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Synthesis of new derivatives of 1,3,4-thiadiazole, 1,2,4-triazolo [4,3-b]isoquinoline, 1,2,4-triazolo[4,3-a]pyrimidinone and 1,2,4-triazolo[4,3-b]-1,2,4-triazine

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ABSTRACT

3,5-Diaryl-2-imino-1,3,4-thiadiazoles **(2a,b)** were synthesized from the reaction of hydrazonyl bromides **(1a,b)** and potassium thiocyanate. **(2a,b)** when were subjected to nitrous acid in acetic acid gave the corresponding nitrozoimino-derivatives **(3a,b)**. **(2a,b)** were acetylated and benzoylated when reacted with acetic anhydride and benzoyl chloride and gave **(5a,b)** and **(6a,b)** respectively. **(1a,b)** reacted with 3,4-dihydro-6,7-dimethoxyisoquinoline **(7)** and 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline **(8)** and give the corresponding 1,2,4-triazolo[4,3-b]isoquinolines **(9a,b)** and **(10a,b)** respectively. 1,2,4-triazolo[4,3-a]pyrimidinones **(15a,b-17a,b)** and 1,2,4-triazolo[4,3-b]-1,2,4-triazines **(18a,b)**, **(19a,b)** were synthesized from the reaction of hydrazonyl bromides **(1a,b)** with compounds containing thiourea moiety **(11-13)**, **(14a,b)** respectively.

KEYWORDS

Thiadiazole;
1,2,4-Triazolo[4,3-b]isoquinoline;
1,2,4-Triazolo[4,3-a]pyrimidinone;
1,2,4-Triazolo[4,3-b]-1,2,4-triazine;
Hydrazonyl bromides;
Antimicrobial activity.

INTRODUCTION

Derivatives of thiadiazoles have been known, to show fungicidal[1,2], anticonvulsant[3] antiinflamatory,[4] antiviral[5] and anti-Rheumatoid arthritis activities.[4] Moreover, isoquinoline derivatives, possess anticancer [6,7], antiinflamatory[8], antidepressant activities[9], act as potential acetylcholinesterase inhibitors[10] (as improvement of Alzheimer's disease) and has antispasmodic effect[11]. Furthermore, the considerable biological activities of fused triazolopyrimidine and triazolotriazine derivatives, since they exhibit antibacterial,[12] antimicrobial[13] activities stimulated our interest to continue our work[14,15] in the synthesis of some new derivatives of these ring systems of expected biological activity, carrying fluoro- and dichloro- substituents on the phenyl group using C-(4-fluorophenyl)[16] and C-(2,4-dichlorophenyl) hydrazonyl bromides[17].

EXPERIMENTAL

All melting points were measured on electrothermal melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in (DMSO-d_6) on a GEMINI-200 spectrometer using TMS as the internal reference. Mass spectra were measured on a GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

Full Paper

Reaction of hydrazonyl bromides (1a,b) with potassium thiocyanate

To a suspension of **(1a,b)** (0.01mol) in ethanol (40ml) potassium thiocyanate (0.97 g, 0.01mol) was added. The mixture was refluxed for 15 min and cooled. The crude product was collected and crystallized. The compounds prepared are listed below together with their physical constants:

5-(4-Fluorophenyl)-2(1H)-imino-3-(4-nitrophenyl)-1,3,4-thiadiazole (2a)

This compound had m.p. 301-3°C (from acetic acid); yield 72 % (yellow); IR (KBr): ν/cm^{-1} 3320.8 (NH), 3114.8, 3032.2 (CH-aromatic), 1622.9 (C=N), 1598.9 (C=C); MS, m\z: 316 (M$^+$, 55.6), 257 (62.4), 211 (10.4), 163 (17.2), 136 (28.5), 123 (40.1), 90 (100.0), 63 (79.7), 62 (23.4), 51 (16.4), 50 (27.4); ^{1}H NMR (DMSO-d$_6$): δ/ppm 7.24-8.31 (m, 8H, ArH's), 8.86 (s, 1H, NH); Anal. for $C_{14}H_9N_4O_2SF$: found: C, 53.13; H, 2.87; N, 17.74; S, 10.10; required: C, 53.16; H, 2.86; N, 17.71; S, 10.11.

5-(2,4-Dichlorophenyl)-2(1H)-imino-3-(4-nitrophenyl)-1,3,4-thiadiazole (2b)

This compound had m.p. 276-7°C (from acetic acid); yield 70 % (yellow crystals); IR (KBr): ν/cm^{-1} 3320.6 (NH), 3080.6 (CH-aromatic), 1639.2 (C=N), 1586.2 (C=C); MS, m\z: 368 (M$^+$+2, 26.2), 366 (M$^+$, 36.5), 307 (50.9), 173 (29.9), 136 (45.1), 90 (100.0), 76 (18.9), 75 (21.7), 64 (37.7), 63 (90.2), 51 (19.6), 50 (43.2); ^{1}H NMR (DMSO-d$_6$): δ/ppm 7.26-8.37 (m, 7H, ArH's), 8.89 (s, 1H, NH); Anal. for $C_{14}H_8N_4O_2SCl_2$: found: C, 45.78; H, 2.18; N, 15.25; S, 8.70; Cl, 19.30; required: C, 45.79; H, 2.19; N, 15.25; S, 8.71; Cl, 19.31.

Nitrosation of 5-aryl-2(1H)-imino-3-(4-nitrophenyl) -1,3,4-thiadiazoles (2a,b)

To a suspension of **(2a,b)** (0.005 mol) in acetic acid (15 ml) a saturated solution of sodium nitrite was added dropwise while stirring in an ice bath. The reddish products formed were collected by filtration, washed with ethanol to give **(3a,b)** respectively. The prepared compounds were used without purification.

