SYNTHESIS OF 1,2,4 - TRIAZOLE, 1,2,4 - TRIAZOLO [3,4 -b] [1,3,4] THIADIAZOLE AND 1,2,4 -TRIAZOLO [3,4 -b] [1,3,4] THIADIAZINE DERIVATIVES OF 3- [5- (BENZOTHIAZOL - 2 - YL) THIENO [2,3-d] PYRIMIDINE - 4- ONE] ACETIC ACID HYDRAZIDE.

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Abstract: Novel 1,2,4-Triazole, 1,2,4-Triazolo [3,4-b] [1,3,4] thiadiazole and 1,2,4-triazolo [3,4-b] [1,3,4] thiadiazine derivatives have been synthesized using 3- [5- (benzothiazol - 2- yl) thieno [2,3-d] pyrimidine - 4- one] acetic acid hydrazide.

Introduction:

The recent literature is enriched with progressive findings about the synthesis and pharmacological action of fused heterocycles. The benzothiazole nucleus is associated with diverse pharmacological activities such as antiviral (1), antibacterial (2) and fungicidal activities (3). They are also useful as anti-allergic(4), anthelmintic (5) anti-inflammatary(6), appetite depressants (7) agents and histamine H_2 antagonists (8). Furthermore,several other publications have also pointed out the value of s-triazolo[3,4-b] [1,3,4] thiadiazoles (9,10) 7H-s-triazolo [3,4-b] [1,3,4] thiadiazines (11) and 1,2,4 -triazole-3-thione (12-17) as biologically active nuclei. Also, diverse biological activities of condensed pyrimidines as sedative, antibacterial and antimalarials are well documented (18-20). Thienopyrimidines have been evaluated pharmacologically and used as analgesic, anti-convulsant and antimicrobial agents (18).

These findings focused particular interest to incorporate thiosemicarbazides, triazoles, s-triazolo [3,4-b][1,3,4] thiadiazoles or, 7H-s-triazolo [3,4-b] [1,3,4] thiadiazines with 5 - (benzothiazol-2-yl) thieno [2,3-d] pyrimidine-4-one in one framework with the hope to obtain compounds of better antimicrobial activity.

Results and Discussion:

2-Acetylbenzothiazole 1 undergoes knoevenagel condensation with ethyl cyanoacetate 2 to afford 3-(benzothiazol -2-yl)-2-ethoxycarbonyl cortonitrile 3. The structure of 3 was confirmed by analytical and spectral data. The IR spectra of 3 showed a presence of cyano absorption band at 2218 cm^{-1}. The reactivity of the methyl group in 3 towards sulfur finds a parallelism in the reported reactivity of the methyl function by Gewald et al (21,22). Thus, the cortonitrile derivative 3 reacts with sulfur in refluxing dioxane containing catalytic amounts of triethylamine to afford one isolable product as evidenced by TLC analysis. The isolated product was identified as ethyl 2-amino -4- (benzothiazol-2-yl) thiophene-3- carboxylate 4.

Both elemental analyses and spectral data were in complete agreement with the assigned structure. The IR spectra of 3 showed two strong absorption bands in the region 3355-3285 cm^{-1} and 1690 cm^{-1} assignable to amino and ester carbonyl functions, respectively. The ^{1}HNMR spectrum of 3 revealed a broad singlet signal at δ_H 6.61 ppm due to NH_2 protons, in addition to a triplet, quartet and multiplet signals at δ_H 1.41, 4.36 and 7.47-8.32 ppm due to CH_3 ; CH_2 of ester and aromatic protons, respectively.

