ISSN 2321-807X

SYNTHESIS AND REACTIONS OF SOME NEW MORPHOLINYLPYRROLYL TETRAHYDROTHIENO[2,3-c] ISOQUINOLINE

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ABSTRACT

Hydrazinolysis of ethyl-5-morpholin-4-yl-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxylate afforded the corresponding carbohydrazide which upon condensation with aromatic aldehydes, acetyl acetone and/ or carbon disulfide gave N- arylidinecarbohydrazide, dimethylpyrazolyl methanone, [1,3,4]oxadiazole-2-thiol and its ethyl ester derivatives respectively. Diazotization of the carbohydrazide with nitrous acid afforded the corresponding carboazide which was used for synthesis of carbamates and substituted carboxamides. Boiling of the carboazide in dry xylene afforded the pyrazinone compound which was used for synthesis of other heterocycles containing pyrrolopyrazinothinoisoquinoline moeity.

KEYWORDS: Tetrahydrothienoisoquinoline, Pyrrole, Pyrazole, Triazole, Synthesis.

Council for Innovative Research

Peer Review Research Publishing System

Journal: Journal of Advances in Chemistry

Vol. 10, No. 3

editorjaconline@gmail.com

www.cirjac.com

ISSN 2321-807X

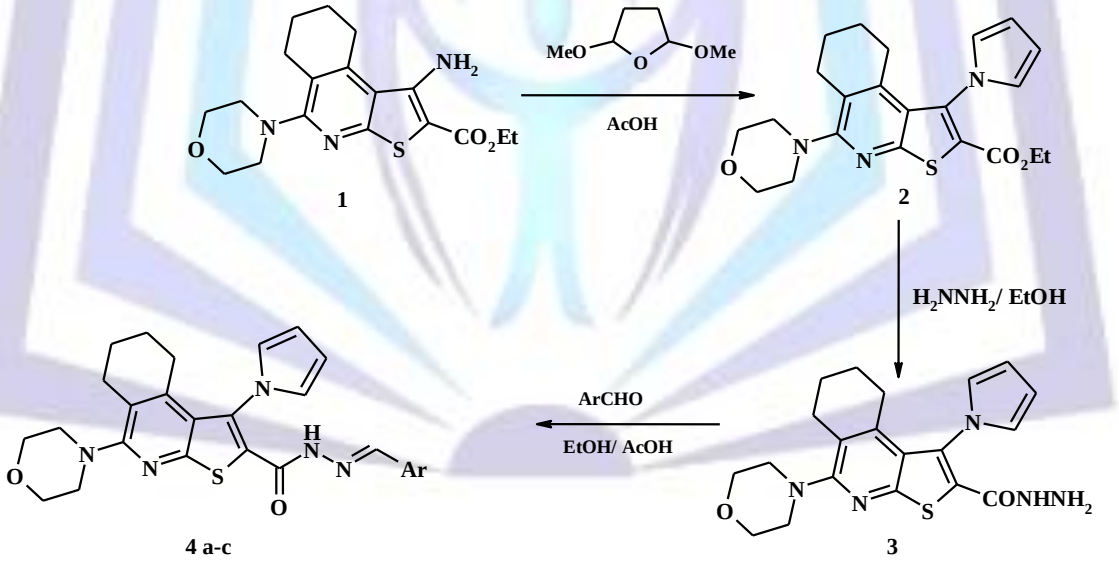
INTRODUCTION

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-leukemic, and anti-tumor properties.[2,3], anti-HIV, and other biological activities [4-7]. Substituted tetrahydroquinolines are the core structures in many important pharmacological agents and drug molecules such as anti-arrhythmic and cardiovascular agents, anticancer drugs, immunosuppressants and as ligands for 5-HTIA and NMDA receptors[8-11]. Thienoquinolines are reported to exhibit a broad spectrum of biological effects. Some of them are useful as memory enhancers,[12] antiallergics,[13] anti-inflammatories, immunoregulators, analgesics and antipyritics.[14] Others are known to possess a good antibacterial [15] and antianaphylactic[16] activities.

RESULTS AND DISCUSSION

In continuation of our work about synthesis of heterocyclic compounds containing morpholinyl- tetrahydrothieno[2,3-c]isoquinoline moiety as described in references [17-21] hoping these new compounds show biological activity. The authors incorporated pyrrolyl ring to the thienotetrahydroisoquinoline system through the reaction of ethyl-1-amino-5-morpholin-4-yl-6,7,8,9-tetrahydrothino[2,3-c]isoquinole-2-carboxylate **1** with 2,5-dimethoxytetrahydrofuran in glacial acetic acid to afford the corresponding pyrrolyl ester **2**. The structure of compound **2** was established by IR, ^{1}H-NMR and mass spectra. IR spectrum showed disappearance of absorption bands characteristic for NH_2 group and absorption band at 1720 cm^{-1} for ester group is still remaining. ^{1}H-NMR in $CDCl_3$ of compound **2** showed singlet signal characteristic for pyrrolyl group at 6.30 and 6.70 ppm. Mass spectrum showed a peak at 411 as molecular ion peak and a base peak. Reaction of pyrrolyl ester **2** with hydrazine hydrate afforded the pyrrolyl carbohydrazide **3**. The structure of **3** was elucidated by elemental and spectral analysis. IR spectrum showed absorption bands at 3400, 3500 and 3100 cm^{-1} characteristic for NH, NH_2 groups and lowering the wave number of CO group in hydrazide from 1720 cm^{-1} in ester compound **2** to 1645 cm^{-1} in carbohydrazide **3**. ^{1}H-NMR spectrum in DMSO-d_6 showed signals at, 5.80 and 4.70 for NH_2, NH groups respectively. Mass spectrum showed at peak at 397 as molecular ion peak.

The pyrrolyl carbohydrazide **3** was used as versatile precursor for synthesis of other hetero cyclic system. Thus, condensation of the carbohydrazide **3** with aromatic aldehydes namely benzaldhyde, *p*-anisaldehyde and/ or cinnamaldehyde afforded the corresponding Schiff's bases (imines) **(4a-c)**. IR spectrum of **4a** revealed disappearance of absorption bands characteristic for NH_2 group in hydrazide **3**. ^{1}H-NMR spectrum in DMSO-d_6 showed multiplet signals at δ 7.30-7.70 characteristic for aromatic protons and at 7.85 for CH benzylidene (scheme 1).

