, 1H, C-2 of Ar'), 7.42 (d, 1H, C-5 of Ar'), 7.8 (d, 1H, C-6 of Ar'), 3.74 (s, 3H, OCH_3 of Ar'), 3.84 (s, 6H, OCH_3 of Ar), 6.96 (d, 1H, CH), 6.8 (d, 1H, CH), 6.14 (s, 1H, OH); MS *m/z*: 410 M^+; Anal. Calcd. (%) for $C_{20}H_{18}N_4O_4S$: C, 58.52; H, 4.42; N, 13.65; S, 7.81. Found: C, 58.43; H, 4.41; N, 13.68; S, 7.78.

3-(3,5-dimethoxy phenyl)-6-(4-hydroxy-3-methoxy cinnamyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (13b)

Yield: 62%; m.p: 188 °C;IR (KBr) ν (cm^{-1}): 3443 (OH stretching), 3040 (aromatic CH stretching), 1614 (C=N stretching), 1588, 1541, 1477, 1452 (C=C ring stretch), 2956, 2909 (methyl CH stretch), 1260 (asymmetric C-O-C stretching), 1019 (symmetric C-O-C stretching), 1290 (N-N=C), 1636 (vinyl group); ^{1}H NMR δ (ppm): 7.24 (d, 2H, C-2 & C-6 of Ar), 6.64 (d, 1H, C-4 of Ar), 7.72 (s, 1H, C-2 of Ar'), 7.46 (d, 1H, C-4 of Ar'), 7.8 (d, 1H, C-6 of Ar'), 6.96 (d, 1H, CH), 6.8 (d, 1H, CH), 3.74 (s, 3H, OCH_3 of Ar'), 3.84 (s, 6H, OCH_3 of Ar), 6.14 (s, 1H, OH); MS *m/z*: 410 M^+; Anal. Calcd. (%) for $C_{20}H_{18}N_4O_4S$: C, 58.52; H, 4.42; N, 13.65; S, 7.81. Found: C, 58.44; H, 4.43; N, 13.61; S, 7.84.

3-(3,4,5-trimethoxy phenyl)-6-(4-hydroxy-3-methoxy cinnamyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (13c)

Yield: 60%; m.p: 146-148 °C;IR (KBr) ν (cm^{-1}): 3437 (OH stretching), 3047 (aromatic CH stretching), 1616 (C=N stretching), 1587, 1549, 1479, 1452 (C=C ring stretch), 2927 (methyl CH stretch), 1263 (asymmetric C-O-C stretching), 1017 (symmetric C-O-C stretching),1280 (N-N=C), 1640 (vinyl group); ^{1}H NMR δ (ppm): 7.30 (s, 2H, C-2 & C-6 of Ar), 7.74 (s, 1H, C-2 of Ar'), 7.46 (d, 1H, C-4 of Ar), 7.8 (d, 1H, C-6 of Ar), 7.0 (d, 1H, CH), 6.86 (d, 1H, CH), 3.74 (s, 3H, OCH_3 of Ar'), 3.88 (s, 9H, OCH_3 of Ar), 6.12 (s, 1H, OH); MS *m/z*: 440 M^+; Anal. Calcd. (%) for $C_{21}H_{20}N_4O_5S$: C, 57.26; H, 4.58; N, 12.72; S, 7.28. Found: C, 57.35; H, 4.54; N, 12.67; S, 7.23.

3-(4-pyridinyl)-6-(4-hydroxy-3-methoxy cinnamyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (13d)

Yield: 64%; m.p: 210 °C; IR (KBr) ν (cm^{-1}): 3445 (OH stretching), 3069 (aromatic CH stretching), 1620 (C=N stretching), 1578, 1554 (C=C ring stretch), 2960, 2844 (methyl CH stretch), 1276 (N-N=C), 1636 (vinyl group); ^{1}H NMR δ (ppm): 8.0 (d, 1H, C-3 & C-5 of Ar), 8.7 (d, 1H, C-2 & C-6 of Ar), 7.74 (s, 1H, C-2 of Ar'), 7.46 (d, 1H, C-4 of Ar), 7.8 (d, 1H, C-6 of Ar), 7.00 (d, 1H, CH) 6.88, (d, 1H, CH), 6.14 (s, 1H, OH), 3.74 (3s, 3H, OCH_3 in Ar'); MS *m/z*: 351 M^+; Anal. Calcd. (%) for $C_{17}H_{13}N_5O_2S$: C, 58.11; H, 3.73; N, 19.93; S, 9.13. Found: C, 57.97; H, 3.71; N, 19.97; S, 9.10.

3-(3,4-dimethoxy phenyl)-6-(2-amino-3,5-dibromo phenyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (14a)

Yield:46%; m.p: 242-246 ^{o}C;IR (KBr) ν (cm^{-1}) : 3290 (NH stretching), 3190, 3060 (aromatic CH stretching), 1614 (C=N stretching), 1584, 1553, 1482, 1456 (C=C ring stretch), 2958, 2932 (methyl CH stretch), 1264 (asymmetric C-O-C stretching), 1020 (symmetric C-O-C stretching), 1280 (N-N=C); ^{1}H NMR δ (ppm): 7.14 (d, 1H C-5 of Ar), 7.56 (s, 1H, C-2 of Ar), 7.68 (d, 1H, C-6 of Ar), 7.88 (s, 1H, C-4 of Ar'), 7.96 (s, 1H, C-6 of Ar'), 6.28 (s, 2H, NH_2), 3.80 (s, 6H, OCH_3); MS *m/z*: 511 M^+, 513 M^{+2}, 515 M^{+4}; Anal. Calcd. (%) for $C_{17}H_{13}N_5O_2SBr_2$: C, 39.94; H, 2.56; N, 13.70; S, 6.27. Found: C, 39.84; H, 2.59; N, 13.65; S, 6.29.

3-(3,5-dimethoxy phenyl)-6-(2-amino-3, 5-dibromo phenyl)-1,2,4-triazolo [3,4-b] 1,3,4-thiadiazole (14b)

Yield: 48%; m.p: 228 ^{o}C; IR (KBr) ν (cm^{-1}): 3298 (NH stretching), 3140, 3074 (aromatic CH stretching), 1610 (C=N stretching), 1590, 1570, 1490, 1465 (C=C ring stretch), 2960 (methyl CH stretch), 1262 (asymmetric C-O-C stretching), 1019 (symmetric C-O-C stretching), 1283 (N-N=C); ^{1}H NMR δ (ppm): 7.24 (d, 2H, C-2 & C-6 of Ar), 6.68 (d, 1H, C-4 of Ar), 7.88 (s, 1H, C-4 of Ar'), 7.96 (s, 1H, C-6 of Ar'), 6.28 (s, 2H, NH_2), 3.84 (s, 6H, OCH_3); MS *m/z*: 511 M^+, 513 M^{+2}, 515 M^{+4}; Anal. Calcd. (%) for $C_{17}H_{13}N_5O_2SBr_2$: C, 39.94; H, 2.56; N, 13.70; S, 6.27. Found: C, 39.86; H, 2.56; N, 13.68; S, 6.24.

3-(3,4,5-trimethoxy phenyl)-6-(2-amino-3, 5-dibromo phenyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (14c)

Yield: 48%; m.p: 202 ^{o}C; IR (KBr) ν (cm^{-1}): 3273 (NH stretching), 3090, 3047 (aromatic CH stretching), 1612 (C=N stretching), 1585, 1575, 1484, 1436 (C=C ring stretch), 2964 (methyl CH stretch), 1290 (N-N=C); 1H NMR δ (ppm): 7.32 (s, 2H, C-2 & C-6 of Ar), 7.86 (s, 1H, C-4 of Ar'), 7.94 (s, 1H, C-6 of Ar'), 6.28 (s, 2H, NH_2), 3.88 (s, 9H, OCH_3); MS *m/z*: 541 M^+, 543 M^{+2}, 545 M^{+4}; Anal. Calcd. (%) for $C_{18}H_{15}N_5O_3SBr_2$: C, 39.95; H, 2.79; N, 12.94; S, 5.92. Found: C, 40.07; H, 2.81; N, 12.86; S, 5.87.

