Synthesis and reactions of novel thienotetrahydroisoquinoline compounds

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Síntesis y reacciones de nuevos compuestos de tienotetrahidroisoquinolina

Síntesi i reaccions de nous derivats de tientetrahidroisoquinolina

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RESUMEN

La cloroacetilación de 1-Aminocarboxamida 1 proporcionó la cloroacetilamina 2 la cual experimentó el cierre del anillo al ser sometida a reflujo con anhídrido acético para proporcionar el derivado clorometilpirimido 3. Este último compuesto experimenta reacciones de sustitución nucleofílica con varias aminas primarias y secundarias que, a través de la reacción de Mannich proporcionaron las imidazopirimidotienoisoquinolinas 5a-c. El compuesto 1 reacciona con anhídrido ftálico en ácido acético y DMF para proporcionar phthalimido- e isoindolopymimidotienotetrahidroisoquinolinas 6, 7 respectivamente.
La reacción con dietilmalonato proporcionó el pirimidocarboxylato 8 que reacciona con hidrato de hidrazina para dar la carbohidrazida 9, la cual reacciona con trietilorthoformato en la síntesis de triazepinopirimido 10. La reacción de 1 con sulfuro de carbono en piridina proporcionó la pirimidintiona 13 que después de doble reacción de Mannich proporciona el nuevo derivado tiadiazinopirimido 14. La reacción de la tetrahidroisoquinolintiona 15 con 2-chlorometilbenzimidazole y posterior ciclación de Thorpe-Zeigler proporcionó el aminobenzoimidazolilo 18 que demostró su versatilidad como material de partida para la síntesis de los nuevos derivados heterocíclicos 19-22.

Palabras clave: Imidazol, Triazepina, Tiadiazina, Pirimidina, síntesis, reacciones

SUMMARY

Chloroacetylation of 1-Aminocarboxamide 1 afforded the chloroacetylamino 2 which underwent ring closure upon reflux with acetic anhydride to afford the chloromethylpyrimido 3. The latter compounds underwent nucleophilic substitution reactions with various primary and secondary amines which underwent Mannich reaction to give the imidazopyrimidothienoisoquinolines 5a-c. Compound 1 react with phthalic anhydride in acetic acid and DMF to afford phthalimido and isoindolopyrimido thienotetrahydroisoquinoline 6, 7 respectively.
Reaction with diethylmalonate afforded the pyrimidocarboxylate 8 which react with hydrazine hydrate to give the carbohydrazide 9 which react with triethyl orthoformate for synthesis of triazepinopyrimido 10. Reaction of 1 with carbon disulfide in pyridine afforded the pyrimidinethione 13 which underwent double Mannich reaction to give the novel thiadiazinopyrimido compound 14. Reaction of tetrahydroisoquinoline thione 15 with 2-chloromethylbenzimidazole followed by Thorpe-Zeigler cyclization to afford the aminobenzoimidazolyl 18 which proved its versatility as starting material for synthesis of novel heterocyclic compounds 19-22.

Keywords: Imidazole, Triazepine, Thiadiazine, Pyrimidine, synthesis, reactions

RESUM

La cloracetilació de la 1-Aminocarboxamida 1 proporciona la cloroacetilamina 2 la qual experimenta el tancament de l'anell al ser sotmesa a reflux amb anhídrid acètic per proporcionar el derivat clorometilpirimido 3. Aquest últim derivat experimenta reaccions de substitució nucleofílica amb varies amines primàries i secundàries que, mitjançant la reacció de Mannich proporcionen les imidazopirimidotienoisoquinolines 5a-c. El producte 1 reacciona amb anhídrid ftàlic en àcid acètic i DMF per proporcionar ftalimido- i isoindolopimimido-tien-tetrahidroisoquinolines 6, 7 respectivament.
La reacció amb dietilmalonat proporcionà el pirimidocarboxylat 8 que reacciona amb hidrat de hidrazina per donar la carbohidrazida 9, la qual reacciona amb trietilortoformat en la síntesi de triazepinopirimido 10. La reacció d'1 amb sulfur de carboni en piridina proporciona la pirimidintiona 13 que després de doble reacció de Mannich proporciona el nou derivat tiadiazinopirimido 14. La reacció de la tetrahidroisoquinolintiona 15 amb 2-clorometilbenzimidazol i subseqüent ciclació de Thorpe-Zeigler proporciona el aminobenzoimidazolil derivat 18 cosa que demostrà la seva versatilitat com material de partida per a la síntesi dels nous derivats heterocíclics 19-22.

Paraules clau: Imidazol, Triazepina, Tiadiazina, Pirimidina, síntesi, reaccions

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INTRODUCTION

The tetrahydroisoquinoline family of alkaloids includes potent cytotoxic agents that display a range of biological properties such as antitumor, antimicrobial, anti-inflammatory and anti-leukemic activities [1,2].

Tetrahydropyrimidothienoisoquinolines and tetrahydropyrimidothienoquinolines are useful compounds as anti-anaphylactics, anti-inflammatories, and bacteriophage inhibitors [3]. Thienoquinolines are reported to exhibit a broad spectrum of biological effects. Some of them are useful as memory enhancers [4], antiallergics [5], anti-inflammatories, immuno regulators, analgesics and antipyritics [6]. Others are known to possess a good antibacterial [7] and antianaphylactic activities [8].

Also, Thienopyrimidines have long been the subject of chemical and biological research. The interest in these compounds is related to their broad range of biological activity, which is displayed by representatives of all the possible structural combinations of the thiophene and pyrimidine systems. Some thienopyrimidines display analgesic [9], antipyretic [10,11], anti-inflammatory [12-15], and anti-allergenic effects [16-18]. These compounds have been studied as anti-neoplastic agents [19] and for lowering the cholesterol level in the cardiovascular system [20,21].

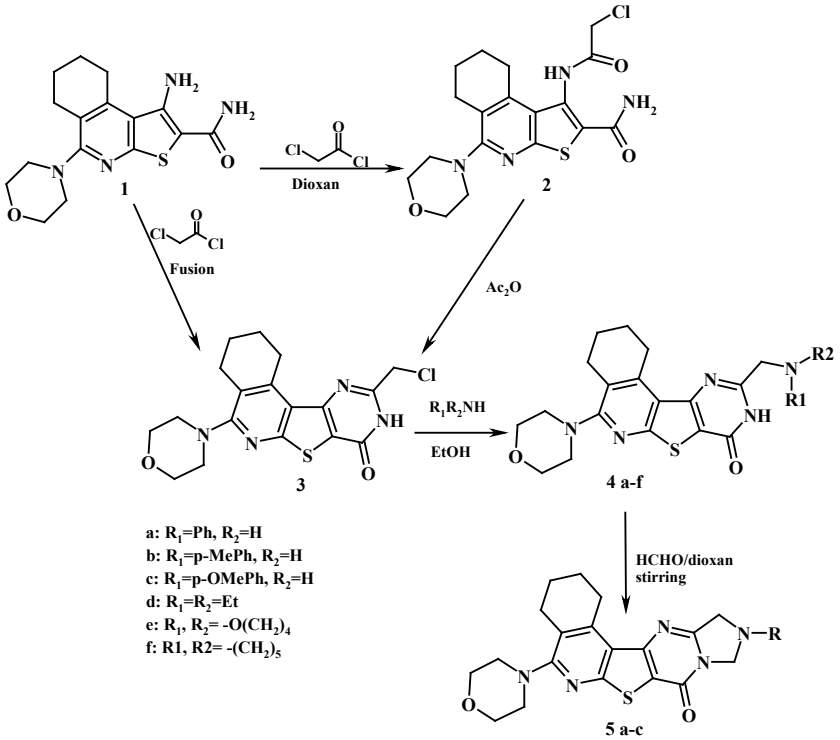
These findings have led us to continue our work on thienopyrimidine derivatives [22]. In continuation of our work, we reported new methods for preparation of thienotetrahydroisoquinolines and incorporating many heterocyclic rings fused to this moiety which were proved to have significant antibacterial and antifungal activities [23-26].

RESULTS AND DISCUSSION:

Reaction of aminocarboxamide **1** with chloro acetylchloride in dioxan followed by treating with sodium carbonate solution afforded the chloroacetylamino derivative **2,** which underwent ring closure using acetic anhydride to afford the chloromethyl compound **3.** The latter can be obtained by heating compound **1** with excess chloro acetylchloride on water bath followed by treatment with sodium carbonate solution. The structure of the produced compound **3** was elucidated on the basis of ^{1}H NMR spectra which revealed the disappearance of signals at δ 6.80 ppm characteristic for NH_2 group and appearance of signals at δ 4.60 ppm characteristic for CH_2 and at 10.70 ppm for NH and confirmed by mass spectrum (m/z) 390.19 (M^+) which in agreement with the postulated structure. Chloroacetyl derivative **3** underwent nucleophilic substitution reactions with various primary and secondary amines in refluxed ethanol to afford 10-arylaminomethyl derivatives **4a-f.** Treatment of compounds **4 a-c** with formaldehyde under *Mannish* conditions afforded imidazopyrimido derivatives **5 a-c (**Scheme 1).