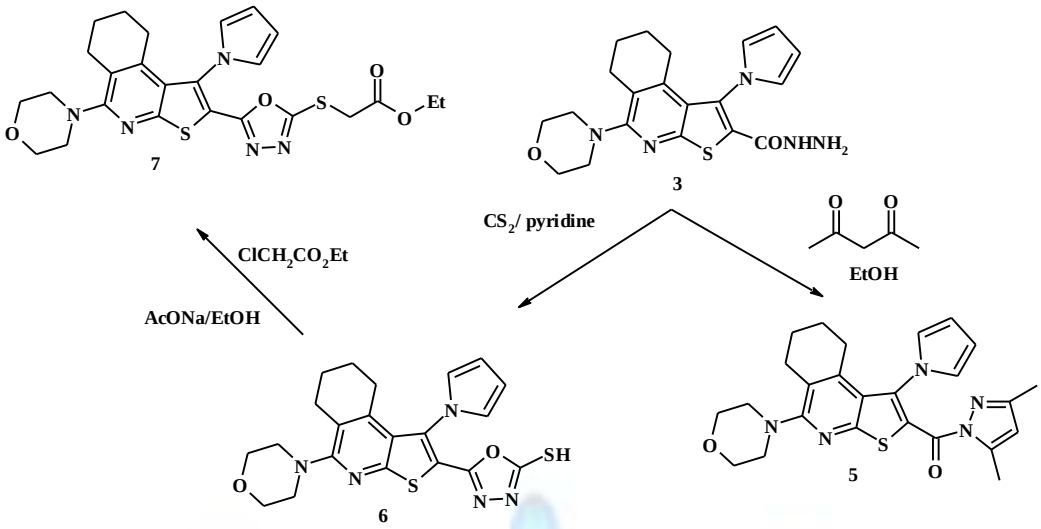


4a Ar: ph
4b Ar :ph(OCH_3)-*p*
4c Ar: -CH=CHph

Scheme 1

Condensation of carbohydrazide **3** with acetyl acetone afforded the dimethylpyrazolyl derivative **5**. The structure of the latter compound was established by elemental and spectral analysis. IR spectrum showed disappearance of absorption bands characteristic for NH, NH_2 group of carbohydrazide **3**. ^{1}H-NMR in $CDCl_3$ showed two singlet signals at δ 2.30 and 2.50 for two methyl groups of pyrazole and singlet signals at 5.95 ppm for CH pyrazole. Also reaction of compound **3** with carbon disulfide in dry pyridine gave the oxadiazole thione **6** which was alkylated using ethyl chloroacetate in presence of ethanol and fused sodium acetate to afford the ethyl sulfanyl acetate 7 (scheme 2).

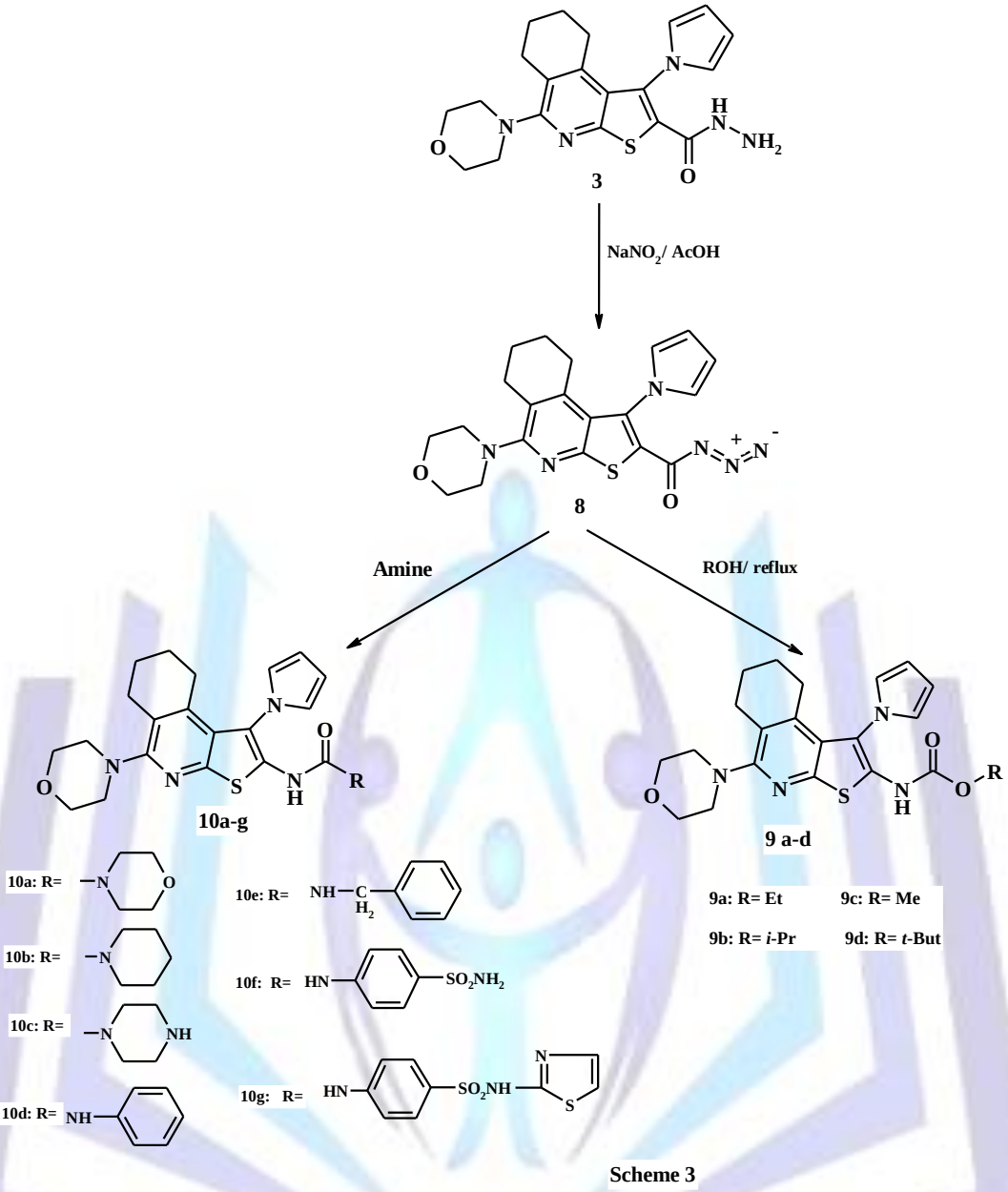
ISSN 2321-807X



Scheme 2

Diazotization of carbohydrazide **3** with sodium nitrite in acetic acid at room temperature afforded the corresponding carboazide **8**. The structure of carboazide **8** was proved by m.p., TLC and IR spectra. IR spectrum revealed disappearance of absorption bands for NH, NH_2 and appearance of absorption band at 2150 cm^{-1} characteristic for azido group. The carboazide compound **8** reacted with various primary, secondary and tertiary alcohols namely: ethanol, methanol, isopropanol and tert-butanol to give the corresponding carbamates **9a-d**. The structure of ethyl carbamate **9a** showed absorption bands at 3230 and 1715 cm^{-1} characteristic for NH and CO carbamate respectively. ^{1}H-NMR of ethyl carbamate **9** in $CDCl_3$ showed triplet and quartet signals at δ 1.30 and 4.20 for ethyl ester group and singlet signal at δ 9.30 for NH group. On the other hand, the carboazide **8** reacts with various cyclic secondary amines and/ or aromatic amines (primary and secondary) to afford the corresponding carboxamide derivatives **10a-f**. The structure of phenyl urea derivative **10c** was elucidated by elemental and spectral data. IR spectrum showed absorption bands at 3350, 3280 for 2NH groups. ^{1}H-NMR spectrum in DMSO-d_6 showed multiplet signals at δ 8.70, 9.80 ppm characteristic for NHph and NHCO respectively (scheme 3).