3-(4-pyridinyl)-6-(2-amino-3,5-dibromophenyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (14d)

Yield: 43%; m.p: 214 ^{o}C;IR (KBr) ν (cm^{-1}): 3280 (NH stretching), 3074 (aromatic CH stretching), 1618 (C=N stretching), 1585, 1554 (C=C ring stretch), 1280 (N-N=C); ^{1}H NMR δ (ppm): 8.04 (d, 1H, C-3 & C-5 of Ar), 8.7 (d, 1H, C-2 & C-6 of Ar), 7.86 (s, 1H, C-4 of Ar'), 7.92 (s, 1H, C-6 of Ar'), 6.28 (s, 2H, NH_2); MS *m/z*: 452 M^+, 454 M^{+2}, 456 M^{+4}; Anal. Calcd. (%) for $C_{14}H_8N_6SBr_2$: C, 37.19; H, 1.78; N, 18.59; S, 7.09. Found: C, 37.12; H, 1.79; N, 18.54; S, 7.69.

3-(3,4-dimethoxy phenyl)-6-(2-nitro-4-methyl phenyl)-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole (15a)

Yield: 65%; m.p: 194-196 ^{o}C;IR (KBr) ν (cm^{-1}): 3076 (aromatic CH stretching), 1613 (C=N stretching), 1586, 1485, 1451 (C=C ring stretch), 2966, 2933 (methyl CH stretch), 1266 (asymmetric C-O-C stretching), 1021 (symmetric C-O-C stretching), 1284 (N-N=C), 1525 (asymmetric Ar-NO_2 stretch), 1346 (symmetric Ar-NO_2 stretch; ^{1}H NMR δ (ppm): 7.12 (d, 1H, C-5 of Ar), 7.54 (s, 1H, C-2 of Ar), 7.70 (d, 1H, C-6 of Ar), 8.22 (s, 1H, C-3 of Ar'), 7.84 (d, 1H, C-5 of Ar'), 7.95 (d, 1H, C-6 of Ar'), 3.80 (s, 6H, OCH_3), 2.82 (s, 3H, CH_3 of Ar'); MS *m/z*: 397 M^+; Anal. Calcd. (%) For $C_{18}H_{15}N_5O_4S$: C, 54.40; H, 3.80; N, 17.62; S, 8.07. Found: C, 54.32; H, 3.82; N, 17.58; S, 8.10.

3-(3,5-dimethoxy phenyl)-6-(2-nitro-4-methyl phenyl)-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole (15b)

Yield: 67%; m.p: 187 ^{o}C; IR (KBr) ν (cm^{-1}): 3075 (aromatic CH stretching), 1609 (C=N stretching), 1586, 1554, 1484, 1453 (C=C ring stretch), 2963, 2930 (methyl CH stretch), 1265 (asymmetric C-O-C stretching), 1027 (symmetric C-O-C stretching), 1286 (N-N=C), 1524 (asymmetric Ar-NO_2 stretch), 1345 (symmetric Ar-NO_2 stretch); ^{1}H NMR δ (ppm): 7.28 (d, 2H, C-2 & C-6 of Ar), 6.68 (d, 1H, C-4 of Ar), 8.22 (s, 1H, C-3 of Ar'), 7.84 (d, 1H, C-5 of Ar'), 7.95 (d, 1H, C-6 of Ar'), 3.84 (s, 6H, OCH_3), 2.82 (s, 3H, CH_3 of Ar'); MS *m/z*: 397 M^+; Anal. Calcd. (%) for $C_{18}H_{15}N_5O_4S$: C, 54.40; H, 3.80; N, 17.62; S, 8.07. Found: C, 54.47; H, 3.78; N, 17.57; S, 8.04.

3-(3,4,5-trimethoxy phenyl)-6-(2-nitro-4-methyl phenyl)-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole (15c)

Yield: 63%; m.p: 174-176 ^{o}C;IR (KBr) ν (cm^{-1}): 3077 (aromatic CH stretching), 1618 (C=N stretching), 1589, 1554, 1483, 1455 (C=C ring stretch), 1259 (asymmetric C-O-C stretching), 1024 (symmetric C-O-C stretching), 2965, 2928 (methyl CH stretch), 1523 (asymmetric Ar-NO_2 stretch), 1343 (symmetric Ar-NO_2 stretch); ^{1}H NMR δ (ppm): 7.34 (s, 2H, C-2 & C-6 of Ar), 8.20 (s, 1H, C-3 of Ar'), 7.84 (d, 1H, C-5 of Ar'), 7.96 (d, 1H, C-6 of Ar'), 3.86 (s, 9H, OCH_3), 2.80 (s, 3H, CH_3 in Ar'); MS *m/z*: 427 M^+; Anal. Calcd. (%) for $C_{19}H_{17}N_5O_5S$: C, 53.39; H, 4.01; N, 16.38; S, 7.50. Found: C, 53.32; H, 3.97; N, 16.46; S, 7.47.

3-(4-pyridinyl)-6-(2-nitro-4-methyl phenyl)-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole (15d)

Yield: 65%; m.p: 206 ^{o}C; IR (KBr) ν (cm^{-1}): 3085 (aromatic CH stretching), 1611 (C=N stretching), 1573, 1562 (C=C ring stretch), 2960, 2842 (methyl CH stretch), 1530 (asymmetric Ar-NO_2 stretch), 1349 (symmetric Ar-NO_2 stretch); ^{1}H NMR δ (ppm): 8.12 (d, 1H, C-3 & C-5 of Ar), 8.86 (d, 1H, C-2 & C-6 of Ar), 8.22 (s, 1H, C-3 of Ar'), 7.84 (d, 1H, C-5 of Ar'), 7.94 (d, 1H, C-6 of Ar'), 7.86 (d, 2H of Ar'), 2.80 (s, 3H, CH_3 of Ar'); MS *m/z*: 338 M^+; Anal. Calcd. (%) for $C_{15}H_{10}N_6O_2S$: C, 53.25; H, 2.98; N, 24.84; S, 9.48. Found: C, 53.18; H, 2.98; N, 24.76; S, 9.45.

3-(3,4-dimethoxy phenyl)-6-[1-(2,4-dichloro phenoxy) ethyl]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (16a)

Yield: 56(%); m.p: 78 ^{o}C; IR (KBr) ν (cm^{-1}): 3078 (aromatic CH stretching), 1612 (C=N stretching), 1585, 1550 (C=C ring stretch), 2954, 2946 (methyl CH stretch), 1260 (asymmetric C-O-C stretching), 1022(symmetric C-O-C stretching), 1281 (N-N=C); ^{1}H NMR δ (ppm): 7.16 (d, 1H, C-5 of Ar), 7.54 (s, 1H, C-2 of Ar), 7.68 (d, 1H, C-6 of Ar), 7.86 (s, 1H, C-3' of Ar), 7.76 (s, 1H, C-5' of Ar), 6.92 (d, 1H, C-6' of Ar'), 5.80 (q, 1H, CH in -CH-CH_3), 1.84 (d, 3H of CH_3 in -CH-CH_3), 3.80 (s, 6H, OCH_3); MS *m/z*: 451 M^+, 453 M^{+2}, 455 M^{+4}; Anal. Calcd. (%) for $C_{19}H_{16}N_4O_3SCl_2$: C, 50.56; H, 3.57; N, 12.41; S, 7.10. Found: C, 50.67; H, 3.59; N, 12.38; S, 7.07.