5-(4-Fluorophenyl)-2(1H)-(nitrosoimino)-3-(4-nitrophenyl)-1,3,4-thiadiazole (3a)

This compound had m.p. 148°C (decom).

5-(2,4-Dichlorophenyl)-2(1H)-(nitrosoimino)-3-(4-nitrophenyl)-1,3,4-thiadiazole (3b)

This compound had m.p. 144-6°C (decom.).

Thermolysis of 5-aryl-2(1H)-(nitrosoimino)-3-(4-nitrophenyl)-1,3,4-thiadiazole (3a,b)

The nitrosoimino compounds **(3a,b)** (0.5 g) was refluxed in xylene (20 ml) till all bubbles of nitrogen ceased to evolve. The excess solvent was then evaporated and the residue was triturated with petroleum ether (40/60°C). The solid formed was collected and crystallized to give the corresponding carbonyl compounds **(4a,b)** respectively.

5-(4-Fluorophenyl)-3-(4-nitrophenyl)-1,3,4-thiadiazol-2(1H)-one (4a)

This compound had m.p. 192-4°C (from acetic acid); yield 65 % (yellow); IR (KBr): ν/cm^{-1} 3121.5, 3077.4 (CH-aromatic), 1706.9 (C=O), 1597.0 (C=C); MS, m\z: 317 (M$^+$, 48.8), 318 (M$^+$+1, 53.5), 258 (78.2), 257 (74.6), 211(13.1), 163(17.5), 136 (38.1), 90 (100.0), 64 (34.5), 63 (72.6), 50 (26.5); ^{1}H NMR (DMSO-d$_6$): δ/ppm 7.36-8.39 (m, 8H, ArH's); ^{13}C NMR (DMSO-d$_6$) δppm 167.56 (C=O), 165.97 (d, J = 250.2Hz, C-F), 149.70, 144.46 (C-NO$_2$, C=N), 141.92 (C-p-NO$_2$), 128.36 (d, J = 9.1 Hz, C-m-F), 125.54 (d, J = 3.1 Hz, C-p-F), 124.30 (C-m-NO$_2$), 120.64 (C-o-NO$_2$), 116.25 (d, J = 22.4 Hz, C-o-F); Anal. for $C_{14}H_8N_3O_3SF$: found: C, 52.98; H, 2.55; N, 13.23; S, 10.10; required: C, 53.00; H, 2.54; N, 13.24; S, 10.08.

5-(2,4-Dichlorophenyl) -3-(4-nitrophenyl)-1,3,4-thiadiazol-2(1H)-one (4b)

This compound had m.p. 184-6°C (from acetic acid); yield 63 % (off white); IR (KBr): ν/cm^{-1} 3086.5 (CH-aromatic), 1699.9 (C=O), 1583.0 (C=C); MS, m\z: 369 (M$^+$+2, 28.6), 367 (M$^+$, 41.6), 309 (44.8), 307 (66.5), 213 (13.7), 189 (26.3), 173 (38.6), 136 (49.9), 90 (95.6), 63 (100.0), 50 (48.9); ^{1}H NMR (DMSO-d$_6$): δ/ppm 7.27-8.38 (m, 8H, ArH's); Anal. for $C_{14}H_7N_3O_3SCl_2$: found: C, 45.66; H, 1.90; N, 11.43; S, 8.70; Cl, 19.25; required: C, 45.67; H, 1.91; N, 11.41; S, 8.69; Cl, 19.26.

Acetylation of 5-aryl-2(1H)-imino-3-(4-nitrophenyl) -1,3,4-thiadiazoles (2a,b)

Compounds **(2a,b)** (0.5g) were refluxed in acetic

anhydride (10 ml) for 20 min and the mixture was cooled and poured on crushed ice. The crude N-acetyl derivative was collected and crystallized to give **(5a,b)** respectively in good yield. Compounds prepared with their physical constants are listed below:

2(1H)-(N-Acetylimino)-5-(4-fluorophenyl)-3-(4-nitrophenyl)-1,3,4-thiadiazole (5a)

This compound had m.p. 248-50°C (from dimethylformamide); yield 74 % (off white); IR (KBr): ν/cm^{-1} 3110.1 (CH-aromatic), 1683.3 (C=O), 1635.7 (C=N), 1595.2 (C=C); MS, m\z: 359 (M^++1, 57.6), 358 (M^+, 56.6) 344 (85.4), 343 (100.0), 298 (11.60, 297 (14.0), 258 (26.4), 257 (27.7), 211 (11.7), 163 (14.2), 136 (23.6), 123 (23.0), 90 (78.3), 63 (64.3), 50 (22.2); ^{1}H NMR (DMSO-d_6): δ/ppm 2.51 (s, 3H, $COCH_3$), 7.44-8.44 (m, 8H, ArH's); Anal. for $C_{16}H_{11}N_4O_3SF$: found: C, 53.61; H, 3.10; N, 15.62; S, 8.91; required: C, 53.63; H, 3.09; N, 15.63; S, 8.93.

2(1H)-(Acetylimino)-5-(2,4-dichlorophenyl)-3-(4-nitrophenyl)-1,3,4-thiadiazole (5b)

This compound had m.p. 218-20°C (from dimethylformamide); yield 71 % (pale yellow); IR (KBr): ν/cm^{-1} 3126.0, 3090.3 (CH-aromatic), 1645.9 (C=O), 1607.3 (C=N), 1585.2 (C=C); MS, m\z: 410 (M^++2, 21.7), 408 (M^+, 28.9), 395 (65.8), 393 (98.6), 348 (10.7), 307 (17.1), 173 (30.3), 136 (43.6), 90 (100.0), 63 (76.2), 50 (27.0); ^{1}H NMR (DMSO-d_6): δ/ppm 2.53 (s, 3H, $COCH_3$), 7.45-8.47 (m, 8H, ArH's); Anal. for $C_{16}H_{10}N_4O_3SCl_2$: found: C, 46.94; H, 2.46; N, 13.71; S, 7.83; Cl, 17.31; required: C, 46.96; H, 2.46; N, 13.69; S, 7.82; Cl, 17.32.