SCHEME 1

Synthesis of the imidazopyrimidothienotetrahydroisoquinoline derivatives

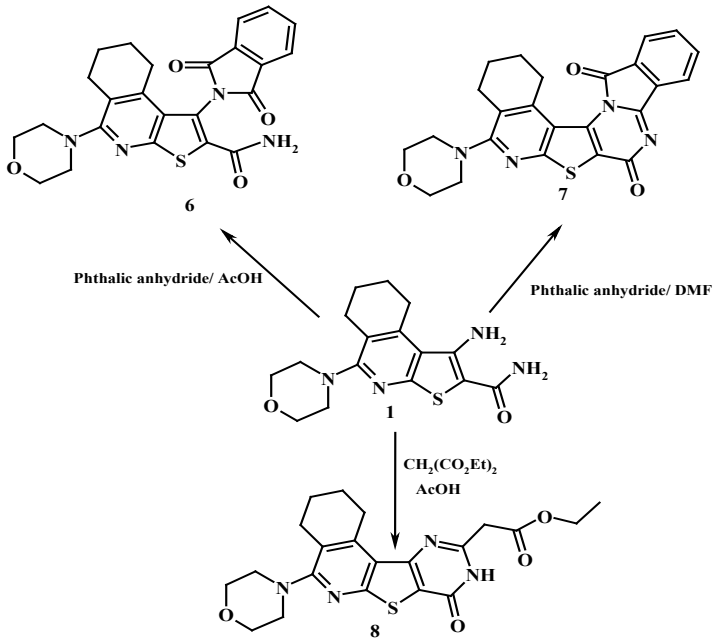


When compound **1** was allowed to react with phthalic anhydride in boiling acetic acid. The reaction stopped at the stage of formation of 3-phthalimido derivative **6,** whereas in boiling DMF a deeper condensation occurs to give a derivative of a new heterocyclic system namely 5-morpholin-4-yl-1,2,3,4-tetrahydro-14-oxoisoindolo [1",2":2',3']pyrimido[4',5':4,5]thieno[2,3-c]isoquinolin-8-one **(7)**. Reaction of compound **1** with diethyl malonate in acetic acid afforded Schiff's base followed by elimination of ethanol to give the S-ethoxycarbonylmethyl derivative **8** (Scheme 2**).**

Compound **8** reacts with hydrazine hydrate to give the corresponding carbohydrazide derivative **9** which was used as versatile starting material for the synthesis of other heterocyclic compounds. Thus, reaction of **9** with triethyl orthoformate in presence of acetic acid yielded the triazepino derivative **10**. While the reaction with acetyl acetone in ethanol gives dimethylpyrazolo derivative **11**. Condensation of compound **9** with aromatic aldehydes gives the corresponding Schiff's base **12** (Scheme 3)**.**

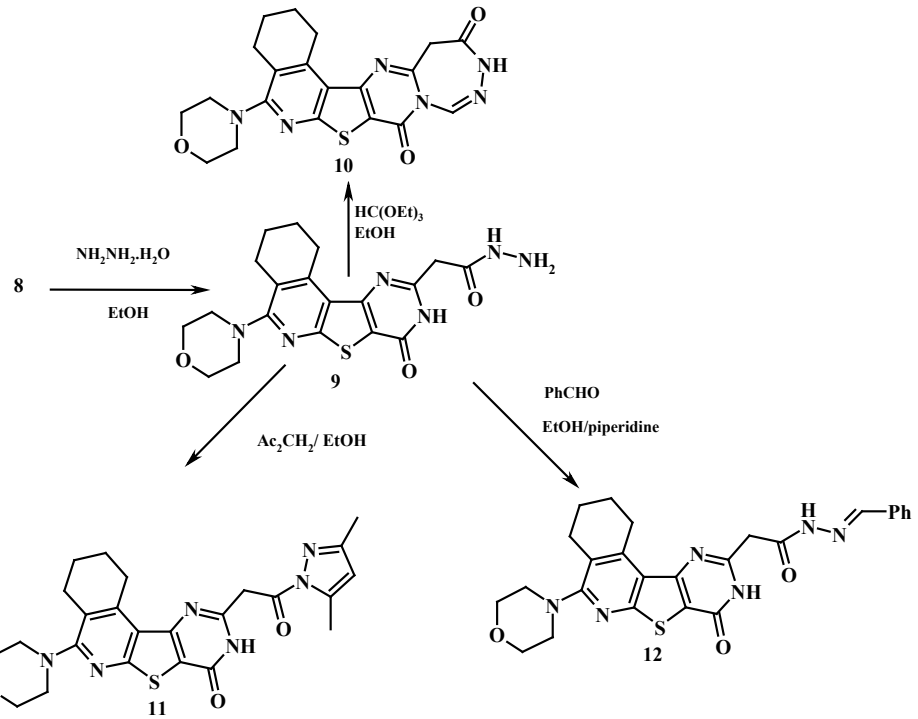
SCHEME 2

Reaction of aminocarboxamide with phthalic anhydride and diethyl malonate



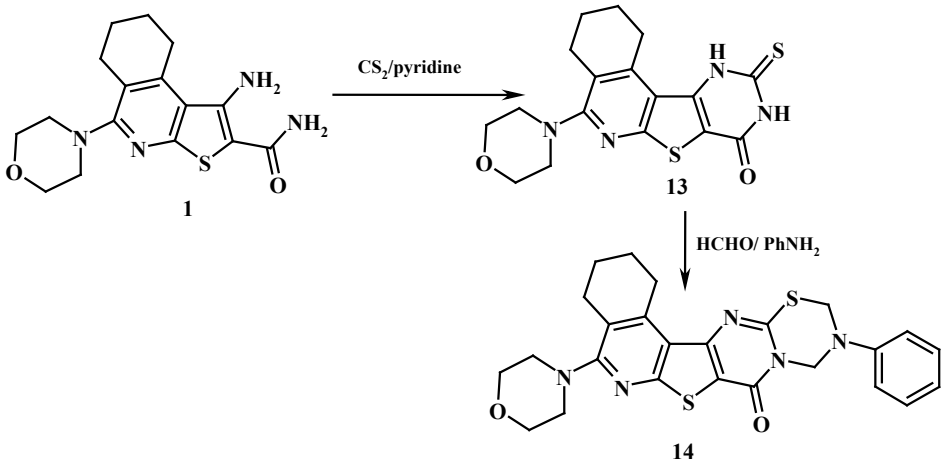
SCHEME 3

Codensation reactions of tetrahydropyrimidothienoisoquinolinecarbohydrazide



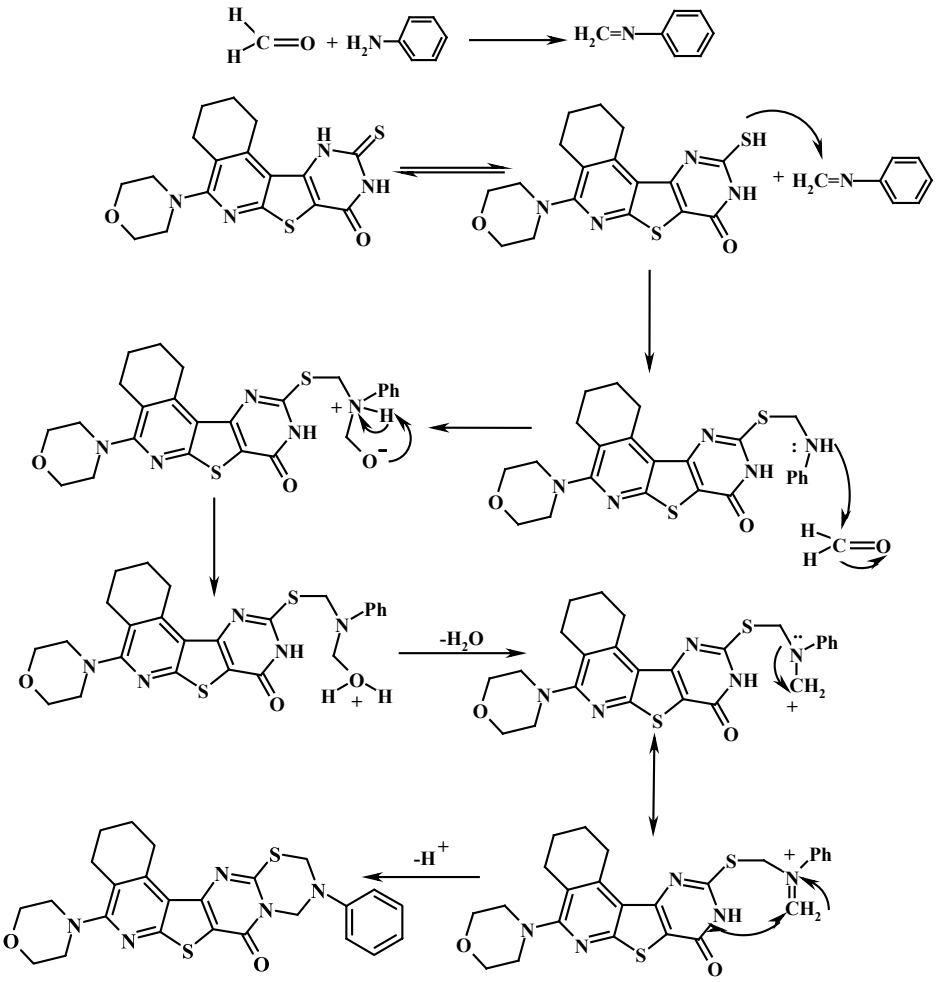
SCHEME 4

Synthesis of tetrahydrothiadiazinopyrimidothienoisoquinoline



SCHEME 5

Mechanism of double Mannish reaction



Reaction of compound **1** with carbondisulfide in pyridine by heating on water bath for 10 hours afforded the pyrimidothione **13** which underwent cyclization under double *Mannish* conditions using formaldehyde and aniline to give thiadiazinopyrimido thienoisoquinoline **14** (Scheme 4).