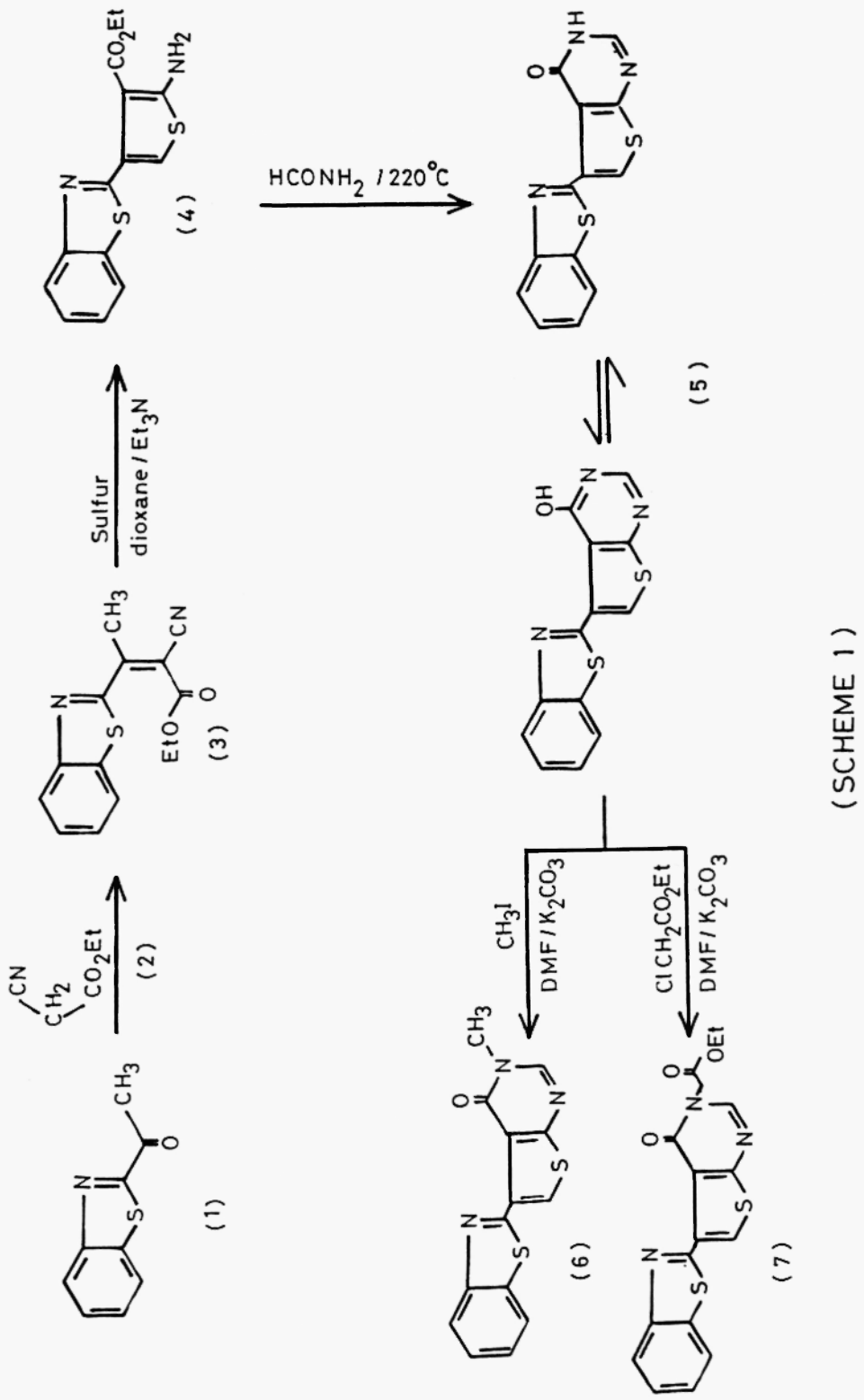
Thiophene derivative 4 reacts with formamide to afford one isolable product that analyzed correctly for $C_{13}H_7N_3S_2O$. The structure of the latter product was identified as 5-(benzothiazol-2-yl) thieno [2,3-d] pyrimidine -4 (3H) one 5 on the basis of its IR and ^{1}HNMR spectra. For example, its IR spectrum showed two characteristic bands at 3495 and 3190 cm^{-1} due to hydroxyl and NH function respectively, in addition to band at 1665 cm^{-1} due to carbonyl function. Its ^{1}HNMR spectrum displayed a broad singlet signal (D_2O - exchangeable) at δ_H 7.96 ppm due to NH (OH) proton and multiplet signal at δ_H 7.46-8.25 ppm due aromatic protons and H-2 of pyrimidine.

Alkylation of 5 with methyl iodide and / or ethyl chloroacetate furnished white precipitate of 5-(benzothiazol-2-yl)-3- methyl thieno [2,3-d] pyrimidine -4- one 6 and ethyl 5-(benzothiazol -2-yl) thieno [2,3-d] pyrimidine -4- one -3- acetate 7 respectively. Both elemental analyses and spectral data are competible with the assigned structures. The IR spectra of the isolated product 6 and 7 showed the absence of NH or OH absorption bands. The ^{1}HNMR spectra of 6 and 7 revealed singlet signal at δ_H 3.92 ppm due to N-CH3 and anthor one at δ_H 4.63 ppm due to N-CH2 respectively (Scheme 1).