Benzoylation of 5-aryl-2(1H)-imino-3-(4-nitro phenyl)-1,3,4-thiadiazoles (2a,b)

A mixture of the imino derivatives **(2a,b)** (0.003 mol) and benzoyl chloride (0.4 g, 0.003 mol) in pyridine (20 ml) was refluxed for 30 min. The reaction mixture was left to cool, then treated with dilute hydrochloric acid (50 ml). The crude product was collected and crystallized to give N-benzoyl derivatives **(6a,b)** respectively.

2(1H)-(N-Benzoylimino)-5-(4-fluorophenyl)-3-(4-nitrophenyl)-1,3,4-thiadiazole (6a)

This compound had m.p. 273-5°C (from dimethyl formamide); yield 75 % (off white); IR (KBr): ν/cm^{-1} 3112.2, 3081.9 (CH-aromatic), 1655.1 (C=O), 1622.8 (C=N), 1602.5 (C=C); MS, m\z: 420 (M^+, 43.7), 257 (15.2), 105 (100.0), 90 (56.3), 63 (31.), 51 (20.3); ^{1}H NMR (DMSO-d_6): δ/ppm 7.41-8.45 (m, 13H, ArH's). Anal. for $C_{21}H_{13}N_4O_3SF$: found: C, 60.00; H, 3.10; N, 13.31; S, 7.59; required: C, 60.00; H, 3.11; N, 13.32; S, 7.61.

2(1H)-(N-Benzoylimino)-5-(2,4-dichlorophenyl)-3-(4-nitrophenyl)-1,3,4-thiadiazole (6b)

This compound had m.p. 196-8°C (from dimethylformamide); yield 72 % (pale yellow); IR (KBr): ν/cm^{-1} 3065.3 (CH-aromatic), 1674.8 (C=O), 1626.3 (C=N), 1608.3 (C=C); MS, m\z: 472 (M^++2, 10.2), 470 (M^+, 13.2), 309 (8.8), 307 (12.3), 105 (100.0), 77 (79.7), 62 (10.7), 51 (22.9); ^{1}H NMR (DMSO-d_6): δ/ppm 7.43-8.48 (m, 13H, ArH's); Anal. for $C_{21}H_{12}N_4O_3SCl_2$: found: C, 53.50; H, 2.57; N, 11.90; S, 6.81; Cl, 15.05; required: C, 53.52; H, 2.56; N, 11.88; S, 6.79; Cl, 15.04.

Reaction of hydrazonyl bromides (1a,b) with 3,4-dihydro-6,7-dimethoxyisoquinoline (7) and 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline (8)

To a solution of hydrazonyl bromides **(1a,b)** (0.005 mol) and the appropriate dipolarophile **(7)** or **(8)** (0.005 mol) in tetrahydrofuran (40 ml) was added triethylamine (1.4 ml, 0.01 mol) at room temperature. The reaction mixture was refluxed for 6 hr. The mixture was washed three times with water, the organic layer was collected, dried over anhydrous sodium sulfate and then filtered. The solvent was evaporated under reduced pressure and the residue was triturated with methanol (10 ml) where it solidified. The crude product was collected and crystallized. The products **(9a,b)** and **(10a,b)** were obtained in good yield.

8,9-Dimethoxy-3-(4-fluorophenyl)-1-(4-nitro phenyl)-1,5,6,10b-tetrahydro-[1,2,4]triazolo[3,4-a] isoquinoline (9a)

This compound had m.p.190-2°C (from dimethylsulfoxide-ethanol); yield 54% (orange); IR (KBr): ν/cm^{-1} 3081.7, 3001.4 (CH-aromatic), 2953.6, 2886.8, 2836.3 (CH-aliphatic), 1594.6 (C=C); MS, m\z: 447 (M^+, 100.0), 416 (24.9), 401 (10.5), 191 (10.0), 176 (16.2), 106 (16.9), 90 (45.1), 79 (12.9), 63 (30.2), 51 (10.6); ^{1}H NMR (DMSO-d_6): δ/ppm 2.68-2.71 (m, 2H, CH_2), 3.40 (m, 1H, 5-H), 3.56 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.78-3.87 (m, 1H, 5-H), 6.66 (s, 1H), 6.83 (s, 1H), 6.86 (s, 1H), 7.19-8.18 (m, 8H, ArH's); Anal. for $C_{24}H_{20}N_4O_4F$: found: C, 64.44; H,

4.51; N, 12.54; required: C, 64.42; H, 4.50; N, 12.52.

