Reactions of 1-amino-5-morpholino-6,7,8,9-tetrahydrothieno[2,3-*c*] isoquinoline- 2-carbonitrile

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1-Amino-5-morpholino-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinoline-2-carbonitrile has been converted to the chloroacetylamino derivative which was subjected to nucleophilic substitution reactions with different amines. Reaction of 1-amino-5-morpholino-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinoline- 2-carbonitrile with triethyl orthoformate followed by cyclisation with hydrazine yielded an aminoiminopyrimidine derivative. The latter was used as a starting material for the synthesis of a variety of fused heterocyclic compounds which include triazolopyrimidothienotetrahydroisoquinolines.

Keywords: tetrahydroisoquinoline, thienotetrahydroisoquinoline pyrimidothieno-tetrahydroisoquinoline, triazolopyrimidothienotetrahydroisoquinoline

Isoquinoline alkaloids are a large family of natural products and display a broad variety of biological activities.[1] Among the members of this class of compounds; tetrahydroisoquinoline derivatives constitute a major group. Many of them exhibit important biological activities, for example, anti-inflammatory, anti-microbial, anti-leukaemic, and anti-tumour properties,[2,3] anti-HIV, and other biological activities.[4–8] Tetrahydroisoquinolines have cardiovascular[9] activities and are useful in the treatment of Parkinson's disease.[10] Tetrahydropyrimidothienoisoquinolines are useful compounds as anti-anaphylactics, anti-inflammatories, and bacteriophage inhibitors.[11] Thienopyrimidines have long been the subject of chemical and biological research. Some thienopyrimidines display analgesic,[12] antipyretic,[13,14] anti-inflammatory,[15,16,17,18] and anti-allergenic effects.[19,20,21] These compounds have been studied as antineoplastic agents[22] and for lowering the cholesterol level in the cardiovascular system.[23,24]

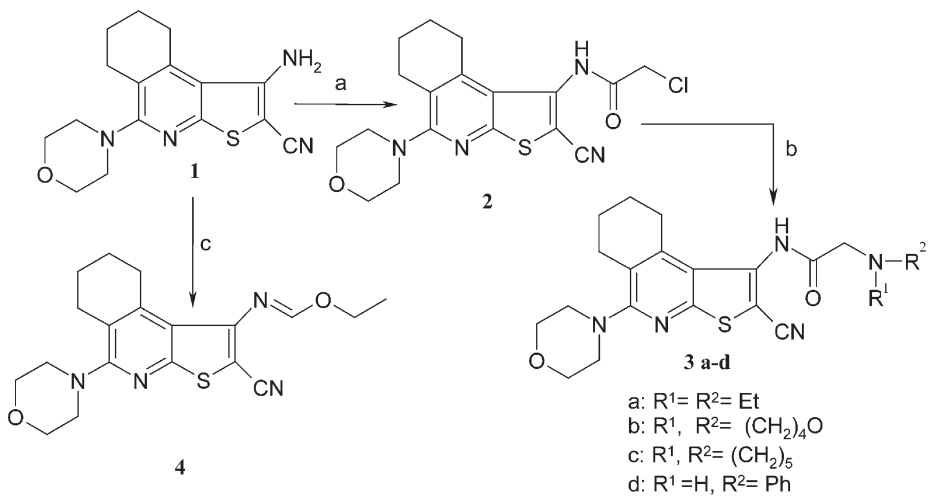
Results and discussion

1-Amino-5-morpholino-6,7,8,9-tetrahydrothieno[2,3-***c***] isoquinoline-2-carbonitrile **1** was chloroacetylated using chloroacetyl chloride in dioxan followed by treatment with sodium carbonate solution to afford the chloroacetamide **2**. The structure of the product was elucidated on the basis of its ^{1}H NMR spectrum, which revealed the disappearance of the signal at δ 6.10 for the NH_2 group and appearance of signals at δ 4.50 characteristic of CH_2 protons and at δ 10.70 for an NH proton.

The chloroacetyl derivative **2** underwent nucleophilic substitution reactions with various primary and secondary amines in refluxing ethanol to afford *N*-alkyl(aryl)aminoacetamides **3a–d**. Heating of compound **1** with a slight excess of trimethyl orthoformate in acetic anhydride gave the (ethoxymethylene) amino derivative **4**, the constitution of which was confirmed by elemental analysis and spectral data. The IR spectrum showed the disappearance of absorption bands at 3470 and 3370 cm^{-1} characteristic for the NH_2 group. The ^{1}H NMR spectrum of compound **4** in $CDCl_3$ revealed the absence of a signal at 6.10 ppm characteristic of the NH_2 group and showed a triplet at 1.50 ppm for a CH_3 group. A quartet at 4.50 ppm for a methylene group and a singlet at δ 8.10 for an azomethine proton were also present. (Scheme 1).

Stirring compound **4** with an equivalent amount of hydrazine hydrate in dioxan at room temperature produced the aminoiminopyrimidine **5**.[25] Formation of compound **5** was established using spectral data. Its IR spectrum revealed the appearance of absorption bands at 3450, 3300 and 3170 cm^{-1} for NH and NH_2 groups and the disappearance of a band characteristic of the CN group in the starting material.

Compound **5** was used as a versatile precursor to synthesise a range of other heterocyclic compounds. Thus, boiling the pyrimidinimine **5** with triethyl orthoformate and also with