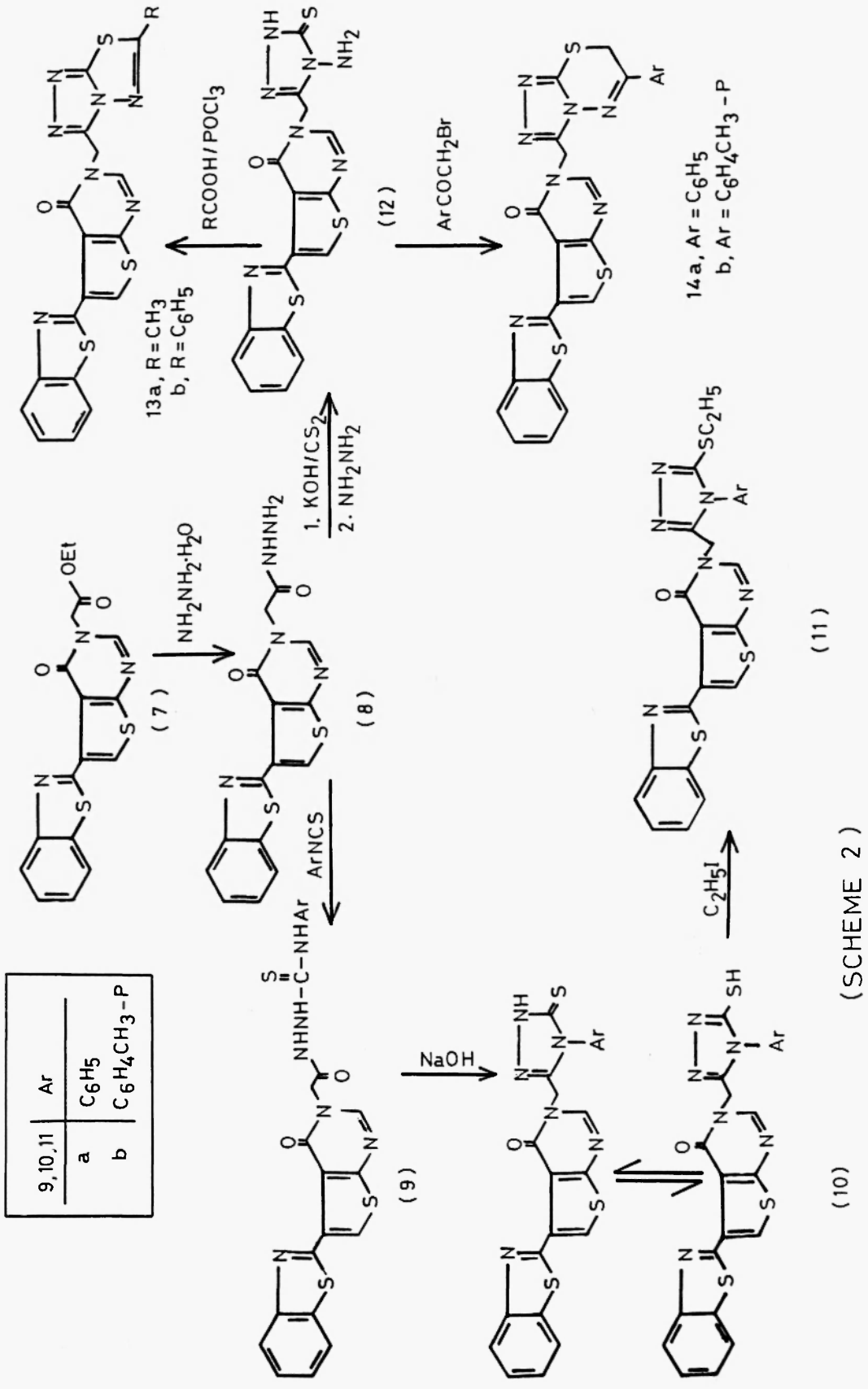
Hydrazinolysis of 7 with hydrazine hydrate in ethanol afforded the corresponding 3-[5-(benzothiazol-2-yl) thieno [2,3-d] pyrimidine -4-one] acetic acid hydrazide 8. The acetic acid hydrazide derivative 8 manifested to be the reasonable structure as confirmed by the elemental analyses, IR, ^{1}HNMR and mass spectra. The IR spectra of 8 revealed absorption bands near 3410-3165 cm^{-1} and 1665-1655 cm^{-1} corresponding to (NH_2,NH) and two carbonyl groups respectively. Also, the ^{1}HNMR spectrum of 8, displayed a broad singlet signal (D_2O-exchangeable) at δ_H 4.18 ppm, singlet one at δ_H 5.12 ppm and anthor broad singlet one (D_2O-exchangeable) at δ_H 9.53 ppm corresponding to NH2; N-CH_2 and NH respectively, in addition to aromatic protons.