3-(2,4-Dichlorophenyl)-8,9-dimethoxy-1-(4-nitrophenyl)-1,5,6,10b-tetrahydro[1,2,4]triazolo [3,4-a]isoquinoline (9b)

This compound had m.p. 142-4°C (from dimethylsulfoxide-ethanol); yield 51 % (orange); IR (KBr): ν/cm^{-1} 3085.4 (CH-aromatic), 2922.1, 2840.5 (CH-aliphatic), 1599.8 (C=C); MS, m\z: 499 (M^++2, 64.0), 497 (M^+, 100.0), 191 (16.2), 190 (15.7), 176 (14.8), 136 (13.1), 90 (38.2), 63 (28.2); ^{1}H NMR (DMSO-d_6): δ/ppm 2.64-2.70 (m, 2H, CH_2), 3.18-3.42 (m, 1H, 5-H), 3.54-3.80 (m, 1H, 5-H), 3.58 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.71 (s, 1H), 6.81 (s, 1H), 6.95 (s, 1H), 7.23-8.18 (m, 7H, ArH's); Anal. for $C_{24}H_{19}N_4O_4Cl_2$: found: C, 57.86; H, 3.82; N, 11.30; Cl, 14.21; required: C, 57.84; H, 3.84; N, 11.29; Cl, 14.22.

8,9-Dimethoxy-3-(4-fluorophenyl)-10b-methyl-1-(4-nitrophenyl)-1,5,6,10b-tetrahydro[1,2,4] triazolo[3,4-a]isoquinoline (10a)

This compound had m.p. 226-8°C (from dimethylsulfoxide-ethanol); yield 77 % (red crystals); IR (KBr): ν/cm^{-1} 3120.8, 3065.1 (CH-aromatic), 2948.0, 2831.0 (CH-aliphatic), 1590.1 (C=C); MS, m\z: 462 (M^++1, 4.1), 447 (M^+-14, 100.0), 400 (7.9), 90 (14.6), 63 (10.7); ^{1}H NMR (DMSO-d_6): δ/ppm 2.23 (s, 3H, CH_3), 2.62 (m, 2H, CH_2), 3.21-3.46 (m, 1H, 5-H), 3.70 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.59-3.82 (m, 1H, 5-H), 6.74 (s, 1H), 6.82 (s, 1H), 7.13-8.16 (m, 8H, ArH's); Anal. for $C_{25}H_{22}N_4O_4F$: found: C, 65.00; H, 4.79; N, 12.15; required: C, 65.06; H, 4.80; N, 12.14.

3-(2,4-Dichlorophenyl)-8,9-dimethoxy-10b-methyl-1-(4-nitrophenyl)-1,5,6,10b-tetrahydro[1,2,4] triazolo[3,4-a]isoquinoline (10b)

This compound had m.p.153-5°C (from dimethylsulfoxide-ethanol); yield 76 % (red crystals); IR (KBr): ν/cm^{-1} 3088.1 (CH-aromatic), 2954.1, 2832.9 (CH-aliphatic), 1587.8 (C=C); MS, m\z: 499 (M^++2(-14), 61.5) 497 (M^+-14, 100.0), 427 (89.4), 232 (12.0), 204 (13.7), 173 (13.0), 103 (19.2), 90 (48.6), 77 (22.6), 63 (44.9), 51 (25.3); ^{1}H NMR (DMSO-d_6): δ/ppm 2.34 (s, 3H, CH_3), 2.45-2.68 (m, 2H, CH_2), 3.41-3.48 (m, 1H, 5-H), 3.58 (s, 3H, OCH_3), 3.63-3.77 (m, 1H, 5-H), 3.71 (s, 3H, OCH_3), 6.68 (s, 1H), 7.07 (s, 1H), 7.50-8.11 (m, 7H, ArH's); Anal.for $C_{25}H_{21}N_4O_4Cl_2$: found: C, 58.63; H, 4.15; N, 10.91; Cl, 13.83; required: C, 58.60; H, 4.13; N, 10.93; Cl, 13.83.

Reaction of hydrazonyl bromides 1a,b with compounds containing thiourea moiety

Triethylamine (0.7 ml, 0.005 mol) at room temperature was added to a stirred solution of hydrazonyl bromides **(1a,b)** (0.005 mol) and the appropriate 2-thiouracil derivatives **(11-13)** and 3-thioxo-1,2,4-triazin-5-one derivatives **(14a,b)** in tetrahydrofuran (50 ml). The reaction mixture was refluxed till hydrogen sulfide ceased to evolve **(12-14 h)**. The reaction mixture was washed with water and the organic layer was collected, dried over anhydrous sodium sulfate and then filtered. The solvent was evaporated under reduced pressure and the residue was treated with methanol. The solid was collected and crystallized from suitable solvent. The products **(15-19)** were obtained in good yields.

6-Cyano-3-(4-fluorophenyl)-1-(4-nitrophenyl)-7-phenyl[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (15a)

This compound had m.p. 306-8°C (from dimethyl formamide); yield 53 % (yellow crystals); IR (KBr): ν/cm^{-1} 3119.3 (CH-aromatic), 2216.5 (C≡N), 1717.4 (C=O), 1656.4 (C=N), 1604.6 (C=C); MS, m\z: 452 (M^+, 100.0), 377 (18.7), 90 (33.8), 77 (14.0), 63 (29.0), 51 (9.9); ^{1}H NMR (DMSO-d_6): δ/ppm 7.46-8.66 (m, 13H, ArH's); Anal. for $C_{24}H_{13}N_3O_6F$: found: C, 63.73; H, 2.91; N, 18.58; required: C, 63.71; H, 2.89; N, 18.57.

6-Cyano-3-(2,4-dichlorophenyl)-1-(4-nitrophenyl)-7-phenyl[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (15b)

This compound had m.p. 314-6°C (from dimethylformamide); yield 56 % (reddish yellow); IR (KBr): ν/cm^{-1} 3089.2 (CH-aromatic), 2216.0 (C≡N), 1725.0 (C=O), 1655.8 (C=N), 1597.4 (C=C); MS, m\z: 504 (M^++2, 3.1), 502 (M^+, 4.0), 467 (100.0), 421 (21.7), 90 (20.4), 63 (17.5), 51 (6.1); ^{1}H NMR (DMSO-d_6): δ/ppm 7.68-8.59(m, 12H, ArH's); Anal. for $C_{24}H_{12}N_6O_3Cl_2$: found: C, 57.28 ; H, 2.40; N, 16.67; Cl, 14.10; required: C, 57.27; H, 2.40; N, 16.69; Cl, 14.08.