ISSN 2321-807X



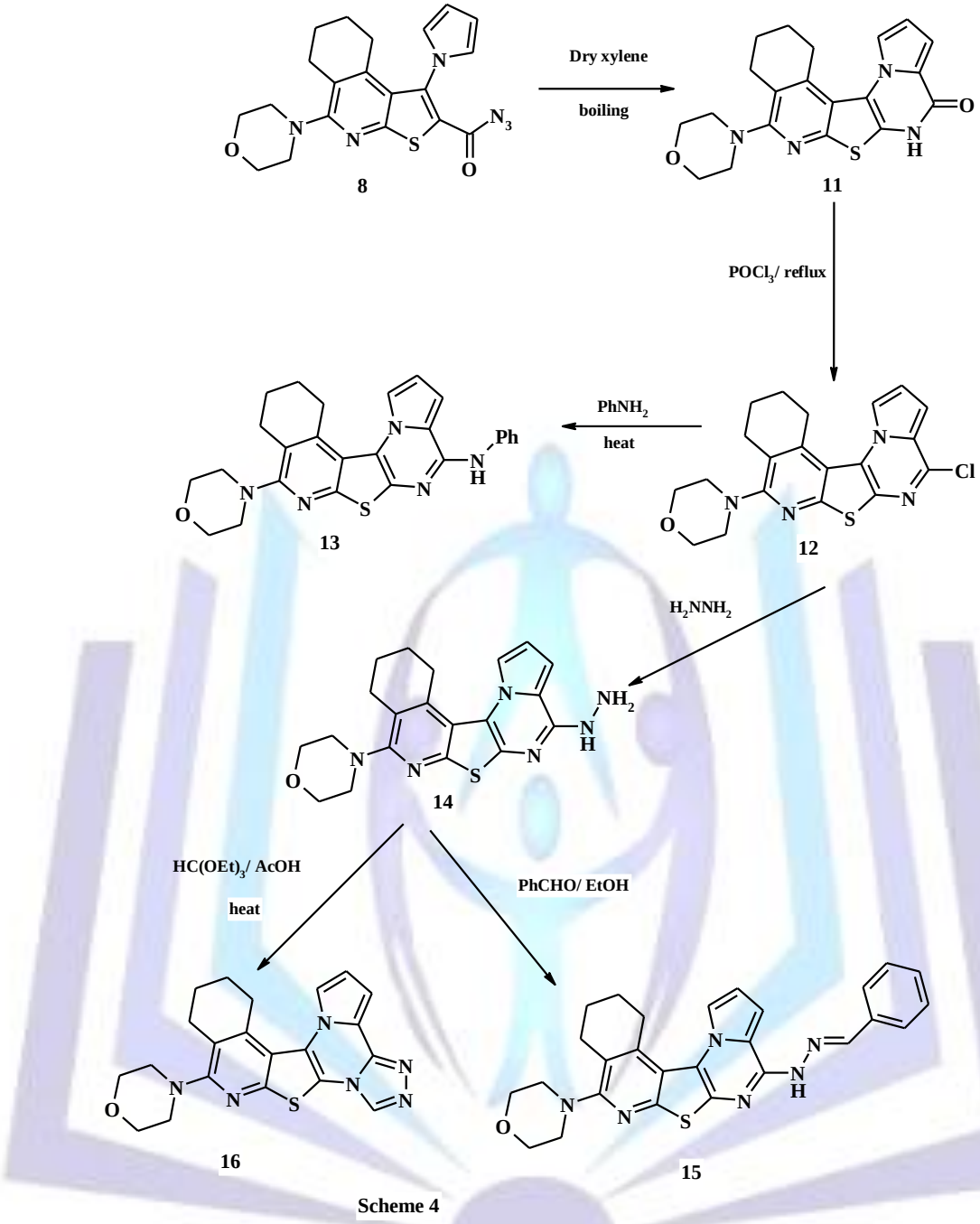
Scheme 3

The carboazide **8** undewent *Curtius* rearrangement upon boiling dry xylene to afford the corresponding pyrrolopyrazinothienoisoquinoline **11**. The structure of the latter compound **11** was established by elemental and spectral analysis. IR spectrum revealed the disappearance of absorption band at 2150 cm^{-1} characteristic for azido group and appearance of absorption band at 3280 cm^{-1} for NH group. ^{1}H-NMR in CF_3CO_2D showed three singlet signals at δ 6.20, 6.50 and 7.00 ppm characteristic for the three CH pyrrolo groups.

Chlorination of the pyrazino compound **11** with phosphorus oxychloride under reflux gave the corresponding chloro derivative **12,** which underwent nucleophilic substitution reactions with primary amines such as aniline and/or hydrazine hydrate to afford the corresponding phenyl amino **13** and hydrazino **14** respectively. The structure of compounds **13**, **14** was proved by IR, ^{1}H-NMR spectra. IR spectrum of compound **13** showed absorption band at 3400 cm^{-1} for NH group. 1H-NMR spectrum in DMSO-d_6 showed multiplet signals at δ 7.20-7.80 ppm characteristic for aromatic protons. While IR spectrum of hydrazine **14** showed absorption band at 3350, 3300 and 3250 for NH, NH_2 groups. ^{1}H-NMR of compound **14** in $CDCl_3$ showed singlet signals at δ 6.50 and δ 7.90 for NH_2 and NH groups respectively.

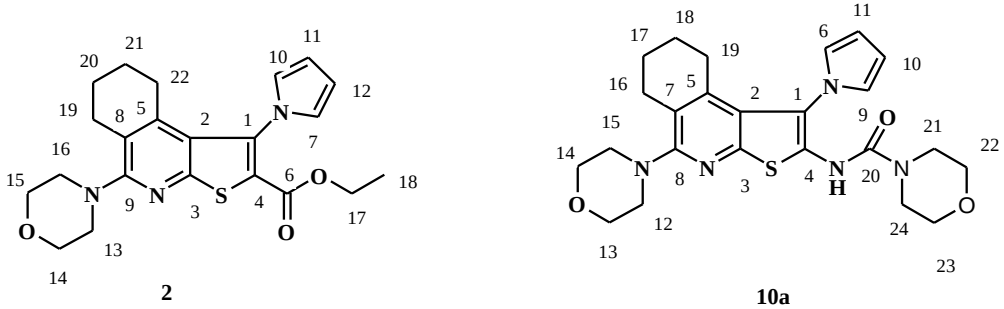
Reaction of hydrazino compound **14** with benzaldehyde afforded the corresponding benzylidene-8-morpholin-4-yl-9,10,11,12-tetrahydropyrrolo[1'',2'':4',5']pyrazino[2',3': 5,4]thieno[2,3-c]isoquinoline-4-ylhydrazide **(15)**, whilst condensation of hydrazino compound **14** with triethyl orthoformate in refluxing acetic acid accompanied by loss of ethanol molecule afforded the corresponding triazolo derivative **16**. The structure of compounds **15**, **16** was established by IR, ^{1}H-NMR spectra. IR spectrum of compound **15** revealed disappearance of absorption bands characteristic for NH, NH_2 groups. 1H-NMR in CF_3CO_2D showed multiplet signals at δ 7.20-7.85 ppm for aromatic protons, while IR spectrum of compound **16** showed absorption band at 1640 cm^{-1} for C=N. ^{1}H-NMR spectrum of compound **16** showed singlet signal at 8.30 for CH triazole (scheme 4).

