SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF TRIAZOLOTHIADIAZINES

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Abstract

It deals with synthesis and spectral studies of 5*H*-[1,2,4] triazolo [3,4b][1,3,4]thiadiazines. A structurally diverse new series of 5*H*-[1,2,4] triazolo[3,4b][1,3,4]thiadiazine heterocycles having medicinally privi-leged nucleus have been synthesized by simple and solvent free environmental benign methods. A mixture of 4-amino-5-substituted-1,2,4-triazolo-3-thiol and β-diketone/ β-ketoester and catalytic amount of hydrazine hydrate exposed to microwave irradiation under solvent free condition in presence of an energy transfer agent DMF to get the product in high yield.

Key Words - 5*H*-[1,2,4] triazolo [3,4b][1,3,4]thiadiazines, β-diketone, β-ketoester.

Introduction

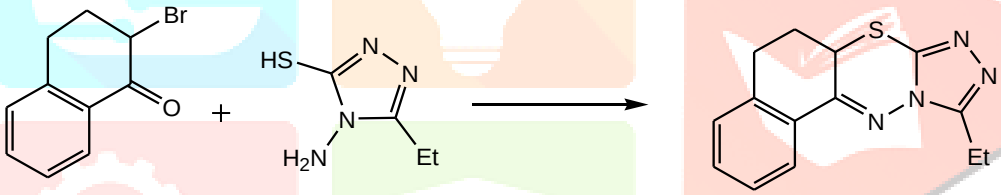
The heterocyclic compounds containing nitrogen and sulphur atoms possess a wide spectrum of biological activities and are specially interesting because of incorporation of these heterocyclic systems into a number of therapeutically interesting drugs[1-8]. Heterocycles containing 1,2,4-triazole and 1,3,4-thiadiazine nucleus have been well studied for a number of pathological conditions including inflammation[9-10], hyper-tension[11] and aching[12]. The 1,3,4-thiadiazine derivatives in which 1,4-thiazines fused with 1,2,4-triazole nucleus are important scaffold in several natural and synthetic compounds of significant pharmacological properties.1,3,4-Thiadiazines have attracted the attention of chemical and medicinal research in view of exhibiting the wide ranging biological activities possibly due to the presence of the -N–C–S- moiety.

Triazoles fused with six-membered ring systems have been reported to possess diverse applications in the field of medicine[13-14]. The literature servey of heterocyclic pharmaceutical agents reveals that the nitrogen and sulphur containing compounds, particularly those incorporating the N–C–S linkage in their skeleton, exhibit a broad spectrum of pharmacological activities such as antimalarial[15], humanimmuno virus-1 (HIV-1) inhibitors[16] and antimicrobial[17-20].

Heterocycles of this category, 1,2,4-triazolo[3,4-b][1,3,4]thia-diazines have been shown to possess antibacterial, antifungal[21-25], analgesic[26], insecticidal[27], anti-viral[28-29], antiparasitic[30], diuretic[31], anti-inflammatory[32], antitubercular[33], anticancer[34-35] and antioxidant activity[36]. It has also been reported that these compounds have marked antidepressant[37], anthelmintic[38] and plant-growth-promoting effects[39].

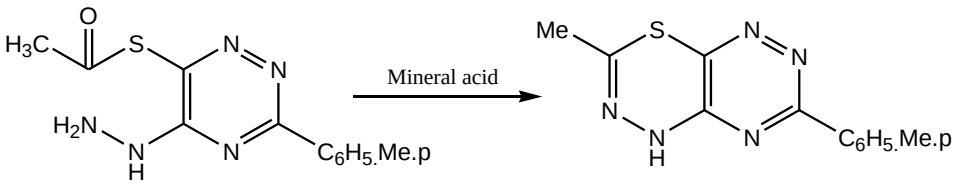
Different methods for the preparation of triazolothiadiazine documented in the literature are as follows –

(1) .1,3,4-thiadiazines were prepared by the reaction of cyclic α-haloketones with 4-amino-5-ethyl-1,2,4-triazole-3-thiol[40] (scheme 3.9).



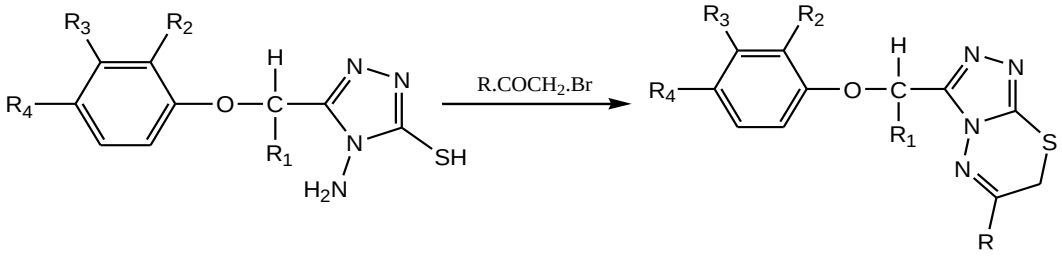
(Scheme: 3.9)

(2) . The cyclization of [(thioacyl) hydrazino] triazines in the presence of mineral acid afforded 1H-1,2,4-triazino[5,6-e][1,3,4]thiadia-zines[41] (scheme 3.10).



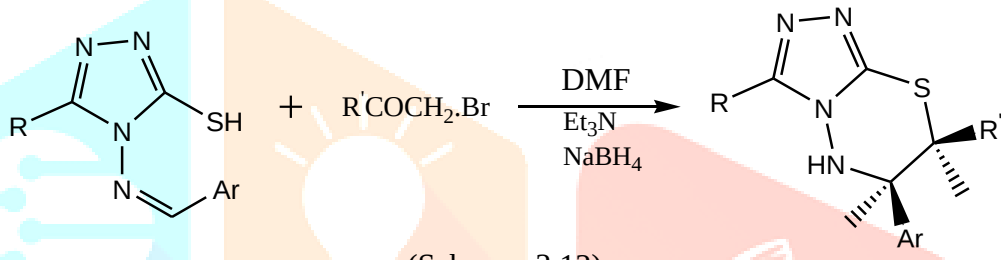
(Scheme: 3.10)

(3) .3-Aryloxyalkyl-6-aryl-7H-s-triazolo[3,4-b][1,3,4]thiadiazines[42] were prepared by the reaction of 4-amino-1,2,4-triazole-5-thiol react with phenacyl bromide (scheme 3.11).



