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

Remon M. Zaki#, Adel M. Kamal El-Dean, Shaban M. Radwan
Chemistry department, Faculty of Science, Assiut University, Assiut 71516, Egypt
E-mail: remonch2003@yahoo.com

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- arylidene carbohydrazide, 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 moiety.

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

Isoquinoline alkaloids are a large family of natural products and display a broad variety of biological activities. 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. Substituted tetrahydroisooquinolines 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. Thienoquinolines are reported to exhibit a broad spectrum of biological effects. Some of them are useful as memory enhancers, antiallergics, immunoregulators, analgesics and antipyretics. Others are known to possess a good antibacterial and antianaphylactic 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 hoping these new compounds show biological activity. The authors incorporated pyrrolyl ring to the thionetetrahydroisoquinoline system through the reaction of ethyl-1-amino-5-morpholin-4-yl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinole-2-carboxylate with 2,5-dimethoxytetrahydrofuram in glacial acetic acid to afford the corresponding pyrrolyl ester. 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 ester. 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 hydrazide 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 hydrazide 3 was used as versatile precursor for synthesis of other heterocyclic system. Thus, condensation of the hydrazide 3 with aromatic aldehydes namely benzaldehyde, 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).

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).
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).
The carboazide 8 underwent Curtius rearrangement upon boiling dry xylene to afford the corresponding pyrrolopyrazinothienoisouquinoline 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\(_3\)CO\(_2\)D showed three singlet signals at \(\delta\) 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. \(^{1}\)H-NMR spectrum in DMSO-\(d_6\) showed multiplet signals at \(\delta\) 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 \(\delta\) 6.50 and \(\delta\) 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-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 triazole 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. \(^{1}\)H-NMR in CF\(_3\)CO\(_2\)D showed multiplet signals at \(\delta\) 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).
Numbering of carbon atoms for compounds 2, 10a needed for $^{13}$C-NMR analysis are described in the following figure:
**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 deuterated 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 procedure1 with melting point 202-204°C.

**Ethyl-5-morpholin-4-yl-1-(1H-pyrro1-1-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]isoquinoline-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 afford white crystals in 69% yield, m.p. 236°C.

The amino ester compound 2 was prepared according to literature procedure2 with melting point 186°C.

**5-Morpholin-4-yl-1-(1H-pyrro-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]iso-quinoline-2-carboxylic acid (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°C.

**N-Arylidene-1-(1H-pyrro1-1-yl)-5-morpholin-4-yl-6,7,8,9-tetrahydrothieno [2,3- c]isoquinoline-2-carboxyhaide (4)**

General procedure:

Carboxyhydrozide compound 3 (0.5 g, 2 mmol) and aromatic aldehyde (2 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-pyrro1-1-yl)-5-morpholin-4-yl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxyhaide (4a)**