3-(3,5-dimethoxy phenyl)-6-[1-(2,4-dichloro phenoxy) ethyl]-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole (16b)

Yield: 56%; m.p: 70 ^{o}C; IR (KBr) ν (cm^{-1}): 3085 (aromatic CH stretching), 1611(C=N stretching), 1581, 1549, 1475, 1439 (C=C ring stretch), 2981, 2934 (methyl CH stretch), 1264 (asymmetric C-O-C stretching), 1028 (symmetric C-O-C stretching), 1280 (N-N=C); ^{1}H NMR δ (ppm): 7.2 (d, 2H, of Ar), 6.7 (d, 1H, of Ar), 7.86 (s, 1H, C-3' of Ar), 7.76 (s, 1H, C-5' of Ar), 6.92 (d, 1H, C-6' of Ar'), 5.80 (q, 1H, CH in -CH-CH_3), 1.84 (d, 3H of CH_3 in -CH-CH_3), 3.84 (s, 6H, OCH_3); MS *m/z*: 451 M^+, 453 M^{+2}, 455 M^{+4}; Anal. Calcd. (%) for $C_{19}H_{16}N_4O_3SCl_2$: C, 50.56; H, 3.57; N, 12.41; S, 7.10. Found: C, 50.68; H, 3.56; N, 12.38; S, 7.07.

3-(3,4,5-trimethoxy phenyl)-6-[1-(2,4-dichlorophenoxy) ethyl]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (16c)

Yield: 52%; m.p: 80 ^{o}C; IR (KBr) ν (cm^{-1}): 3069 (aromatic CH stretching), 1613 (C=N stretching), 1587, 1525, 1485, 1451 (C=C ring stretch), 2974, 2865 (methyl CH stretch), 1261 (asymmetric C-O-C stretching), 1017 (symmetric C-O-C stretching), 1282 (N-N=C); ^{1}H NMR δ (ppm): 7.34 (s, 2H, C-2 & C-6 of Ar), 7.86 (s, 1H, C-3' of Ar), 7.74 (d, 1H, C-5' of Ar), 6.92 (d, 1H, C-6' of Ar'), 5.80 (q, 1H, CH in -CH-CH_3), 1.84 (d, 3H of CH_3 in -CH-CH_3), 3.86 (s, 9H, OCH_3); MS *m/z*: 481 M^{+}, 483 M^{+2}, 485 M^{+4}; Anal. Calcd. (%) for $C_{20}H_{18}N_4O_4SCl_2$: C, 49.90; H, 3.77; N, 11.64; S, 6.66. Found: C, 49.84; H, 3.76; N, 11.63; S, 6.68.

3-(4-pyridinyl)-6-[1-(2,4-dichlorophenoxy)ethyl]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole(16d)

Yield: 54%; m.p: 148 ^{o}C; IR (KBr) ν (cm^{-1}): 3075 (aromatic CH stretching), 1610 (C=N stretching), 1580, 1565 (C=C ring stretch), 1282 (N-N=C); ^{1}H NMR δ (ppm): 8.04 (d, 1H, C-3 & C-5 of Ar), 8.72 (d, 1H, C-2 & C-6 of Ar), 7.86 (s, 1H, C-3' of Ar), 7.76 (d, 1H, C-5' of Ar), 6.94 (d, 1H, C-6' of Ar'), 5.80 (q, 1H, CH in -CH-CH_3), 1.84 (d, 3H of CH_3 in -CH-CH_3); MS *m/z*: 392 M^{+}, 394 M^{+2}, 396 M^{+4}; Anal. Calcd. (%) for $C_{16}H_{11}N_5OSCl_2$: C, 48.99; H, 2.83; N, 17.85; S, 8.17. Found: C, 49.09; H, 2.82; N, 17.78; S, 8.14.

General method for the preparation of 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole 17 (a-d)

An equimolecular mixture of substituted triazole (0.02 mol) and 2-furfuraldehyde (0.02 mol), DMF (30 mL) and a catalytic amount of *p*-toluenesulphonic acid (10 mg) were taken in a round bottom flask. Refluxed the mixture for about 10-12h. The reaction mixture was concentrated to half its volume and cooled to room temperature. Poured the cooled mixture gradually into crushed ice cubes with stirring. Allowed the mixture to stand, solid was separated. It was filtered, washed thoroughly with cold water, dried and recrystallized from hot ethanol. Similarly 18-20 (a-d) were synthesized and characterized.

3-(3,4-dimethoxy phenyl)-6-[2-furanyl]- 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (17a)

Yield: 55(%); m.p: 172^{o}C;IR (KBr) ν (cm^{-1}): 3370 (NH stretching), 3056 (aromatic CH stretching), 1618 (C=N stretching), 1580, 1535 (C=C ring stretch), 1264 (asymmetric C-O-C stretching), 1017 (symmetric C-O-C stretching); ^{1}H NMR δ (ppm): 7.1 (d, 1H of C-5 of Ar), 7.5 (s, 1H, C-2 of Ar), 7.68 (d, 1H, C-6 of Ar), 6.84 (d, 1H, C-3' of furan), 7.24 (m, 1H of C-4' of furan), 7.78 (d, 1H C-5'of furan), 5.56 (s, 1H, CH in -CH-NH), 6.20 (s, 1H of NH in -NH-CH), 3.84 (s, 6H, OCH_3); MS *m/z*: 330 M^{+}; Anal. Calcd. (%) for $C_{15}H_{14}N_4O_3S$: C, 54.53; H, 4.27; N, 16.96; S, 9.71. Found: C, 54.46; H, 4.29; N, 16.92; S, 9.74.

3-(3,5-dimethoxy phenyl)-6-[2-furanyl]- 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (17b)

Yield: 52%; m.p: 160^{o}C; IR (KBr) ν (cm^{-1}): 3350 (NH stretching), 3076 (aromatic CH stretching), 1617(C=N stretching), 1576, 1552, 1480 (C=C ring stretch), 1262 (asymmetric C-O-C stretching), 1020 (symmetric C-O-C stretching); ^{1}H NMR δ (ppm): 7.12 (s, 2H, C-2 & C-6 of Ar), 6.7 (s, 1H, C-4 of Ar), 6.90 (d, 1H, C-3' of furan), 7.24 (m, 1H of C-4' of furan), 7.76 (d, 1H C-5'of furan), 5.58 (s, 1H, CH in -CH-NH), 6.18 (s, 1H of NH in -NH-CH), 3.80 (s, 6H, OCH_3); MS *m/z*: 330 M^{+}; Anal. Calcd. (%) for $C_{15}H_{14}N_4O_3S$: C, 54.53; H, 4.27; N, 16.96; S, 9.71. Found: C, 54.62; H, 4.29; N, 17.03; S, 9.68.

3-(3,4,5-trimethoxy phenyl)-6-[2-furanyl]- 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (17c)

Yield: 59%; m. p: 172°C; IR (KBr) ν (cm^{-1}): 3328 (NH stretching), 3080 (aromatic CH stretching), 1620 (C=N stretching), 1580, 1552, 1484 (C=C ring stretch), 1258 (asymmetric C-O-C stretching), 1023 (symmetric C-O-C stretching); ^{1}H NMR δ (ppm): (d, 7.32 (s, 2H, C-2 & C-6 of Ar), 6.90 (d, 1H, C-3' of furan), 7.20 (m, 1H of C-4' of furan), 7.7 (d, 1H C-5'of furan), 5.58 (s, 1H, CH in -CH-NH), 6.16 (s, 1H of NH in -NH-CH), 3.86 (s, 9H, OCH_3); MS *m/z*: 360 M^+; Anal. Calcd. (%) for $C_{16}H_{16}N_4O_4S$: C, 53.32; H, 4.47; N, 15.55; S, 8.90. Found: C, 53.25; H, 4.48; N, 15.48; S, 8.86.