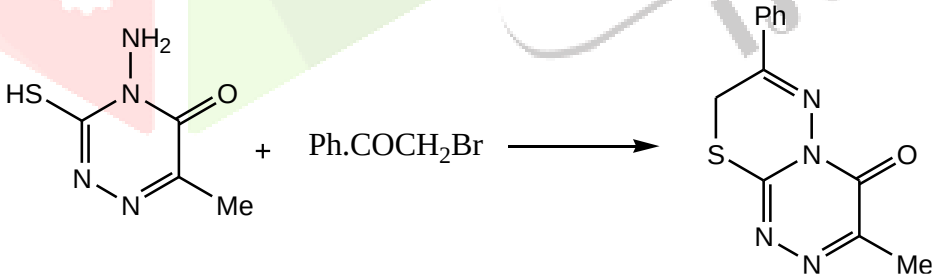
(Scheme: 3.11)

(4) . Ibrahim et al.[43] repoted stereospecific synthesis of 6,7-dihydro-5H-1,2,4-triazolo [3,4-b] [1,3,4] thiadiazines (scheme 3.12).



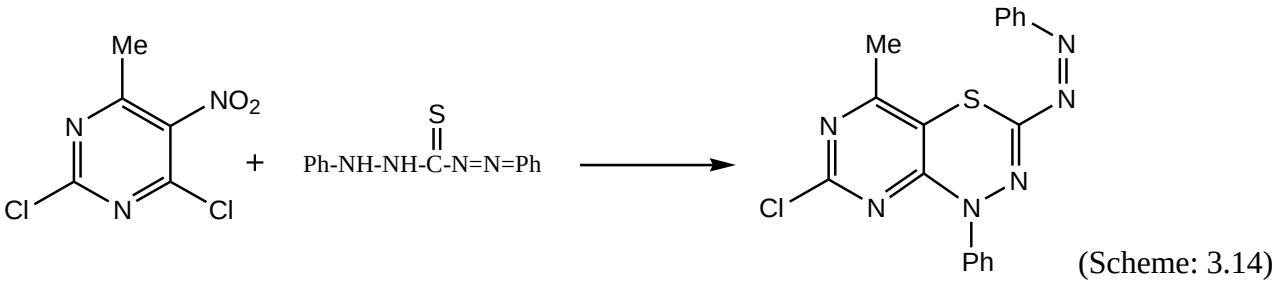
(Scheme: 3.12)

(5) . The reaction of 4-amino-3-mercapto-6-methyl [1,2,4] triazin-5-one with phenacyl bromide also provided triazinothiadiazines[44] (scheme 3.13).



(Scheme: 3.13)

(6) . Rahimizadeh et al.[45] prepared 1,3,4-thiadiazines by the cyclization of 2,4-dichloro-6-methyl-5-nitropyrimidine with dithizone (scheme 3.14).



(Scheme: 3.14)

In view of diverse biological importance of these heterocycles, a number of hitherto unknown 1,3,4-thiadizine derivatives containing 1,2,4-triazole nucleus were synthesized by environmental benign solvent free method. The synthesized compounds were characterized and screened for their biological activities to explore potent biologically active molecules.

EXPERIMENTAL

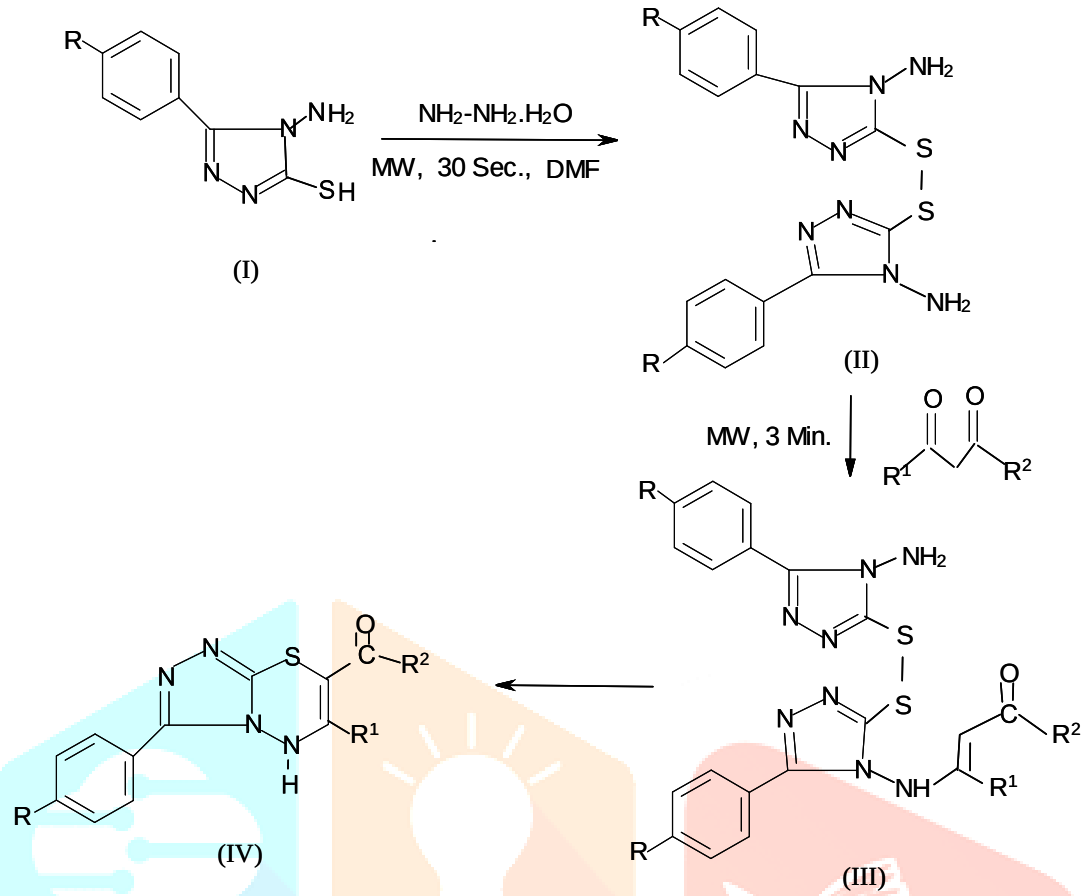
Melting points of all the synthesized compounds were determined on open aluminum block and are uncorrected. The purity was checked by thin layer chromatography using Merck silica gel G-60. IR spectra we recorded in KBr on Shimdzu Affinity-1 FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini 400 spectrometer (300 MHz) using TMS as an internal standard. The mass spectra were recorded using Jeol SX 102 spectrometer at 70 ev.