Reagents and conditions: a = $ClCH_2COCl$; b = R^1R^2NH; c = $CH(OEt)_3/Ac_2O$

Scheme 1

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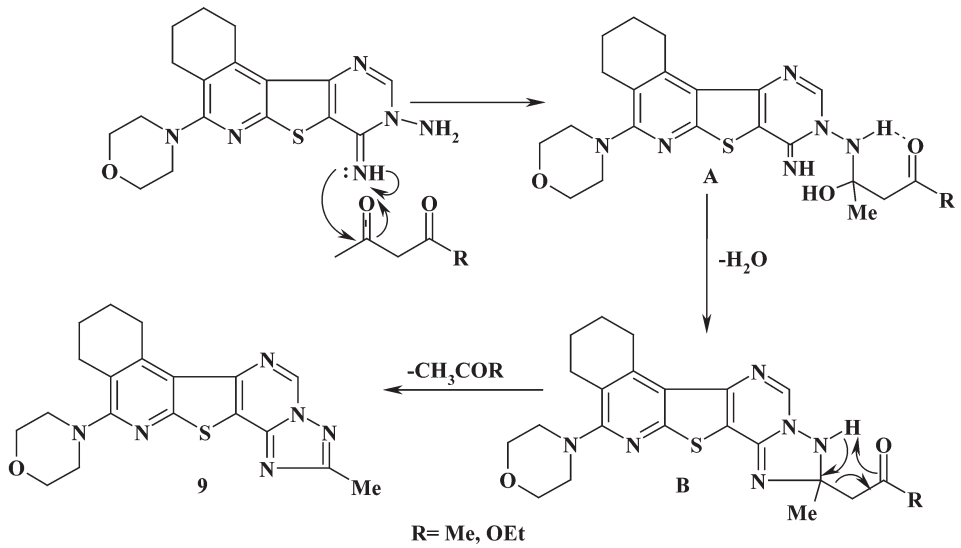
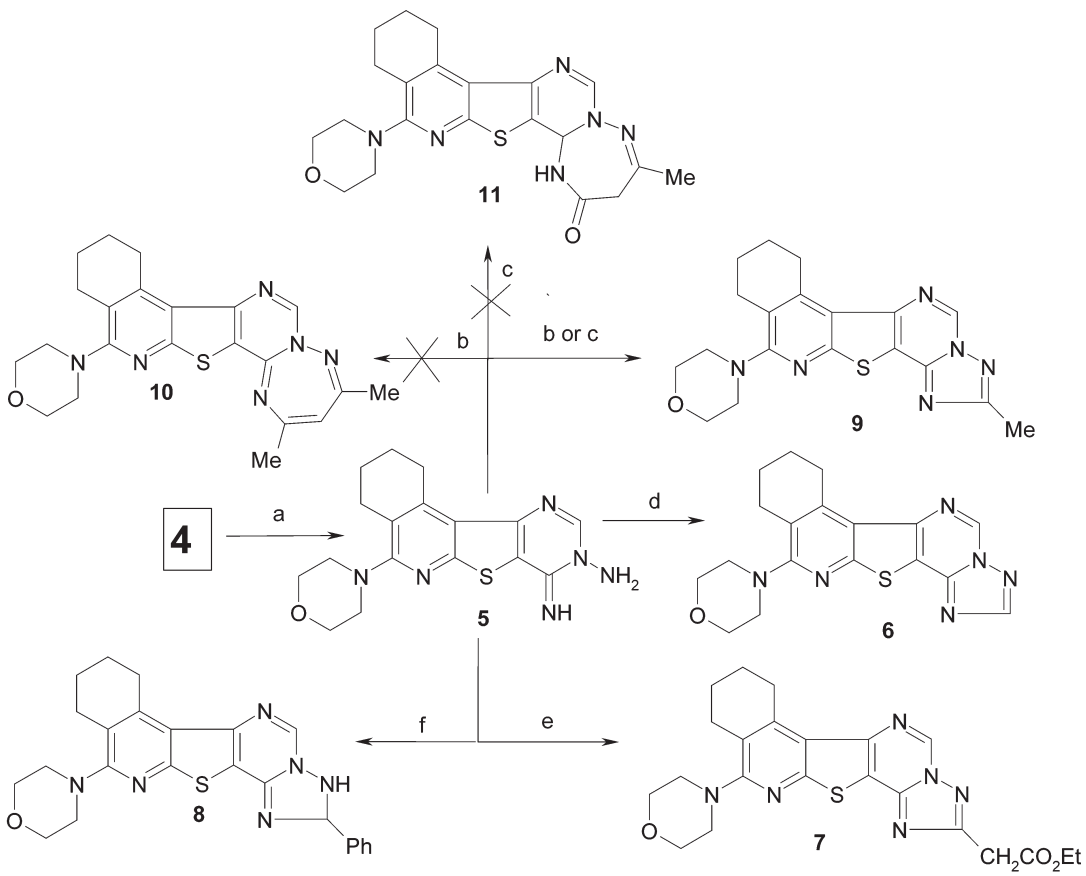


Scheme 2

diethyl malonate afforded the triazolo derivatives **6** and **7** respectively. Reaction of compound **5** with benzaldehyde in refluxing ethanol in presence of piperidine gave the hexahydrotriazolopyrimidoisoquinoline **8**. Reaction of imine **5** with acetylacetone afforded the methyltriazolo derivative **9** rather than the triazepine **10**. Compound **9** was also obtained from the reaction of **5** with ethyl acetoacetate instead of acetylacetone in the above reaction.

These condensations proceed via cyclisation of the imine with a retro aldol-type elimination of acetone, in the case of acetylacetone and elimination of ethyl acetate in the case of ethyl acetoacetate as shown in Scheme 2.

The structure of compound **9** was established by its ^{1}H NMR and mass spectra. The former showed a sharp methyl group signal at 2.85 ppm, whilst the mass spectrum showed a molecular ion peak at *m/z* 379 as the base peak (Scheme 3).



Reagent and conditions: a = $NH_2NH_2.H_2O$/dioxan; b =CH_2Ac_2; c= $AcCH_2CO_2Et$; d = $HC(OEt)_3$; e= $CH_2(CO_2Et)_2$/fusion; f= PhCHO/EtOH/piperidine

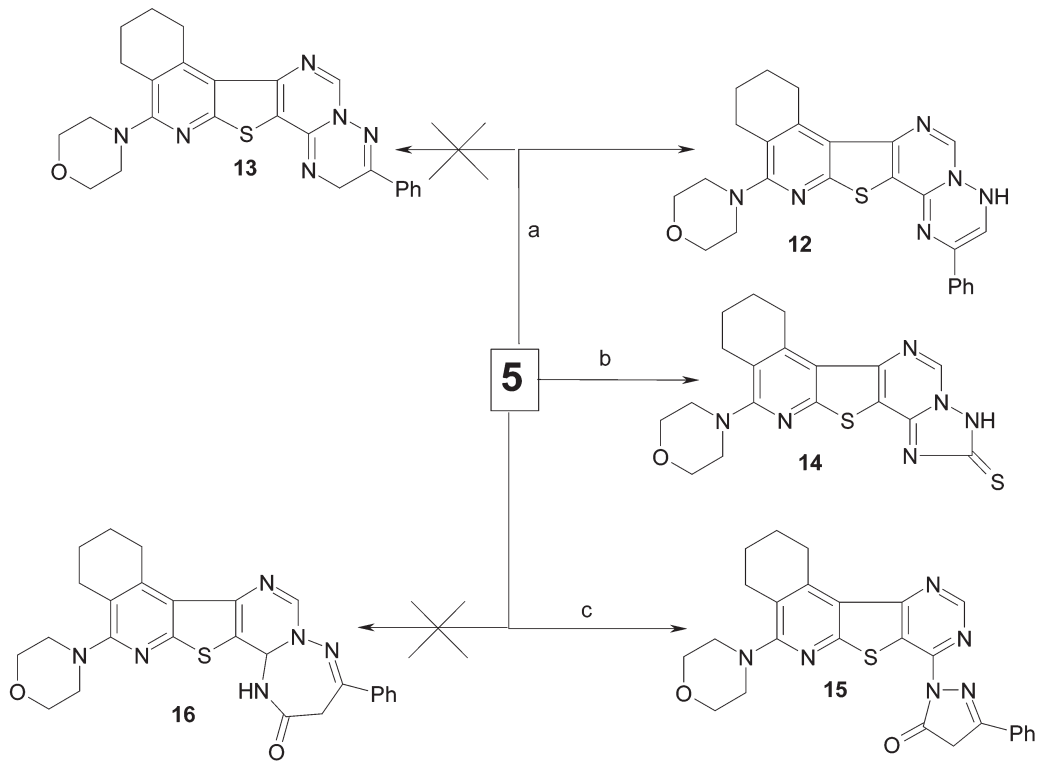
Scheme 3

Reaction of compound **5** with phenacyl bromide in refluxing ethanol and triethylamine gave the 2-phenyltriazinopyrimidothienoisoquinoline **12** rather than the 3-phenyltriazino derivative **13**. The structure of compound **12** was elucidated on the basis of IR and ^{1}H NMR spectra. The IR spectrum showed an absorption band at 3450 cm^{-1} for the NH group. Singlets at δ 4.80 characteristic for H-3 and at δ 9.80 for an NH proton were present in the ^{1}H NMR spectrum.

On the other hand, reaction of compound **5** with carbon disulfide in pyridine (steam bath) afforded the triazolopyrimidothienoisoquinolinthione **14**, whilst reaction of **5** with ethyl benzoylacetate in ethanol and piperidine gave the pyrazolone derivative **15** rather than triazepinone **16** (Scheme 4).