3-(4-Fluorophenyl)-7-methyl-1-(4-nitrophenyl) [1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (16a)

This compound had m.p. 310-2°C (from dimethylsul-

foxide-ethanol); yield 74 % (dark yellow); IR (KBr): ν/cm^{-1} 3064.8 (CH-aromatic), 2920.4 (CH-aliphatic), 1718.7 (C=O), 1654.2 (C=N), 1608.2 (C=C); MS, m\z: 365 (M$^+$, 100.0), 337 (12.9), 205 (11.6), 199 (10.9), 183 (6.8), 148 (7.9), 123 (10.1), 90 (32.6), 63 (33.3), 50 (10.2); ^{1}H NMR (DMSO-d$_6$): δ/ppm 2.39 (s, 3H, CH$_3$), 6.01 (s, 1H, pyrimidinone), 7.33-8.59 (m, 8H, ArH's); Anal. for $C_{18}H_{12}N_5O_3F$: found: C, 59.20; H, 3.32; N, 19.20; required: C, 59.17; H, 3.31; N, 19.17.

3-(2,4-Dichlorophenyl)-7-methyl-1-(4-nitrophenyl) [1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (16b)

This compound had m.p. 282-4°C (from tetrahydrofuran); yield 69 % (yellow crystals); IR (KBr): ν/cm^{-1} 3102.8 (CH-aromatic), 2925.2 (CH-aliphatic), 1723.7 (C=O), 1612.1 (C=N), 1581.6 (C=C); MS, m\z: 417 (M$^+$+2, 2.6), 415 (M$^+$, 3.3), 382 (41.6), 38 (100.0), 334 (22.2), 90 (20.7), 63 (16.9), 50 (5.3); ^{1}H NMR (DMSO): δ/ppm 2.41 (s, 3H, CH$_3$), 6.3 (s, 1H, pyrimidine), 7.55-8.63 (m, 7H, ArH's); Anal. for $C_{18}H_{11}N_5O_3Cl_2$: found: C, 51.98; H, 2.64; N, 16.81; Cl, 16.98; required: C, 51.94; H, 2.66; N, 16.82; Cl, 17.03.

3-(4-Fluorophenyl)-1-(4-nitrophenyl)-7-phenyl [1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (17a)

This compound had m.p. 319-21°C (from dimethyl sulfoxide); yield 67 % (dark yellow); IR (KBr): ν/cm^{-1} 3096.0 (CH-aromatic), 1693.5 (C=O), 1611.7 (C=N); MS, m\z: 427 (M$^+$, 100.0), 426(M$^+$-1, 72.0), 399 (16.4), 380 (13.8), 261 (4.6), 214 (4.9), 187 (7.6), 90 (30.0), 77 (14.1), 63 (24.5), 51 (10.3), 50 (10.1); ^{1}H NMR (DMSO-d$_6$): δ/ppm 6.09 (s, 1H, pyrimidinone), 7.34-8.63 (m, 18H, ArH's); Anal. for $C_{23}H_{14}N_5O_3F$: found: C, 64.49; H, 3.32; N, 16.32; required: C, 64.63; H, 3.30; N, 16.38.

3-(2,4-Dichlorophenyl)-1-(4-nitrophenyl)-7-phenyl-[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (17b)

This compound had m.p. 293-5°C (from dimethylsulfoxide); yield 62 % (off white); IR (KBr): ν/cm^{-1} 3115.0, 3076.9 (CH-aromatic), 1707.8 (C=O), 1608.3 (C=N); MS, m\z: 477 (M$^+$, 12.5), 445 (14.1), 427 (75.0), 399 (82.8), 261 (67.2), 230 (53.1), 192 (35.9), 171 (100.0), 147 (26.6), 122 (29.7), 101 (56.3), 75 (93.8), 64 (57.8), 52 (14.1); ^{1}H NMR (DMSO-d$_6$): δ/ppm 6.73 (s, 1H, pyrimidinone), 7.56-8.67 (m, 12H, ArH's); Anal. for $C_{23}H_{13}N_5O_3Cl_2$: found: C, 57.72; H, 2.71; N, 14.66; Cl, 14.80; required: C, 57.75; H, 2.73; N, 14.64; Cl, 14.82.

3-(4-Fluorophenyl)-6-(4-methylbenzyl)-1-(4-nitrophenyl)-[1,2,4]triazolo-[4,3-b][1,2,4]triazine-7(1H)-one 18a

This compound had m.p. 282-4°C (from dimethylsulfoxide-ethanol); yield 65 % (yellow crystals); IR (KBr): ν/cm^{-1} 3110.8, 3081.1 (CH-aromatic), 2923.2, 2858.9 (CH-aliphatic), 1663.6 (C=O), 1599.1 (C=C); MS, m\z: 456 (M$^+$, 100.0), 325 (50.9), 257 (11.5), 131 (13.8), 90 (28.9), 63 (24.4); ^{1}H NMR (DMSO-d$_6$): δ/ppm 2.33 (s, 3H, CH$_3$), 4.09 (s, 2H, CH$_2$), 7.17-8.52 (m, 12H, ArH's); Anal. for $C_{24}H_{17}N_6O_3F$: found: C, 63.16; H, 3.74; N, 18.48; required: C, 63.15; H, 3.75; N, 18.49.