The mechanism of double *Mannish* reaction to afford compound **14** was suggested in the following scheme.

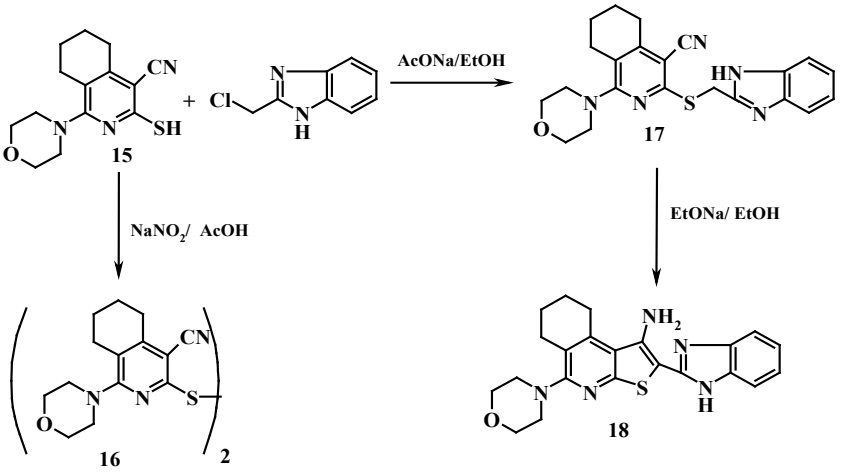
Stirring a solution of isoquinolinethione **15** in acetic acid with sodium nitrite solution afforded the dimerized compound **16**. Also, Alkylation of **15** with 2-chloromethyl

benzoimidazole in ethanol in presence of fused sodium acetate gave the S-benzoimidazolyl derivative **17**, which underwent *Thorpe-Ziegler* cyclization by using ethanolic sodium ethoxide solution to give aminobenzimidazolyl tetrahydro thienoisoquinoline **18**. Cyclization of compound **17** was confirmed using spectral analysis. IR of compound **17** revealed an absorption band at 2210 cm^{-1} for the CN group, which disappeared upon being cyclized into **18** and showing bands characteristic of the NH, NH_2 groups at 3450-3200 cm^{-1}. ^1H NMR spectra of **18** showed the disappearance of signals characteristic for the SCH_2 group in the starting material and appearance of new signals at δ 7.70 ppm corresponding to NH_2 group (Scheme 6).

Condensation of compound **18** with benzaldehyde in refluxing ethanol afforded the corresponding Schiff's base which underwent *Michael* addition to afford hexahydrobenzimidazo derivative **19** which refluxing in n-butanol losses hydrogen molecule to afford the corresponding tetrahydrobenzoimidazo derivative **20.** While reaction with triethyl orthoformate gave benzimidazopyrimidothienoisoquinoline **21.** The structure of compound **21** was established on the basis of spectral analysis. IR spectrum of compound **21** revealed disappearance an absorption bands for the NH_2 group. ^1H NMR spectrum of **21** showed singlet signal at 10.05 corresponding to CH pyrimidine. Compound **18** was converted to the corresponding triazino derivative **22** using sodium nitrite in acetic acid (Scheme 7).

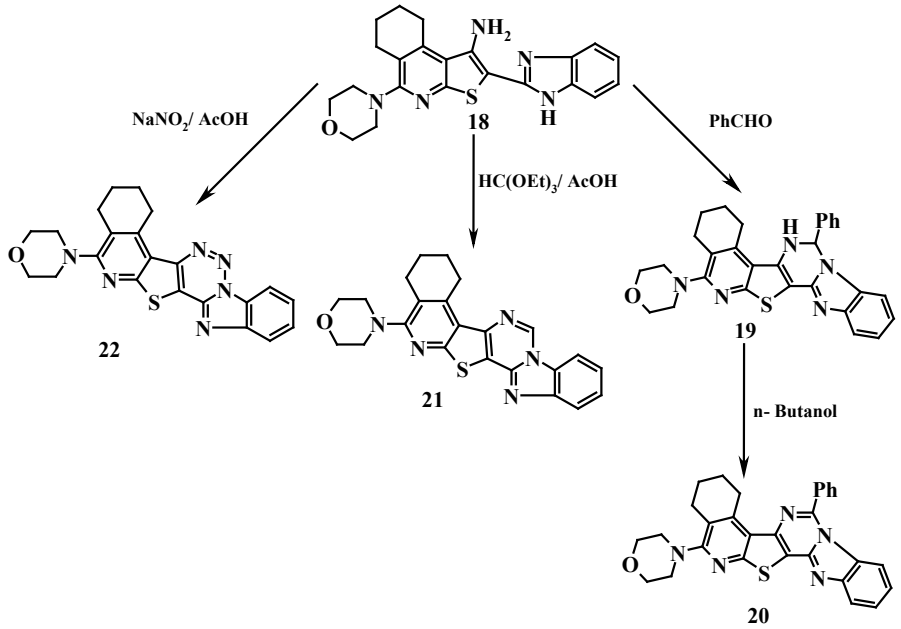
SCHEME 6

Synthesis of benzimidazolyltetrahydrothienoisoquinoline



SCHEME 7

Synthesis of tetrahydrobenzimidazopyrimido and tetrahydrobenzimidazotriazinothienoisoquionline



EXPERIMENTAL

Materials and Instruments

All melting points are corrected and measured on a Fisher-John apparatus. IR spectra were recorded (KBr) with a Perkin-Elmer 1430 Spectrophotometer. ^{1}H NMR and $^{13}CNMR$ spectra were obtained on a Varian EM-390 MHz (90 MHz) and Joel 400 MHz spectrometers in $CDCl_3$, DMSO-d_6 and CF_3CO_2D using Me_4Si as internal standard, and chemical shifts are expressed as ppm. Mass spectra were measured on a Joel-JMS 600 spectrometer. Analytical data were obtained on Elemental Analyze system GmbH-VarioEL V.3 microanalyzer in the central lab of Assiut University; aminocarboxamide **1** and tetrahydroisoquinolinethione **15** were obtained as reported procedure [23]. Numbering of carbon atoms for compounds **8**, **10** and **14** is shown in fig. 1