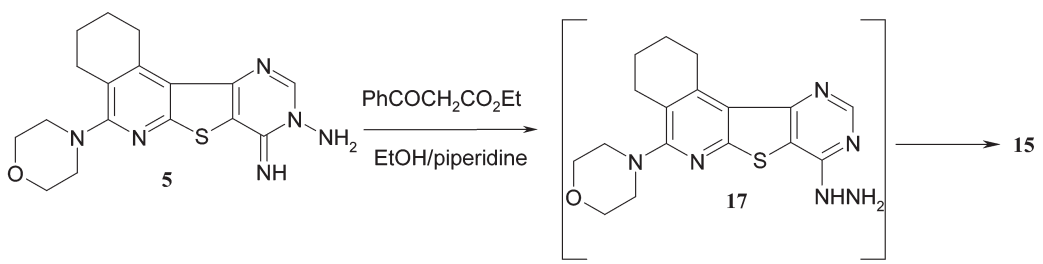
The structure of compound **15** was confirmed by an alternative route involving fusion of the hydrazinopyrimidothienoisoquinoline **17**[26] with ethyl benzoylacetate. The pyrazolone derivative **15** obtained by the two routes was identical in all aspects. This finding confirmed that the rearrangement of the imine **5** into the intermediate hydrazinopyrimidine derivative **17** (not isolated) upon reaction with ethyl benzoylacetate under neat, basic conditions occurs by a Dimroth pathway[25]. Formation of the pyrazolone **15** was deduced from elemental analysis and spectral data. Its IR spectrum revealed the disappearance of absorption bands characteristic of an $NHNH_2$ group and the appearance of an absorption band at 1690 cm^{-1} was characteristic of a carbonyl group. The mass spectrum showed a molecular ion peak at *m/z* 483 [M$^+$, 44%] (Scheme 5)**.**

When compound **17** was allowed to react with triethyl orthoformate in the presence of a catalytic amount of acetic acid, the triazolopyrimidine **18** was obtained. The cyclisation of the hydrazinopyrimidine compound to produce compound **18** was confirmed by spectral data and elemental analysis. The IR spectrum showed the disappearance of absorption bands at, 3350, 3200 and 3080 cm^{-1} characteristic of NH and NH_2 functions. The hydrazino compound **17** reacted with carbon disulfide in pyridine to afford the corresponding isoquinolinethione **19**, which was alkylated with ethyl chloroacetate, in the presence of anhydrous potassium carbonate in refluxing ethanol to give the *S*-(ethoxycarbonyl)methyl derivative **20**. The structure of the latter was elucidated on the basis of its ^{1}H NMR spectrum which showed triplet and quartet signals at δ 1.30 and 4.20 for the ethyl group and a singlet at δ 3.90 for the SCH_2 unit.



Reagents: a = $PhCOCH_2Br$/EtOH/piperidine; b=CS_2/pyridine
c = $PhCOCH_2CO_2Et$/EtOH/piperidine

Scheme 4



Scheme 5

When compound **17** was allowed to react with acetylacetone in ethanol, the dimethylpyrazolyl derivative **21** was obtained. The formation of compound **21** was established by elemental analysis and spectral data. The IR spectrum revealed the disappearance of absorption bands characteristic for an $NHNH_2$ group. Also, the formation of pyrazolyl ring was established by the presence of two signals at δ 2.30 and 2.70 characteristic for two methyl groups and a singlet at δ 5.90 for the pyrazole ring proton. Condensation of hydrazino compound **17** with benzaldehyde produced the corresponding hydrazone **22** (Scheme 6).

Annulation of fused pyrimidine rings onto the tetrahydrothieno[2,3-*c*]isoquinoline system was achieved by the reaction of the *o*-aminocarbonitrile **1** with 1,3-diaminopropane in presence of carbon disulfide to give the tetrahydropyrimido derivative **23**. The latter, when allowed to react separately with triethyl orthoformate, with benzaldehydes, and with nitrous acid yielded the pyrimido derivatives **24**, **25** and **26** respectively. Chloroacetylation of compound **23** using chloroacetyl chloride in dioxan afforded the chloroacetylamino derivative **27** which reacted with aniline to give the phenylaminoacetamide derivative **28** (Scheme 7).

Experimental

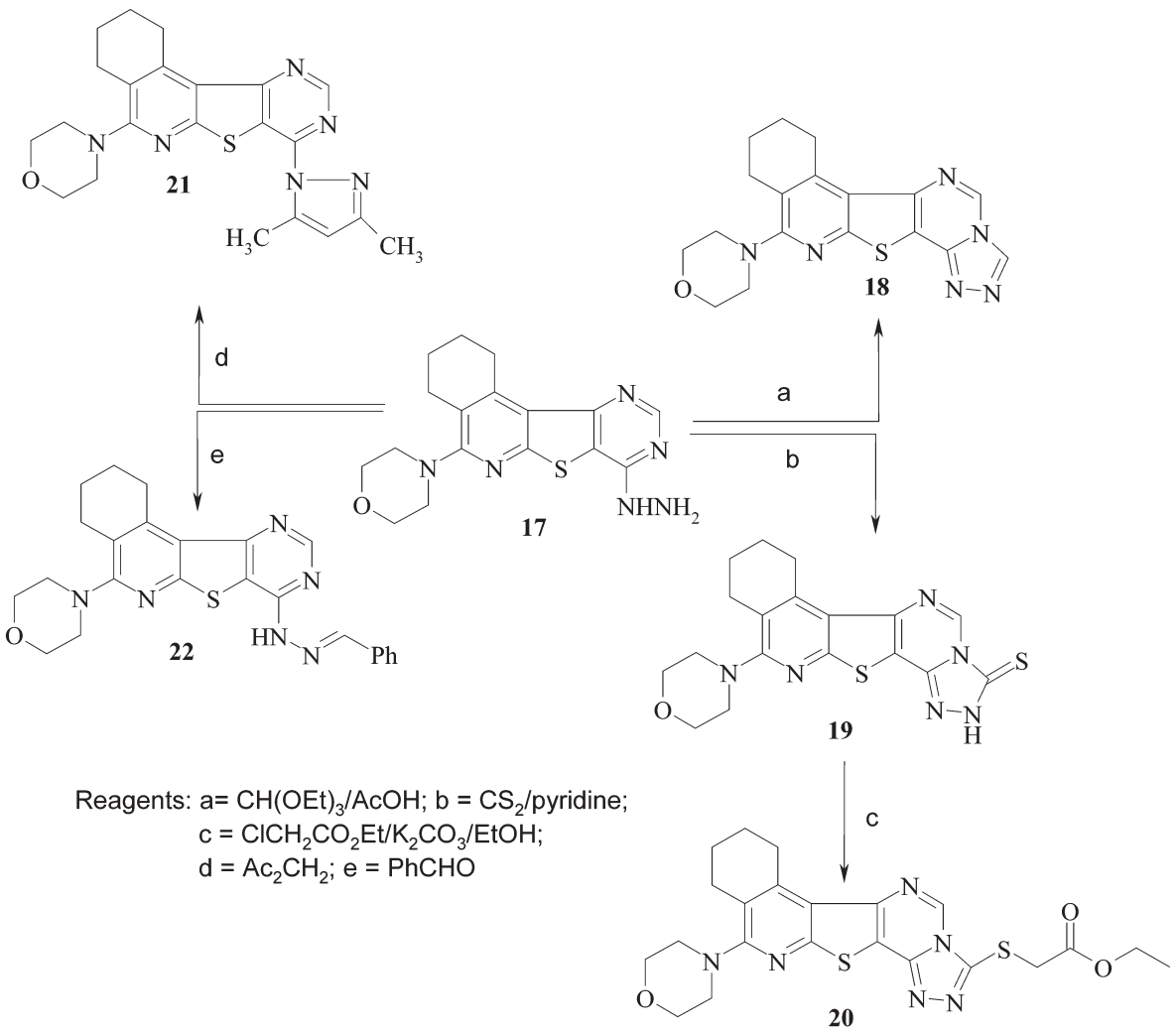
All melting points are uncorrected. IR spectra were recorded (KBr) with a Perkin-Elmer 1430 Spectrophotometer. ^{1}H NMR spectra were obtained on a Varian EM-390 MHz (390 MHz) spectrometer in $CDCl_3$ and DMSO-d_6 using Me_4Si as internal standard, and chemical shifts are expressed as ppm. Mass spectra were measured on a Jeol-JMS 600 spectrometer. Analytical data were obtained on Elementar Analyse system GmbH-VarioEL V.3 microanalyser in the central laboratory of Assiut University.