ISSN 2321-807X



Scheme 4

Numbering of carbon atoms for compounds **2, 10a** needed for ^{13}C-NMR analysis are described in the following figure:



2 **10a**

Figure 1

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EXPERIMENTAL

All melting points are uncorrected and measured on a Fisher-John apparatus. Elemental analyses were determined on an Elementar Analysensystem GmbH-VarioEL V.3 microanalyzer in the central lab of Assiut University. Their results were found to be in good agreement (±0.2%) with the calculated values. IR spectra were recorded on a Pye-Unicam Sp-100 spectrophotometer using KBr wafer technique. NMR spectra were recorded on a varian EM-390 90 MHz and Joel 400 MHz spectrometers in a suitable deutrated solvent using TMS as internal standard (chemical shifts in ppm). MS spectra were recorded on Jeol JMS-600 apparatus. The amino ester compound **1** was prepared according to literature procedure[17] with melting point 202-204^{o}C.

Ethyl-5-morpholin-4-yl-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c] isoquinoline-2-carboxylate (2)

A mixture of ethyl-1-amino-5-morpholin-4-yl-6,7,8,9-tetrahydrothieno[2,3-c]iso quinoline-2-carboxylate **(1)** (3.6 g, 0.01 mol) and 2,5-dimethoxytetrahydrofuran (1.50 ml, 0.011 mol) in acetic acid (15 ml) was refluxed for 1 hr. The solid product which formed on cold was filtered off, dried and recrystallized from ethanol to give white needles in 83% yield, m.p. 186-188^{o}C. Anal. Calcd. For: $C_{22}H_{25}N_3O_3S$ (411.53): C, 64.21; H, 6.12; N, 10.21; S, 7.79%. Found: C, 64.25; H, 6.10; N, 10.16; S, 7.83%. IR ν (cm^{-1}): 2950, 2850 (CH aliphatic), 1720 (CO ester), 1620 (C=N). ^{1}H-NMR ($CDCl_3$): 1.10-1.30 (t, *J*= 9.00 Hz, 3H, CH_3 ester), 1.70 (m, 4H, $2CH_2$ cyclohexeno), 2.65 (m, 4H, $2CH_2$ cyclohexeno), 3.35 (m, 4H, 2 x CH_2-N morpholine), 3.80 (m, 4H, 2 x CH_2-O morpholine), 4.05-4.30 (q, *J*= 7.50 Hz, 2H, CH_2 ester), 6.30 (s, 2H, 2CH=C pyrrolyl), 6.70 (s, 2H, 2CH-N pyrrolyl). ^{13}C-NMR ($CDCl_3$, 400 MHz): 13.91 (C18, CH3 ester), 22.03, 22.27, 22.32, 26.45 (C19-C22 cyclohexeno), 50.10 (C13: C16, $(CH_2)_2$-N morpholino), 61.29 (C17, CH_2 ester), 66.96 (C14:C15, $(CH_2)_2$-O morpholino), 109.15 (C11, C12 pyrrolyl), 122 (C7, C10 pyrrolyl), 124.90 (C2), 136.79 (C5), 144.96 (C1, C4), 156.03 (C3), 161 (C9), 161.64 (C6, CO ester). EI-MS: *m/z (%)* = 411 (M^+, 100), 381 (M^+-Et, 11), 366 (M^+-OEt, 10), 354 (M^+-COEt, 22), 325 (M^+-morpholino, 4), 86 (morpholino, 3).

5-Morpholin-4-yl-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]iso- quinoline-2-carbo hydrazide (3)

A mixture of pyrrol-1-yl ester compound **2** (1 g, 2.5 mmol) and hydrazine hydrate (5 ml, 0.1 mol) was heated under neat conditions for 1 hr then ethanol absolute (10 ml) was added and reflux continued for additional 2 hrs. The solid product which formed on cold was filtered off, dried and recrystallized from ethanol to afford white crystals in 69% yield, m.p. 236-238^{o}C. Anal. Calcd. For: $C_{20}H_{23}N_5O_2S$ (397.50) C, 60.43; H, 5.83; N, 17.62; S, 8.07%. Found: C, 60.40; H, 5.79; N, 17.65; S, 8.00%. IR ν (cm^{-1}): 3400, 3300, 3100 (NH, NH_2), 2950, 2850 (CH aliphatic), 1645 (CO hydrazide), 1620 (C=N). ^{1}H-NMR (DMSO-d_6): 1.50 (m, 4H, 2 x CH_2 cyclohexeno), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 x CH_2-N morpholine), 3.70 (m, 4H, 2 x CH_2-O morpholine), 5.80 (S, 2H, NH_2), 6.30 (s, 2H, 2CH=C pyrrrolyl), 6.95 (s, 2H, 2CH-N pyrrolyl), 7.40 (s, 1H, NH). EI-MS: *m/z (%)* = 398 (M^++1, 20.1), 397 (M^+, 34), 396 (M^+-1, 30), 368 (22), 366 (M^+-N_2H_3, 100), 361 (21), 353 (M^+-$CONH_2$, 14), 297 (M^+-$C_4H_8N_2O$, 21), 281 (17), 253 (23), 225 (16).

N-Arylidene-1-(1H-pyrrol-1-yl)-5-morpholin-4-yl--6,7,8,9-tetrahydrothieno [2,3-c]isoquinoline-2-carbohydraide (4)

General procedure:

Carbohydrazide compound **3** (0.5 g, 2 mmol) and aromatic aldehyde (2.5 mmol) were refluxed in ethanol (20 ml) and acetic acid (0.5 ml) for 2 hrs. The solid precipitate which is formed during reflux was filtered off, dried and recrystallized from the proper solvent.

N-Benzylidene-1-(1H-pyrrol-1-yl)-5-morpholin-4-yl--6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carbohydraide (4a)

Obtained from carbohydrazide **3** and benzaldehyde. The solid precipitate which is formed during reflux was filtered off, dried and recrystallized from acetic acid as white crystals. IR ν (cm^{-1}): 3300 (NH), 3050 (CH aromatic), 2950, 2850 (CH aliphatic), 1650 (CO hydrazide), 1610 (C=N). ^{1}H-NMR (DMSO-d_6): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.80 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 x CH2-N morpholine), 3.80 (m, 4H, 2 x CH_2-O morphoine), 6.50 (s, 2H, 2 CH=C pyrrolyl), 6.95 (s, 2H, 2CH-N pyrrolyl), 7.30-7.70 (m, 5H, ArH), 7.85 (s, 1H, N=CHph), 8.00 (s, 1H, NH).