3-(2,4-Dichlorophenyl)-6-(4-methylbenzyl)-1-(4-nitrophenyl)[1,2,4]-triazolo[4,3-b][1,2,4]triazine-7(1H)-one (18b)

This compound had m.p. 274-6°C (from dimethylsulfoxide-ethanol); yield 62 % (pale yellow); IR (KBr): ν/cm^{-1} 3113.4, 3078.1 (CH-aromatic), 2903.7, 2857.2 (CH-aliphatic), 1663.4 (C=O), 1609.1 (C=C); MS, m\z: 507 (M$^+$+1, 38.5), 505 (M$^+$-1, 86.9), 468 (11.8), 374 (70.1), 309 (38.0), 306 (30.0), 253 (18.6), 204 (21.7), 199 (19.0), 185 (15.8), 173 (23.1), 136 (32.1), 131 (100.0), 90 (64.7), 78 (18.6), 63 (14.5), 51 (19.0); ^{1}H NMR (DMSO-d$_6$): δ/ppm 2.35 (s, 3H, CH$_3$), 4.10 (s, 2H, CH$_2$), 7.26-8.62 (m, 11H, ArH's); Anal. for $C_{24}H_{16}N_6O_3Cl_2$: found: C, 57.01; H, 3.16; N, 16.55; Cl, 13.98; required: C, 56.81; H, 3.17; N, 16.56; Cl, 13.97.

3-(4-Fluorophenyl)-6-(4-methoxybenzyl)-1-(4-nitrophenyl)[1,2,4]triazolo[4,3-b][1,2,4]triazine-7(1H)-one (19a)

This compound had m.p. 250-2°C (from dimethylsulfoxide-ethanol); yield 52 % (greenish yellow); IR (KBr): ν/cm^{-1} 3113.2, 3083.3 (CH-aromatic), 2940.4, 2841.4 (CH-aliphatic), 1666.0 (C=O), 1609.0 (C=C); MS, m\z: 472 (M$^+$, 100.0), 325 (22.3), 257 (10.8), 236 (9.4), 146 (51.9), 132 (13.4), 121 (48.4), 90 (23.4), 63 (27.8); ^{1}H NMR (DMSO-d$_6$): δ/ppm 3.78 (s, 3H, OCH$_3$), 4.07 (s, 2H, CH$_2$), 6.92-8.49 (m, 12H, ArH's); Anal. for $C_{24}H_{17}N_6O_4F$: Found: C, 61.00; H, 3.63; N, 17.80; required: C, 61.01; H, 3.62; N, 17.79.

3-(2,4-Dichlorophenyl)-6-(4-methoxybenzyl)-1-(4-nitrophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazine-7(1H)-one (19b)

This compound had m.p. 254-6°C (from dimethylsul-

foxide-ethanol); yield 57 % (pale yellow); IR (KBr): ν/cm^{-1} 3115.8, 3084.7 (CH-aromatic), 2940.6, 2841.9 (CH-aliphatic), 1667.2 (C=O), 1609.7 (C=C); ^{1}H NMR (DMSO-d_6): δ/ppm 3.71 (s, 3H, OCH_3), 4.03 (s, 2H, CH_2), 6.88-8.46 (m, 11H, ArH's); Anal. for $C_{24}H_{16}N_6O_4Cl_2$: found: C, 55.10; H, 3.06; N, 16.04; Cl, 13.55; required: C, 55.08; H, 3.08; N, 16.05; Cl, 13.54.

RESULTS AND DISCUSSION

Treatment of hydrazonyl bromides **(1a,b)** with potassium thiocyanate in ethanol at reflux afforded compounds which correctly analyzed for **(2a,b)**. The structure of **(2a,b)** was confirmed on the basis of elemental and spectral data. Thus, the IR spectra of **(2a,b)** revealed the absence of the absorption band in the region of ν 2000-2250 cm^{-1} due to free SCN[18]. However, they showed an imino band near ν 3320 cm^{-1} (Experimental part).

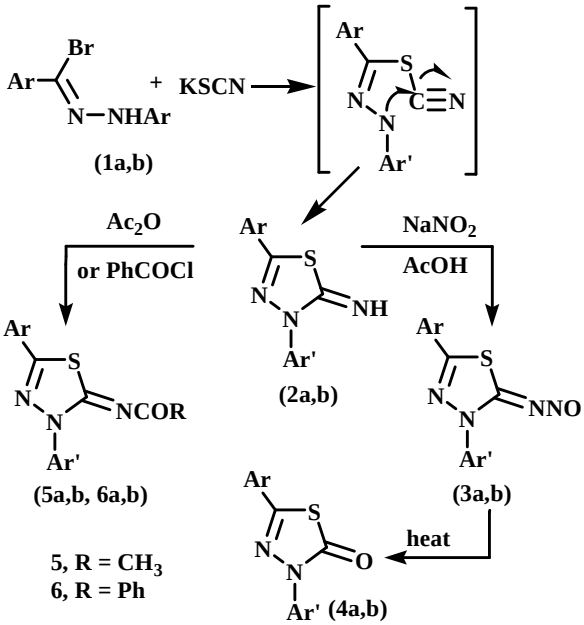
Nitrosation of 5-aryl-2(3H)-imino-3-(4-nitrophenyl)-1,3,4-thiadiazoles **(2a,b)** at 0-5°C gave the corresponding N-nitrosoimino derivatives **(3a,b)** respectively (SCHEME 1). Compounds **(3a,b)** were used without purification. Upon refluxing in xylene, N-nitrosoimino derivatives **(3a,b)** gave the corresponding 5-aryl-3-(4-nitrophenyl)-1,3,4-thiadiazol-2(3H)-ones **(4a,b)** respectively in almost quantitative yield (SCHEME 1). The IR spectra showed strong C=O absorption band near ν 1700 cm^{-1}.