1-Amino-5-morpholino-6,7,8,9-tetrahydro-thieno[2,3-*c*]isoquinoline-2-carbonitrile **1** and 8-hydrazino-5-morpholino-1,2,3,4-tetrahydropyrimido[4′,5′:4,5]thieno- [2,3-*c*]isoquinoline **18** were prepared according to the reported procedure.[27]

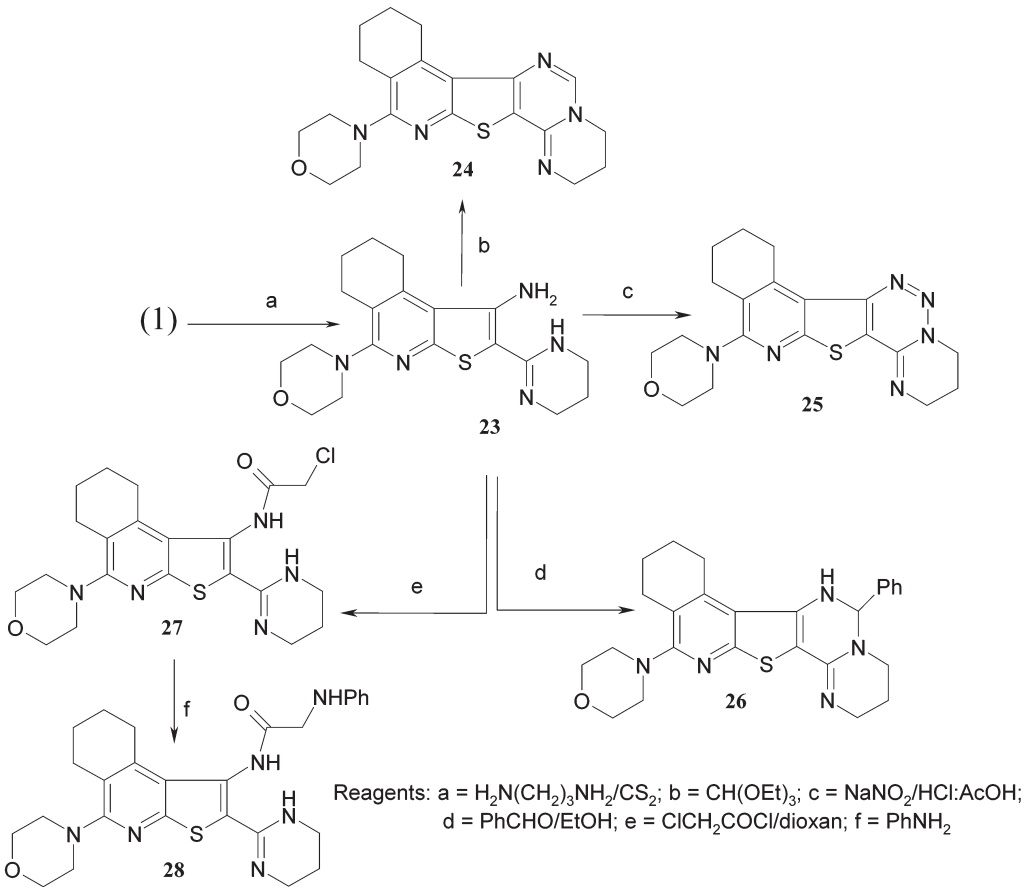
2-Chloro-N-*(2-cyano*-5-morpholino-*6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolin-1-yl)acetamide* (**2**): A mixture of compound **1** (1.60 g, 5 mmol) and of chloroacetyl chloride (0.7 mL, 6 mmol) in dioxan (30 mL) was heated on water bath for 2 h. The solid precipitate which was formed by pouring into dilute sodium carbonate solution was filtered off, dried and recrystallised from ethanol–benzene mixture giving pale brown crystals in 78% yield, m.p. 177–179 °C. Anal. Calcd for $C_{18}H_{19}ClN_4O_2S$ (390.89): C, 55.31; H, 4.90; Cl, 9.07; N, 14.33; S, 8.20. Found: C, 55.57; H, 5.00; Cl, 8.95; N, 14.50%. IR (cm^{-1}): ν =3380 (NH), 2920, 2850 (CH aliphatic), 2190 (CN), 1665 (CO amidic). ^{1}H NMR (DMSO-d_6): δ = 1.70–1.85 (m, 4H, $2CH_2$), 2.65–2.75 (m, 4H, $2CH_2$), 3.10–3.20 (m, 4H, $2CH_2$), 3.75–3.80 (m, 4H, $2CH_2$), 4.50 (s, 2H, CH_2Cl), 10.70 (s, 1H, NH).

N-*(2-Cyano*-5-morpholino-*6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolin-1-yl)-2-alkyl(aryl)aminoacetamides* (**3**): A mixture of the chloroacetamide derivative (**2**) (0.50 g, 1.3 mmol) and the corresponding amine (2 mmol) was dissolved in ethanol (20 mL) and refluxed for 3 h. The solid precipitate which was formed was filtered off, dried and recrystallised from ethanol.

N-*(2-Cyano*-5-morpholino-*6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolin-1-yl)-2-(diethylamino)acetamide* (**3a**): Obtained from the reaction of **2** with diethylamine and recrystallised from ethanol as buff crystals in 78% yield, m.p. 110–112 °C. Anal. Calcd for $C_{22}H_{29}N_5O_2S$



Scheme 6



Scheme 7

(427.57): C, 61.80; H, 6.84; N, 16.38; S, 7.50. Found: C, 61.63; H, 6.95; N, 16.17; S, 7.41%. IR (cm^{-1}): ν = 3450 (NH), 2920, 2850 (CH aliphatic), 2210 (CN), 1630 (C=N). ^{1}H NMR ($CDCl_3$): 1.10–1.30 (t, *J* = 7.5 Hz, 6H, $2CH_3$), 1.65–1.80 (m, 4H, $2CH_2$), 2.60–2.70 (m, 8H, $2CH_2$ cyclohexeno + 2 × CH_2CH_3), 3.15–3.25 (m, 6H, $2CH_2$+$COCH_2N$), 3.80–3.85 (m, 4H, $2CH_2$), 10.80 (s, 1H, NH).

N-*(2-Cyano-*5-morpholino-*6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolin-1-yl)-2-morpholin-4-yl-acetamide* (**3b**): Obtained from the reaction of **2** with morpholine and recrystallised from ethanol as white needles in 75% yield, m.p. 195–196°C. Anal. Calcd for $C_{22}H_{27}N_5O_3S$ (441.56): C, 59.84; H, 6.16; N, 15.86; S, 7.26. Found: C, 60.00; H, 6.28; N, 16.00; S, 7.00%. IR (cm^{-1}): ν = 3380 (NH), 2920, 2850 (CH aliphatic), 2190 (CN), 1640 (C=O), 1625 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.70–1.80 (m, 4H, $2CH_2$), 2.70–2.80 (m, 8H, $2CH_2$ cyclohexeno + 2 × CH_2N-morpholine), 3.15–3.25 (m, 6H, 2 × CH_2N-morpholine CH_2CO), 3.70–3.80 (m, 8H, 4 × CH_2O-morpholine), 9.40 (s, 1H, NH).