Condensation of the acid hydrazide 8 with aryl isothiocyanates afforded a novel aryl 3-[5-(benzothiazol-2-yl) thieno [2,3-d] pyrimidine-4-one] carbonylmethylthiosemicarbazide 9a,b. The IR spectra of 9a,b showed in each case the presence of absorption bands at 3420,3350, 3200 cm^{-1} due to NH groups and anthor ones at 1680-1700 cm^{-1} due to carbonyl absorption bands. Their ^{1}HNMR spectra exhibited, in each case besides an aromatic multiplet at δ_H 7.35-8.41 ppm, two D_2O-exchangeable doublet signal in the regions at δ_H 9.63 ppm assignable to 2NH protons and anthor D_2O-exchangeable broad singlet one at δ_H 10.43 ppm due to SCNH-proton.

Cyclization of these thiosemicarbazides with sodium hydroxide (16,23) afforded 3- (4-aryl-4H-3-thione -1,2,4- triazol-5-(benzothiazol -2-yl) thieno [2,3-d] pyrimidine-4-one 10a,b which smoothly alkylated with ethyl iodide (16) to give 3-(4-aryl-3-ethylthio-4H-1,2,4- triazol-5-yl) methyl-5- (benzothiazol-2-yl)thieno [2,3-d] pyrimidine-4-one 11a,b. The structure of 10a,b were established on the basis of their elemental analyses and spectral data. The IR spectra of 10a,b showed in each case absorption bands in the region 3215-3190 cm^{-1} assignable to NH groups. However, in compounds 12a-c NH absorption bands were absent. The ^{1}HNMR spectra of 10a,b and 11a,b revealed the presence of, in each case, in addition to an aromatic multiplet at δ_H 7.42-8.35 ppm, singlet signal at δ_H 5.68-5.92 ppm due to (-CH_2-) and D_2O - exchangeable singlet signal in 10a,b at δ_H 13.96-14.05 ppm assignable to SH, while the latter SH signal disapearance in 11a,b.


CO2Et
NH2
(4)
HCONH2 / 220°C
Sulfur
dioxane / Et3N
CH3
CN
EtO
O
(3)
(5)
CN
CH2
CO2Et
(2)
(1)
CH3I
DMF / K2CO3
ClCH2CO2Et
DMF / K2CO3
(6)
(7)

(SCHEME 1)


9,10,11 | Ar
a | C6H5
b | C6H4CH3-P
13a, R=CH3
b, R=C6H5
RCOOH/POCl3
(12)
ArCOCH2Br
14a, Ar=C6H5
b, Ar=C6H4CH3-P
(7)
NH2NH2·H2O
(8)
1. KOH/CS2
2. NH2NH2
ArNCS
(9)
NaOH
(10)
C2H5I
(11)

(SCHEME 2)

Next, we investigated the applicability of acid hydrazide **8** as a precursor for the construction of variety of polyfimctionally substituted fused herterocycles containing thieno [2,3-d] pyrimidine moiety. Thus, the hydrazide **8** reacts with carbon disulphide and potassium hydroxide followed by hydrazine hydrate (24) afforded 3-(4-amino-4H-3-thione-1,2,4-triazol -5-yl) methyl-5-(benzothiazol-2-yl) thieno [2,3-d] pyrimidine- 4- one **12** . The structure of **12** was established on the basis of their elemental analyses and spectral data, as well as their chemical transformations. The ^{1}HNMR spectra of **12** displayed, D_2O - exchangeable two singlet signal around δ_H 5.53 ppm and δ_H 14.05 ppm corresponding to NH_2 and SH, protons, respectively, in addition to aromatic and methylene protons at δ_H 7.6-8.31 ppm and δ_H 5.92 ppm respectively.

Condensation of **12** with carboxylic acids in the presence of phosphorusoxychloride (25) afforded 6-substituted -3-[5-(benzothiazol-2-yl) thieno [2,3-d] pyrimidine-4-one] methyl -1,2,4- triazolo [3,4-b] [1,3,4] thiadiazoles **13a,b** ; while its condensation with substituted phenacyl bromides (11) afforded the fused heterocycles, 6-substituted phenyl -3- [5-(benzothiazol-2-yl) thieno [2,3-d] pyrimidine -4-one] methyl- 1,2,4- triazolo [3,4-b] [1,3,4] thiadiazines **14a,b**. The structures of triazolo [3,4-b] [1,3,4] thiadiazoles **13a,b** and triazolo [3,4-b] [1,3,4] thiadiazines **14a,b** derivatives were established based on its elemental analyses and spectral data. Their IR spectra showed, in each case, absorption bands assignable to NH_2 and NH groups are absent. The ^{1}HNMR spectra of **13a,b** revealed the presence singlet signal at δ_H 5.93-5.96 ppm due to CH_2 protons, singlet signal in **13a** at δ_H 2.61 ppm due to CH_3 and the ^{1}HNMR also revealed singlet signal in **14a,b** at δ_H 4.13-4.16 ppm due to C-7 triazolothiadizne (scheme 2).