1. Synthesis of 4-amino-1,2,4-triazole-3-thiols

Synthesis of substituted 4-amino-1,2,4-triazole-3-thiols required for the preparation of triazolothiadiazine has been given in part (B) of chapter-2

2. Synthesis of 5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines

A mixture of compound I (10 mmol), catalytic amount of hydrazine hydrate (1 mmol) and DMF (5 ml) as an energy transfer medium was exposed to microwave irradiations for 30 seconds. After that β-diketone/ β-ketoester (10 mmol) was added to the reaction mixture and again exposed to microwave irradiations intermittently at 30 seconds for three minutes. After completion of reaction as monitored by TLC, the reaction mixture was cooled and transferred to crushed ice. The solid separated out was filtered, washed with 50% ethanol and crystallized from ethanol to get pure product (scheme 3.15).



(Scheme: 3.15)

In present investigation following 5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines have been synthesized :

(1). 7-Ethoxycarbonyl-3-(4-methoxyphenyl)-6-methyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(2). 7-Ethoxycarbonyl-3-(4-fluorophenyl)-6-methyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(3). 3-(4-Chlorophenyl)-7-ethoxycarbonyl-6-methyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(4). 3-(4-Bromophenyl)-7-ethoxycarbonyl-6-methyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(5). 7-Ethoxycarbonyl-6-methyl-3-(4-nitrophenyl)-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(6). 7-Ethoxycarbonyl-3-(4-methoxyphenyl)-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(7). 7-Ethoxycarbonyl-3-(4-fluorophenyl)-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(8). 3-(4-Chlorophenyl)-7-ethoxycarbonyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(9). 3-(4-Bromophenyl)-7-ethoxycarbonyl-6-pheny-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(10). 7-Ethoxycarbonyl-3-(4-nitrophenyl)-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(11). 3-(4-Methoxyphenyl)-6-methyl-7-methylcarbonyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(12). 3-(4-Fluorophenyl)-6-methyl-7-methylcarbonyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(13). 3-(4-Chlorophenyl)-6-methyl-7-methylcarbonyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

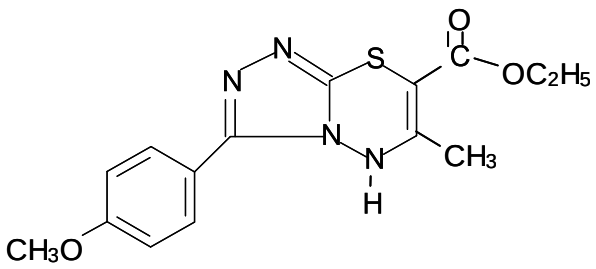
(14). 3-(4-Bromophenyl)-6-methyl-7-methylcarbonyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

(15). 6-Methyl-7-methylcarbonyl-3-(4-nitrophenyl)-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Physical and spectral data of the synthesized compounds -

(1). 7-Ethoxycarbonyl-3-(4-methoxyphenyl)-6-methyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{15}H_{16}N_4O_3S$



Yield 65%, M.P. 135^0C

IR (KBr, ν_{max}., cm^{-1}): 3380 (N-H), 1225, 1030 (C-O-C), 2990 (C-H

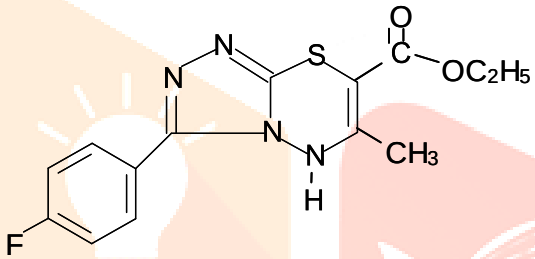
aliphatic), 3070 (C-H aromatic), 1597 (C=N), 1680 (>C=O), 1058 (N-N); ^{1}H NMR ($CDCl_3$) δ: 7.2-7.9 (4H, m, Ar-H), 8.7 (1H, s, N-H), 2.20 (3H, s, CH_3 at C_6), 3.8 (3H, s, OCH_3 at 4'), 4.10 (2H, q, CH_2 at C_7), 1.20 (3H, t, CH_3 at C_7);

MS (m/z): 332 [M^+], 331 [M^+-H], 303[M^+ -C_2H_5], 304 [M^+ -C_2H_4], 287 [M^+ -OC_2H_5], 285 [M^+ -C_2H_5OH+CO], 225 [M^+ -$C_6H_4OCH_3$]

Anal. Calculated (%) for $C_{15}H_{16}N_4O_3S$: C, 54.21; H, 4.81; N, 16.86. Found (%): C, 53.95; H , 4.76; N, 16.79.

(2). 7-Ethoxycarbonyl-3-(4-fluorophenyl)-6-methyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{14}H_{13}FN_4O_2S$



Yield 60%, M.P.132^{0}C

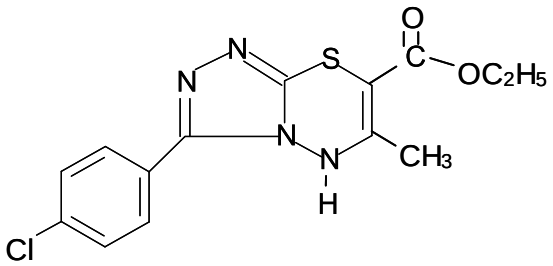
IR (KBr, ν_{max}., cm^{-1}): 3385 (N-H), 1230, 1035 (C-O-C), 2995 (C-H aliphatic), 3050 (C-H aromatic), 1588 (C=N), 1675 (>C=O), 1055 (N-N); ^{1}H NMR ($CDCl_3$) δ: 7.8-8.5 (4H, m, Ar-H), 8.75 (1H, s, N-H), 2.2 (3H, s, CH_3 at C_6), 4.05 (2H, q, CH_2 at C_7), 1.15 (3H, t, CH_3 at C_7);

MS (m/z): 320 [M^+], 319 [M^+ -H], 291 [M^+ -C_2H_5], 292 [M^+ -C_2H_4], 275 [M^+ -OC_2H_5], 247 [M^+ -C_2H_5OH+CO], 225 [M^+ -C_6H_4F].