Acetylation of **(2a,b)** with acetic anhydride yielded the corresponding N-acetyl derivatives **(5a,b)** respectively in excellent yield (SCHEME 1). The structures of the latter products followed from their method of preparation and their spectral data. For example, the IR spectrum of **(5))** showed an absorption band at ν 1630 cm^{-1} assignable to acetyl carbonyl group. The NH absorption band observed in the spectrum of **(2)** was absent in the spectrum of the product **(5)**. The ^{1}H NMR spectrum of **(5)** showed a singlet signal at δ2.5 ppm corresponding to methyl protons of the acetyl group.

Also, **(2a,b)** underwent benzoylation when treated with benzoyl chloride in pyridine. The products were identified as 5-aryl-2-(N-benzoylimino)-3-(4-nitrophenyl)-1,3,4-thiadiazole **(6a,b)** respectively (SCHEME 1). The spectral data (Experimental part) were in accordance with their assigned structures.

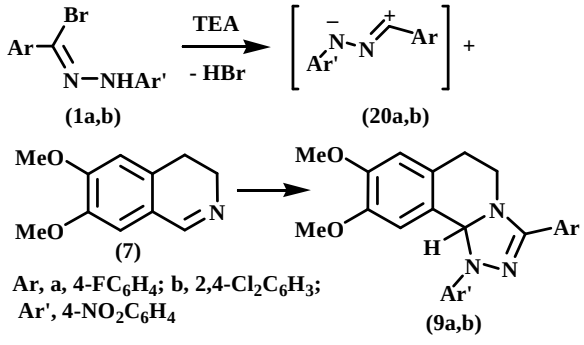
Treatment of hydrazonyl bromides **(1a,b)** with 3,4-dihydro-6,7-dimethoxyisoquinoline **(7)** in tetrahydrofuran in the presence of triethylamine at reflux for **(6)** hours afforded, in each case, a single product (SCHEME 2) as evidenced by TLC. The isolated cycloadducts **(9)** gave satisfactory elemental analyses and spectral data (IR, ^{1}H NMR, MS) for the proposed structures. For example, the ^{1}H NMR spectrum of each compound showed a singlet signal at δ near 6.8-6.9 ppm assignable to the proton 10b (SCHEME 2). This chemical shift value is higher than that of CH-1 in the starting dipolarophile **(7)**[19].

Next the reaction of hydrazonyl bromides **(1a,b)** with dipolarophile having active group at C-1, namely 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline **(8)** was studied. Thus, when these reactions were carried out in a similar manner as that of **(7)** with **(1a,b)**, they



Ar, a, 4-FC_6H_4; b, 2,4-$Cl_2C_6H_3$; Ar', 4-$NO_2C_6H_4$

SCHEME 1



Ar, a, 4-FC_6H_4; b, 2,4-$Cl_2C_6H_3$; Ar', 4-$NO_2C_6H_4$

SCHEME 2

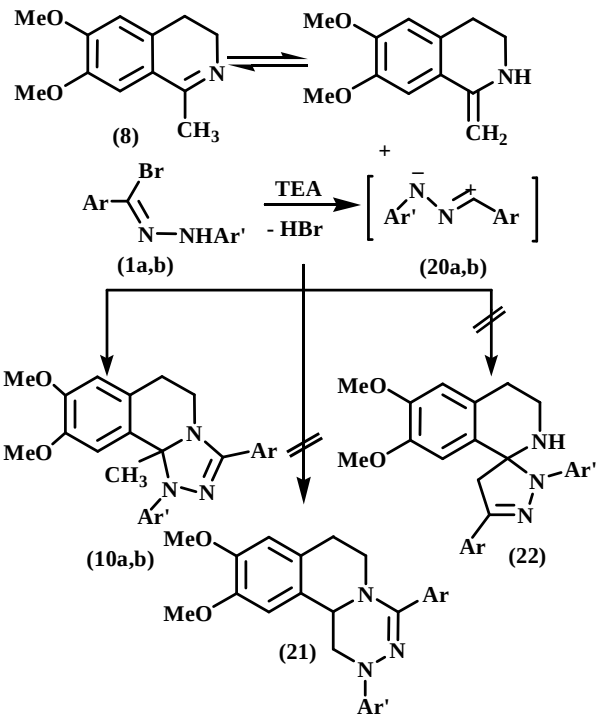
gave products whose elemental analyses and spectral data were compatible with the triazole derivatives **(10a,b)**. Neither triazine derivatives **(21)** nor spiro derivatives **(22)** were detected (SCHEME 3).

The structure of the products was confirmed on the basis of ^{1}H NMR evidence. For example, while structure **(21)** is expected to reveal doublet and triplet assignable to C1-2H and C11b-1H protons, the other isomeric structure **(22)** will reveal two singlet signals assignable to CH_2 and NH protons. Such signals were absent in the ^{1}H NMR spectra of the product isolated from reaction of **(1a,b)** with **(8)**. Instead of these signals, the ^{1}H NMR spectra of the products showed one singlet signal at δ 2.2-2.3 ppm which is compatible with the assigned structure **(10)**.

Next, the reactions of hydrazonyl bromides **(1a,b)** with reagents containing thiourea moiety were studied. Treatment of **(1a,b)** with 2-thiouracil derivatives **(11-13)** in tetrahydrofuran in the presence of triethylamine at reflux till hydrogen sulfide gas ceased to evolve gave one isolable product as evidenced by TLC analysis. The spectral and elemental analyses data of the products are compatible with their assigned structures namely **(15-17)** respectively (SCHEME 4). The reaction pathway that leading to the formation of the latter were outlined in SCHEME 4. The products **(15-17)** are formed most probably via the cycloaddition of nitrilimines **(20)** to the C=S double bond of **(11-13)** to give the spiroad ducts **(23)** which rearranges to give the thiohydrazide 24. Cyclization of the latter intermediates followed by elimination of H_2S would then give the end products.