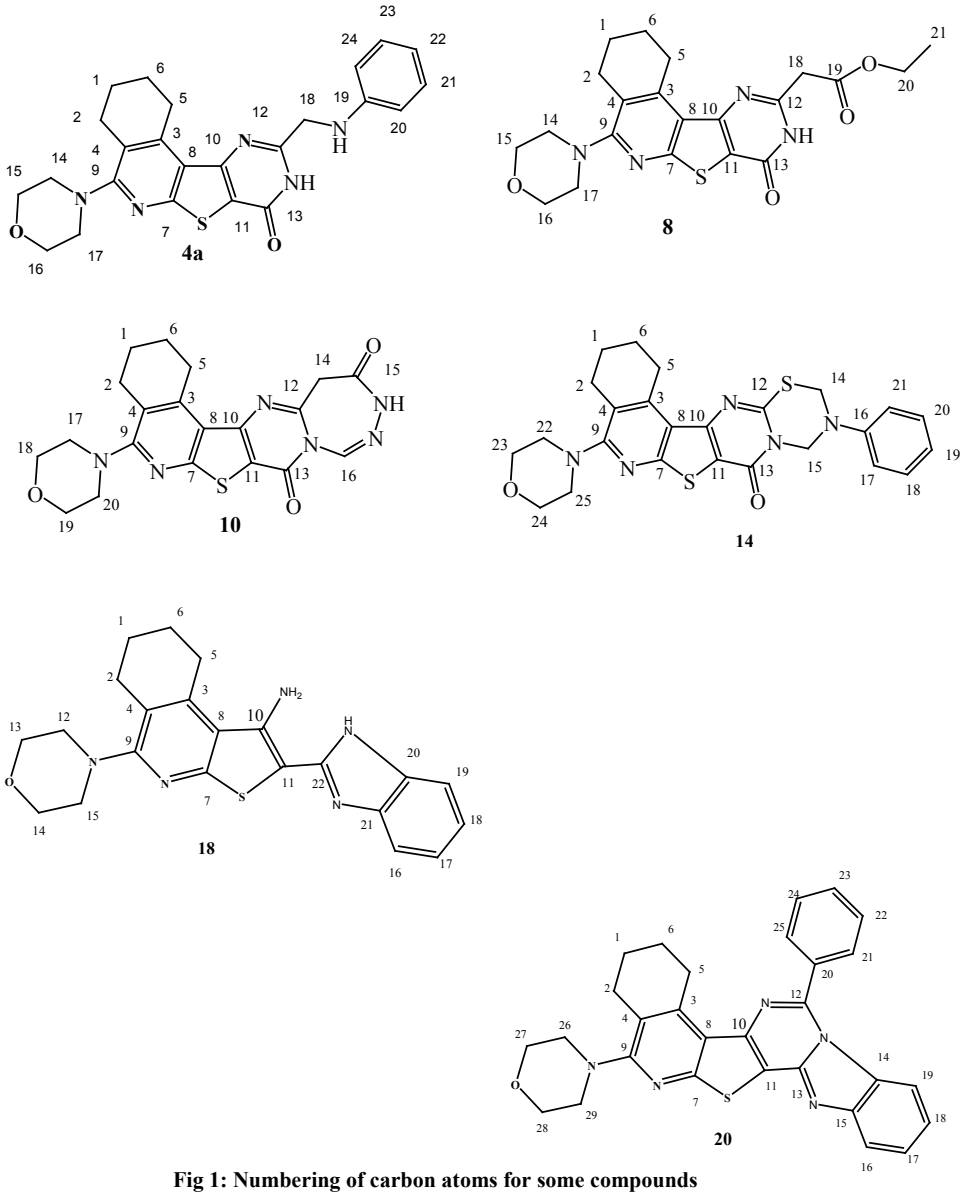


Fig 1: Numbering of carbon atoms for some compounds

1-(2-Chlorocetylamino)-5-morpholin-4-yl-6,7,8,9-tetrahydrothieno[2,3-c]iso- quinoline-2-carboxylic acid amide (2)

A solution of aminocarboxamide **1** (1 g, 3 mmol) and chloroacetyl chloride (0.4 mL, 3.5 mmol) in dioxane (30 mL) was heated on water bath for 2 hrs. The solid product which obtained by cooling and pouring on diluted sodium carbonate solution was filtered off, dried and recrystallized from ethanol to give white crystals in (81 %, 1.00 g) yield, m.p.: 250-252°C.

Anal. Calcd. for $C_{18}H_{21}ClN_4O_3S$ (408.91): C; 52.87, H; 5.18, Cl; 8.67, N; 13.7, S; 7.84, Found: C; 53.05, H; 5.32, Cl; 8.43, N; 13.54, S; 7.93%. IR ν: 3400, 3271 cm^{-1} (NH, NH_2 amides), 2950, 2860 cm^{-1} (CH aliphatic), 1664 cm^{-1} (C=O amide). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.80 (m, 4H, $2CH_2$), 2.70 (m, 4H, $2CH_2$), 3.50 (4H, m, $2CH_2$), 3.80 (m, 4H, $2CH_2$), 4.40 (s, 2H, CH_2Cl), 7.50 (s, 2H, NH_2), 10.60 (s, 1H, NH).

10-Chloromethyl-5-morpholin-4-yl-1,2,3,4-tetrahydro-pyrimido[4',5":4,5]thieno [2,3-c]isoquinolin-8(9H)-one (3)

Method A:

A mixture of **2** (4 g**,** 0.01 mol) in of acetic anhydride (20 mL) was refluxed for 2 hrs. The solid product which was

formed on cooling filtered off, dried and recrystallized from dioxane to give white crystals in (78.5 %, 3 g) yield.

Method B:

A mixture of of **1** (3.32 g, 0.01 mol) and chloro acetyl-chloride (3 mL, 38 mmol) was heated on water bath for 3 hrs, then poured into cold water (100 mL), neutralized with 10% sodium carbonate solution to just alkaline. The solid product was filtered off, dried and recrystallized from dioxane to give white crystals in (77%, 3.00 g) yield. m.p.: 308-310°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; 55.52, H; 5.12, Cl; 8.87, N; 14.10, S; 8.00%. IR ν: = 3450 (NH), 2950, 2850 cm^{-1} (CH aliphatic), 1650 cm^{-1} (CO), 1600 cm^{-1} (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 1.82 (4H, m, 2 x CH_2 cyclohexeno), 2.70 (4H, m, 2 x CH_2 cyclohexeno), 3.20 (4H, m, 2 x CH_2-N morpholine), 3.80 (4H, m, 2 x CH_2O- morpholine), 4.60 (2H, s, CH_2Cl), 10.70 (1H, s, NH.; EI-MS: *m/z (%)* = 393 (M^{+2}, 14), 391 (M^+, 25), 359 (13), 347 (4), 335 (24), 333 (51), 304 (7), 256 (5), 207 (9), 186 (26), 128 (19), 115 (30), 97 (47), 88 (53), 73 (41), 71 (25), 69 (72), 67 (28), 61 (76), 59 (5), 57 (92), 55 (100).

10-Phenylaminomethyl-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimido[4',5':4,5] thieno[2,3-c]isoquinoline-8(9H)-one (4a)

A mixture of **3** (3.90 g, 0.01 mol), and aniline (2.00 mL, 0.02 mol) was heated for 5 min, then ethanol (20 mL) was added. The mixture was refluxed for 2 hrs. The solid product which is formed on hot filtered off, dried and recrystallized from dioxane to give (71%, 3.2 g) as white crystals. m.p.: 288-290°C.

Anal. Calcd. for $C_{24}H_{25}N_5O_2S$ (447.56): C; 64.41, H; 5.63, N; 15.65, S; 7.10, Found: C; 64.20, H; 5.85, N; 15.80; S; 7.30%. IR ν: 3400, 3350 cm^{-1} (2NH), 3050 cm^{-1} (CH aromatic), 2920, 2850 cm^{-1} (CH aliphatic), 1650 cm^{-1} (CO amide). ^1H NMR (DMSO-d_6, 400 MHz,) δ (ppm): 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.60 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 x CH_2-N morpholine), 3.80 (m, 4H, 2 x CH_2-O morpholine), 4.30 (s, 2H, CH_2NH), 5.90 (s, 1H, NH), 7.05-7.50 (m, 5H, ArH), 11.20 (s, 1H, NH pyrimidine); ^{13}C-NMR (DMSO-d_6, 400 MHz) δ (ppm): 22.15 (CH_2, C1 cyclohexeno), 22.86 (CH_2, C-6 cyclohexeno), 27.01 (CH_2, C-2 cyclohexeno), 28.24 (CH_2, C-5 cyclohexeno), 50.35 ($2CH_2$-N morpholine C-14, C17), 52.43 (CH_2NH), 66.78 ($2CH_2O$ morpholine C15, C16), 113.5 (2CH , C-20, C-24 aromatic), 116.32 (CH_2, C-4 cycloexeno), 117.24 (CH, C-22 aromatic), 121.18 (C-8), 123.89 (C-3), 129.60 (2CH, C-21, C-23 aromatic), 142.63 (C-10), 146.85 (C-11), 148.00 (CH, C-19 aromatic), 153.23 (C-7), 155.97 (C-9), 160.67 (CO amide).

10-(p-Tolylaminomethyl)-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimido[4',5':4,5] thieno[2,3-c]isoquinolin-8(9H)-one (4b)

A mixture of **3** (1 g, 2.5 mmol), of *p*-toluidine (0.3 g, 2.8 mmol) in ethanol (20 mL) and few drops of triethylamine was refluxed for 4 hrs. The solid product which formed on hot was filtered off and recrystallized from dioxane to give white crystals in (74%, 0.87 g) yield. m.p. 260-262°C.

Anal. Calcd. for $C_{25}H_{27}N_5O_2S$ (461.59): C; 65.05, H; 5.90, N; 15.17, S; 6.95, Found: C; 65.27, H; 6.15, N; 14.97, S; 7.05%. IR ν: 3450, 3400 cm^{-1} (NH), 2920, 2820 cm^{-1} (CH aliphatic), 1660 cm^{-1}(CO amide), 1600 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) δ (ppm): 1.80 (s, 3H, CH_3 *p*-tolyl), 2.30 (m, 4H, 2 x CH_2 cyclohexeno), 2.65 (m, 4H, 2 x CH_2 cyclohexeno), 3.25 (m, 4H, 2 x CH_2N-morpholine), 3.70 (m, 4H, 2 x CH_2-N morpholine), 4.30 (s, 2H, CH_2NH), 6.20 (s, 1H, NH *p*-tolyl), 6.55-6.80 (2d, 4H, ArH), 12.50 (s, 1H, NH pyrimidine).