Anal. Calculated (%) for $C_{14}H_{13}FN_4O_2S$: C, 52.5; H, 4.1; N, 17.5. Found (%):C, 52.1; H, 3.95; N, 17.31.

(3.) 3-(4-Chlorophenyl)-7-ethoxycarbonyl-6-methyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine.

Molecular Formula : $C_{14}H_{13}ClN_4O_2S$



Yield 66%, M.P.129^{0}C

IR (KBr, ν_{max}., cm^{-1}): 3380 (N-H), 1220, 1030 (C-O-C), 2990 (C-H aliphatic), 3060 (C-H aromatic), 1590 (C=N), 1675 (>C=O), 740 (C-Cl), 1043 (N-N);

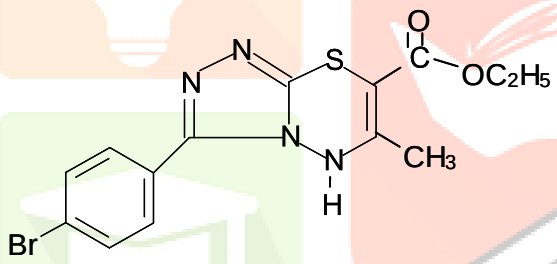
^{1}H NMR ($CDCl_3$) δ: 7.6-8.1 (4H, m, Ar-H,), 8.7 (1H, s, N-H), 2.25 (3H, s, CH_3 at C6), 4.0 (2H, q, CH_2 at C_7), 1.25 (3H, t, CH_3 at C_7);

MS(m/z): 336 [M^+] 335 [M^+ -H], 307 [M^+ -C_2H_5], 308 [M^+ -C_2H_4], 291[M^+ -OC_2H_5], 262 [M^+ -C_2H_5OH+CO], 35 [Cl], 255 [M^+ -C_6H_4Cl].

Anal. Calculated (%) for $C_{14}H_{13}ClN_4O_2S$:C, 49.9; H,3.8; N,16.6. Found (%): C, 50.52; H, 3.5; N, 16.2.

(4). 3-(4-Bromophenyl)-7-ethoxycarbonyl-6-methyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{14}H_{13}BrN_4O_2S$



Yield 70%, M.P.139^{0}C

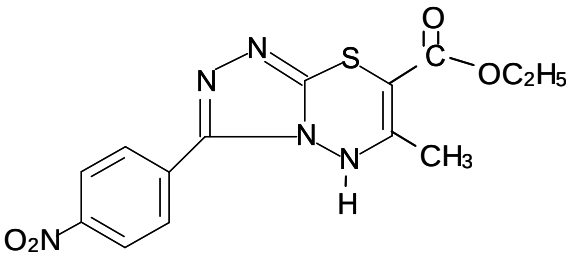
IR (KBr, ν_{max}., cm^{-1}): 3340 (N-H), 1230, 1035 (C-O-C), 2995 (C-H aliphatic), 3070 (C-H aromatic), 1593 (C=N), 1665 (>C=O), 1060 (N-N), ^{1}H NMR ($CDCl_3$) δ: 7.3-7.9 (4H, m, Ar-H), 8.65 (1H, s, N-H), 2.15 (3H, s, CH_3 at C_6), 4.15 (2H, q, CH_2 at C_7), 1.25 (3H, t, CH_3 at C_7,);

Anal. Calculated (%) for $C_{14}H_{13}BrN_4O_2S$: C, 44.0; H, 3.4; N, 14.6.

Found (%): C, 43.84; H, 3.21; N, 14.35.

(5). 7-Ethoxycarbonyl-6-methyl-3-(4-nitrophenyl)-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{14}H_{13}N_5O_4S$



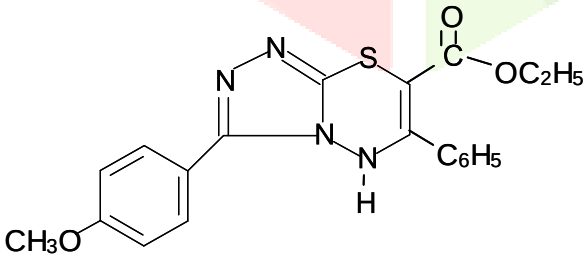
Yield 63%, M.P.124^{0}C

IR (KBr, ν_{max}., cm^{-1}): 3370 (N-H), 1230, 1040 (C-O-C), 3070 (C-H aromatic), 2990 (C-H aliphatic), 1590 (C=N), 1680 (>C=O), 1060 (N-N); ^{1}H NMR ($CDCl_3$) δ: 7.45-8.25 (4H, m, Ar-H), 8.5 (1H, s, N-H), 2.20 (3H, s, CH_3 at C_6), 4.05 (2H, q, CH_2 at C_7,), 1.15 (3H, t, CH_3 at C_7);

Anal. Calculated (%) for $C_{14}H_{13}N_5O_4S$: C, 48.41; H, 3.74; N, 20.17. Found (%): C, 48.34; H, 3.71;N, 20.14.

(6). 7-Ethoxycarbonyl-3-(4-methoxyphenyl)-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{20}H_{18}N_4O_3S$



Yield 65%, M.P. 141 ^{0}C

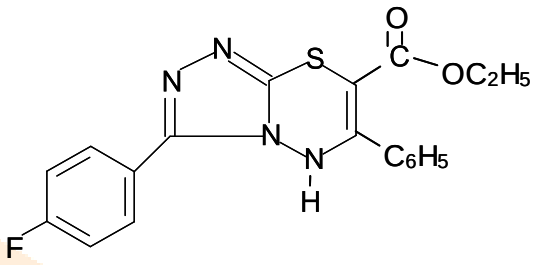
IR (KBr, ν_{max}., cm^{-1}): 3385 (N-H), 1235, 1040 (C-O-C), 2998 (C-H aliphatic), 3090 (C-H aromatic), 1595 (C=N), 1670 (>C=O), 1065 (N-N); ^{1}H NMR ($CDCl_3$) δ: 7.8-8.2 (10H, m, Ar-H), 8.8 (1H, s, N-H,), 3.75 (4H, s, OCH_3 at 4'), 4.1 (2H, q, CH_2 at C_7,), 1.18 (3H, t, CH_3 at C_7);

MS(m/z): 394 [M^+], 393 [M^+ -H], 365 [M^+ -C_2H_5], 366 [M^+ -C_2H_4], 349 [M^+ -OC_2H_5], 320 [M^+ -C_2H_5OH+CO], 317 [M^+ -C_6H_5], 287 [M^+ -$C_6H_4OCH_3$].