ISSN 2321-807X

Table 1: Physical constants of compounds 4a-c, 9a-d, 10a-g

compound	Empirical Formula	Found, % / Calculated, %				Mp, °C	Yield
		C	H	N	S		
4a	$C_{27}H_{27}N_5O_2S$ (485.61)	66.72 / 66.78	5.65 / 5.60	14.38 / 14.42	6.67 / 6.60	260-262	0.44 g (72%)
4b	$C_{28}H_{29}N_5O_3S$ (515.64)	65.10 / 65.22	5.71 / 5.67	13.64 / 13.58	6.28 / 6.22	268-270	0.52 g (80%)
4c	$C_{29}H_{29}N_5O_2S$ (511.62)	67.94 / 68.08	5.80 / 5.71	13.75 / 13.69	6.33 / 6.27	280-282	0.49 g (76%)
9a	$C_{22}H_{26}N_4O_3S$	62.00 / 61.95	6.22 / 6.14	13.24 / 13.14	7.58 / 7.52	232-234	0.43 g (83%)
9b	$C_{21}H_{24}N_4O_3S$	61.05 / 61.15	5.90 / 5.86	13.64 / 13.58	7.85 / 7.77	210-212	0.4 g (80%)
9c	$C_{23}H_{28}N_4O_3S$	62.76 / 62.70	6.50 / 6.41	12.68 / 12.72	7.40 / 7.28	216-218	0.46 g (86%)
9d	$C_{24}H_{30}N_4O_3S$	63.48 / 63.41	6.54 / 6.65	12.25 / 12.32	6.96 / 7.05	226-228	0.42 g (76%)
10a	$C_{24}H_{29}N_5O_3S$	61.57 / 61.65	6.00 / 6.25	15.10 / 14.98	6.92 / 6.86	208-210	0.39 g (68%)
10b	$C_{24}H_{30}N_6O_2S$	61.82 / 61.78	6.54 / 6.48	17.92 / 18.01	7.00 / 6.86	224-226	0.34 g (60%)
10c	$C_{25}H_{31}N_5O_2S$	64.56 / 64.49	6.66 / 6.71	14.97 / 15.04	7.00 / 6.89	220-222	0.37 g (64%)
10d	$C_{26}H_{27}N_5O_2S$	66.00 / 65.94	5.62 / 5.75	14.85 / 14.79	6.70 / 6.77	218-220	0.42 g (70%)
10e	$C_{27}H_{29}N_5O_2S$	66.62 / 66.51	6.08 / 5.99	14.47 / 14.36	6.48 / 6.58	230-232	0.48 g (80%)
10f	$C_{26}H_{28}N_6O_4S_2$	56.61 / 56.50	5.20 / 5.11	15.15 / 15.21	11.73 / 11.60	234-236	0.44 g (65%)

10g	$C_{29}H_{29}N_7O_4S_3$	54.86 54.79	4.51 4.60	15.36 15.42	15.00 15.13	238-240	0.44 g (56%)

N-(4-Methoxybenzylidene-1-(1H-pyrrol-1-yl)-5-morpholin-4-yl--6,7,8,9-tetra hydrothieno[2,3-c]isoquinoline-2-carbohydraide (4b)

Obtained from carbohydrazide **3** and *p*-.anisaldehyde. The solid precipitate which is formed during reflux was filtered off, dried and recrystallized from acetic acid as white crystals. IR ν (cm^{-1}): 3280 (NH), 3030 (CH aromatic), 2950, 2850 (CH aliphatic), 1645 (CO hydrazide), 1600 (C=N). ^{1}H-NMR (CF_3CO_2D): 1.95 (m, 4H, 2 x CH_2 cyclohexeno), 2.90 (m, 4H, 2 x CH_2 cyclohexeno), 3.90 (m, 4H, 2 x CH_2-N morpholine), 4.25 (s, 3H, OCH_3), 4.50 (m, 4H, 2 x CH_2-O morpholine), 6.95 (s, 2H, 2CH=C pyrrolyl), 7.30 (s, 2H, 2CH-N pyrrolyl), 7.70-8.00 (m. 5H, ArH), 8.25 (s, 1H, N=CH).

2-Morholin-4-yl-N-(3-phenylallylidene)-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydro thieno[2,3-c] isoquinoline-2-carbohydrazide (4c)

Obtained from carbohydrazide **3** and cinnamaldehyde. The solid precipitate which is formed during reflux was filtered off, dried and recrystallized from dioxane as yellow crystals. IR ν (cm-1): 3300 (NH), 3050 (CH aromatic), 1655 (CO), 1600 (C=N). ^{1}H-NMR (CF_3CO_2D): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.80 (m, 4H, 2 x CH_2 cyclohexeno), 3.30 (m, 4H, 2 x CH_2-N morpholine), 3.90 (m, 4H, 2 x CH_2-O morpholine), 6.30 (s, 2H, 2 x CH=C pyrrolyl), 6.90 (s, 2H, 2 x CH-N pyrrolyl), 7.20-7.80 (m, 7H, ArH+ CH=CH), 8.30 (s, 1H, N=CH).

(3,5-Dimethyl-1H-pyrazol-1-yl)(5-morpholino-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydro thieno[2,3-c]isoquinolin-2-yl)methanone (5)

A mixture of carbohydrazide compound **3** (0.5 g, 1.2 mmol) and acetyl acetone (0.2 ml, 2 mmol) in ethanol (20 ml) was refluxed for 3 hrs. The solid product which formed during reflux was filtered off, dried and recrystallized from ethanol-dioxane mixture in 79% yield, m.p. 178-180^{o}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, 65.00; H, 6.00; N, 15.23; S, 7.00%. IR ν (cm^{-1}): 3920, 2820 (CH aliphatic), 1695 (CO), 1620 (C=N). ^{1}H-NMR ($CDCl_3$): 1.65 (m, 4H, 2 x CH_2 cyclohexeno), 2.30, 2.50 (2s, 6H, 2 x CH_3 pyrazole), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.25 (m, 4H,2 x CH_2-N morpholine), 3.80 (m, 4H, 2 x CH_2-O morpholine), 5.95 (s, 1H, CH pyrazole), 6.35 (s, 2H, 2CH=C pyrrolyl), 6.80 (s, 2H, CH-N pyrrolyl). EI-MS: *m/z (%)* =462 (M^++1, 11), 461 (M^+, 100), 446 (M^+-CH_3, 45), 431 (M^+-2CH_3, 9.2), 397 (M^+-C_5H_4, 11), 375 (M^+-morpholino, 21.6), 366 (M+-$C_5H_7N_2$, 4.6), 338 (M^+-$C_6H_7N_2O$, 15), 252 (M+-$C_{10}H_{15}N_3O_2$, 9).

5-(5-Morpholin-4-yl-1-pyrrol-1-yl-6,7,8,9-tetrahydrothieno[2,3-c]iso quinolin-2-yl)-[1,3,4]oxadiazole-2-thiol (6)

A mixture of carbohydrazide compound **3** (1.0 g, 1.20 mmol) and carbon disulfide (2 ml) in dry pyridine (4 ml) was heated on steam bath for 6 hrs. The solid product which formed during heating washed with ethanol, filtered off, dried and recrystallized from ethanol into pale yellow crystals in 81% yield, m.p. 312-314^{o}C. Anal. Calcd. For: $C_{12}H_{21}N_5O_2S_2$ (439.56) C, 57.38; H, 4.82; N, 15.93; S, 14.59%. Found: C, 57.30; H, 4.86; N, 16.00; S, 14.64%. IR ν (cm^{-1}): 2920, 2850 (CH aliphatic), 1600 (C=N). ^{1}H-NMR (CF_3CO_2D): 2.00 (m, 4H, 2 x CH_2 cyclohexeno), 2.80 (m, 4H, 2 x CH_2 cyclohexeno), 3.65 (m, 4H, 2 x CH_2-N morpholine), 4.20 (m, 4H, 2 x CH_2-O morpholine), 6.70 (s, 2H, 2CH=C pyrrolyl), 7.05 (s, 2H, 2CH-N pyrrolyl).