Experimental:

Mps are uncorrected. IR spectra were measured as KBr pellets on a Pye Unicam SP 3-300 spectrophotometer. ^{1}HNMR spectra were recorded in deuterated chloroform or dimethylsulfoxide at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were performed on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. 2- Acetyl benzothiazole **1**(26) was prepared according to literature procedures.

3-(Benzothiazol-2-yl) -2-ethoxy carbonyl cortonitrile 3. To (1.772 g,10 mmol) of 2-acetylbenzothiazole **1** that have been throughly dried, piperidine (1ml) and ethyl cyanoacetate (1.36g, 12 mmol) were added. The reaction mixture was heated in an oil bath at 150°C for 1h. The solid product formed upon trituration with methanol was filtered off, washed with ethanol, dried and finally recrystallized from ethanol to afford **3** (63%), pale brown crystals, m.p 182-3°C; vmax/ cm^{-1} (KBr) 2989,2872 (CH_3, CH_2), 2218 (C ≡N), 1696 (C=O), 1645 (C=C) and 1613 (C=N) ; δ_H ($CDCl_3$) 1.61 (3H,t) , 3.36 (3H,s), 4.35 (2H,q) and 7.41 - 8.12 (4H,m); m/z 272 (M^+) (Found: C,61.63 ; H, 4.39 ;N, 10.12; S, 11.71. $C_{14}H_{12}N_2O_2S$ requires C,61.75; H, 4.44; N, 10.29; S, 11.77 %).

Ethyl 2-amino-4-(benzothiazol-2-yl) thiophene-3- carboxylate 4. To a solution of the cortonitrile **3** (2.723g, 10 mmol) in dioxane (40 ml), elemental sulphur (0.32g, 10 mmol) and a catalytic amount of triethylamine were added. The reaction mixture was heated at reflux for 3h. (TLC control). The solid product, formed on dilution with water, was filtered off, washed with water and dried. Recrystallization from ethanol afforded **4** (81%) , brown-red crystals, m.p 220-1 C; vmax/ cm^{-1} (KBr) 3355,3280 (NH_2) , 1690 (C=O)

and 1610 (C=N); δ_H (DMSO) 1.41 (3H,t), 4.36 (2H,q), 6.61 (2H,s), 7.12 (1H,s) and 7.47-8.32 (4H,m); m/z 305 (M^++1) (Found: C,55.30; H, 3.96 ;N, 9.15; S 21.12 $C_{14}H_{12}N_2O_2S_2$ requires C,55.24; H, 3.97; N, 9.20; S,21.07%).

5-(Benzothiazol-2-yl) thieno [2,3-d] pyrimidine-4(3H) one 5. A mixture of 4 (1.52g, 5 mmol) in formamide (15ml) was heated at 220-240°C for 2h. On cooling, a white crystals was fittered off, washed with ethanol and dried. Recrytallization from ethanol afforded 5 (71%), white crystals, m.p 237 °C; vmax/ cm^{-1} (KBr) 3495 (OH), 3190 (NH), 3100 (CH-ar.). 1665 (C=O) and 1605 (C=N); δ_H (DMSO) 7.46-8.25 (6H,m) and 8.96 (1H,s) ; m/z 286 (M^++1) (Found: C,54.71; H, 2.46; N,14.61; S. 22.38. $C_{13}H_7N_3S_2O$ requires C,54.72; H, 2.47; N, 14.73; S, 22.47%).

5-(Benzothiazol-2-yl)-3-methyl thieno [2,3-d] pyrimidine -4- one 6. Amixture of 5 (1.43g, 5 mmol) and methyl iodide (1.42 g, 10 mmol) was stirred in dry dimethylformamide (25 ml) in the presence of anhydrous potassium carbonate (1.38 g, 10 mmol) for 12hrs. The solid product formed upon trituration with water was filtered off, washed with aqueous ethanol, dried and finally recrystallized from DMF to afford 6 (65%), pale yellow crystals, m.p 252° C;vmax/ cm^{-1} (KBr) 2975,2878 (CH_3), 1685 (C=O) and 1618 (C=N); δ_H (DMSO) 3.92 (3H,s), 7.30 (1H,s) and 7.35 - 8.41 (5H,m); m/z 300 (M^++1) (Found: C,56.14; H, 3.01; N, 14.02; S, 21.40. $C_{14}H_9N_3OS_2$ requires C,56.17; H, 3.03; N, 14.04; S, 21.42%).