3-(4-pyridinyl)-6-[2-furanyl]- 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (17d)

Yield: 58%; m.p: 218°C;IR (KBr) ν (cm^{-1}): 3356 (NH stretching), 3082 (aromatic CH stretching), 1614 (C=N stretching), 1580, 1547 (C=C ring stretch), 1261 (asymmetric C-O-C stretching), 1020 (symmetric C-O-C stretching); ^{1}H NMR δ (ppm): 8.00 (d, 2H, C-2 & C-6 of Ar), 8.64 (d, H, C-3 & C-5 of Ar), 6.86 (d, 1H, C-3' of furan), 7.26 (m, 1H of C-4' of furan), 7.74 (d, 1H C-5'of furan), 5.58 (s, 1H, CH in -CH-NH), 6.20 (s, 1H of NH in -NH-CH); MS *m/z*: 271 M^+; Anal. Calcd. (%) for $C_{12}H_9N_5OS$: C, 53.13; H, 3.34; N, 25.81; S, 11.82. Found: C, 53.05; H, 3.34; N, 25.74; S, 11.85.

3-(3,4-dimethoxy phenyl)-6-[5-nitro-2-furanyl]- 5,6-dihydro- 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (18a)

Yield:59%; m.p: 224°C; IR (KBr) ν (cm^{-1}): 3338 (NH stretching), 3086 (aromatic CH stretching), 1619 (C=N stretching), 1590, 1558 (C=C ring stretch), 1265 (asymmetric C-O-C stretching), 1017(symmetric C-O-C stretching), 1527 (asymmetric NO_2 stretch), 1347 (symmetric NO_2 stretch); ^{1}H NMR δ (ppm): 7.12 (d, 1H of C-5 of Ar), 7.58 (s,1H, C-2 of Ar), 7.74 (d, 1H, C-6 of Ar), 7.36 (d, 1H, C-3' of furan), 7.90 (d, 1H of C-4' of furan), 5.58 (s, 1H, CH in -CH-NH), 6.20 (s, 1H of NH in -NH-CH), 3.82 (s, 6H, OCH_3); MS *m/z*: 375 M^+; Anal. Calcd. (%) for $C_{15}H_{13}N_5O_5S$: C, 48.00; H, 3.49; N, 18.66; S, 8.54. Found: C, 48.13; H, 3.51; N, 18.62; S, 8.51.

3-(3,5-dimethoxy phenyl)-6-[5-nitro-2-furanyl]- 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (18b)

Yield:56%; m.p: 218°C;IR (KBr) ν (cm^{-1}): 3350 (NH stretching), 3079 (aromatic CH stretching), 1615(C=N stretching), 1584, 1547, 1492 (C=C ring stretch), 1258 (asymmetric C-O-C stretching), 1021 (symmetric C-O-C stretching), 1519 (asymmetric NO_2 stretch), 1348 (symmetric NO_2 stretch); ^{1}H NMR δ (ppm): 7.20 (s, 2H, C-2 & C-6 of Ar), 6.76 (s, 1H, C-4 of Ar), 7.40 (d, 1H, C-3' of furan), 7.94 (d, 1H of C-4' of furan), 5.58 (s, 1H, CH in -CH-NH), 6.16 (s, 1H of NH in -NH-CH), 3.80 (s, 6H, OCH_3); MS *m/z*: 375 M^+; Anal. Calcd. (%) for $C_{15}H_{13}N_5O_5S$: C, 48.00; H, 3.49; N, 18.66; S, 8.54. Found: C, 47.91; H, 3.51; N, 18.72; S, 8.48.

3-(3,4,5-trimethoxy phenyl)-6-[5-nitro-2-furanyl]- 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (18c)

Yield:60%; m.p: 214°C;IR (KBr) ν (cm^{-1}): 3345 (NH stretching), 3084 (aromatic CH stretching), 1620 (C=N stretching), 1580, 1542, 1490 (C=C ring stretch), 1530 (asymmetric NO_2 stretch), 1340 (symmetric NO_2 stretch); ^{1}H NMR δ (ppm): 7.28 (s, 2H, C-2 & C-6 of Ar), 7.42 (d, 1H, C-3' of furan), 7.92 (d, 1H of C-4' of furan), 5.60 (s, 1H, CH in -CH-NH), 6.18 (s, 1H of NH in -NH-CH), 3.84 (s, 9H, OCH_3); MS *m/z*: 405 M^+; Anal. Calcd. (%) for $C_{16}H_{15}N_5O_6S$: C, 47.40; H, 3.73; N, 17.28; S, 7.91. Found: C, 47.41; H, 3.76; N, 17.24; S, 7.87.

3-(4-pyridinyl)-6-[5-nitro-2-furanyl]- 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (18d)

Yield: 57%; m.p: 234°C; IR (KBr) ν (cm^{-1}): 3327 (NH stretching), 3068 (aromatic CH stretching), 1620 (C=N stretching), 1590, 1560 (C=C ring stretch), 1526 (asymmetric NO_2 stretch), 1342 (symmetric NO_2 stretch); ^1H NMR δ (ppm): 8.00 (d, 2H, C-2 & C-6 of Ar), 8.64 (d, H, C-3 & C-5 of Ar), 7.40 (d, 1H, C-3' of furan), 7.92 (d, 1H of C-4' of furan), 5.58 (s, 1H, CH in -CH-NH), 6.16 (s, 1H of NH in -NH-CH); MS *m/z*: 316 M^+; Anal. Calcd. (%) for $C_{12}H_8N_6O_3S$: C, 45.57; H, 2.55; N, 26.57; S, 10.14. Found: C, 45.48; H, 2.55; N, 26.62; S, 10.11.

3-(3,4-dimethoxy phenyl)-6-[pyrol-2-yl]- 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (19a)

Yield: 53%; m.p: 176 °C; IR (KBr) ν (cm^{-1}): 3352 (NH stretching), 3070 (aromatic CH stretching), 1619 (C=N stretching), 1586, 1554 (C=C ring stretch), 1263 (asymmetric C-O-C stretching), 1019 (symmetric C-O-C stretching); ^1H NMR δ (ppm): 7.20 (d, 1H of C-5 of Ar), 7.58 (s,1H, C-2 of Ar), 7.76 (d, 1H, C-6 of Ar), 6.42 (d, 1H, C-3' of pyrrole), 6.60 (m, 1H of C-4' of pyrrole), 7.04 (d, 1H of C-5' of pyrrole), 5.60 (s, 1H, CH in -CH-NH), 6.16 (s, 1H of NH in -NH-CH), 9.8 (d, 1H, -NH of pyrrole), 3.80 (s, 6H, OCH_3); MS *m/z*: 329 M^+; Anal. Calcd. (%) for $C_{15}H_{15}N_5O_2S$: C, 54.70; H, 4.59; N, 21.26; S, 9.74. Found: C, 54.62; H, 4.61; N, 21.18; S, 9.71.

3-(3,5-dimethoxy phenyl)-6-[pyrol-2-yl]- 5,6-dihydro-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole (19b)

Yield: 50%; m.p: 162°C; IR (KBr) ν (cm^{-1}): 3365 (NH stretching), 3083 (aromatic CH stretching), 1617(C=N stretching), 1586, 1550, 1470 (C=C ring stretch), 1257 (asymmetric C-O-C stretching), 1021 (symmetric C-O-C stretching); ^1H NMR δ (ppm): 7.26 (s, 2H, C-2 & C-6 of Ar), 6.80 (s, 1H, C-4 of Ar), 6.46 (d, 1H, C-3' of pyrrole), 6.60 (m, 1H of C-4' of pyrrole), 7.06 (d, 1H of C-5' of pyrrole), 5.60 (s, 1H, CH in -CH-NH), 6.16 (s, 1H of NH in -NH-CH), 9.6 (d, 1H, -NH of pyrrole), 3.80 (s, 6H, OCH_3); MS *m/z*: 329 M^+; Anal. Calcd. (%) for $C_{15}H_{15}N_5O_2S$: C, 54.70; H, 4.59; N, 21.26; S, 9.74. Found: C, 54.63; H, 4.60; N, 21.32; S, 9.71.