Ethyl[5-(5-Morpholin-4-yl-1-pyrrol-1-yl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl)-[1,3,4]oxadiazol-2-ylsulfanyl] acetate (7)

A mixture of thiol compound **6** (0.50 g, 1.13 mmol) and ethyl chloroacetate (0.2 ml, 1.6 mmol) in ethanol (20 ml) in presence of fused sodium acetate (0.3 g, 4 mmol) was refluxed for 2 hrs. The solid precipitate which formed on cooling and dilution with water was filtered off, dried and recrystallized from ethanol into white crystals in 76% yield, m.p. 224-226^{o}C. Anal. Calcd. For: $C_{25}H_{27}N_5O_4S_2$ (525.65) C, 57.12; H, 5.18; N, 13.32; S, 12.20%. Found: C, 57.30; H, 5.38; N, 13.08; S, 12.23%; IR ν (cm^{-1}): 2950, 2850 (CH aliphatic), 1730 (CO ester), 1620 (C=N). ^{1}H-NMR ($CDCl_3$): 1.30 (t, *J*= 7.50 Hz, 3H, CH_3 ester), 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.70 (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), 4.10 (s, 2H, SCH_2), 4.20 (q, *J*= 6.00 Hz, 2H, CH_2 ester), 6.30 (s, 2H, 2CH=C pyrrolyl), 6.90 (s, 2H, 2CH-N pyrrolyl).

Morpholin-4-yl-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]iso quinoline-2-carboazide (8)

Sodium nitrite solution (0.30 g, 4.20 mmol, 10%) was added dropwise with stirring to a solution of carbohydrazide compound **3** (0.50 g, 1.20 mmol) in glacial acetic acid (20 ml) at 0^{o}C in an ice bath for 5 minutes. The solid product which formed during stirring was filtered off, dried and used without recrystallization in 56% yield, m.p. 140-142^{o}C. Anal. Calcd. For: $C_{20}H_{20}N_6O_2S$ (408.49) C, 58.81; H, 4.94; N, 20.57; S, 7.85%. IR ν (cm^{-1}): 2950, 2850 (CH aliphatic), 2150 (N_3), 1665 (CO azide), 1580 (C=N).

ISSN 2321-807X

Alkyl-5-morpholino-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl carbamate (9 a-d)

General procedure:

A solution of carboazide compound **8** (0.5 g, 1.2 mmol) in an alcohol (20 ml) was refluxed for 2 hrs. The solid product which formed during reflux was filtered off, dried and recrystallized from ethanol-dioxane 1:1.

Ethyl-5-morpholino-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]iso quinolin-2-yl carbamate (9a)

Obtained from carboazide **8** and ethanol. The solid product was recrystallized from ethanol-dioxane 1:1 mixture as white crystals. IR ν (cm^{-1}): 3230 (NH), 2920, 2820 (CH aliphatic), 1715 (CO carbamate), 1590 (C=N). ^{1}H-NMR ($CDCl_3$): 1.30 (t, *J*= 7.5 Hz, 3H, CH_3), 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.75 (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), 4.20 (q, *J*= 6.0 Hz, 2H, CH_2 ester), 6.30 (s, 2H, 2CH=C pyrrolyl), 6.90 (s, 2H, 2CH-N pyrrolyl), 9.30 (s, 1H, NH).

Methyl-5-morpholino-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl carbamate (9b)

Obtained from carboazide **8** and methanol. The solid product was recrystallized from ethanol as pale brown crystals. IR ν (cm^{-1}): 3200 (NH), 2920, 2850 (CH aliphatic), 1720 (CO ester), 1600 (C=N). ^{1}H-NMR ($CDCl_3$): 1.50 (m, 4H, 2 x CH_2 cyclohexeno), 2.60 (m, 4H, 2 x CH_2 cyclohexeno), 3.00 (m, 4H, 2 x CH_2-N morpholine), 3.70 (m, 4H, 2 x CH_2-O morpholine), 6.25 (s, 2H, 2CH=C pyrrolyl), 6.70 (s, 2H, 2CH-N pyrrolyl), 9.60 (s,1H, NH).

Isopropyl-5-morpholino-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl carbamate (9c)

Obtained from carboazide **8** and isopropanol. The solid product was recrystallized from ethanol-dioxane 1:1 mixture into pale red crystals. IR ν (cm^{-1}): 3250 (NH), 2980, 29220, 2850 (CH aliphatic), 1715 (CO carbamate). 1H-NMR ($CDCl_3$): 1.30,1.35 (d, 6H, $2CH_3$ isopropyl), 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.15 (m, 4H, 2 x CH_2-N morpholine), 3.80 (m, 4H, 2 x CH_2-O morpholine), 5.00 (s, 1H, CH isopropyl), 6.30 (s, 2H, 2CH=C pyrrolyl), 6.70 (s, 2H, CH-N pyrrolyl), 9.55 (s, 1H, NH) . EI-MS: *m/z (%)* = 440 (M+, 100), 412 (M+-C2H4, 12), 397 (M^+-C_3H_7, 15), 381 (M^+-C_3H_7O, 3), 354 (M^+-$C_4H_6O_2$, 21), 338 (M^+-$C_4H_8NO_2$).

t-Butyl-(5-Morpholin-4-yl-1-pyrrol-1-yl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl) carbamate (9d)

Obtained by the reaction of carboazide **8** with tert-butanol. The solid product was recrystallized from ethanol-dioxane 1:1 mixture into white crystals. IR ν (cm^{-1}): 3300 (NH), 2920, 28510 (CH aliphatic), 1710 (CO carbamate), 1590 (C=N). ^{1}H-NMR ($CDCl_3$): 1.50 (s, 9H, $3CH_3$), 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.10 (m, 4H, 2 x CH_2-N morpholine), 3.85 (m, 4H, 2 x CH_2-O morpholine), 6.30 (s, 2H, 2CH=C pyrroyl), 6.70 (s, 2H, 2CH-N pyrrolyl), 9.60 (s, 1H, NH).

N-(5-Morpholino-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]iso- quinolin-2-yl) substituted-4-carboxamide (10a-g)

General procedure:

A mixture of pyrrol-1-ylcarboazide **8** (0.5 g, 1.2 mmol) and primary (secondry) amine (1.25 mmol) was refluxed in dry toluene for 2 hrs. The solid product which formed on cooling was filtered off, dried and recrystallized from the proper solvent.

N-(5-Morpholino-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl) morpholine-4-carboxamide (10a)

Obtained from carboazide **8** and morpholine. The solid product was recrystallized from ethanol as pale green crystals. IR ν (cm^{-1}): 3400-3300 (br NH), 2920, 2850 (CH aliphatic), 1640 (CO amide). ^{1}H-NMR ($CDCl_3$): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.75 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 8H, $4CH_2$-N morpholine), 3.90 (m, 8H, $4CH_2$-O morpholine), 6.30 (s, 2H, 2CH=C pyrrolyl), 6.75 (s, 2H, 2CH-N pyrrolyl), 9.50 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$): 21.93, 22.27, 23.33, 26.45 (C16-C19 cyclohexeno), 50.31 (C12, C15, C21, C24 :2 x $(CH_2)_2$-N morpholino), 66.52, 66.96 (C13, C14, C22, C23: 2 x $(CH_2)_2$-O morpholino), 109.69 (C10, C11 pyrrolyl), 123 (C6, C9 pyrrolyl), 123.76 (C2), 129.87 (C5), 144.51 (C3, C4), 160.46 (C8), 161.30 (C20, CO). EI-MS: *m/z (%)* = 467.18 (M+, 10), 441 (100).