10-[p-Anisylaminomethyl]-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimido[4',5': 4,5]thieno [2,3-c]isoquinolin-8(9H)-one (4c)

Obtained by the reaction of **3** with p-anisidine to give white crystals in (77%, 0.94 g) yield. m.p.: 238-240°C.

Anal. Calcd. for $C_{25}H_{27}N_5O_3S$ (477.59): C; 62.87, H; 5.70, N; 14.66, S; 6.71, Found: C; 63.07, H; 5.93, N; 14.46, S; 6.58%. IR ν: 3480, 3450 cm^{-1} (2NH), 2920, 2850 (CH aliphatic), 1655 (CO amide), 1620 (C=N). ^1H NMR ($CDCl_3$) δ (ppm): 1.80 (m, 4H, $2CH_2$ cyclohexeno), 2.65 (m, 4H, 2 x CH_2 cyclohexeno), 3.10 (m, 4H, 2 x CH_2-N morpholine), 3.60 (m, 4H, $2CH_2$-O morpholine), 3.80 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2NH), 6.20 (s, 1H, NH *p*-anisyl), 6.55-6.80 (2d, 4H, ArH), 12.50 (s, 1H, NHpyrimidine).

10-Diethylaminomethyl-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimido[4',5':4,5] thieno[2,3-c]isoquinolin-8(9H)-one (4d)

A solution of **3** (3.9 g, 0.01 mol) in ethanol (20 mL) and diethyl amine (1.4 mL, 0.02 mol) was refluxed for 2 hrs, and then the mixture was allowed to cool. The solid product was filtered off, dried and recrystallized from ethanol to give green crystals in(75%, 0.82 g) yield. m.p. 260-262°C.

Anal. Calcd. for $C_{22}H_{29}N_5O_2S$ (427.57): C;, 61.80, H; 6.84, N; 16.38, S; 7.50, Found: C; 62.02, H; 7.00, N; 16.52, S; 7.35%. IR ν: 3450 cm^{-1} (NH), 2950, 2850 cm^{-1} (CH aliphatic), 1650 cm^{-1} (CO). ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, 6H, *J* = 9 Hz, $2CH_3$ diethyl amino), 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.85 (m, 4H, 2 x CH_2 cyclohexeno), 3.15 (m, 4H, 2 x CH_2N-morpholine), 3.60 (m, 4H, 2 x CH_2O-morpholine), 4.10 (s, 2H, CH_2N), 4.60 (q, 4H, *J* = 7.5 Hz, 2 x CH_2 diethyl amino), 11.80 (s, 1H, NH pyrimidine).

10-Morpholin-4-yl-methyl-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimido[4',5': 4,5]thieno[2,3-c]isoquinolin-8(9H)-one (4e)

Obtained by the reaction of **3** with morpholine. The product was recrystallized from ethanol to give (72%, 0.81 g) as green crystals. m.p.: 316-318°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; 6.34, N; 16.10, S; 7.42%. IR ν: 3470 cm^{-1} (NH pyrimidine), 2950, 2850 cm^{-1} (CH aliphatic), 1640 cm^{-1} (C=O amide). ^1H NMR ($CDCl_3$) δ (ppm): 1.60 (m, 4H, 2 x CH_2 cyclohexeno), 1.75 (m, 4H, 2 x CH_2 cyclohexeno), 2.15 (m, 4H, 2 x CH_2N-morpholine C-5), 2.50 (m, 4H, 2 x CH_2O-morpholine C-5), 3.10 (m, 4H, 2 x CH_2N-morpholine C-11), 3.60 (m, 4H, 2 x CH_2O-morpholine C-11), 3.70 (s, 2H, CH_2N), 11.30 (s, 1H, NH pyrimidine).

10-Piperidin-1-ylmethyl-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimido[4',5':4,5] thieno[2,3-c]isoquinoline (4f)

Obtained by the reaction of **3** with piperidine. The product was recrystallized from ethanol to afford green crystals in (79%, 0.89 g) yield. m.p.: 320-322°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; 63.04, H; 6.86, N; 16.15, S; 7.43%. IR ν: 3480 cm^{-1} (NH), 2920, 2850 cm^{-1} (CHaliphatic), 1650 cm^{-1} (C=O amide). ^1H NMR ($CDCl_3$) δ (ppm): 1.50 (m, 6H, 3 x CH_2 piperidine H3: H5), 1.80 (m, 4H, $2CH_2$ cyclohexeno), 2.20 (m, 4H, 2 x CH_2 piperidine H2, H-6), 2.60 (m, 4H, 2 x CH_2 cyclohexeno), 3.30 (m, 4H, 2 x CH_2N-

morpholine), 3.70 (m, 4H, 2 x CH_2O-morpholine), 3.85 (s, 2H, CH_2N), 12.30 (s, 1H, NHpyrimidine).

5-Morpholin-4-yl-11-aryl-1,2,3,4,10,12-hexahydro-imidazo[5"1":2',3']pyrimido [5',6':2,3]thieno[5,4-c]isoquinolin-8-one (5 a-c)

General Procedure:

A mixture of **4 a-c** (1 g, 2.2 mmol) was dissolved in warm ethanol (20 mL) then formaldehyde (2mL, 35%) was added drop wise with stirring for 15 min. then the mixture was heated for 2 h. at 50-60°C. The solid product which is formed on hot was filtered off, dried and recrystallized from chloroform to give white crystals.

5-Morpholin-4-yl-11-phenyl-1,2,3,4,10,12-hexahydro-imidazo[5"1":2',3'] pyrimido[5',6':2,3]thieno[5,4-c]isoquinolin-8-one (5a)

Yield: (35%, 0.36 g); m.p.: 334-336°C.

Anal. Calcd. for: $C_{25}H_{25}N_5O_2S$ (459.57): C; 65.34, H; 5.48, N; 15.24, S; 6.98, Found: C; 65.54, H; 5.25, N; 15.44, S; 7.21%. ^{1}H NMR (CF_3CO_2D): δ (ppm): 2.10 (m, 4H, 2CH_2 cyclohexeno), 2.95 (m, 4H, 2 x CH_2 cyclohexeno), 3.95 (m, 4H, 2 x CH_2N-morpholine), 4.25 (m, 4H, 2 x CH_2O-morpholine), 5.10, 6.05 (2s, 4H, 2 x CH_2 imidazole), 7.00-7.50 (m, 5H, ArH). IR ν: 3030 cm^{-1} (CH aromatic), 2920, 2820 cm^{-1} (CH aliphatic), 1680 cm^{-1} (C=O), 1600 cm^{-1} (C=N).

5-Morpholin-4-yl-11-(p-tolyl)-1,2,3,4,10,12-hexahydroimidazo[5"1":2',3'] pyrimido[5',6':2,3]thieno[5,4-c] isoquinolin-8-one (5b)

Yield: (58%, 0.60 g); m.p.: 308-310°C.

Anal. Calcd. for: $C_{26}H_{27}N_5O_2S$ (473.60) C; 65.94, H; 5.75, N; 14.79, S; 6.77, Found: C; 66.13, H; 5.55, N; 15.00, S; 6.97%. IR ν: 2920, 2850 cm^{-1} (CH aliphatic), 1670 cm^{-1} (CO amide). ^{1}H NMR (CF_3CO_2D) δ (ppm): 1.70 (s, 3H, CH_3 *p*-tolyl) 2.05 (m, 4H, 2CH_2 cyclohexeno), 3.10 (m, 4H, 2 x CH_2 cyclohexeno), 3.80 (m, 4H, 2 x CH_2N-morpholine), 4.30 ((m, 4H, 2 x CH_2O-morpholine), 5.05, 6.10 (2s, 4H, 2 x CH_2 imidazole), 7.50-7.70 (m, 4H, ArH).

5-Morpholin-4-yl-11-(p-anisyl)-1,2,3,4,10,12-hexahydroimidazo[5"1":2',3'] pyrimido[5',6':2,3]thieno[5,4-c] isoquinolin-8-one (5c)

Yield: (62%, 0.63 g); m.p.: 312-314°C.