3-(3,4,5-trimethoxy phenyl)-6-[pyrol-2-yl]- 5,6-dihydro- 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (19c)

Yield: 55%; m.p: 180°C; IR (KBr) ν (cm^{-1}): 3348 (NH stretching), 3076 (aromatic CH stretching), 1615 (C=N stretching), 1580, 1568, 1490 (C=C ring stretch), 1259 (asymmetric C-O-C stretching), 1024 (symmetric C-O-C stretching); ^1H NMR δ (ppm): ^1H NMR δ (ppm): 7.34 (s, 2H, C-2 & C-6 of Ar), 6.42 (d, 1H, C-3' of pyrrole), 6.59 (m, 1H of C-4' of pyrrole), 7.06 (d, 1H of C-5' of pyrrole), 5.60 (s, 1H, CH in -CH-NH), 6.18 (s, 1H of NH in -NH-CH), 9.8 (d, 1H, -NH of pyrrole), 3.84 (s, 9H, OCH_3); MS *m/z*: 359 M^+; Anal. Calcd. (%) for $C_{16}H_{17}N_5O_3S$: C, 53.47; H, 4.77; N, 19.49; S, 8.92. Found: C, 53.45; H, 4.77; N, 19.42; S, 8.87.

3-(4-pyridinyl)-6-[pyrol-2-yl]- 5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (19d)

Yield: 53%; m. p: 206°C; IR (KBr) ν (cm^{-1}): 3365 (NH stretching), 3086 (aromatic CH stretching), 1618 (C=N stretching), 1588, 1566 (C=C ring stretch); ^1H NMR δ (ppm):7.96 (d, 2H, C-2 & C-6 of Ar), 8.68 (d, H, C-3 & C-5 of Ar), 6.40 (d, 1H, C-3' of pyrrole), 6.62 (m, 1H of C-4' of pyrrole), 7.04 (d, 1H of C-5' of pyrrole), 5.60 (s, 1H, CH in -CH-NH), 6.18 (s, 1H of NH in -NH-CH), 9.8 (d, 1H, -NH of pyrrole); MS *m/z*: 270 M^+; Anal. Calcd. (%) for $C_{12}H_{10}N_6S$: C, 53.32; H, 3.73; N, 31.09; S, 11.86. Found: C, 53.25; H, 3.73; N, 31.14; S, 11.80.

3-(3,4-dimethoxy phenyl)-6-[N-methyl-pyrol-2-yl]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (20a)

Yield: 57(%); m.p: 184°C; IR (KBr) ν (cm^{-1}): 3364 (NH stretching), 3062 (aromatic CH stretching), 1610 (C=N stretching), 1580, 1553 (C=C ring stretch), 1266 (asymmetric C-O-C stretching), 1021 (symmetric C-O-C stretching), 2963, 2847 (methyl CH stretch); ^{1}H NMR δ (ppm): 7.24 (d, 1H of C-5 of Ar), 7.56 (s,1H, C-2 of Ar), 7.72 (d, 1H, C-6 of Ar), 6.88 (d, 1H, C-5' of pyrrole), 6.56 (m, 1H, C-4' of pyrrole), 6.40 (d, 1H, C-3' of pyrrole), 5.62 (s, 1H, of -CH-NH), 6.20 (s, 1H of NH in -NH-CH), 3.56 (s, 3H of N-CH_3), 3.82 (s, 6H, OCH_3); MS *m/z*: 343 M^+; Anal. Calcd. (%) for $C_{16}H_{17}N_5O_2S$: C, 55.96; H, 4.99; N, 20.39; S, 9.34. Found: C, 56.10; H, 5.01; N, 20.31; S, 9.31.

3-(3,5-dimethoxyphenyl)-6-[N-methyl-pyrol-2-yl]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole(20b)

Yield: 52%; m.p: 174°C;IR (KBr) ν (cm^{-1}): 3364 (NH stretching), 3058 (aromatic CH stretching), 1615(C=N stretching), 1589, 1565, 1480 (C=C ring stretch), 1258 (asymmetric C-O-C stretching), 1025 (symmetric C-O-C stretching), 2958, 2849 (methyl CH stretch); ^{1}H NMR δ (ppm): 7.22 (s, 2H, C-2 & C-6 of Ar), 6.76 (s, 1H, C-4 of Ar), 6.9 (d, 1H, C-5' of pyrrole), 6.52 (m, 1H, C-4' of pyrrole), 6.38 (d, 1H, C-3' of pyrrole), 5.48 (s, 1H, of -CH-NH), 6.18 (s, 1H of NH in -NH-CH), 3.60 (s, 3H of N-CH_3), 3.82 (s, 6H, OCH_3); MS *m/z*: 343 M^+; Anal. Calcd. (%) for $C_{16}H_{17}N_5O_2S$: C, 55.96; H, 4.99; N, 20.39; S, 9.34. Found: C, 56.05; H, 5.01; N, 20.34; S, 9.32.

3-(3,4,5-trimethoxyphenyl)-6-[N-methyl-pyrol-2-yl]-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (20c)

Yield: 61%; m. p: 162°C; IR (KBr) ν (cm^{-1}): 3345 (NH stretching), 3072 (aromatic CH stretching), 1616 (C=N stretching), 1587, 1549, 1480 (C=C ring stretch), 1264 (asymmetric C-O-C stretching), 1022 (symmetric C-O-C stretching), 2965, 2850 (methyl CH stretch); ^{1}H NMR δ (ppm): 7.3 (s, 2H, C-2 & C-6 of Ar), 7.06 (d, 1H, C-5' of pyrrole), 6.82 (m, 1H, C-4' of pyrrole), 6.64 (d, 1H, C-3' of pyrrole), 5.50 (s, 1H, of -CH-NH), 6.16 (s, 1H of NH in -NH-CH), 3.60 (s, 3H of N-CH_3), 3.86 (s, 9H, OCH_3); MS *m/z*: 373 M^+; Anal. Calcd. (%) for $C_{17}H_{19}N_5O_3S$: C, 54.68; H, 5.13; N, 18.75; S, 8.59. Found: C, 54.61; H, 5.13; N, 18.67; S, 8.61.

3-(4-pyridinyl)-6-[N-methyl-pyrol-2-yl]-5,6-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (20d)

Yield: 59%; m. p: 200°C; IR (KBr) ν (cm^{-1}): 3369 (NH stretching), 3045 (aromatic CH stretching), 1614 (C=N stretching), 1590, 1563 (C=C ring stretch), 2964, 2840 (methyl CH stretch); ^{1}H NMR δ (ppm): 8.02 (d, 2H, C-2 & C-6 of Ar), 8.66 (d, H, C-3 & C-5 of Ar), 6.86 (d, 1H, C-5' of pyrrole), 6.56 (m, 1H, C-4' of pyrrole), 6.38 (d, 1H, C-3' of pyrrole), 5.48 (s, 1H, of -CH-NH), 6.16 (s, 1H of NH in -NH-CH), 3.50 (s, 3H of N-CH_3), MS *m/z*: 284 M^+; Anal. Calcd. (%) for $C_{13}H_{12}N_6S$: C, 54.91; H, 4.25; N, 29.56; S, 11.28. Found: C, 54.81; H, 4.22; N, 29.52; S, 11.25.