*N-(2-Cyano-*5-morpholino-*6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolin-1-yl)-2-piperidin-4-yl-acetamide* (**3c**): Obtained from the reaction of **2** with piperidine and recrystallised from ethanol as white crystals in 72% yield, m.p. 150–152 °C. Anal. Calcd for $C_{23}H_{29}N_5O_2S$ (439.58): C, 62.84; H, 6.65; N, 15.93; S, 7.29. Found: C, 61.90; H, 6.25; N, 16.64; S, 7.70%. IR (cm^{-1}): ν = 3380 (NH), 2920, 2850 (CH aliphatic), 2210 (CN), 1690 (CO amide). ^{1}H NMR ($CDCl_3$): δ = 1.70–1.95 (m, 8H, $4CH_2$), 2.60–2.70 (m, 8H, $4CH_2$), 3.10–3.20 (m, 6H, $2CH_2$N-mopholine + CH_2CO), 3.70–3.80 (m, 4H, $2CH_2$), 9.60 (s, 1H, NH).

N-*(2-Cyano-*5-morpholino-*6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolin-1-yl)-2-phenylaminoacetamide* (**3d**): Obtained from the reaction of **2** with aniline and recrystallised from ethanol as white needles in 76% yield, m.p. 214–216 °C. Anal. Calcd for: $C_{24}H_{25}N_5O_2S$ (447.56): C, 64.41; H, 5.63; N, 15.65; S, 7.16. Found: C, 64.28; H, 5.62; N, 15.50; S, 7.30%. IR (cm^{-1}): ν = 3480, 3390 (NH), 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 2190 (CN), 1650 (CO amide), 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ = 1.75–1.90 (m, 4H, $2CH_2$), 2.50–2.60 (m, 4H, $2CH_2$), 3.20–3.30 (m, 4H, $2CH_2$), 3.75–3.85 (m, 4H, $2CH_2$), 4.35 (s, 2H, $COCH_2$), 6.60 (s, 1H, NH), 7.10–7.80 (m, 5H, ArH), 9.20 (s, 1H, NHCO).

*1-Ethoxymethyleneamino-5-morpholino-6,7,8,9-tetrahydrothieno [2,3-*c*]isoquinoline-2-carbonitrile* (**4**): A mixture of the aminocarbonitrile **1** (3.14 g, 0.01 mol) and triethyl orthoformate (6 mL, 0.04 mol) was refluxed for 2 h in the presence of few drops of acetic anhydride. The solid product which formed on cooling was filtered off, dried and recrystallised from ethanol to afford white crystals in 84% yield, m.p. 139–141°C. Anal. Calcd for $C_{19}H_{22}N_4O_2S$ (370.48): C, 61.60; H, 5.99; N, 15.12; S, 8.65. Found: C, 61.75; H, 6.20; N, 15.35; S, 8.52%. IR (cm^{-1}): ν = 3100 (NH), 2950, 2870 (CH aliphatic), 2220 (CN), 1600 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.30–1.50 (t, *J* = 9.00, 3H, CH_3), 1.90 (m, 4H, $2CH_2$), 2.80 (m, 4H, $2CH_2$), 3.30 (m, 4H, $2CH_2$), 3.95 (m, 4H, $2CH_2$), 4.50 (q, *J* = 7.50 Hz, 2H, CH_2), 8.10 (s, 1H, NH). MS (M^+): *m/z* 370.

*9-Amino-8-imino-5-morpholino-1,2,3,4-tetrahydropyrimido[4',5':4,5] thieno [2,3-*c*]isoquinoline* (**5**): A solution of **4** (3.70 g, 0.01 mol) in warm dioxan was stirred at room temperature and hydrazine hydrate (0.8 mL, 0.016 mol) was added to the solution. Stirring of the mixture was continued for 2 h. The solid precipitate which formed was filtered off, dried and recrystallised from ethanol–dioxan to give white crystals in 61% yield, m.p. 218–220 °C. Anal. Calcd for $C_{17}H_{20}N_6OS$ (356.45): C, 57.28; H, 5.66; N, 23.58; S, 9.00. Found: C, 57.02; H, 5.78; N, 23.79; S, 9.23%. IR (cm^{-1}): ν = 3450, 3300, 3170 (NH+NH_2), 2920, 2820 (CH aliphatic), 1615 (C=N). ^{1}H NMR (CF_3CO_2D): δ = 1.80–1.90 (m, 4H, $2CH_2$), 3.40–3.50 (m, 4H, $2CH_2$), 3.80–3.90 (m, 4H, $2CH_2$), 8.90 (s, 1H, NH).

*11-Morpholino-7,8,9,10-tetrahydro[1,2,4]triazolo[2'',3'':1',6']pyrimido-[4',5':4,5]thieno[2,3-*c*]isoquinoline* (**6**): Compound **5** (0.70 g, 0.002 mol) and triethyl orthoformate (5 mL) were heated under reflux for 3 h. The solid product obtained from the hot mixture was filtered off and recrystallised from ethanol as white crystals in 84% yield, m.p. 250–252 °C. Anal. Calcd for $C_{18}H_{18}N_6OS$ (366.45): C, 59.00, H, 4.95; N, 22.93; S, 8.75. Found: C, 58.86; H, 5.11; N, 23.23; S, 8.58%. IR (cm^{-1}): ν = 2920, 2820 (CH aliphatic), 1615 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.75–1.90 (m, 4H, $2CH_2$), 2.70–2.80 (m, 4H, $2CH_2$), 3.20–3.30 (m, 4H, $2CH_2$), 3.80–3.95 (m, 4H, $2CH_2$), 8.50 (s, 1H, pyrimidine H-5), 9.40 (s, 1H, triazole H-2).

Ethyl {11-morpholino-7,8,9,10-tetrahydro[1,2,4]triazolo[2″,3″:1′,6′] pyrimido-[4′,5′:4,5]thieno[2,3-c]isoquinolin-2-yl}acetate (**7**): Compound **5** (0.70 g, 0.002 mol) and diethyl malonate (5 mL) were heated under reflux for 2 h. Then the reaction mixture was allowed to cool. The solid product was filtered off and recrystallised from ethanol to give brown crystals in 68% yield, m.p. 159–160°C. Anal. Calcd for $C_{22}H_{24}N_6O_3S$ (452.54): C, 58.39; H, 5.35; N, 18.57; S, 7.09. Found: C, 58.50; H, 5.18; N, 18.70; S 7.18%. IR (cm^{-1}): ν = 2920, 2850 (CH aliphatic), 1735 (CO ester), 1620 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.30–1.45 (t, *J* = 6.0Hz, 3H, CH_3 ester), 1.70–1.80 (m, 4H, $2CH_2$), 2.70–2.80 (m, 4H, $2CH_2$), 3.20–3.30 (m, 4H, $2CH_2$), 3.75–3.90 (m, 4H, $2CH_2$), 4.10 (s, 2H, CH_2CO), 4.20-4.40 (q, *J* = 6.0Hz, 2H, CH_2 ester), 9.40 (s, 1H, pyrimidine H-5). MS (M^+) *m/z*: 451.