N-(5-Morpholino-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl) piperazine-4-carboxamide (10b)

Obtained from carboazide **8** and piperazine. The solid product was recrystallized from ethanol as white crystals. IR ν (cm^{-1}): 3400, 3300 (2NH), 2920, 2850 (CH aliphatic), 1650 (CONH), 1580 (C=N). ^{1}H-NMR (DMSO-d_6): 1.90 (m, 4H, 2x CH_2 cyclohexeno), 2.60 (m, 4H, 2 x CH_2 cyclohexeno), 2.90 (m, 4H, $2CH_2$-NH piperazine), 3.20 (m, 8H, $(CH_2)_2$-N piperazine + $(CH_2)_2$-N morpholine), 3.80 (m, 4H, $(CH_2)_2$-O morpholine), 6.70 (s, 2H, 2CH=C pyrrolyl), 6.95 (s, 2H, 2CH-N pyrrolyl), 7.40 (s, 1H, NH piperazine), 9.40 (s, 1H, NH amide).

N-(5-Morpholino-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl) piperidine-4-carboxamide (10c)

Obtained from carboazide **8** and piperidine. The solid product was recrystallized from ethanol as white crystals. IR ν (cm^{-1}): 3400 (NH), 2950, 2850 (CH aliphatic), 1630 (CO amide), 1560 (C=N). ^{1}H-NMR ($CDCl_3$): 1.50 (m, 4H, 2 x CH_2 C2, C4

piperidine), 1.60 (m, 2H, CH_2 C3 piperidine), 1.75 (m, 4H, 2 x CH_2 cyclohexeno), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 x CH_2-N morpholine), 3.40 (m, 4H, 2 x CH_2 C1, C5 piperidine), 3.80 (m, 4H, 2 x CH_2-O morpholine), 6.30 (s, 2H, 2CH=C pyrrolyl), 6.90 (s, 2H, 2CH-N pyrrolyl), 9.60 (s, 1H, NH).

1-(5-Morpholin-4-yl-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl)-3-phenylurea (10d)

Obtained from carboazide **8** and aniline. The solid product was recrystallized from dioxane as white needles. IR ν (cm^{-1}): 3350, 3280 (2NH), 3030 (CH aromatic), 2920, 2850 (CH aliphatic), 1690 (CO), 1590 (C=N). ^{1}H-NMR (DMSO-d_6): 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.65 (m, 4H, 2 x CH_2 cyclohexeno), 3.25 (m, 4H, 2 x CH_2-N morpholine), 3.70 (m, 4H, 2 x CH_2-O morpholine), 6.30 (s, 2H, 2 x CH=C pyrrolyl), 6.85 (s, 2H, 2 x CH-N pyrrolyl), 7.30-7.70 (m, 5H, ArH), 8.70 (s, 1H, NHph), 9.80 (s, 1H, NHCO).

1-Benzyl-3-(5-morpholin-4-yl-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]iso quinolin-2-yl)urea (10e)

Obtained from carboazide **8** and benzyl amine. The solid product was recrystallized from ethanol-dioxane 1:1 mixture as yellow needles. IR ν (cm^{-1}): 3400, 3300 (2NH), 3020 (CH aliphatic), 2920, 2850 (CH aliphatic), 1630 (CO). ^{1}H-NMR ($CDCl_3$): 1.70 (m, 4H, 2 x CH_2cyclohexeno), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 x CH_2-N morpholine), 3.90(m, 4H, 2 x CH_2-O morpholine), 4.30 (s, 2H, CH_2ph), 6.30 (s, 2H, 2 x CH=C pyrrolyl), 6.80 (s, 2H, 2 x CH-N pyrrolyl), 7.10-7.40 (m, 5H, ArH), 8.00 (s, 1H, NH benzyl), 9.60 (s, 1H, NHCO).

4-(3-(5-Morpholin-4-yl-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin -2-yl) ureido)benzenesulfonamide (10f)

Obtained from carboazide **8** and sulfanilamide. The solid product was recrystallized from dioxane as pale brown needles. IR ν (cm^{-1}): 3400, 3350, 3250 (NH, NH_2), 3030 (CH aromatic), 2920, 2850 (CH aliphatic), 1695 (CO). ^{1}H-NMR (DMSO-d_6): 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.70 (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), 5.90 (s, 2H, NH_2), 6.20 (s, 2H, 2 x CH=C pyrrolyl), 6.80 (s, 2H, 2 x CH-N pyrrolyl), 8.85 (s, 1H, NHph), 9.60 (s, 1H, CONH).

4-(3-(5-Morpholin-4-yl)-1-(1H-pyrrol-1-yl)-6,7,8,9-tetragydrothieno[2,3-c]isoquinolin -2-yl)ureido)-N-(thiazol-2-yl)benzenesulfanamide (10g)

Obtained from carboazide **8** and sulfathiazole. The solid product was recrystallized from dioxane as white crystals. IR ν (cm^{-1}): 3400, 3350, 3250 (3NH), 3030 (CH aromatic), 2920, 2850 (CH aliphatic), 1705 (CONH). ^{1}H-NMR (DMSO-d_6): 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), 3.85 (m, 4H, 2 x CH_2-O morpholine), 6.30 (s, 2H, 2 x CH=C pyrrolyl), 6.70 (s, 2H, 2CH-N pyrrolyl), 7.20-7.80 (m, ,6H, ArH+ 2CH thiazole), 8.90 (NHph), 9.60 (NHCO), 10.60 (s, 1H, NH thiazole).

8-Morpholin-4-yl-9,10,11,12-tetrahydropyrrolo[1'',2'':4',5']pyrazino[2',3' :5,4] thieno[2,3-c] isoquinolin-4(5H)-one (11)

A suspension of caboazide compound **8** (1 g, 2.45 mmol) in xylene (5 ml) was refluxed for 2 hrs. The solid product which formed during reflux was filtered off, dried and recrystallized from dioxane into white crystals in 38% yield, m.p. 320-322^{o}C. Anal. Calcd. For: $C_{20}H_{20}N_4O_2S$ (380.47) C, 63.14; H, 5.30; N, 14.73; S, 8.43%. Found: C, 63.22; H, 5.38; N, 14.86; S, 8.50%. IR ν (cm^{-1}): 3280 (NH), 2920, 2850 (CH aliphatic), 1640 (CO pyrazine), 1585 (C=N). ^{1}H-NMR (CF_3CO_2D): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.50 (m, 4H, 2 x CH_2 cyclohexeno), 3.65 (m, 4H, 2CH2-N morpholine), 4.20 (m, 4H, 2 x CH_2-O morpholine), 6.20 (s, 1H, CH C:2 pyrrole), 6.50 (s, 1H, CH C:1 pyrrole), 7.30 (s, 1H, CH C:3 pyrrole).