Anal. Calcd. for: $C_{26}H_{27}N_5O_3S$ (489.60): C; 63.78, H; 5.56, N; 14.30, S; 6.55, Found: C; 63.56, H; 5.73, N; 14.52, S; 6.74%. IR ν: 2950, 2820 cm^{-1} (CH aliphatic), 1665 cm^{-1} (CO). ^{1}H NMR (CF_3CO_2D) δ (ppm): 1.60 (s, 3H, CH_3 *p*-anisyl), 2.00 (s, 4H, 2CH_2 cyclohexeno), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.50 (m, 4H, 2 x CH_2N-morpholine), 4.10 (m, 4, 2 x CH_2O-morpholine), 5.20, 6.35 (2s, 4H, 2 x CH_2 imdazole), 7.30-7.60 (m, 4H, ArH);

1-Phthalimido-5-morpholin-4-yl-6,7,8,9-tetrahydrothieno[2,3-c] isoquinolin-2-carboxamide (6)

A mixture of **1** (1.60 g, 5 mmol) and phthalic anhydride (0.80 g, 5 mmol) in glacial acetic acid (20 mL) was refluxed for 3 hrs. The solid product which is formed on hot filtered off, dried and recrystallized from dioxane to give green crystals in (65%, 1.40 g) yield. m.p. 256-258°C.

Anal. Calcd. for: $C_{24}H_{22}N_4O_4S$ (462.53): C; 62.32, H; 4.79, N; 12.11, S; 6.93, Found: C; 62.50, H; 5.00, N; 11.93, S; 7.11%. IR ν: 3250, 3180 cm^{-1} (NH_2), 3050 cm^{-1} (CH aromatic), 2920, 2850 cm^{-1} (CH aliphatic) 1720, 1685 cm^{-1} (3CO); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.90 (4H, m, 2 x CH_2 cyclohexeno), 2.70 (4H, m, 2 x CH_2 cyclohexeno), 3.20 (4H, m, 2 x CH_2N-morpholine), 3.80 (4H, m, 2 x CH_2O-morpholine), 7.30 (2H, s, NH_2), 7.60-8.10 (4H, m, ArH).

5-Morpholin-4-yl-1,2,3,4-hexahydroisoindolo[1",2":2',3']pyrimido[4',5':4,5] thieno[2,3-c]isoquinolin-8,14-dione (7)

A mixture of **1** (1.6 g, 5 mmol) and phthalic anhydride (0.80 g, 5 mmol) in DMF (20 mL) was refluxed for 10 hrs. The solid product which is formed by cooling filtered off, dried and recrystallized from ethanol to give yellow crystals in (56%, 1.20 g) yield. m.p.: 180-182°C.

Anal. Calcd. for: $C_{24}H_{20}N_4O_3S$ (444.52): C; 64.85, H; 4.54, N; 12.60, S; 7.21, Found: C; 65.00, H; 4.32, N; 12.82, S; 7.40%. IR ν: 3030 cm^{-1} (CH aromatic), 2950, 2856 cm^{-1} (CH aliphatic), 1722, 1670 cm^{-1} (2CO). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.80 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (4H, m, 2 x CH_2N-morpholine), 3.90 (4H, m, 2 x CH_2O-morpholine), 7.30 -8.10 (m, 4H, ArH), EI-MS: *m/z (%)* = 444 (M^{+1}, 8), 443 (M^+, 100), 442 (M^{-1}, 17), 429 (41), 419 (23), 410 (57), 405 (24), 398 (56), 384 (32), 373 (26), 360 (17), 342 (23), 332 (96), 311 (15), 275 (34), 256 (23), 230 (18), 218 (10), 201 (11), 143 (12), 130 (12), 104 (20), 55 (3).

(5-Morpholin-4-yl-8-oxo-1,2,3,4,9-pentahydropyrimido[4',5':4,5]thieno[2,3-c] isoquinolin-10-yl)acetic acid ethyl ester (8)

A mixture of **1** (0.5 g, 1.5 mmol) and diethyl malonate (1.0 ml, 6 mmol) in acetic acid (5 mL) was heated under reflux for 1hr. The solid product was formed on hot was filtered off and recrystallized from dioxane to give yellow crystals in (68%, 0.44 g) yield. m.p.: 270-272°C.

Anal. Calcd. for: $C_{21}H_{24}N_4O_4S$ (428.51): C; 58.86, H; 5.65; N; 13.07, S; 7.48, Found: C; 59.09, H; 5.86, N; 12.84, S; 7.70%. IR ν: 3450 cm^{-1} (NH), 2920, 2850 cm^{-1} (CH aliphatic), 1740 cm^{-1} (CO ester), 1640 cm^{-1} (CO amide). ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm): 1.20 (t, 3H, *J* = 9 Hz, CH_3 ester), 1.85 (m, 4H, 2 x CH_2 cyclohexeno), 2.72 (m, 4H, 2 x CH_2 cyclohexeno), 3.34 (m, 4H, 2 x CH_2N-morpholine), 3.65 (m, 4H, 2 x CH_2O-morpholine), 3.84 (s, 2H, CH_2CO), 4.15 (q, 2H, *J* = 7.5 Hz, CH_2 ester) 11.30 (s, 1H, NH pyrimidine), ^{13}C NMR (DMSO-d_6, 400 MHz) δ (ppm): 14.60 (CH_3 ester), 22.00 (CH_2, C-1 cyclohexeno), 22.62 (CH_2, C-6 cyclohexeno), 26.60 (CH_2, C-2 cyclohexeno), 27.37 (CH_2, C-5 cyclohexeno), 40.45 (CH_2CO), 50.29 (2CH_2N-morpholine, C-14, C-17), 61.44 (CH_2 ester), 66.66 (2CH_2O-morpholine, C-15, C-16), 117.97 (C-4), 120.97 (C-8), 122.67 (C-3), 143.32 (C-10), 146.70 (C-11), 152.90 (C-7), 153.03 (C-9), 161.79 (CO amide), 168.45 (CO ester). EI-MS: *m/z (%)* = 429 (M^{+1}, 40), 428 (M^+, 100), 427 (M^{-1}, 19), 397 (36), 383 (53), 371 (79), 355 (27), 343 (34), 325 (24), 311 (27), 297 (42), 270 (35), 256 (17), 240 (13), 226 (19), 212 (12), 174 (16), 128 (10), 103 (8), 86 (24), 68 (9), 57 (4).

(5-Morpholin-4-yl-8-oxo-1,2,3,4,9-pentahydropyrimido[4',5':4,5]thieno[2,3-c]iso quinolin-10-yl)-acetic acid hydrazide (9)

A sample of **8** (0.5 g, 1.2 mmol) and hydrazine hydrate (1 mL, 85%) was fused for 3 min. then ethanol (20 mL) was added. The mixture was refluxed for 2 hrs. The solid product, which formed on hot was filtered off and recrystallized from ethanol to give white crystals in (56%, 0.27 g). m.p. 296-298°C.

Anal. Calcd. for: $C_{19}H_{22}N_6O_3S$ (414.49): C; 55.06, H; 5.35, N; 20.28, S; 7.74, Found: C; 55.25, H; 5.55, N; 20.15, S; 7.94%. IR ν: 3350-3150 cm^{-1} (NH, NH_2), 2920, 2850 cm^{-1} (CH aliphatic), 1660, 1640 cm^{-1} (2 CO amide). EI-MS: *m/z (%)* = 414 (M^+, 34), 332 (19), 325 (31), 294 (66), 271 (28), 256 (23), 207 (21), 183 (28), 154 (30), 140 (17), 109 (59), 93 (40), 71 (74), 57 (100).

5-Morpholin-4-yl-1,2,3,4,12,14-hexahydro[1,2,4]triazepino[4",5":1',2']pyrimido [4',5':4,5]thieno[2,3-c]isoquinolin-8,13-dione (10)

A mixture of **9** (0.4 g, 1 mmol), triethyl orthoformate (2 mL, 13.5 mmol) and few drops of acetic acid was heated under reflux for 1 hr. The solid product was filtered off and recrystallized from dioxane to give yellow crystals in (50%, 0.20 g) yield. m.p. > 360°C.

Anal. Calcd. for: $C_{20}H_{20}N_6O_3S$ (424.48): C; 56.59, H; 4.75, N; 19.80, S; 7.55, Found: C; 57.10, H; 5.00, N; 19.63, S; 7.72%. IR ν: 3120 cm^{-1} (NH), 2920, 2850 cm^{-1} (CH aliphatic), 1670 cm^{-1} (CO amide). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.85 (4H, m, 2 x CH_2 cyclohexeno), 2.65 (m, 4H, 2 x CH_2 cyclohexeno), 3.30 (m, 4H, 2 x CH_2N-morpholine), 3.50 (m, 4H, 2 x CH_2O-morpholine), 3.80 (s, 2H, triazepine H-14), 8.20 (s, 1H, triazepine H-15), 12.40 (s, 1H, NH triazepine); ^{13}C NMR (DMSO-d_6, 400 MHz) δ (ppm): 22.19 (CH_2, C-1 cyclohexeno), 22.40 (CH_2, C-6 cyclo- hexeno), 26.70 (CH_2, C-2 cyclohexeno), 27.67 (CH_2, C-5 cyclohexeno), 40.67 (CH_2CO triazepine), 50.27 (2CH_2N-morpholine, C-17, C-20), 66.67 (2CH_2O-morpholine, C-18, C-19), 116.78 (C-4), 120.62 (C-8), 122.64 (C-3), 145.98 (C-11), 151.48 (C-7), 153.77 (C-9), 159.77 (CO pyrimidine), 161.86 (CO triazepine). EI-MS: *m/z (%)* = 425 (M^{+1}, 3), 424 (M^+, 4), 403 (10), 351 (87), 321 (26), 306 (22), 279 (8), 252 (7), 238 (4), 225 (6), 169 (8), 140 (11), 127 (12), 108 (26), 90 (44), 79 (70), 70 (81), 57 (100).