2-Phenyl-11-morpholino-2,3,7,8,9,10-hexahydro[1,2,4]triazolo[2″, 3″:1′,6′] pyrimido[4′,5′:4,5]thieno[2,3-c]isoquinoline (**8**): Compound **5** (0.70 g, 0.002 mol), excess benzaldehyde (4 mL) and few drops of piperidine were fused for 10 minutes then absolute ethanol (10 mL) was added. The mixture was refluxed for 2 h. The solid product which was formed whilst hot was filtered off and recrystallised from dioxan to give yellow crystals in 70% yield, m.p. 260–262 °C. Anal. Calcd for $C_{24}H_{24}N_6OS$ (444.56): C, 64.84; H, 5.44; N, 18.90; S, 7.21. Found: C, 65.00; H, 5.22; N, 19.00; S, 7.43%. IR (cm^{-1}): ν = 3100 (NH), 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 1615 (C=N). ^{1}H NMR (CF_3CO_2D): δ = 1.90–2.10 (m, 4H, $2CH_2$), 2.90–3.15 (m, 4H, $2CH_2$), 3.70–3.85 (s, 4H, $2CH_2$), 4.10–4.25 (m, 4H, $2CH_2$), 4.30 (s, 1H, triazole H-2), 7.60–8.50 (m, 5H, ArH), 9.05 (s, 1H, pyrimidine H-5). MS (M^+) *m/z*: 444.

2-Methyl-11-morpholino-7,8,9,10-tetrahydro[1,2,4]triazolo[2″,3″: 1′,6′] pyrimido[4′,5′:4,5]thieno[2,3-c]isoquinoline (**9**): *Method A*: Compound **5** (0.70 g, 2 mmol) and acetylacetone (3 mL, 30 mmol) were gently refluxed for 3 h. The solid product formed after cooling was filtered off and recrystallised from ethanol to give brown crystals in 73% yield, m.p. 258–260 °C.

Method B: A mixture of **5** (0.70 g, 0.002 mol) and ethyl acetoacetate (4 mL, 30 mmol) were refluxed in ethanol (20 mL), containing a few drops of piperidine (0.3 mL), for 3 h. The solid product formed after cooling was filtered off and recrystallised from ethanol to give brown crystals in 69% yield, m.p. 258–260 °C. Anal. Calcd for $C_{19}H_{20}N_6OS$ (380.47): C, 59.98; H, 5.30; N, 22.09; S, 8.43. Found: C, 60.17; H, 5.46; N, 21.95; S, 8.54%. IR (cm^{-1}): ν = 2920, 2850 (CH aliphatic), 1620 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.85–2.00 (m, 4H, $2CH_2$), 2.70–2.85 (m, 3H, CH_3), 3.10–3.20 (m, 4H, $2CH_2$), 3.35–3.50 (m, 4H, $2CH_2$), 3.70–3.80 (m, 4H, $2CH_2$), 9.30 (s, 1H, pyrimidine H-5). MS (M^+) *m/z*: 379.

2-Phenyl-12-morpholino-4,8,9,10,11-pentahydro[1,2,4]triazino[2″, 3″:1′,6′] pyrimido[4′,5′:4,5]thieno[2,3-c]isoquinoline (**12**): The aminoimine **5** (0.70 g, 2.0 mmol), phenacyl bromide (0.40 g, 2.0 mmol) in ethanol (20 mL) and piperidine (0.3 mL) were refluxed for 3 h. The solid product which was formed whilst hot was filtered off, dried and recrystallised from ethanol to afford yellow crystals in 63% yield, m.p. 253–255 °C. Anal. Calcd for: $C_{25}H_{24}N_6OS$ (456.57) C, 65.77; H, 5.30; N, 18.41; S, 7.02. Found: C, 65.55; H, 5.56; N, 18.62; S, 7.24%. IR (cm^{-1}): ν = 3450 (NH), 3050 (CH aromatic), 2920, 2830 (CH aliphatic), 1655 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.70–1.80 (m, 4H, $2CH_2$), 2.60–2.70 (m, 4H, $2CH_2$), 3.05–3.20 (m, 4H, $2CH_2$), 3.80–3.90 (m, 4H, $2CH_2$), 4.80 (s, 1H, triazine H-3), 7.50–7.90 (m, 5H, ArH), 8.10 (s, 1H, pyrimidine H-6), 9.80 (s, 1H, NH). MS (M^+) *m/z*: 456.

11-Morpholino-7,8,9,10-tetrahydro[1,3,5]triazolo[1″,2″:1′,6′]pyrimido [4′,5′:4,5]thieno[2,3-c]isoquinolin-2(3H)-thione (**14**): A mixture of the aminoimine **5** (0.70 g, 2 mmol) and carbon disulfide (1.5 mL) in pyridine (3 mL) was refluxed for on a steam bath for 8 h. The solid precipitate which formed was filtered off and recrystallised from ethanol to afford orange needles in 66% yield, m.p. 261–263 °C. Anal. Calcd for $C_{18}H_{18}N_6OS_2$ (398.51): C, 54.256; H, 4.55; N, 21.09; S, 16.09. Found: C, 54.38; H, 4.70; N, 21.00; S, 15.90%. IR (cm^{-1}): ν = 3120 (NH), 2920, 2840 (CH aliphatic), 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ = 1.70–1.80 (m, 4H, $2CH_2$), 2.45–2.60 (m, 4H, $2CH_2$), 3.00–3.20 (m, 4H, $2CH_2$), 3.55–3.70 (m, 4H, $2CH_2$), 7.20 (s, 1H, NH), 8.50 (s, 1H, pyrimidine H-5).

8-(3-Phenyl-4,5-dihydro-5-oxopyrazol-1-yl)-1,2,3,4-tetrahydro-5-morpholino-pyrimido [4′,5′:4,5]thieno[2,3-c]isoquinoline (**15**): *Method A:* Compound **5** (0.70 g, 2 mmol) and ethyl benzoylacetate (1.0 mL, 5.2 mmol) were gently refluxed for 3 h then absolute ethanol (10 mL) and few drops of piperidine were added and refluxing was continued for additional 1 h. The solid product which was formed was filtered off, dried and recrystallised from ethanol to afford pale yellow crystals in 74% yield, m.p. 262–264 °C.

Method B: A mixture of **17** (0.7 g, 2 mmol) and ethyl benzoylacetate (0.38 mL, 2 mmol) in ethanol (20 mL) and piperidine (0.25 mL) were refluxed for 6 h. The solid precipitate which formed was filtered off, dried and recrystallised from dioxan to give pale yellow crystals in 68% yield, m.p. 262–264 °C. Anal. Calcd for $C_{26}H_{24}N_6O_2S$ (484.58): C, 64.44; H, 4.99; N, 17.34; S, 6.62. Found: C, 64.66; H, 5.21; N, 17.52; S, 6.85%. IR (cm^{-1}): ν = 3030 (CH aromatic), 2910, 2830 (CH aliphatic), 1630 (unsaturated CO), 1600 (C=N). ^{1}H NMR (CF_3CO_2D): δ = 1.70–1.80 (m, 4H, $2CH_2$), 2.65–2.80 (m, 4H, $2CH_2$), 3.55–3.70 (m, 4H, $2CH_2$), 4.00–4.20 (m, 4H, $2CH_2$), 5.75 (s, 2H, pyrazole 2H-4), 7.30–7.70 (m, 5H, ArH), 8.95 (s, 1H, pyrimidine H-10). MS (M^+): *m/z* 483.