Anal. Calculated (%) for $C_{20}H_{18}N_4O_3S$: C, 60.91; H, 4.56; N, 14.21. Found (%): C, 60.78; H, 4.52; N, 14.16.

(7). 7-Ethoxycarbonyl-3-(4-fluorophenyl)-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{19}H_{15}FN_4O_2S$



Yield 62%, M.P.138^{0}C

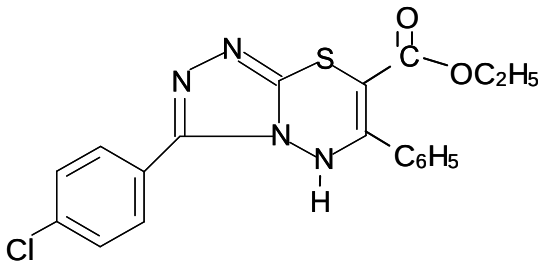
IR (KBr, ν_{max}., cm^{-1}): 3385 (N-H), 1240, 1045 (C-O-C), 3090 (C-H aromatic), 2985 (C-H aliphatic), 1610 (C=N), 1685 (>C=O), 1075 (N-N); ^{1}H NMR ($CDCl_3$) δ: 8.0-8.7 (9H, m, Ar-H), 8.75 (1H, s, N-H), 4.10 (2H, q, CH_2 at C_7), 1.20 (3H, t, CH_3 at C_7);

MS (m/z): 382 [M^+], 381 [M^+ -H], 353 [M^+ -C_2H_5],354 [M^+ -C_2H_4], 337 [M^+ -OC_2H_5], 308 [M^+ -C_2H_5OH], 305 [M^+ -C_6H_5], 287 [M^+ -C_6H_4F].

Anal. Calculated (%) for $C_{19}H_{15}FN_4O_2S$: C, 59.5; H, 3.9; N, 14.6. Found (%): C, 59.32; H, 3.78; N, 14.49.

(8). 3-(4-Chlorophenyl)-7-ethoxycarbonyl-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{19}H_{15}ClN_4O_2S$



Yield 67%, M.P.134^{0}C

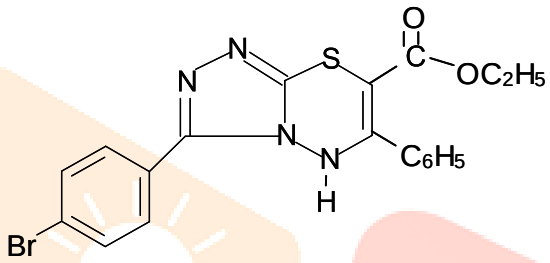
IR (KBr, ν_{max}., cm-1): 3390 (N-H), 1245, 1035 (C-O-C), 3045 (C-H aromatic), 2980 (C-H aliphatic), 1605 (C=N), 1685 (>C=O), 1060 (N-N), 765 (C-Cl);

^{1}H NMR ($CDCl_3$) δ: 7.7-8.2 (9H, m, Ar-H), 8.70 (1H, s, N-H), 4.05 (2H, q, CH_2 at C_7), 1.15 (3H, t, CH_3 at C_7); MS (m/z): 398 [M^+], 397 [M^+ -H], 369 [M^+ -C_2H_5], 370 [M^+ -C_2H_5], 353 [M^+ -OC_2H_5], 324 [M^+ -C_2H_5OH+CO], 321 [M^+ -C_6H_5], 287 [M^+-C_6H_4Cl].

Anal. Calculated (%) for $C_{19}H_{15}ClN_4O_2S$: C, 57.5; H, 3.7; N, 14.0. Found (%): C, 56.98; H, 3.6; N, 13.89.

(9). 3-(4-Bromophenyl)-7-ethoxycarbonyl-6-pheny-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{19}H_{15}BrN_4O_2S$



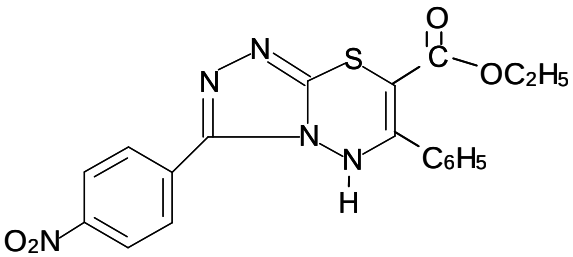
Yield 69%, M.P.145^{o}C

IR (KBr, ν_{max}., cm^{-1}): 3390 (N-H), 1240, 1035 (C-O-C), 3080 (C-H aromatic), 2985 (C-H aliphatic), 1598 (C=N), 1665 (>C=O), 1068 (N-N); ^{1}H NMR ($CDCl_3$) δ: 7.4-6.98 (9H, m, Ar-H), 8.75 (1H, s, N-H), 4.10 (2H, q, CH_2 at C_7), 1.15 (3H, t, CH_3 at C_7);

Anal. Calculated (%) for $C_{19}H_{15}BrN_4O_2S$: C, 51.4; H, 3.3; N, 12.6. Found (%): C, 51.05; H, 3.12; N, 12.48.

(10). 7-Ethoxycarbonyl-3-(4-nitrophenyl)-6-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{19}H_{15}N_5O_4S$



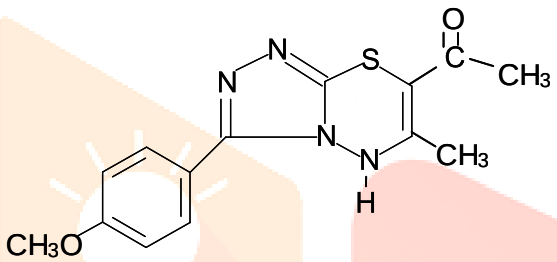
Yield 63%, M.P.151^{0}C

IR (KBr, ν_{max}., cm^{-1}): 3360 (N-H), 1240, 1035 (C-O-C), 3085 (C-H aromatic), 2985 (C-H aliphatic), 1585 (C=N), 1675 (>C=O), 1065 (N-N); ^{1}H NMR ($CDCl_3$) δ: 7.5-8.2 (9H, m, Ar-H), 8.65 (1H, s, N-H), 4.0 (2H, q, CH_2 at C_7), 1.20 (3H, t, CH_3 at C_7);

Anal. Calculated (%) for $C_{19}H_{15}N_5O_4S$: C, 55.74; H,3.66; N,17.11. Found (%): C,55.68;3.64; N,17.04.