Ethyl 5-(benzothiazol-2-yl) thieno [2,3-d] pyrimidine-4- one -3-acetate 7. A mixture of 5 (1.43g,5 mmol) and ethyl chloroacetate (1.23 g, 10 mmol) in dry pyridine (25ml) was stirred for 3 hrs. at 0-5°C. The reaction mixture was heated at reflux on water bath for 2 hrs. The solid product formed upon dilution with ice water was filtered off, washed with water, dried and finally recrystallized from dioxane to afford 7 (76%), yellow crystals, m.p. 279°C; vmax/ cm^{-1} (KBr) 3040 (CH-ar.) , 2910-3000 (CH-ali.), 1725, 1672 (2 C=O) and 1610 (C=N), δ_H (DMSO) 1.31 (3H,t), 4.31 (2H,q) 4.63 (2H,s), 7.25 (1H,s) and 7.45-8.36 (5H,m); m/z 371 (M^+) (Found: C,54.81; H, 3.40; N, 11.21; S, 17.23. $C_{17}H_{13}N_3S_2O_3$ requires C,54.97; H, 3.53; N, 11.31; S, 17.26%).

3-[5-(Benzothiazol-2-yl) thieno [2,3-d] pyrimidine- 4-one] acetic acid hydrazide 8. Hydrazine hydrate (1 g, 20 mmol) was added to a solution of ethyl 5-(benzothiazol-2-yl) thieno [2,3-d] pyrimidine -4- one -3-acetate 7 (1.86g, 5 mmol) in ethanol (20 ml). The reaction mixture was heated under reflux for about 4 hrs. The solid product formed upon cooling, ditution with water was filtered off, washed with ice water, dried and finally recrystallized from ethanol to afford 8 (91%), white crystals, m.p 251°C;vmax/ cm^{-1} (KBr) 3410-3165 (NH_2 and NH), 1665-1655 (2C=O), and 1605 (C=N); δ_H (DMSO) 4.18 (2H, brs, D_2O- exchangeable), 5.12 (2H,s) 7.25 (1H,s), 7.41-8.35 (5H,m) and 9.53 (1H, brs, D_2O- exchangeable); m/z 356 (M^+) (Found: C,50.52; H,2.80; N,19.63; S,17.95. $C_{15}H_{11}N_5O_2S_2$ requires C, 50.55; H, 2.83; N, 19.65; S, 17.99 %).

Aryl 3-[5-(benzothiazol-2-yl) thieno [2,3-d] pyrimidine -4-one] carbonylmethylthio semicarbazide 9a,b (General procedure). A solution of acetic acid hydrazide 8 (1.78g, 5 mmol) and the appropriate isothiocyanate (5 mmol) in dioxane (20 ml) was heated under

reflux for 4 hrs. and then left at room temperature overnight. The solid product formed was filtered off, washed with ethanol, dried and finally recrystallized from aqueous dioxane to afford 9a,b .

9a: (68%), yellow crystals, m.p 286°C;vmax / cm^{-1} (KBr) 3420, 3350, 3200 (3-NH), 3015 (CH-ar.), 1685, 1695 (2 C=O) and 1605 (C=N); δ_H (DMSO) 5.2 (2H,s), 7.21 (1H,s) , 7.35-8.36 (10 H,m), 9.63 (1H,d, D_2O- exchangeable), 9.68 (1H,d, D_2O -exchangeable) and 10.38 (1H, brs, D_2O - exchangeable); m/z 493 (M^+) (Found: C,53.61; H, 3.26; N, 17.00; S, 19.51. $C_{22}H_{16}N_6O_2S_3$ requires C,53.64; H, 3.27; N, 17.06; S, 19.53%)

9b:(71%), white-yellow crystals, m.p 261°C;vmax/ cm^{-1} (KBr) 3415,3310,3180 (3-NH), 3050 (CH-ar.) , 1680, 1700 (2 C=O) and 1618 (C=N); δ_H (DMSO) 2.32 (3H,s), 5.41 (2H,s), 7.25 (1H,s) , 7.36 - 8.41 (9H,m), 9.42 (1H,d-D_2O- exchangeable), 9.61 (1H,d,D_2O- exchangeable) and 10.21 (1H, broads, D_2O-exchangeable) and m/z 506 (M^+) (Found: C,54.51; H, 3.57; N, 16.50; S, , 18.97. $C_{23}H_{18}N_6O_2S_3$ requires C, 54.53; H, 3.58; N, 16.59; S, 18.99%).