Results and Discussion

In the IR spectra of the cyclized products showed absorption band at 3270-3290cm^{-1} due to NH functional group and the weak broad absorption band around 2580cm^{-1} due to SH group were absent. This confirmed the involvement of NH_2 and SH groups of the parent amino mercapto triazole in the ring formation. An absorption band was observed for all the synthesized compounds in the range of 3060-3090 cm^{-1} may be attributed for aromatic stretching vibration, while that seen at 1610-1614cm^{-1} corresponds to C=N linkage. Thus, the formation of iminomethine functional group in the compound was indicated.

In the ^{1}H NMR spectra of synthesized compound, the peaks due to NH_2 and SH, which were present in the amino mercapto triazole were absent that further confirmed the involvement of these functional groups in the cyclization of triazole to triazolo thiadiazoles. Similarly the absence of SH proton and the down fielding of NH_2 protons (integration for one proton) in the ^{1}H NMR spectra established that -CHO group of the aromatic aldehydes reacted with -SH & -NH_2 groups of triazoles and thus converted to dihydro triazolo thiadiazoles (17-20). The ^{1}H NMR, mass spectra, IR and elemental analysis supported the structure of various synthesized triazolo thiadiazoles and their dihydro analogues.

The antimicrobial results showed that some of the compounds are active against the tested microbes. It can be concluded that none of the prepared compounds were superior to positive controls against various tested microbial strains, but was interesting to note that compounds 8d, 9a, 9b, 9d, 14d & 16d were very sensitive to all the tested organisms comparable to the standards used at the concentration of 30µg/mL. Antimicrobial effects of the some of the synthesized compounds were reported in Table 3 & 4 as zone of inhibition against various bacterial and fungal strains respectively.

Anti-inflammatory and analgesic activity screening indicated that some of the tested compound 10d, 12d, 14a, 14b, 14d, 16a, 16b and 16d showed good anti-inflammatory and analgesic activities. Other compounds had moderate anti-inflammatory and analgesic activities. Anti-inflammatory and analgesic effects of the newly synthesized compounds were reported in Table 1 & 2 respectively.

Table 1. Anti-inflammatory activity of compounds

Compd	Change in paw volume (in mL) after (±SE)#				Percentage inhibition of oedema volume after			
	1h	2h	3h	4h	1h	2h	3h	4h
8a	0.71±0.02	0.98±0.03	1.39±0.02	1.52±0.02	11.4	16.2	20.7	26.5
8b	0.73±0.02	1.02±0.04	1.41±0.03	1.56±0.03	8.8	12.9	19.5	24.6
8c	0.74±0.02	1.00±0.06	1.45±0.04	1.64±0.03	7.8	13.9	17.4	20.5
8d	0.71±0.02	0.97±0.05	1.36±0.02	1.52±0.02	11.3	16.8	22.3	26.4
10a	0.80±0.02	1.07±0.07	1.43±0.02	1.66±0.02	11.2	16.5	20.7	26.4
10b	0.79±0.05	1.07±0.03	1.42±0.03	1.65±0.04	12.3	16.9	21.1	26.8
10c	0.82±0.05	1.10±0.07	1.49±0.02	1.77±0.03	8.6	14.0	17.1	21.5
10d	0.77±0.02	1.02±0.02	1.32±0.03	1.53±0.04	14.9*	20.5*	26.7*	31.9*
12a	0.76±0.02	1.00±0.02	1.32±0.03	1.58±0.07	15.6*	22.1*	26.8*	29.8*
12b	0.77±0.04	1.01±0.03	1.32±0.04	1.61±0.05	14.7*	21.2*	26.4*	28.5*
12c	0.78±0.04	1.06±0.02	1.39±0.03	1.70±0.03	13.3*	17.1	22.8	24.4
12d	0.74±0.03	0.93±0.02	1.19±0.05	1.44±0.02	17.8	27.9	33.9**	36.2**
14a	0.61±0.02	0.83±0.03	1.08±0.03	1.33±0.03	17.4***	23.5*	29.6*	32.8*
14b	0.60±0.03	0.83±0.02	1.10±0.07	1.36±0.05	17.8***	23.2*	27.9*	31.6*
14c	0.62±0.03	0.89±0.03	1.17±0.05	1.46±0.023	15.3**	18.3	23.8	26.4
14d	0.58±0.02	0.79±0.06	1.04±0.02	1.26±0.02	20.3***	26.7**	32.3**	36.6**
16a	0.62±0.02	0.85±0.05	1.09±0.02	1.35±0.04	15.9**	21.7*	29.0*	32.1*
16b	0.61±0.02	0.82±0.04	1.07±0.02	1.32±0.02	16.9**	24.7**	29.9*	33.2*
16c	0.63±0.04	0.86±0.02	1.16±0.02	1.45±0.02	14.4*	20.6*	24.0	26.8
16d	0.55±0.03	0.82±0.02	1.07±0.05	1.30±0.04	18.9***	24.3**	30.1*	34.6**
Phenyl butazone	0.72±0.03	0.92±0.03	0.97±0.04	1.00±0.00	21.2***	33.5***	40.8***	48.0***

= ± Standard error ; * = P<0.05; ** = P<0.01; *** = P<0.001; For all other comparison P>0.05.

Table 2. Analgesic activities of compounds

Compd	Reaction time (sec) after drug administration			Percent increase in reaction time		
	30 min± SE[#]	60 min± SE[#]	90 min ± SE[#]	30min	60min	90min
8d	5.98±0.43	6.30±0.43	6.64±0.21	19.2	23.3*	27.3*
9d	7.81±0.31	8.37±0.34	8.68±0.45	19.0	24.4*	27.1*
10d	8.23±0.33	8.84±0.55	9.29±0.45	19.1	24.7*	28.3*
12a	8.70±0.73	9.27±0.43	9.73±0.35	17.7	22.8	26.4*
12b	7.23±0.24	8.02±0.45	8.46±0.34	14.8	23.2*	27.2*
12c	7.47±0.56	7.77±0.50	8.63±0.61	11.6	19.1	23.5
12d	3.98±0.33	4.29±0.60	4.57±0.31	20.5	26.2**	30.7*
14a	8.34±0.34	9.20±0.21	10.03±0.40	20.1	27.6**	33.6**
14b	8.54±0.52	9.08±0.45	9.48±0.60	23.9	28.4**	31.4**
14c	9.53±0.34	10.16±0.42	10.52±0.34	21.3	26.2**	28.7*
14d	8.39±0.15	9.21±0.42	10.09±0.45	26.6	33.1***	38.9**
15d	4.44±0.47	4.75±0.56	5.06±0.37	17.6	22.9	27.7
16a	5.60±0.15	6.26±0.42	6.63±0.45	22.7	30.8**	34.7**
16b	9.60±0.33	10.69±0.48	11.42±0.17	20.2	28.3*	32.9**
16c	7.19±0.34	8.13±0.37	8.47±0.21	16.6	26.2*	29.2*
16d	5.91±0.34	6.89±0.42	7.28±0.34	23.9	34.7***	38.2**
17d	6.24±0.17	6.92±0.21	7.84±0.40	5.68	15.18	26.14
18d	6.17±0.34	6.85±0.56	8.70±0.37	5.34	15.68	26.85
diclofenac sodium	4.74±0.50	5.58±0.43	7.33±0.21	26.2***	37.3***	52.3***

[#] = Standard error; ***=** P<0.05. *****=**P<0.01. *** = P<0.001. For all other comparison P>0.05.

Pharmacology

Anti-inflammatory activity

All the synthesized compounds were evaluated for their anti-inflammatory activity against carrageenan-induced acute paw oedema in albino rats (Wistar strain) weighing 150-200g[15,16]. The animals were weighed and numbered into various groups and each group contained six animals. One group served as control and received 0.1mL of 1% gum acacia suspension orally. Group II served as standard and received phenylbutazone at a dose of 5mg/kg suspension in gum acacia orally. One hour after the administration of test compounds at a dose of 5mg/kg as suspension in gum acacia, 0.1 mL of 1% carrageenan in normal saline was given subcutaneously to the sub plantar region of right hind paw. The paw volume was measured immediately ('0' h) and after 1, 2, 3 and 4th h respectively by using plethysmograph. The amount of oedema in the drug-treated groups was compared in relation to the control group with the corresponding time intervals. The percentage of inhibition by the drugs was calculated by using the formula,

$$\text{Percentage inhibition} = 100\,(1-V_{test} / V_{control}),$$

Where V_{test} = mean increase in paw volume of drug treated group;

$V_{control}$ = mean increase in paw volume of control group.