11-Morpholino-7,8,9,10-tetrahydro[1,2,4]triazolo[3″,4″:6′,1′]pyrimido[4′,5′:-4,5]thieno[2,3-c]isoquinoline (**18**): A mixture of hydrazino compound **17** (1.00 g, 2.8 mmol) and triethyl orthoformate (3 mL) containing a few drops of acetic acid were refluxed for 1 h. A white precipitate which was formed was filtered off, dried and recrystallised from acetic acid to give pale yellow crystals in 85% yield; m.p. 291–293 °C. Anal. Calcd for $C_{18}H_{18}N_6OS$ (366.45): C, 59.00; H, 4.95; N, 22.93; S, 8.75. Found: C, 59.18; H, 5.00; N, 23.02; S, 8.66%. IR (cm^{-1}): ν = 2930, 2850 (CH aliphatic), 1660 (C=N). ^{1}H NMR (CF_3CO_2D): δ = 1.80–1.95 (m, 4H, $2CH_2$), 2.75–2.90 (m, 4H, $2CH_2$), 3.80–3.90 (m, 4H, $2CH_2$), 4.00–4.20 (m, 4H, $2CH_2$), 9.70 (s, 1H, triazole H-3), 9.80 (s, 1H, pyrimidine H-5).

11-Morpholino-7,8,9,10-tetrahydro[1,2,4]triazolo[3″,4″:6′,1′]pyrimido-[4′,5′:4,5]thieno[2,3-c]isoquinolin-3(2H)-thione (**19**): A mixture of the hydrazino compound **17** (0.50 g, 1.4 mmol) and carbon disulfide (1 mL) in pyridine (2 mL) was refluxed for on a steam bath for 8 h. The solid precipitate which formed was recrystallised from ethanol to afford green needles in 66% yield, m.p. >360 °C. Anal. Calcd for $C_{18}H_{18}N_6OS_2$ (398.51): C, 54.25; H, 4.55; N, 21.09; S, 16.09. Found: C, 54.05; H, 4.63; N, 21.00; S, 16.27%. IR (cm^{-1}): ν = 3400 (NH), 2950, 2870 (CH aliphatic), 1660 (C=N). ^{1}H NMR (CF_3CO_2D): δ = 2.00–2.20 (m, 4H, $2CH_2$), 2.80–2.95 (m, 4H, $2CH_2$), 3.70–3.80 (m, 4H, $2CH_2$), 4.15–4.30 (m, 4H, $2CH_2$), 9.20 (s, 1H, pyrimidine H-5).

Ethyl {11-morpholino-7,8,9,10-tetrahydro[1,2,4]triazolo[3″,4″:6′,1′] pyrimido-[4′,5′:4,5]thieno[2,3-c]isoquinolin-3-ylsulfanyl}acetate (**20**): A mixture of compound **19** (0.40 g, 1 mmol), ethyl chloroacetate (0.13 mL, 1 mmol) and anhydrous potassium carbonate (0.50 g, 3.6 mmol) in ethanol (20 mL) were refluxed for 2 h. The solid precipitate which formed was recrystallised from ethanol to give white crystals in 74% yield, m.p. 222–224 °C. Anal. Calcd for $C_{22}H_{24}N_6O_3S_2$ (484.60): C, 54.53; H, 4.99; N, 17.34; S, 13.23. Found: C, 54.68; H, 5.14; N, 17.16; S, 13.50%. IR (cm^{-1}): ν = 2920, 2850 (CH aliphatic), 1720 (CO ester), 1640 (C=N). ^{1}H- NMR ($CDCl_3$): δ = 1.20–1.40 (t, *J* = 6.6Hz, 3H, CH_3), 1.70–1.80 (m, 4H, $2CH_2$), 2.30–2.45 (m, 4H, $2CH_2$), 2.70–2.85 (m, 4H, $2CH_2$), 3.10–3.20 (m, 4H, $2CH_2$), 3.90 (s, 2H, CH_2S), 4.00–4.20 (q, *J* = 6.0 Hz, 2H, CH_2), 9.25 (s, 1H, pyrimidine H-5).

8-(3,5-Dimethylpyrazol-1-yl)-5-morpholino-1,2,3,4-tetrahydropyrimido[4′,5′:-4,5]thieno[2,3-c]isoquinoline (**21**): Compound **17** (0.71 g, 2 mmol) and acetylacetone (0.2 mL, 2 mmol) were refluxed in ethanol (20 mL) for 3 h. The solid precipitate which was formed was recrystallised from ethanol to give green crystals in 73% yield, m.p. 232–234 °C. Anal. Calcd for $C_{22}H_{24}N_6OS$ (420.54): C, 62.83; H, 5.75; N, 19.98; S, 7.62. Found: C, 63.00; H, 5.67; N, 20.05; S, 7.86%. IR (cm^{-1}): ν = 2950, 2850 (CH aliphatic), 1620 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.70–1.80 (m, 4H, $2CH_2$), 2.10–2.30 (m, 4H, $2CH_2$), 2.50, 2.70 (2s, 6H, $2CH_3$), 3.10–3.30 (m, 4H, $2CH_2$), 3.70–3.80 (m, 4H, $2CH_2$), 5.90 (s, 1H, pyrazole H-4), 8.80 (s, 1H, pyrimidine H-10).

1-Benzylidene-2-(5-morpholino-1,2,3,4-tetrahydropyrimido[4′,5′: 4,5]thieno-[2,3-c]isoquinolin-8-yl)hydrazone (**22**): Hydrazino compound **17** (0.70 g, 2 mmol) and benzaldehyde (1.0 mL, 0.01 mol) in ethanol (20 mL) were refluxed for 3 h. The solid product which formed was recrystallised from dioxan as yellow crystals in 78% yield. m.p. 297–300°C. Anal. Calcd for: $C_{24}H_{24}N_6OS$ (444.56): C, 64.84; H, 5.44; N, 18.90; S, 7.21. Found: C, 65.00; H, 5.24; N, 19.05; S, 7.00%. IR (cm^{-1}): ν = 3190 (NH), 3040 (CH aromatic), 2920, 2850 (CH aliphatic). ^{1}H NMR (CF_3CO_2D): δ = 2.00–2.15 (m, 4H, $2CH_2$), 2.70–2.80 (m, 4H, $2CH_2$), 3.70–3.90 (m, 4H, $2CH_2$), 4.10–4.30 (m,

4H, $2CH_2$), 7.60–7.85 (m, 5H, ArH), 8.50 (s, 1H, NH), 8.90 (s, 1H, pyrimidine H-10).

1-Amino-5-morpholino-2-(1,4,5,6-tetrahydropyrimidin-2-yl)-6,7,8,9-tetra-hydrothieno[2,3-c]isoquinoline (**23**): A mixture of compound **1** (3.14 g, 0.01 mol), 1,3-diaminopropane (5 mL, .067 mol) and carbon disulfide (1 ml) was heated on water bath for 4 h. After cooling, the mixture was triturated with ethanol and the product obtained was filtered off and recrystallised from ethanol–benzene mixture to give brilliant yellow crystals in 81% yield, m.p. 218–220 °C. Anal. Calcd for $C_{19}H_{25}N_5OS$ (371.51): C, 61.43; H, 6.78; N, 18.85; S, 8.63. Found: C, 61.28; H, 7.00; N, 19.05; S, 8.57%. IR (cm^{-1}): ν = 3466, 3392, 3180 (NH,NH_2), 2937, 2853 (CH aliphatic), 1590 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.65–1.85 (m, 6H, $2CH_2$ cyclohexeno + CH_2 tetrahydropyrimidine), 2.60–2.70 (m, 2H, CH_2 tetrahydropyrimidine), 3.15–3.30 (m, 6H, $2CH_2$ cyclohexeno + CH_2 tetrahydropyrimidine), 3.50–3.55 (m, 4H, 2 × CH_2N-morpholine), 3.75–3.85 (m, 4H, 2 × CH_2O-morpholine), 5.40 (s, 2H, NH_2), 8.50 (s, 1H, NH). MS (M^+-1): *m/z* 370.