3- (4-aryl-4H-3-thione -1,2,4 - triazol- 5-yl) methyl -5- benzothiazol-2-yl) thieno [2,3-d] pyrimidine- 4-one 10a,b (General procedure). A suspension of the appropriate thiosemicarbazide 9a,b (2mmol) in sodium hydroxide solution (5%, 25ml) was heated under reflux for 2 hrs. The reaction mixture was allowed to cool, then neutralized with 20% hydrochloric acid and left at room temperature overnight. The solid product formed was filtered off, washed with water, dried and finally recrystallized from aqueous dioxane to afford 10a,b .

10a: (67%), pale yellow crystals, m.p. 259°C;vmax / cm^{-1} (KBr)3215 (NH) 1610 (C=N), 1540, 1275, 1160 (N-C=S), δ_H (DMSO) 5.68 (2H,s), 7.12 (1H,s), 7.61 - 8.35 (10 H,m) and 13.96 (1H, s, D_2O-exchangeable); m/z 474 (M^+) (Found: C,55.64; H, 2.91; N, 17.70; S, 20.19. $C_{22}H_{14}N_6OS_3$ requires C, 55.68; H, 2.97; N, 17,71; S, 20.27%)

10b: (69%), white-yellow crystals, m.p 263 °C;vmax /cm^{-1} (KBr) 3190 (NH), 1605 (C=N) and 1270 (N-C=S); δ_H (DMSO) 2.36 (3H,s), 5.92 (2H,s), 7.11 (1H,s), 7.42-3.31 (9H,m) and 14.05 (1H,s, D_2O - exchangeable); m/z 488 (M^+) (Found: C,56.52; H, 3.27; N, 17.18; S, 19.59. $C_{23}H_{16}N_6OS_3$ requires C, 56.55; H, 3.28; N, 17.20; S, 19.69%).

3- (4-arly - 3- ethylthio - 4H- 1,2,4 - triazol - 5- yl) methyl - 5- (benzothiazol-2-yl) thieno [2,3-d] pyrimidine - 4- one 11a,b. The appropriate mercaptotriazole 10a,b (1 mmol) was dissolved in an ethanolic solution of sodium ethoxide in ethanol (25ml) and then ethyl iodide (0.3 g, 2mmol) was added gradually to the resulting solution. The reaction mixture was heated under reflux for 3h., concentrated, cooled, diluted with ice water and left overnight. The precipitate obtained was filtered, washed with water and recrystallized from dioxane to afford 11a,b.

11a: (64%), pale yellow crystals, m.p. 172-3°C ; ν max / cm^{-1} (KBr) 1605 (C=N) 1596 (C=C), δ_H ($CDCl_3$) 1.41 (3H,s), 3.61 (2H,q), 5.82 (2H,s), 7.62-8.31 (11 H,m); m/z 503 (M^++1) (Found : C,57.32; H, 3.59; N, 16.70; S, 18.71. $C_{24}H_{18}N_6OS_3$ requires C, 57.35; H, 3.61; N, 16.72; S 18.73%)

11b: yellow crystals, mp. 179°C; vmax/ cm^{-1} (KBr) 1610 (C=N), 1590 (C=C), δ_H ($CDCl_3$), 1.36 (3H,s) 2.26 (3H,s), 3.58 (2H,q), 5.76 (2H,s), 7.51 - 8.25 (10H,m); m/z 514 (M^+) (Found: C, 58.10; H, 3.89; N, 16.25; S, 18.59. $C_{25}H_{20}N_6OS_3$ requires C,58.12; H,3.91; N, 16.27; S, 18.62%)