(11). 3-(4-Methoxyphenyl)-6-methyl-7-methylcarbonyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{14}H_{14}N_4O_2S$



Yield: 64%, M.P.122^{0}C

IR (KBr, ν_{max}.,cm^{-1}): 3390 (N-H), 2970 (C-H aliphatic), 3080 (C-H aromatic), 1590 (C=N), 1660 (>C=O), 1060 (N-N);

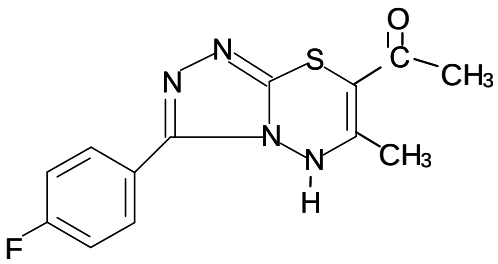
^{1}H NMR (CDCl) δ: 7.8-8.5 (4H, m, Ar-H), 8.7 (1H, s, N-H), 2.15 (3H, s, CH_3 at C_6), 3.8 (3H, s, OCH_3 at 4'), 3.5 (3H, s, $COCH_3$ at C_7);

MS (m/z): 302 [M^+], 301 [M^+ -H], 287 [M^+ -CH_3], 259 [M^+ -$COCH_3$], 242 [M^+ -CH_3OH+CO], 195 [M^+ -$C_6H_4OCH_3$].

Anal. Calculated (%) for $C_{14}H_{14}N_4O_2S$: C, 55.6; H, 4.63; N, 18.54. Found (%): C, 55.54; H, 4.59; N, 18.48.

(12). 3-(4-Fluorophenyl)-6-methyl-7-methylcarbonyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{13}H_{11}FN_4OS$



Yield: 62%, M.P. 114^{0}C

IR (KBr, ν_{max}., cm^{-1}): 3380 (N-H), 2995 (C-H aliphatic), 3065 (C-H aromatic), 1590 (C=N), 1650 (>C=O), 1070 (N-N);

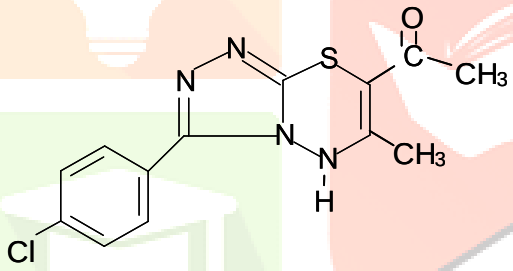
^{1}H NMR ($CDCl_3$) δ: 7.9-7.5 (4H, m, Ar-H), 8.7 (1H, s, N-H), 2.20 (3H, s, CH_3 at C_6), 3.6 (3H, s, $COCH_3$ at C_7);

MS (m/z): 290[M^+], 289 [M^+-H], 275 [M^+-CH_3], 247 [M^+-$COCH_3$], 230 [M^+-CH_3OH+CO], 195 [M^+-C_6H_4F].

Anal. Calculated (%) for $C_{13}H_{11}FN_4OS$: C, 53.7; H, 3.7; N, 19.3. Found (%): C, 53.59; H, 3.62; N, 19.12.

(13). 3-(4-Chlorophenyl)-6-methyl-7-methylcarbonyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{13}H_{11}ClN_4OS$



Yield: 65%, M.P.119^{0}C

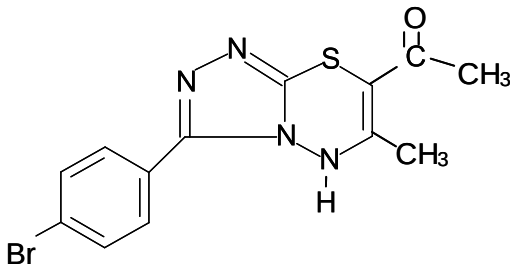
IR (KBr, ν_{max}., cm^{-1}): 3370 (N-H), 2985 (C-H aliphatic), 3065 (C-H aromatic), 1595 (C=N), 1660 (>C=O), 1065 (N-N);

^{1}H NMR ($CDCl_3$) δ: 7.7-8.3 (4H, m, Ar-H), 8.8 (1H, s, N-H), 2.15 (3H, s, CH_3 at C_6), 3.45 (3H, s, $COCH_3$ at C_7);

Anal. Calculated (%) for $C_{13}H_{11}ClN_4OS$: C, 50.8; H, 3.5; N, 18.2. Found (%): C, 50.68; H, 3.43; N, 18.13.

(14). 3-(4-Bromophenyl)-6-methyl-7-methylcarbonyl-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{13}H_{11}BrN_4OS$



Yield: 6%, M.P. 135°C

IR (KBr, ν_{max}., cm^{-1}): 3385 (N-H), 2985 (C-H aliphatic), 3075 (C-H aromatic), 1598 (C=N), 1655 (>C=O), 1065 (N-N);

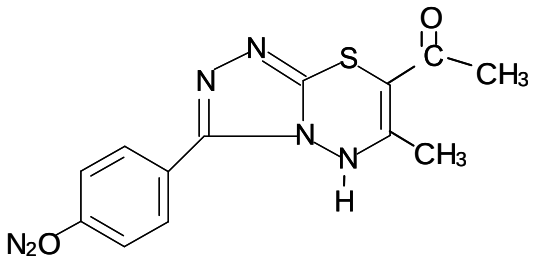
^{1}H NMR (CDCl) δ: 7.6-8.3 (4H, m, Ar-H), 8.7 (1H, s, N-H), 2.25 (3H, s, CH_3 at C_6), 3.4 (3H, s, $COCH_3$ at C_7);

MS (m/z): 351[M^+], 350 [M^+ -H], 336 [M^+ -CH_3], 308 [M^+ -$COCH_3$], 291 [M^+ -CH_3OH+CO], 195 [M^+ -C_6H_4Br], 272 [M^+ -Br].

Anal. Calculated (%) for $C_{13}H_{11}BrN_4OS$: C, 44.4; H, 3.1; N, 15.9. Found (%): C, 44.15; H, 2.98; N, 15.81.