12-Morpholino-2,3,4,5,8,9,10,11-octahydropyrimido[1",2":1',6'] pyrimido-[4',5':4,5] thieno[2,3-c]isoquinoline (**24**): Compound **23** (0.37 g, 0.001 mol) and triethyl orthoformate (5 mL) were refluxed for 3 h. The solid precipitate which was formed on cooling was collected and recrystallised from ethanol to give green crystals in 79% yield, m.p. >300°C. Anal. Calcd for $C_{20}H_{23}N_5OS$ (381.50): C, 62.97; H, 6.08; N, 18.36; S, 8.40. Found: C, 63.18; H, 5.93; N, 18.47; S, 8.55%. IR (cm^{-1}): ν = 2920, 2850 (CH aliphatic), 1640 (C=N). ^{1}H- NMR ($CDCl_3$): δ =1.60–1.80 (m, 6H, $2CH_2$ cyclohexeno + CH_2 tetrahydro pyrimidine), 2.65–2.70 (m, 2H, CH_2 tetrahydropyrimidine), 3.00–3.20 (m, 6H, $2CH_2$ cyclohexeno + CH_2 tetrahydropyrimidine), 3.65–3.85 (m, 4H, 2 × CH_2N-morpholine), 4.10–4.25 (m, 4H, 2 × CH_2O-morpholine), 8.60 (s, 1H, H-6). MS (M^+-1): *m/z* 380

12-Morpholino-2,3,4,5,8,9,10,11-octahydropyrimido[1",2":1',6'] [1,2,3]triazino [4',5':4,5]thieno[2,3-c]isoquinoline (**25**): To ice-cooled solution of amino compound **23** (0.74 g, 2 mmol) in an acetic acid (10 mL) and hydrochloric acid (2 mL) mixture, a solution of sodium nitrite (0.31 g , 4 mmol in H_2O, 5 mL) was added during 5 minutes. After the addition, the ice bath was removed and stirring was continued for 5 h. The mixture was diluted with water and the solid product obtained was collected and recrystallised from ethanol to give yellow needles in 38% yield, m.p. 170–172 °C. Anal. Calcd for $C_{19}H_{22}N_6OS$ (382.49): C, 59.66; H, 5.80; N, 21.97; S, 8.38. Found: C, 59.48; H, 6.00; N, 22.23; S, 8.50%. IR (cm^{-1}): ν = 2920, 2850 (CH aliphatic), 1635 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.65–1.80 (m, 6H, $2CH_2$ cyclohexeno + CH_2 tetrahydropyrimidine), 2.70–2.80 (m, 2H, CH_2 tetra hydropyrimidine), 3.15–3.30 (m, 4H, $2CH_2$ cyclohexeno +CH_2 tetrahydropyrimidine), 3.80–3.90 (m, 4H, 2 × CH_2N–morpholine), 4.40–4.50 (m, 4H, 2 × CH_2O-morpholine).

12-Morpholin-4-yl-6-phenyl-2,3,4,5,6,7,8,9,10,11-decahydropyrimido[1",2":1',6']- pyrimido[4',5': 4,5]thieno[2,3-c]isoquinoline (**26**): Amino derivative **23** (0.74 g, 2 mmol) and excess benzaldehyde (1.10 mL, 10 mmol) were gently refluxed for 30 minutes then absolute ethanol (20 mL) was added and reflux was continued for additional 2 h. The solid product which was formed after cooling was collected and recrystallised from ethanol as yellow crystals in 83% yield, m.p. >300 °C. Anal. Calcd for $C_{26}H_{29}N_5OS$ (461.63): C, 67.65; H, 6.77; N, 15.17; S, 6.95. Found: C, 67.50; H, 6.56; N, 15.00; S, 7.18%. IR (cm^{-1}): ν =. 3450 (NH), 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 1660 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.20–1.35 (m, 2H, CH_2 tetrahydropyrimidine), 1.65–1.75 (m, 4H, $2CH_2$ cyclohexeno), 2.55–2.70 (m, 6H, $2CH_2$ cyclohexeno + CH_2 tetrahydropyrimidine), 3.10–3.20 (m, 6H, $2CH_2$N–morpholine + CH_2 tetrahydropyrimidine), 3.75–3.80 (m, 4H, 2 × CH_2O–morpholine), 5.50 (s, 1H, H-6), 7.20–7.80 (m, 5H, ArH), 10.1 (s, 1H, NH).

2-Chloro-N-*[2-(5-morpholino-1,4,5,6-tetrahydropyrimidin-2-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-1-yl]acetamide* (**27**): A mixture of compound **23** (0.74 g, 2 mmol) and chloroacetyl chloride (0.4 mL, 3 mmol) in dioxan (20 mL) was heated on water bath for 1 h, then poured into dilute sodium carbonate solution. The solid precipitate was filtered off and recrystallised from ethanol to give yellow crystals in 64% yield, m.p. 258–260 °C. Anal. Calcd for $C_{21}H_{26}ClN_5O_2S$ (447.99): C, 56.30; H, 5.85; Cl, 7.91; N, 15.63; S, 7.16. Found: C, 56.52; H, 6.10; Cl, 8.14; N, 15.52; S, 7.30%. IR (cm^{-1}): ν = 3420, 3350 (2NH), 2920, 2850 (CH aliphatic), 1635 (CO amide), 1600 (C=N). ^{1}H NMR ($CDCl_3$): δ = 1.70–1.85 (m, 6H, $2CH_2$ cyclohexeno +CH_2 tetrahydropyrimidine), 2.50–2.60 (m, 2H, CH_2 tetrahydropyrimidine), 3.20-3.35 (m, 6H, $2\underline{CH_2}$ cyclohexeno + $\underline{CH_2}$ pyrimidine), 3.65–3.75 (m, 4H, 2 × CH_2N-morpholine), 3.85–3.95 (m, 4H, 2 × CH_2O-morpholine), 5.10 (s, 2H, CH_2Cl), 9.9 (s, 1H, NH).

2-(Phenylamino)-N-*[2-(5-morpholino-1,4,5,6-tetrahydropyrimidin-2-yl)thieno[2,3-c]isoquinolin-1-yl]acetamide* (**28**): Compound **27** (0.90 g, 2 mmol) and excess of aniline (1 mL, 10 mmol) was gently refluxed for 15 minutes, then absolute ethanol (20 mL) was added. The solid product was filtered off, dried and recrystallised from dioxan to give white crystals in 52% yield, m.p. 260–262 °C. Anal. Calcd for $C_{27}H_{32}N_6O_2S$ (504.66): C, 64.26; H, 6.39; N, 16.65; S, 6.35. Found: C, 64.07; H, 6.55; N, 16.48; S, 6.16%. IR (cm^{-1}): ν = 3400 (NH), 3030 (CH aromatic), 2920, 2850 (CH aliphatic), 1635 (CO amide). ^{1}H NMR (DMSO-d_6): δ = 1.3–1.50 (m, 2H, CH_2 tetrahydropyrimidine), 1.60–1.70 (m, 4H, $2CH_2$ cyclohexeno), 2.30–2.50 (m, 6H, $2CH_2$ cyclohexeno + CH_2 tetrahydropyrimidine), 3.00–3.25 (m, 6H, 2 × CH_2N–morpholine + CH_2 tetrahydropyrimidine), 3.75–3.90 (m, 4H, 2 × CH_2O–morpholine), 4.60 (s, 2H, $COCH_2$), 6.70–7.20 (m, 5H, ArH), 7.40 (s, 1H, NH-Ph), 11.20 (s, 1H, NHCO).

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