3-(4-Amino-4H-3-thione-1,2,4-triazol-5-yl)methyl-5-(benzothiazol-2-yl) thieno [2,3-d] pyrimidine-4- one 12. To a cold stirred solution of acetic acid hydrazide **8** (1.78g, 5mmol) in absolute ethanol (50ml) containing potassium hydroxide (0.28g, 5mmol), carbon disulphide (0.38g, 5mmol) was added gradually. The reaction mixture was stirred at room temperature for 24h. whereupon a yellow precipitate of the corresponding potassium dithiocarbazate was separated. Dry ether (50ml) was then added to complete the precipitation of the formed salt. The obtained product was filtered, washed with dry ether and dried in a desiccator. The salt was then suspended in hydrazine hydrate (10 mmol), stirred and heated under reflux for 4h. The reaction mixture was cooled, diluted with ice cold water (100 ml) and neutralized with dilute hydrochloric acid. The solid product formed was filtered off, washed thoroughly with cold water, dried and finally recrystallized from ethanol to afford **12** (72%) yellow crystals, m.p. 261°C:vmax/ cm^{-1} (KBr) 3305,3170 (NH_2 and NH), 1675 (C=O), 1640 (C=O) , 1280, 1175, 1010 (N-C=S), δ_H (DMSO) 5.53 (2H, brs,D_2O -exchangeable), 5.92 (2H, s), 7.12 (1H,s) , 7.61 - 8.31 (2H,m) 14.05 (1H, brs, D_2O - exchangeable); m/z 414 (M^++1) (Found:C,46.41; H, 2.61; 23.63; S, 23.12. $C_{16}H_{11}N_7OS_3$ requires C, 46.48 ; H, 2.68; N, 23.71; S, 23.26%) .

6-Substituted-3-[5-(benzothiazol-2-yl)thieno[2,3-d]pyrimidine-4-one]methyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles 13a,b

(General procedure). A mixture of 3-(4-amino-4H-3-thione-1,2,4-triazol-5-yl)methyl-5-(benzothiazol-2-yl)thieno[2,3-d] pyrimidine-4-one **12** (2.07g, 5mmol) and the appropriate carboxylic acid (5 mmol) in phosphorusoxychloride (15 ml) was heated under reflux at 110°C for 1.5 h. The reaction mixture was cooled, poured gradually with stirring into an ice cold sodium bicarbonate solution. The separated product was filtered, washed thoroughly with water, dried and recrystallized from dioxane to afford **13a,b**.

13a: (71%), pale brown crystals, m.p. 293°C;vmax / cm^{-1} (KBr) 1670 (C=O), 1635 (C=N), 1590 (C=C); δ_H (DMSO) 2.61 (3H,s), 5.93 (2H,s), 7.21 (1H,s), 7.81-8.15 (5H,m); m/z 438 (M^++1) (Found: C, 49.39; H, 2.51; N, 22.38; S, 21.97 $C_{18}H_{11}N_7OS_3$ requires C, 49.42; H, 2.53; N, 22.41; S, 21.98 %)

13b: (67%), yellow crystals, m.p 298°C; vmax / cm^{-1} (KBr) 1667 (C=O), 1615 (C=N), 1585 (C=C); δ_H (DMSO) 5.96 (2H,s), 7.23 (1H,s), 7.7 - 8.21 (10H,m); (Found: C,55.11; H, 2.60; N, 19.58; S, 18.36 $C_{23}H_{13}N_7OS_3$ requires C, 55.30; H, 2.62; N, 19.63 ; S, 18.42 %).

6-Substituted phenyl-3-[5-(benzothiazol-2-yl)thieno[2,3-d]pyrimidine-4-one]methyl-1,2,4-triazolo [3,4-b] [1,3,4] thiadiazines 14a,b (General proedure). A solution of 3- (4-amino- 4H-3 thione- 1,2,4- triazol-5-yl) methyl -5- (benzothiazol-2-yl) thieno [2,3-d] pyrimidine-4-one **12** (2.07g, 5 mmol) and the appropriate phenacyl bromide derivative (5 mmol) in absolute ethanol (30ml) was heated under reflux for 1h. The reaction mixture was then cooled , adjusted to pH 8 by the addition of a cold saturated solution of sodium acetate and left overnight. The product which precipitated was filtered, washed with water, dried and recrystallized from ethanol to afford **14a,b**.

14a: (65%) brown crystals, m.p. 286°C;vmax/ cm^{-1} (KBr) 1660 (C=O) , 1630 (C=N) , 1050 (C=C); δ_H (DMSO) 4.13 (2H,s), 5.93 (2H,s), 7.21-8.31 (11H,m); m/z 513 (M^+) (Found: C,56.09; H, 2.85; N, 18.98; S, 18.68 $C_{24}H_{15}N_7OS_3$ requires C, 56.13; H, 2.94; N, 19.09 ; S, 18.73 %) .

14b: (61%), brown crystal, m.p. 279°C;vmax/cm^{-1} (KBr) 1663 (C=O), 1610 (C=N), 1590 (C=C); δ_H (DMSO) 2.35 (3H,s) , 4.16 (2H,s), 6.12 (2H,s) 7.15- 8.32 (10 H,m); (Found: C, 56.86; H, 3.19; N, 18.56; S, 18.21 $C_{25}H_{17}N_7OS_3$ requires C, 56.91 ; H, 3.25; N, 18.58; S, 18.23%).

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