(15). 6-Methyl-7-methylcarbonyl-3-(4-nitrophenyl)-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine

Molecular Formula : $C_{13}H_{11}N_5O_3S$



Yield 67%, M.P.128 ^{0}C

IR (KBr, ν_{max}., cm-1): 3370 (N-H), 3070 (C-H aromatic), 2990 (C-H aliphatic), 1580 (C=N), 1665 (>C=O), 1050 (N-N);

^{1}H NMR ($CDCl_3$) δ: 7.60-8.30 (4H, m, Ar-H), 8.5 (1H, s, N-H), 2.20

(3H, s, CH_3 at C_6), 3.45 (3H, s, $COCH_3$ at C_7);

MS (m/z) 317 [M^+], 316 [M^+ -H], 302 [M^+ -CH_3], 274 [M^+ -$COCH_3$], 257 [M^+ -CH_3OH+CO], 195 [M^+ -$C_6H_4NO_2$], 271 [M^+ -NO_2], 287 [M^+ -NO];

Anal. Calculated (%) for $C_{13}H_{11}N_5O_3S$: C,49.21; H,3.47; N,22.08. Found (%): C,49.12; H,3.44; N,21.02

Spectral analysis

The structures of the synthesized compounds were confirmed by IR, NMR and MS spectral data and further supported by correct elemental analysis. The infrared spectra of all the synthesized triazolothiadiazines invariably showed a N-H stretching absorption peak in the region of 3390-3340 cm^{-1} and for C=O stretching absorption peak in the region 1685-1650 cm^{-1}. In compounds 1 to 10 bands appearing in the region 1240-1220 cm^{-1} and 1045-1030 cm^{-1} are attributed to C-O-C asymmetric and symmetric vibrations respectively.

In the ^1H NMR spectra of synthesized compounds dispearance of the peaks due to NH_2 and SH which were present in the amino triazolo thiols further confirmed the involvement of these functional groups in the cyclization of triazole to triazolothiadiazines. A broad singlet peak in the region of 8.5-8.8 δ is observed in all the synthesized compounds for N-H proton and multiplets in the region 6.3-7.8 δ are due to aromatic ring protons. A singlet peak at about 3.7 δ is observed in methoxy derivatives due to OCH_3 group at 4'.

In mass spectra of all the synthesized triazolothiadiazines the observed molecular ion peak (M^+) conform the assigned molecular formulae of respective compounds. Other peaks like M^+ - C_2H_4, M^+ - C_2H_5, M^+ - COC_2H_5, M^+ - OC_2H_5, M^+ - $COCH_3$, M^+ - $C_6H_4NO_2$, M^+ - C_6H_4Br were also observed in the mass spectra of related compounds in conformity of assigned structure.

Antimicrobial Activity

All the synthesized thiadiazines derivatives evaluated for antimicrobialactiveities in vitro using agar-plate diffusion technique 18 by measuring the zone of inhibition in mm. The antibacterial activity was evaluated against bacteria Escherichia coli ATCC25922 (E. coli), Pseudomonas aeruginosa ATCC 27853 (P. aeruginosa), Staphylococcus aureus ATCC 25923 (S. aureus) and Bacillus megaterium ATCC 14518 (B. megaterium) at 40 µg/ml concentration of samples with standard drugs amoxicillin and ciprofloxacin. After completion of incubation period, the zone of inhibition of growth in the form of diameter in mm was measured (table- 1).

Antifungal activities was evaluated against Aspergillusneiger (A. neiger) and Canadidaalbicans (C. albicans) at 40 µg/ml concentration of samples using Griseofulvin as standard drug. After completion of the incubation period, the zone of inhibition of growth in the form of diameter in mm was measured (table-1).

Table-1: Antimicrobial activities of 5H- [1,2,4]triazolo[3,4b][1,3,4]-thiadiazines derivatives **(1-15)**

Comp.	Zone of Inhibition in mm					
	Antibacterial Activity				Antifungal Activity	
	E. coli	P. aeruginosa	S. aureus	B.megaterium	A. niger	C. albicans
1.	10.00	12.25	13.00	11.50	9.50	9.00
2.	16.00	17.25	18.00	16.25	14.50	16.50
3.	13.50	12.50	13.00	12.00	11.50	11.00
4.	12.50	13.00	12.50	11.75	10.00	10.75
5.	15.00	15.50	16.00	15.00	13.00	14.75
6.	11.20	10.75	11.75	10.50	9.00	9.25
7.	17.00	18.00	19.00	17.75	15.75	16.00
8.	13.00	14.25	15.25	14.75	12.00	11.75
9.	11.50	12.75	12.00	12.25	11.00	11.25
10.	16.50	16.00	16.75	15.50	13.00	12.75
11.	10.75	10.75	11.50	11.25	9.75	10.00
12.	18.00	18.00	19.00	18.25	16.25	16.00
13.	14.25	14.25	14.00	13.75	10.50	11.25
14.	12.50	13.00	13.25	13.50	10.75	10.25
15.	15.75	15.50	16.00	17.00	14.00	13.75