10-[2-(3,5-dimethylpyrazol-1-yl)-2-oxoethyl]-5-morpholin-4-yl-1,2,3,4tetrahydro pyrimido [4',5':4,5]thieno [2,3-c]isoquinolin-8 (9H)-one (11)

A mixture of compound **9** (0.5 g**,** 1.2 mmol) and acetylacetone (0.5 mL, 5 mmol) was fused for 5 min. then absolute ethanol (20 mL) was added and reflux continued for additional 2 hrs. The solid product formed on hot filtered off, dried and recrystalized from dioxane to give 0.39 g (67%) **11** as yellow crystals. m.p. 246-248°C.

Anal. Calcd. for: $C_{24}H_{26}N_6O_3S$ (478.58) C; 60.23, H; 5.48, N; 17.56, S; 6.70, Found: C; 60.46, H; 5.70, N; 17.35, S; 6.87%. IR ν: 3400 cm^{-1} (NH), 2940, 2860 cm^{-1} (CH aliphatic), 1660, 1640 cm^{-1} (2CO). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.60 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 x CH_2N-morpholine), 3.60 (m, 4H, 2 x CH_2O-morpholine), 2.50, 2.70 (2s, 6H, pyrazole 2CH_3), 4.00 (s, 2H, CH_2), 6.50 (s, 1H, pyrazole H-4), 11.50 (s, 1H, NH pyrimidine)

10-(2-Benzylidenehydrazinylmethyl-5-morpholin-4-yl--1,2,3,4-tetrahydro pyrimido[4',5':4,5]thieno[2,3-c]isoquinolin-8(9H)-one (12)

A mixture of carbohydrazide compound **9** (0.5 g**,** 1.2 mmol), benzaldehyde (0.5 mL, 5 mmol) in absolute ethanol (20 mL) in presence of catalytic amount of piperidine was refluxed for 2 hrs. The solid product formed on hot filtered off, dried and recrystallized from dioxane to give yellow crystals in (48%, 0.29 g) yield. m.p. 264-266°C.

Anal. Calcd. for $C_{26}H_{26}N_6O_3S$ (502.60): C; 62.13, H; 5.21, N; 16.72, S; 6.38, Found: C; 62.35, H; 5.00, N; 16.88, S; 6.55%. IR ν: 3450, 3250 cm^{-1} (2NH), 3050 cm^{-1} (CH aromatic), 2920, 2820 cm^{-1} (CH aliphatic) 1670, 1650 cm^{-1} (2CO). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.50 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 x CH_2N-morpholine), 3.50 (m, 4H, 2 x CH_2O-morpholine), 3.80 (s, 2H, H-14), 7.30-7.60 (m, 5H, ArH), 7.90 (s, 1H, CHPh), 9.10 (s, 1H, NH hydrazone), 11.80 (s, 1H, NH pyrimidine).

8-Oxo-5-morpholin-4-yl-1,2,3,4-tetrahydropyrimido[4',5':4,5]thieno[2,3-c]iso quinoline-10(11H)-thione (13)

A mixture of **1** (0.66 g, 2 mmol) and carbon disulphide (2 mL) was refluxed on water bath for 5 hrs. in presence of anhydrous pyridine (4 mL). The solid product which was formed on hot filtered off and recrystallized from ethanol to give white crystals in (67.5%, 0.5 g) yield. m.p. 338-340°C. Anal. Calcd. for $C_{17}H_{18}N_4O_2S_2$ (374.49): C; 54.53, H; 4.84, N; 14.96, S; 17.12, Found: C; 54.74, H; 4.68, N; 15.15, S; 17.30%. IR ν: 3450, 3350 cm^{-1} (2NH), 2950, 2850 cm^{-1} (CH aliphatic), 1685 cm^{-1} (CONH), 1225 cm^{-1} (C=S). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.60 (m, 4H, 2 x CH_2 cyclohexeno), 3.30 (m, 4H, 2 x CH_2N-morpholine), 3.60 (m, 4H, 2 x CH_2O-morpholine), 7.50 (s, 1H, NHCS pyrimidine) 8.80 (s, 1H, NHCO pyrimidine).

5-Morpholin-4-yl-11-phenyl-1,2,3,4-tetrahydro[1,3,5]thiadiazino[2",3":2',1'] pyrimido[4',5':4,5]thieno[2,3-c]isoquinolin-8(9H)-one (14)

A mixture of **13** (0.5 g, 1 mmol), formaldehyde (2 mL) and aniline (0.2 mL, 2 mmol) in ethanol (20 mL) in presence of few drops of acetic acid was refluxed for 30 min.. The solid precipitate which is formed on hot filtered off, dried and recrystallized from dioxan in (59%, 0.39 g) yield. m.p.>360°C. Anal. Calcd. for $C_{25}H_{25}N_5O_2S_2$ (491.64): C; 61.08, H; 5.13, N; 14.24, S; 13.04, Found: C; 61.30, H; 5.25, N; 14.05, S; 13.20%. IR ν: 3030 cm^{-1} (CH aromatic), 2920, 2820 cm^{-1} (CH aliphatic), 1660 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 x CH_2N-morpholine), 3.60 (m, 4H, 2 x CH_2O-morpholine), 5.45, 5.80 (2s, 4H, thiadiazine H-14, H-15), 6.90-7.30 (m, 5H, ArH). ^{13}C NMR (DMSO- d_6, 400 MHz) δ (ppm): 21.91 (CH_2, C-1 cyclohexeno), 22.58 (CH_2, C-6 cyclohexeno), 26.63 (CH_2, C-2 cyclohexeno), 27.28 (CH_2, C-5 cyclohexeno), 40.68 (2CH_2N-morpholine, C-22, C-25), 66.64 (2CH_2O-morpholine, C-23, C-24), 114.30 (2CH, C17, C-21 aromatic), 116.70 (C-4), 119.97 (C-19 aromatic), 120.67 (C-8), 122.23 (2CH, C-18, C-20 aromatic), 123.05 (C-3), 143.94 (C-10), 146.88 (C-11), 151.46 (C-16), 155.67 (C-12), 151.90 (C-7), 153.87 (C-9), 162.01 (CO pyrimidine). EI-MS: *m/z (%)* = 492 (M^{+1}, 68), 491 (M^+, 100), 435 (29), 358 (37), 341 (13), 329 (21), 300 (30), 245 (3), 187 (1), 118 (10), 105 (29), 95 (11), 85 (10), 71 (14), 57 (18).

3,3'-Disulfanediylbis(1-morpholino-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile) (16)

Sodium nitrite solution (0.7 g, 10%, 0.01 mol) was added drop wise to a solution of tetrahydroisoquinolinethione **15** (1 g, 3.63 mmol) in glacial acetic acid (20 mL) for 5 min. at room temperature. The solid product which was formed filtered off, dried and recrystallized from ethanol to afford brown crystal in 89% yield. m.p. 192-194°C.

Anal. Calcd. for: $C_{28}H_{32}N_6O_2S_2$ (548.73): C; 61.29, H; 5.88, N; 15.32, S; 11.69, Found: C; 61.14, H; 6.00, N; 15.49, S; 11.54%. IR ν: 2920, 2850 cm^{-1} (CH aliphatic), 2200 cm^{-1} (CN), 1620 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) δ (ppm): 1.80 (m, 8H, 4 x CH_2 cyclohexeno), 2.50 (m, 4H, 2 x CH_2 cyclohexeno), 2.80 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 8H, 4 x CH_2N-morpholine), 3.60 (m, 8H, 4 x CH_2O-morpholine).

3-(1H-Benzoimidazol-2-ylmethylsulfanyl)-1-morpholin-4-yl-5,6,7,8-tetrahydroiso quinoline-4-carbonitrile (17)

A mixture of **15** (4 g, 0.01 mol) and 2-chloromethylbenzo[d] imidazole (1.66 g, 0.01 mol) in presence of fused sodium acetate (4.10 g, 0.05 mol) was refluxed in ethanol (30 mL) for 30 min. The solid product which formed on hot filtered off, dried and recrystallized from ethanol to afford white crystals in 47% yield. m.p.: 160-162°C.