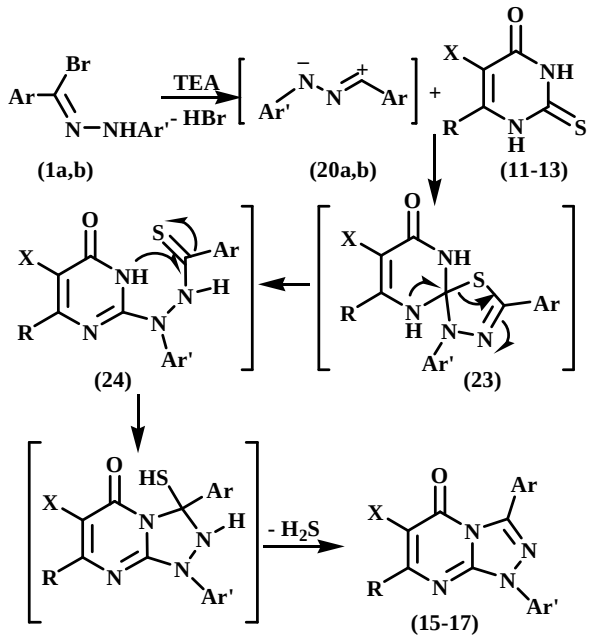
Similarly, treatment of hydrazonyl bromides **(1a,b)** with the appropriate 3-thioxo-1,2,4-triazin-5-one derivatives **(14a,b)** (SCHEME 5) in tetrahydrofuran in the presence of triethylamine afforded a single product, in each case, as evidenced on the basis of TLC. Both mass spectroscopy and elemental analyses confirmed the absence of sulfur in all products[20,21]. Thus, the products were assigned the structures **(18a,b)** and **(19a,b)** respectively. It is undoubtedly the most nucleophilic property of N-1 of 2-thiouracil derivatives **(11-13)** and N-2 of 3-thioxo-1,2,4-triazin-5-one derivatives **(14a,b)** due to electronic effect of the carbonyl group cause the preferential ring closure route to form the products **(15-19)**. The structures of the products **(15-19)** were assigned on the basis of correct elemental analyses and spectroscopic data.

For example, compounds **(18,19)** showed an intense IR absorption at 1660 cm^{-1}, which is characteris-



Ar, a, 4-FC_6H_4; b, 2,4-$Cl_2C_6H_3$; Ar', 4-$NO_2C_6H_4$

SCHEME 3

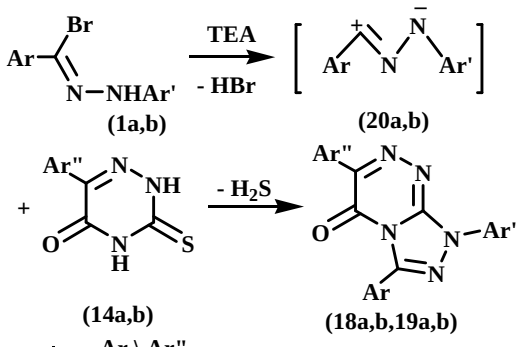


	X/R		X/R		X/R
15a	CN/Ph	16a	H/CH_3	17a	H/Ph
15b	CN/Ph	16b	H/CH_3	17b	H/Ph

Ar, a, 4-FC_6H_4; b, 2,4-$Cl_2C_6H_3$; Ar', 4-$NO_2C_6H_4$

SCHEME 4

Full Paper



	Ar \ Ar"	
18a	a \ 4-$CH_3C_6H_4CH_2$	Ar, a, 4-FC_6H_4;
18b	b \ 4-$CH_3C_6H_4CH_2$	b, 2,4-$Cl_2C_6H_3$;
19a	a \ 4-$CH_3OC_6H_4CH_2$	Ar', 4-$NO_2C_6H_4$
19b	b \ 4-$CH_3OC_6H_4CH_2$	

SCHEME 5

tic for a triazinone. In the ^{1}H NMR spectra, two singlets appeared at δ 4.0 and 2.3 or 3.7ppm assignable to methylene and methyl protons respectively.

ANTIMICROBIAL ACTIVITY

Compounds **(10a)**, **(16b)** and **(17a)** taking as examples were screened for antibacterial activity (nutrient agar broth) and antifungal activity (Dox's medium and Saboured's agar) by agar diffusion method[22] at a concentration 20 mg/ml using DMSO as a solvent. The compounds were tested for their activities against gram +ve bacteria, *Staphylococcus aureus* and gram -ve bacteria, *Escherichia coli* in addition to the pathogenic fungi *Aspergillus flavus* and *Candida albicans*. The results of antimicrobial screening were recorded as average diameter of inhibition zone in mm and presented in TABLE 1.

As shown in the results, the tested compounds displayed significant activities against *E.coli, S.aureus* and *C.albicans* while only compound **(17a)** was very active against *A.flavus* and showed almost the same activity when compared with the usually used antifungal agents at the same concentration.

TABLE 1: Antimicrobial screening results of the tested compounds

Comp.no.	*E.coli*	*S.aureus*	*A.flavus*	*C.albicans*
10a	13	14	0	9
16b	9	11	0	10
17a	10	9	13	11
Tetracycline	32	34	-	-
Flucoral	-	-	14	16
Amphotricine	-	-	16	20

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