REFERENCES

1. A. T. C. Olak, F. C. Olak, N. Atar, A. Olgun, Acta Chim. Slov., **57**, 212-221 (2010).
2. H. M. Gaber, I. S. A. Hafiz, K. M. ElSawy, S. M. Sherif, Acta Chim. Slov., **57**, 230-243 (2010).
3. R. Rohini, P. M. Reddy, K. Shanker, V. Ravinder, Acta Chim. Slov., **56**, 900-907 (2009).
4. E. R. Kotb, M. A. EI-Hashash, M. A. Salama, H. S. Kalf, N. A. M. A. Wahed, Acta Chim. Slov., **56**, 908-919 (2009).
5. P. Anderluh, G. Vilfan, A. Prezelj, U. Urleb, Acta Chim. Slov., **56**, 669-673 (2009).
6. A. R. B. A. EI-Gazzar, H. N. Hafez, Acta Chim. Slov., **55**, 359-371 (2008).
7. M. Palcut, L. Rabara, Acta Chim. Slov., **56**, 845-851 (2009).
8. M. Abdel-Magid, M. Awas, M. Seada, K. Elmahdy, M. El-Sayed, Acta Chim. Slov. **56**, 852-859 (2009).
9. Labanauskas, V. Kalcas, E. Udrenaite , P. Gaidelis , A. Brukstus, V. Dauksas , Pharmazie, **56**, 617-619 (2001).
10. S. Schenone , O. Bruno , A. Ranise, F. Bondavalli, W. Filppelli , G. Falcone , L. Giordano, M. R. Vitelli, Bioorg. Med Chem., **9,** 2149-2153 (2001).
11. A. Varvaresou , A. Tsantili-Kakoulidou , T. Siatra-Papastasikoudi E. Tiligada, Arznemittelforschung, **50**, 48 (2000).
12. J. J. Baldwin, E. L. Engelhardt, G. S. Ponticello, J. G. Atkinson, B. K. Wasson, C. S. Sweet, A. Scriabine, J. Med. Chem., **23**, 65-70 (1980).
13. A. K. Sadana, Y. Mirza, K. R. Aneja, O. Prakash, Eur. J. Med. Chem., **38,** 533-536 (2003).
14. M. Koufaki, A. Detsi, E. Theodorou, C. Kiziridi, T. Calogeropoulou, A. Vassilopoulos, A. P. Kourounakis, E. Rekka, P. N. Kourounakis, C. Gaitanaki, P. Papazafiri, Bioorg. Med.Chem., **12**, 4835-4841 (2004).
15. Z. A. Kaplancykly, G. Turan-Zitouni, A. Ozdemir, G. Revial, Eur. J. Med. Chem., **43**, 155-159 (2008).
16. J. L.Vennerstrom, M. T. Maklet, C. K. Angerhofer, J. A. Williams, Antimicrob. Agents Chemother., **39**, 2671-2676 (1995).

17. B. Kunze, R. Jansen, L. Pridzum, E. Jurkiewicz, G. Hunsmann, G. Hofle, H. J. Reichenboch, Antibiot., **46**, 1752-1759 (1993).

18. P. Karegoudar, D. J .Prasad, M. Ashok, M. Mahalinga, B. Poojary, B. S. Holla, Eur. J. Med. Chem., **43**, 808-815 (2008).

19. M. Amir, H. Kumar, S. A. Javeed, Eur. J. Med. Chem., **43**, 2056-2066 (2008).

20. N. Demirbas, A. Demirbas, S. A. Karaoglu, E. Celik, ARKIVOC, **75**, 91 (2005).

21. Collins, C. H. Lyne, P. M. Grange, J. M. Falkinham, J. O. Collins , Butterworth, London, (1970).

22. J. Mohan, G. S. R. Gsranjaneyulu, R. Kiran, Indian J. Chem., Sect. (B), Org. Chem. Incl. Med. Chem., **27**, 128 (1988).

23. M. Kidwai, Y. Goel, K. Kumar, Indian J. Chem., Sect. (B), Org. Chem. Incl. Med. Chem., **36,** 782 (1997).

24. M. Jag, Indian J. Chem., Sect. (B), Org. Chem. Incl. Med. Chem., **22**, 270 (1983).

25. K. Prakash, P. D. Jagdeesh, A. Mithun, M. Manjuathuru, P. Boja, H. B. Shivarama, Eur. J. Med. Chem. **43**, 808 (2008).

26. A. Mifhun, H. B. Shivarama, Indian J. Pharm. Toxicol. **2**, 256 (2007).

27. K. C. Ravindra, H. M. Vagdevi, V. P. Vaidya, Indian J. Chem., Sect. B. Org. Chem. Incl. Med. Chem., **47**, 1271 (2008).

28. H. B. Shivarama, C. S. Prasanna, P. Boja, K. S. Rao, K. Shridhara, Indian J. Chem., Sect. (B), Org. Chem. Incl. Med. Chem., **45**, 2071 (2006).

29. A. R. Farghaly, E. De Clercq, H. El-Kashef, ARKIVOC, **(x)**, 137 (2006).

30. K. P. Vijaya, R. V. Rajeswar, Indian J. Chem., Sect. B. Org. Chem. Incl. Med. Chem., **47**, 106 (2008).

31. M. A. El-Dawy, A. M. Omar, A. M. Ismail, A. A. B.Hazzaa, J. Pharm. Sci., **72**, 45 (1983).

32. M. Jag, Chim. Acta Turc. **16**, 91 (1988).

33. A. R. Prasad,T. Ramalingam, A. B. Rao, P. V. Diwan, P. V. P. B. Sattur, Eur. J. Med. Chem., **24**, 199 (1989).

34. H. B. Shivarama, R. B. Sooryanarayana, B. K.Sarojini, P. M. Akberali, K. N. Suchetha, Eur. J. Med. Chem., **41**, 657 (2006).

35. H. B. Shivarama, R. B. Sooryanarayana, B. K. Sarojini, P. M. Akberali, K. N. Suchetha, V. Shetty, Farmaco, **56**, 565 (2001).

36. A. M. Demchenko, V. O. Yanchenko, O. S Smolskii, V.O.Ageev, M. O. Lozinskii, Farmatsevtichnii Zh. **6**, 41 (2003).

37. W. L. Albrecht, F. W. Sweet, US 3954983, (1976)

38. R. G. Ramana, R. K. Srinivasa, Indian Drugs, **26**, 220 (1989).

39. Y. Xiao-Xia, Z. Jin, Z. An- Jiang, Z. Li-Xue, J. Heterocycl. Chem., **45**, 987 (2008).

40. W. L. Alberecht, W. D. Jones, F. W. Jr. Sweet, J. Heterocycl. Chem., **15(2)**, 209-15 (1978); Chem. Abstr., **89**, 24265d (1978).

41. N. Hans, D. Marita, H. Heinz, Synthesis, 10, 778-82 (1988), Chem. Abstr., **110**, 212771s (1989).

42. A. R. Prasad, T. Ramalingam, A. B. Rao, Eur. J. Med. Chem., **24(2)**, 199-201 (1989), Chem. Abstr., **112**, 35816d (1990).

43. Y. A. Ibrahim, A. H. M. Elwahy, A. E. M. El-Fiky, Heteroat. Chem., **5(4)**, 321-5 (1994), Chem. Abstr., **122**, 81332x (1995).

44. M. M. Hervi, P. Khosrofar, J. Sci. Islamic Repub. Iran., **7(2)**, 86-88 (1996), Chem. Abstr., **125**, 195597e (1996).

45. M. Rahimizadeh, M. M. Heravi, A. Malekan, Indian J. Heterocycl. Chem., **6**, 223-224 (1997).