The results were expressed as percentage inhibition of oedema over the untreated control group.

Table 3. Antifungal activities of compounds

Compd	*C. albicans*[1]			*A. niger*[2]		
	10 , µg /mL ±SD*	20, µg /mL ±SD*	30, µg /mL ±SD*	10, µg /mL ±SD*	20, µg /mL ±SD*	30, µg/mL ±SD*
4a	5.64±1.16	12.84±1.73	18.78±1.53	6.04±0.58	11.63±0.58	17.58±1.16
4b	5.82±0.58	11.37±0.58	17.95±1.73	6.14±1.16	11.54±1.53	16.72±0.58
4d	6.27±0.58	14.84±1.16	19.36±1.53	5.92±0.58	11.00±0.00	17.67±0.58
5a	6.18±1.16	13.82±0.58	18.75±0.61	5.62±0.47	12.62±0.58	18.54±0.27
5b	5.84±0.53	12.62±0.58	19.00±2.00	6.00±1.00	13.46±0.58	17.42±1.16
5d	5.48±0.58	12.00±1.00	17.48±1.53	6.25±0.58	13.00±1.00	16.72±0.27
6a	6.48±0.58	13.92±1.73	18.00±1.00	6.40±0.61	12.85±0.58	19.10±1.53
6b	6.14±0.58	13.66±0.47	17.82±0.27	6.32±0.61	13.00±1.00	19.00±0.00
6d	5.78±0.58	11.00±1.00	19.24±1.53	6.14±0.58	12.00±1.00	19.10±0.58
7d	5.34±0.58	10.00±2.00	17.28±1.53	5.14±0.58	9.48±0.58	16.84±0.58
8a	7.14±0.47	13.72±0.58	19.28±0.47	6.64±0.58	11.84±1.73	18.42±1.16
8b	6.82±0.58	12.88±0.61	19.36±0.61	7.23±0.58	13.00±0.00	18.38±0.27
8c	5.66±0.47	11.62±0.58	17.28±1.73	6.12±0.47	10.68±0.58	15.62±1.16
8d	7.26±0.58	14.00±2.00	21.86±1.53	7.38±0.27	14.26±0.58	20.66±0.58
9a	7.68±0.58	14.46±1.16	21.68±1.16	6.68±0.58	12.57±0.58	20.48±1.73
9b	8.14±0.47	14.75±0.58	21.72±1.16	7.14±0.58	12.44±0.58	20.96±0.58
9c	6.14±0.61	11.62±0.58	17.36±0.58	5.84±1.16	10.74±1.53	17.85±0.27
9d	8.82±0.58	16.58±0.58	23.76±1.53	7.36±0.58	13.00±0.00	22.66±0.58
10a	5.44±0.58	9.26±0.58	17.16±1.16	5.38±1.73	10.12±0.61	16.94±0.61
10b	5.76±0.58	9.38±0.47	18.00±2.00	5.16±0.47	9.18±0.58	17.36±1.53
10d	6.12±0.58	10.83±0.61	19.47±1.53	5.62±0.58	10.86±0.61	18.74±0.58
11a	4.35±0.58	8.72±1.16	16.73±1.16	4.57±2.08	9.24±1.16	15.26±2.08
11b	4.69±0.58	9.16±2.08	16.16±1.16	4.93±0.58	8.58±1.16	15.78±1.53
11d	5.14±0.58	9.86±1.16	17.14±1.53	5.85±0.58	11.00±2.00	16.42±0.58
12a	5.86±0.58	11.48±1.16	17.47±1.53	5.18±0.58	11.12±0.17	16.94±0.58
12b	6.10±0.58	11.24±0.47	17.22±1.53	5.24±0.58	10.62±0.27	17.12±0.58
12d	6.38±0.58	13.37±0.27	19.72±0.27	5.64±0.58	13.86±0.61	19.16±1.16
13d	4.72±0.27	7.37±1.73	12.46±1.16	4.82±0.58	9.38±0.61	14.35±0.27
14a	6.72±0.47	13.85±0.61	19.06±0.61	6.41±0.58	12.35±0.47	18.49±0.58
14b	6.88±1.73	12.69±0.58	19.28±0.27	6.05±0.58	13.06±0.27	17.35±1.53
14c	5.14±0.61	10.17±0.27	16.36±0.47	4.76±1.73	8.49±1.16	14.06±0.61
14d	7.96±0.58	14.00±1.00	20.31±1.16	8.16±0.58	15.72±0.47	19.84±0.58
15d	5.62±0.58	9.38±0.61	16.49±0.27	6.86±0.58	9.63±1.73	17.54±0.58
16a	7.36±0.61	11.92±1.16	18.17±1.53	7.46±0.47	12.15±0.61	18.12±0.58
16b	7.42±0.58	11.88±0.47	19.02±0.27	7.56±0.58	13.00±0.00	18.30±0.27
16c	5.84±0.27	9.63±1.73	16.47±0.58	5.63±0.561	11.37±0.27	15.10±0.61
16d	8.72±0.47	13.96±1.16	21.36±0.61	7.85±0.27	13.94±0.61	20.82±0.27
Griseofulvin	-	-	24.67±1.16	-	-	23.14±2.00

*SD = Standard Deviation; 1 = *Candida albicans*; 2 = *Aspergillus niger*

Table 4. Antibacterial activity of compounds.