Anal. Calcd. for $C_{22}H_{23}N_5OS$ (405.53): C; 65.16, H; 5.72, N; 17.27, S; 7.91, Found: C; 65.05, H; 5.86, N; 17.38, S; 8.05%. IR ν: 3450 cm^{-1} (NH), 3050 cm^{-1} (CH aromatic), 2920, 2820 cm^{-1} (CH aliphatic), 2210 cm^{-1} (CN), 1640 cm^{-1} (C=N). ^1H NMR (DMSO-d_6) δ (ppm): 1.65 (4H, m, 2 x CH_2 cyclohexeno), 2.70 (4H, m, 2 x CH_2 cyclohexeno), 3.30 (4H, m, 2 x CH_2N-morpholine), 3.70 (m, 4H, 2 x CH_2O-morpholine), 4.70 (s, 2H, H-15), 7.10-7.60 (4H, m, ArH), 12.50 (s, 1H, NH benzimidazole).

1-Amino-2-(1H-benzimidazol-2-yl)-5-morpholin-4-yl-6,7,8,9-tetrahydrothieno [2,3-c]isoquinoline (18)

A solution of compound **17** (0.7 g, 1.7 mmol) in absolute ethanol (20 mL) and few drops of sodium ethoxide solution (prepared from 0.5 gm of finely divided sodium metal dissolved in 20 mL absolute ethanol) was refluxed for 2 hrs. The solid product which formed after cooling was filtered off, dried and recrystallized from ethanol to afford yellow crystals in 71% yield. m.p. 278-280°C.

Anal. Calcd. () for $C_{22}H_{23}N_5OS$ (405.53): C; 65.16, H; 5.72, N; 17.27, S; 7.91, Found: C; 65.30, H; 5.83, N; 17.08, S; 8.00%. IR ν: 3450, 3200, 3250 cm^{-1} (NH, NH_2), 3050 cm^{-1} (CH aromatic), 2920, 2850 cm^{-1} (CH aliphatic), 1600 cm^{-1} (C=N). ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.76 (m, 4H, 2 x CH_2 cyclohexeno), 2.83 (m,4H, 2 x CH_2 cyclohexeno), 3.34 (m, 4H, 2 x CH_2N-morpholine), 3.88 (m, 4H, 2 x CH_2O-morpholine), 7.08-7.43 (m, 4H, ArH), 7.64 (s, 2H, NH_2), 11.66 (s, 1H, NH benzimidazole); ^{13}C-NMR (DMSO-d_6, 400 MHz): 22.53 (CH_2, C1 cyclohexeno), 23.10 (CH_2, C-6 cyclohexeno), 27.93 (CH_2, C-2 cyclohexeno), 29.10 (CH_2, C-5 cyclohexeno), 49.38 ($2CH_2$-N morpholine C-12, C15, 66.54 ($2CH_2$O morpholine C13, C14), 115.52 (2CH , C-16, C-19 aromatic), 116.62 (CH_2, C-4 cycloexeno), 121.29 (2CH, C-17, C-18 aromatic), 121.18 (C-8), 123.23 (C-3), 123.46 (C-NH_2), 138.51 (C-22 imidazole), 143.25 (C-10), 145.54 (C-11), 150.52 (C-7), 153.87 (C-9).

8-Phenyl-2-morpholin-4-yl-3,4,5,6,7,8-hexahydrobenzoimidazo[1",2":1',6'] pyrimido[4',5':4,5]thieno[2,3-c] isoquinoline (19)

Aminobenzoimidazolyl compound **18** (0.4 g, 1 mmol) and benzaldehyde (1 mL, 0.01 mol) was gently refluxed for 15 min. then ethanol (20 mL) was added and reflux continued for additional 2 hrs. The solid product which formed on cold filtered off, dried and recrystallized from dioxane to give yellow needles in 75% yield. m.p. 310-312°C.

Anal. Calcd. for $C_{29}H_{27}N_5OS$ (493.64): C; 70.56, H; 5.51, N; 14.19, S; 6.50, Found: C; 70.77, H;5.63, N; 14.32, S; 6.67%. IR ν: 3250 cm^{-1} (NH), 3050 cm^{-1} (CH aromatic), 2920, 2850 cm^{-1} (CH aliphatic), 1630 cm^{-1} (C=N). ^1H NMR (DMSO-d_6) δ (ppm): 1.90 (m, 4H, 2 x CH_2 cyclohexeno), 2.80 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 x CH_2N-morpholine), 3.80 (m, 4H, 2 x CH_2O-morpholine), 7.10 (s, 1H, pyrimidine H12), 7.30-7.70 (m, 9H, ArH), 12.20 (s, 1H, NH pyrimidine).

8-Phenyl-2-morpholin-4-yl-3,4,5,6-tetrahydrobenzoimidazo[1",2":1',6'] pyrimido[4',5':4,5]thieno[2,3-c]isoquinoline (20)

Compound **19** (0.49 g, 1 mmol) was refluxed in n-butanol for 3 hrs. The solid product which formed on hot was recrystallized from dioxane to give green crystals in 40% yield. m.p.>360°C.

Anal. Calcd. () for: $C_{29}H_{25}N_5OS$ (491.62): C; 70.85, H; 5.13, N; 14.25, S; 6.52, Found: C; 71.00, H; 4.98, N; 14.43, S; 6.35%. IR ν: 3030 cm^{-1} (CH aromatic), 2920, 2860 cm^{-1} (CH aliphatic), 1640 cm^{-1} (C=N). ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 1.78 (m, 4H, 2 x CH_2 cyclohexeno), 2.94 (m, 4H, 2 x CH_2 cyclohexeno), 3.37 (m, 4H, 2 x CH_2N-morpholine), 3.88 (m, 4H, 2 x CH_2O-morpholine), 7.46-7.80 (m, 9H, ArH); ^{13}C-NMR (DMSO-d_6, 400 MHz): 22.43 (CH_2, C1 cyclohexeno), 22.94 (CH_2, C-6 cyclohexeno), 26.36 (CH_2, C-2 cyclohexeno), 28.68 (CH_2, C-5 cyclohexeno), 48.55 ($2CH_2$-N morpholine C-26, C-29), 66.30 ($2CH_2$O morpholine C-27, C-28), 115.43 (2CH , C-16, C-19 benzimidazole), 116.62 (CH_2, C-4 cyclohexeno), 120.60 (C-8), 121.29 (2CH, C-17, C-18 benzimidazole), 122.82 (C-3), 127.60 (2CH, C-21, C-25 phenyl), 127.93 (CH, C-23 phenyl), 128.62 (2CH, C-22, C-24 phenyl), 129.88 (C-20 phenyl), 141.32 (C-13), 143.68 (C-10), 146.76 (C-11), 152.08 (C-7), 154.54 (C-9), 156.34 (C-12).

5-Morpholin-4-yl-1,2,3,4-tetrahydrobenzimidazo[1",2":1',2']pyrimido[4',5': 4,5]thieno[2,3-c]isoquinoline (21)

A mixture of of aminobenzoimidazolyl compound **18** (0.4 g, 1 mmol) and triethyl orthoformate (2 mL) was refluxed for 1hr. The solid product which formed on hot was collected and recrystallized from dioxane to afford yellow crystals in 63% yield. m.p. 280-282°C.

Anal. Calcd. (%) for: $C_{23}H_{21}N_5OS$ (415.52): C; 66.48, H; 5.09, N; 16.85, S; 7.72, Found: C; 66.57, H; 4.95, N; 17.00, S; 7.88. IR ν: 3030 cm^{-1} (CH aromatic), 2920, 2850 cm^{-1} (CH aliphatic), 1625 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D): δ (ppm): 2.00 (m, 4H, 2 x CH_2 cyclohexeno), 2.90 (m, 4H, 2 x CH_2 cyclohexeno), 3.90 (m, 4H, 2 x CH_2N-morpholine), 4.20 (m, 4H, 2 x CH_2O-morpholine), 8.00-8.50 (m, 4H, ArH), 10.05 (s, 1H, pyrimidine H-12).

2-Morpholin-4-yl-3,4,5,6-tetrahydrobenzimidazo[1",2":1',6']triazino[4',5':4,5] thieno[2,3-c]isoquinoline (22)

Sodium nitrite (0.2 g, 4%) solution was added drop wise with stirring to a solution of benzimidazolyl compound **18** (1 g, 2.5 mmol) in glacial acetic acid (10 mL) and HCl (1 mL). Stirring was continued for 15 min. at room temperature. The solid precipitate which was formed by stirring was collected and recrystallized from acetic acid to give yellow crystals in 45% yield. m.p. 248-250°C.

Anal. Calcd. for: $C_{22}H_{20}N_6OS$ (416.51) C; 63.44, H; 4.84, N; 20.18, S; 7.70, Found: C; 63.29, H; 5.00, N; 20.34, S; 7.58%. IR ν: 3050 cm^{-1} (CH aromatic), 2920, 2850 cm^{-1} (CH aliphatic), 1620 cm^{-1} (C=N). ^1H NMR (CF_3CO_2D) δ (ppm):

1.85 (m, 4H, 2 x CH_2 cyclohexeno), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.25 (m, 4H, 2 x CH_2N-morpholine), 3.80 (m, 4H, 2 x CH_2O-morpholine), 7.50-8.30 (m, 4H, ArH).

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