4-Chloro-8-morpholin-4-yl-9,10,11,12-tetrahydropyrrolo[1'',2'':4',5'] pyrazino[2',3':5,4]thieno[2,3-c]isoquinoline (12)

A solution of pyrrolopyrazinothienoisoquinolinone **11** (1.00 g, 2.50 mmol) in phosphorus oxychloride (3 ml) was refluxed for 2 hrs. The solid precipitate which formed on cooling and dilution with water was filtered off, dried and recrystallized from ethanol into green crystals in 60%, m.p. 116-118^{o}C. Anal. Calcd. For: $C_{20}H_{19}ClN_4OS$ (398.92) C, 60.22; H, 4.80; N, 14.04; S, 8.04%. Found: C, 60.30; H, 5.00; N, 13.92; S, 8.15%. IR ν (cm^{-1}): 2920, 2850 (CH aliphatic), 1620 (C=N). ^{1}H-NMR ($CDCl_3$): 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.60 (m, 4H, 2 x CH_2 cyclohexeno), 3.25 (m, 4H, 2 x CH_2-N morpholine), 3.80 (m, 4H, 2 x CH_2-O morpholine), 6.35 (s, 1H, CH C:2 pyrrole), 6.90 (s, 1H, CH C:3 pyrrole), 7.20 (s, 1H, CH C:1 pyrrole).

4-Phenylamino-8-morpholin-4-yl-9,10,11,12-tetrahydropyrrolo[1'',2'' :4',5']pyrazino[2',3':5,4]thieno[2,3-c]isoquinoline (13)

A mixture of chloro compound **12** (0.5 g, 1.26 mmol) and aniline (0.25 ml, 2.70 mmol) was heated under neat conditions for 5 minutes then ethanol (15 ml) was added and reflux was continued for additional 2 hrs. The solid product which formed on cooling was filtered off, dried and recrystallized from ethanol: dioxane mixture into white crystals in 74% yield, m.p. 262-264^{o}C. Anal. Calcd. For: $C_{26}H_{25}N_5OS$ (455.59) C, 68.55; H, 5.53; N, 15.37; S, 7.04%. Found: C, 68.60; H, 5.48; N, 15.44; S, 7.20%. IR ν (cm^{-1}): 3400 (NH), 3030 (CH aromatic) 2920, 2850 (CH aliphatic), 1595 (C=N). ^{1}H-NMR (DMSO-d_6): 1.70 (m, 4H, 2 x CH_2 cyclohexeno), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 x CH_2-N morpholine), 3.80 (m,

4H, 2x CH_2-O morpholine), 6.35 (s, 1H, CH C:2 pyrrole), 6.90 (s, 1H, CH C:3 pyrrole), 7.20-7.80 (m, 6H, ArH+ CH C:1 pyrrole), 9.70 (s, 1H, NH).

4-Hydrazino-8-morpholin-4-yl-9,10,11,12-tetrahydropyrrolo[1'',2'':4',5'] pyrazino[2',3':5,4]thieno[2,3-c]isoquinoline (14)

A solution of chloro compound (13) (0.50 g, 1 mmol) and hydrazine hydrate (0.25 g, 5 mmol) in ethanol was refluxed for 2 hrs. The solid product formed on cooling was filtered off, dried and recrystallized from ethanol into white crystals in 52% yield, m.p. 242-244^{o}C. Anal. Calcd. For: $C_{20}H_{22}N_6OS$ (394.50) C, 60.89; H, 5.62; N, 21.30; S, 8.13%. Found: C, 60.97; H, 5.58; N, 21.38; S, 8.25%. IR v (cm-1): 3350, 3300, 3250 (NH, NH_2), 2920, 2850 (CH aliphatic), 1640 (C=N). ^{1}H-NMR ($CDCl_3$): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.70 (m, 4H, 2 x CH_2 cyclohexeno), 3.25 (m, 4H, 2 x CH_2-N morpholine), 3.85 (m, 4H, 2 x CH_2-O morpholine), 6.35 (s, 1H, CH C:2 pyrrole), 6.50 (s, 2H, NH_2), 6.85 (s, 1H, CH C:3 pyrrole), 7.20 (s, 1H, CH C:1 pyrrole), 7.90 (s, 1H, NH).

Benzylidene-8-morpholin-4-yl-9,10,11,12-tetrahydropyrrolo[1'',2'':4',5'] pyrazino[2',3':5,4]thieno[2,3-c]isoquinoline-4-ylhydrazide (15)

A mixture of hydrazine compound 14 (0.50 g, 1.27 mmol) and benzaldehyde (0.5 ml, 4.7 mmol) was heated under neat conditions for 5 minutes then ethanol (10 ml) was added and reflux was continued for 2 hrs. The solid product formed on cooling was filtered off, dried and recrystallized from ethanol: dioxane mixture as yellow crystals in 75% yield. Anal. Calcd. For: $C_{27}H_{26}N_6OS$ (482.61) C, 67.20; H, 5.43; N, 17.41; S, 6.64%. Found: C, 67.12; H, 5.50; N, 17.26; S, 6.85. IR v (cm^{-1}): 3030 (CH aromatic), 1640 (C=N). ^{1}H-NMR (CF_3CO_2D): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.75 (m, 4H, 2 x CH_2 cyclohexeno), 3.20 (m, 4H, 2 xCH_2-N morpholine), 3.85 (m, 4H, 2 x CH_2-O morpholine), 6.35 (s, 1H, CH C:2 pyrrole), 6.95 (s, 1H, CH C:3 pyrrole), 7.20-7.80 (m, 7H, ArH + CHph + CH C:1 pyrrole).

10-Morpholin-4-yl-11,12,13,14-tetrahydro[1,2,4]triazolo[3''',4''':6',1'] pyrrolo[1'',2'':4',5']pyrazino[2',3':5,4]thieno[2,3-c]isoquinoline (16)

A mixture of hydrazino compound 15 (0.5 g, 1 mmol) and triethylortho formate (2 ml) in presence of glacial acetic acid (0.5 ml) was refluxed for 2 hrs. The solid product which formed during reflux was filtered off, dried and recrystallized from ethanol: dioxane mixture as white crystals in 74% yield, m.p. 332-334^{o}C. Anal. Calcd. For: $C_{21}H_{20}N_6OS$ (404.50) C, 62.36; H, 4.98; N, 20.78; S, 7.93%. Found: C, 62.45; H, 5.10; N, 20.63; S, 8.10%. IR v (cm^{-1}): 2950, 2850 (CH aliphatic), 1640 (C=N). ^{1}H-NMR (CF_3CO_2D): 1.80 (m, 4H, 2 x CH_2 cyclohexeno), 2.75 (m, 4H, 2 x CH_2 cyclohexeno), 3.30 (m, 4H, 2 x CH_2-N morpholine), 3.95 (m, 4H, 2 x CH_2-O morpholine), 6.35 (s, 1H, CH C:2 pyrrole), 6.90 (s, 1H, CH C:3 pyrrole), 7.20 (s, 1H, CH C:1 pyrrole), 8.30 (s, 1H, CH triazole).

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