Compd	*E.coli* [1]			*P. aeruginosa* [2]			*B. subtilis* [3]			*S. aureus*[4]		
	10µg/mL ±SD*	20µg/mL ±SD*	30µg/mL ±SD*	10µg/mL ±SD*	20µg/mL ±SD*	30µg/mL ±SD*	10µg/mL ±SD*	20µg/mL ±SD*	30µg/mL ±SD*	10µg/mL ±SD*	20µg/mL ±SD*	30µg/mL ±SD*
4a	6.86±1.73	11.72±2.52	16.52±2.65	6.72±1.16	11.38±0.58	15.49±0.58	6.82±0.47	11.15±1.16	16.16±1.53	5.82±0.58	10.12±0.58	16.36±0.58
4b	6.08±0.58	11.28±0.47	16.86±1.16	5.92±0.61	10.85±0.58	16.04±1.16	5.76±0.58	10.24±1.53	15.92±0.47	5.12±0.26	10.26±0.61	16.74±0.58
4c	5.16±1.16	9.84±1.53	14.18±2.52	6.10±0.58	10.63±0.58	14.48±0.58	4.80±0.58	9.02±1.16	14.00±1.00	5.04±0.58	10.36±1.16	16.60±0.58
4d	7.64±0.26	13.18±0.58	17.36±0.45	7.12±0.26	12.04±1.16	17.26±2.09	6.16±0.61	11.84±0.58	16.86±1.53	6.18±0.58	12.69±0.17	17.48±0.58
5a	5.16±1.73	9.12±2.52	16.67±2.89	5.31±1.16	10.26±1.53	16.11±0.58	7.06±1.71	11.10±0.61	16.38±0.45	6.89±0.58	12.06±0.17	16.10±1.16
5b	5.25±1.15	8.80±0.00	16.00±0.00	5.26±0.57	10.12±1.15	16.05±1.15	6.29±.57	10.18±1.15	16.12±0.57	6.72±0.57	11.68±0.57	16.60±0.57
5c	5.84±0.58	8.19±0.58	14.20±1.53	4.67±0.45	9.10±0.58	15.53±1.16	5.48±1.16	9.63±0.58	15.80±1.73	6.78±0.58	11.29±0.61	16.00±2.00
5d	6.28±0.45	10.48±0.58	17.00±1.00	6.00±0.00	11.84±0.17	16.82±1.73	7.38±1.16	12.48±0.17	17.10±1.53	7.10±0.58	13.73±0.63	17.92±0.26
6a	8.28±0.26	14.48±0.58	18.78±0.45	7.82±0.26	13.27±1.16	18.71±2.09	7.68±0.61	13.06±0.58	18.80±1.53	7.21±0.58	13.19±0.17	18.12±0.58
6b	7.85±1.73	14.36±2.52	18.64±2.89	7.70±1.16	14.10±1.53	18.16±0.58	7.40±1.71	13.26±0.61	18.66±0.45	6.96±0.58	12.61±0.17	18.27±1.16
6c	7.22±1.1.6	13.96±0.47	16.72±0.21	6.90±0.58	12.92±1.16	16.73±2.09	7.10±1.16	12.50±1.73	16.82±0.45	6.48±0.17	12.10±1.16	17.85±0.26
6d	8.74±0.58	15.27±1.16	19.41±0.58	8.17±2.09	14.15±0.17	19.10±0.58	8.14±1.53	14.10±0.45	19.79±1.71	8.16±0.58	14.10±1.16	19.12±0.58
8a	6.39±2.09	12.23±0.17	19.21±0.58	7.02±0.26	12.48±1.16	19.11±0.58	7.12±1.53	13.84±0.58	18.63±1.16	6.98±0.58	13.70±1.16	18.58±0.26
8b	6.72±0.61	12.82±1.16	19.67±2.09	6.93±0.45	12.19±0.58	19.39±0.61	7.19±0.47	13.92±0.17	18.91±0.63	7.05±0.26	13.61±1.16	18.14±1.53
8c	6.06±2.09	11.73±1.16	18.68±0.47	6.15±1.16	12.02±2.09	18.52±0.26	6.48±1.16	12.71±0.58	16.85±0.63	6.82±0.45	12.72±1.16	17.36±0.61
8d	7.48±0.58	14.78±0.47	20.19±0.17	7.79±0.61	13.78±0.47	20.59±0.26	7.82±1.17	14.55±0.58	20.38±1.16	7.82±0.63	14.66±0.17	19.23±0.58
9a	8.10±0.45	14.65±1.17	19.67±1.16	8.68±1.16	14.92±0.58	19.52±1.73	7.78±1.16	14.12±1.16	19.16±1.53	7.29±2.09	14.11±0.61	19.25±0.17
9b	7.96±0.26	14.39±0.47	19.29±0.61	8.21±0.17	14.88±2.09	19.26±0.58	7.64±1.53	14.38±0.47	19.26±0.47	7.10±0.61	13.85±1.61	19.19±0.17
9c	7.08±0.47	13.85±0.58	18.80±1.16	7.85±1.16	14.19±0.58	18.83±0.58	6.90±1.16	13.81±0.58	18.78±0.47	6.82±0.58	13.57±0.58	17.95±1.73
9d	8.54±0.47	14.27±0.58	20.79±1.16	8.39±1.53	15.21±0.45	21.29±0.61	8.12±1.16	14.76±0.58	19.86±1.73	7.90±0.58	14.18±2.09	20.17±1.53
14a	7.14±0.26	13.72±1.16	17.92±0.58	6.82±0.58	12.88±0.61	18.10±2.09	6.97±1.53	12.28±0.45	18.19±1.16	6.49±0.47	12.37±1.16	18.24±0.58
14b	6.89±0.17	12.17±2.09	17.24±1.16	6.70±1.17	12.62±0.58	18.28±1.73	6.82±1.16	12.39±1.16	18.07±1.53	6.55±0.45	12.46±0.61	18.35±0.26
14c	6.15±0.58	11.27±0.45	16.93±0.61	5.96±0.58	12.05±0.45	17.85±1.16	6.18±0.17	11.48±0.47	17.21±1.53	5.79±.61	11.72±0.47	17.49±0.17
14d	7.37±0.61	13.89±0.58	18.21±1.16	7.38±1.73	13.48±0.58	19.71±0.21	7.80±1.16	13.60±0.58	19.38±0.61	7.12±0.58	13.70±0.58	19.81±0.47
16a	6.85±0.58	13.18±0.63	19.00±1.16	6.60±1.53	12.17±0.58	18.38±1.16	6.45±0.47	13.30±1.53	18.27±2.09	6.16±1.73	12.60±0.61	18.86±0.58
16b	6.71±1.17	12.85±1.16	18.19±1.16	6.16±1.53	12.43±0.58	18.45±0.45	6.17±1.16	13.11±1.53	18.28±1.73	6.02±0.47	12.91±0.61	18.66±0.58
16c	6.10±0.58	11.90±1.16	17.65±1.53	5.56±0.47	11.65±0.58	17.68±1.53	5.80±0.58	11.82±0.61	17.45±0.58	5.85±1.16	11.47±0.58	17.94±1.73
16d	7.12±0.26	13.36±0.58	19.26±0.47	7.19±0.45	13.28±0.17	19.10±1.73	7.31±0.58	13.27±0.47	19.10±1.53	6.86±0.47	12.90±2.09	18.15±0.26
18d	5.78±1.53	11.02± 2.09	16.85±1.16	6.12±1.53	11.82±0.58	17.14±0.58	6.25±1.16	11.52±1.16	17.23±1.73	6.11±0.61	11.51±0.47	17.48±0.58
Vancomycin	-	-	-	-	-	-	-	-	23.33±1.53	-	-	22.48±0.58
Amikacin	-	-	22.67±0.58	-	-	24.00± -1.00	-	-	-	-	-	

*SD = Standard Deviation; # Zone of inhibition in mm; 1= *Escherichia coli*; 2 = *Pseudomonas aeruginosa*; 3 = *Staphylococcus aureus*; 4 = *Bacillus subtilis*

Analgesic activity

All the compounds were tested for their analgesic activity using Eddy's hot plate technique[17]. Mice (Swiss strain) of either sex weighing between 25-35g were used for the experiment. In this method heat is used as a source of pain. Animals were individually placed on a hot plate maintained at constant temperature (55 ^{0}C) and the reaction of animals, such as paw licking or jump response (whichever appears first) was taken as the end point. A cut off - time of 15 seconds (sec) was taken as maximum analgesic response to avoid injury to the paws. Tested compounds and diclofenac sodium (standard) at a dose of 5mg/kg body weight in 1% gum acacia was given as suspension orally to animals and observed the reaction time of animals on the hot plate at 15, 30, 60, 90 and 120 minutes (min) after the compound administration. Percentage analgesic activity shown by the tested compounds is recorded in Table 2.

Antibacterial and antifungal activities

Applying the agar plate diffusion technique[18] all of the newly synthesized compounds were screened *in vitro* for antibacterial activity against *Escherichia coli (E.coli), Pseudomonas aeruginosa (P. aeruginosa)* (Gram negative), *Staphylococcus aureus (S.aureus)*, *Bacillus Subtilis (B.subtilis)* (Gram positive) at 10µg/mL, 20µg/mL, 30µg/mL concentrations respectively. Under identical conditions the positive control antibiotics Amikacin at 30µg/mL showed zone of inhibition 23-24mm for gram-negative organism and Vancomycin at 100µg/mL showed zone of inhibition 23mm for gram-positive organism. Similarly, the antifungal screening of the compounds were carried out *in vitro* by paper disc method against two fungai *Aspergillus niger (A.niger)* and *Candida albicans (C.albicans)* by using Griseofulvin (30µg/mL) as the positive control, which showed (23mm and 25mm respectively) as the zone of inhibition.

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