Obtained from carboxyhydrozide 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). ¹H-NMR (DMSO-d₆): 1.80 (m, 4H, 2 x CH₂ cyclohexeno), 2.80 (m, 4H, 2 x CH₂O morpholine), 3.20 (m, 4H, 2 x CH₂-N morpholine), 6.50 (s, 2H, 2 CH=N pyrrolyl), 6.95 (s, 2H, 2CH=N morpholine), 7.30-7.70 (m, 5H, ArH), 7.85 (s, 1H, N=CH₂pH), 8.00 (s, 1H, NH).
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_{5}O_{2}S | 66.72   | 5.65 | 14.38 | 6.67 | 260-262 | 0.44 g (72%) |
|          | (485.61)          | 66.78   | 5.60  | 14.42 | 6.60 |        |        |
| 4b       | C_{28}H_{28}N_{5}O_{2}S | 65.10   | 5.71  | 13.64 | 6.28 | 268-270 | 0.52 g (80%) |
|          | (515.64)          | 65.22   | 5.67  | 13.58 | 6.22 |        |        |
| 4c       | C_{29}H_{29}N_{5}O_{2}S | 67.94   | 5.80  | 13.75 | 6.33 | 280-282 | 0.49 g (76%) |
|          | (511.62)          | 68.08   | 5.71  | 13.69 | 6.27 |        |        |
| 9a       | C_{22}H_{22}N_{4}O_{3}S | 62.00   | 6.22  | 13.24 | 7.58 | 232-234 | 0.43 g (83%) |
|          |                  | 61.95   | 6.14  | 13.14 | 7.52 |        |        |
| 9b       | C_{21}H_{22}N_{4}O_{3}S | 61.05   | 5.90  | 13.64 | 7.85 | 210-212 | 0.4 g (80%) |
|          |                  | 61.15   | 5.86  | 13.58 | 7.77 |        |        |
| 9c       | C_{23}H_{23}N_{4}O_{3}S | 62.76   | 6.50  | 12.68 | 7.40 | 216-218 | 0.46 g (86%) |
|          |                  | 62.70   | 6.41  | 12.72 | 7.28 |        |        |
| 9d       | C_{24}H_{24}N_{4}O_{3}S | 63.48   | 6.54  | 12.25 | 6.96 | 226-228 | 0.42 g (76%) |
|          |                  | 63.41   | 6.55  | 12.32 | 7.05 |        |        |
| 10a      | C_{24}H_{24}N_{5}O_{3}S | 61.57   | 6.00  | 15.10 | 6.92 | 208-210 | 0.39 g (68%) |
|          |                  | 61.65   | 6.25  | 14.98 | 6.86 |        |        |
| 10b      | C_{24}H_{24}N_{5}O_{2}S | 61.82   | 6.54  | 17.92 | 7.00 | 224-226 | 0.34 g (60%) |
|          |                  | 61.78   | 6.48  | 18.01 | 6.86 |        |        |
| 10c      | C_{25}H_{25}N_{5}O_{2}S | 64.56   | 6.66  | 14.97 | 6.89 | 220-222 | 0.37 g (64%) |
|          |                  | 64.49   | 6.71  | 15.04 | 6.89 |        |        |
| 10d      | C_{26}H_{26}N_{5}O_{2}S | 66.00   | 5.62  | 14.85 | 6.70 | 218-220 | 0.42 g (70%) |
|          |                  | 65.94   | 5.75  | 14.79 | 6.77 |        |        |
| 10e      | C_{27}H_{27}N_{5}O_{2}S | 66.62   | 6.08  | 14.47 | 6.48 | 230-232 | 0.48 g (80%) |
|          |                  | 66.51   | 5.99  | 14.36 | 6.58 |        |        |
| 10f      | C_{28}H_{28}N_{5}O_{4}S_{2} | 56.61   | 5.20  | 14.47 | 11.73 | 234-236 | 0.44 g (65%) |
|          |                  | 56.50   | 5.11  | 15.21 | 11.60 |        |        |
N-(4-Methoxybenzylidene-1-(1H-pyrrol-1-yl)-5-morpholin-4-yl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carbohydrazide (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). ¹H-NMR (CF₃COCD₃): 1.95 (m, 4H, 2 x CH₂ cyclohexeno), 2.90 (m, 4H, 2 x CH₂ cyclohexeno), 3.90 (m, 4H, 2 x CH₂-N morpholine), 4.25 (s, 3H, OCH₃), 4.50 (m, 4H, 2 x CH₂-O morpholine), 6.95 (s, 2H, 2CH=pyrrol), 7.30 (s, 2H, 2CH-N pyrrol), 7.70-8.00 (m, 5H, ArH), 8.25 (s, 1H, N=CH).

2-Morpholin-4-yl-N-(3-phenylallylidene)-1-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[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=O). ¹H-NMR (CDCl₃): 2.80 (m, 4H, 2 x CH₂ cyclohexeno), 3.60 (m, 4H, 2 x CH₂-N morpholine), 3.80 (m, 4H, 2 x CH₂-O morpholine), 3.90 (s, 2H, 2 x CH-N pyrrol), 6.20-7.80 (m, 17H, ArH+CH=CH), 8.30 (s, 1H, N=CH).

(3,5-Dimethyl-1H-pyrazol-1-yl)(5-morpholin-1-yl-1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxamide (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°C. Anal. Calcd. For: C₂₀H₂₃N₂O₄S (462.59) C, 56.05; H, 5.90; N, 15.17; S, 6.95%. Found: C, 56.00; H, 6.00; N, 15.23; S, 7.00%. IR ν (cm⁻¹): 3920, 2820 (CH aliphatic), 1695 (CO), 1620 (C=O). ¹H-NMR (CDCl₃): 1.65 (m, 4H, 2 x CH₂ cyclohexeno), 2.30, 2.50 (2s, 6H, 2 x CH₂ pyrrole), 2.70 (m, 4H, 2 x CH₂ cyclohexeno), 2.35 (m, 4H, 2 x CH₂-N morpholine), 3.80 (m, 4H, 2 x CH₂-O morpholine), 5.95 (s, 1H, CH pyrrole), 6.35 (s, 2H, 2CH=C pyrrole), 6.80 (s, 2H, CH=CH pyrrole), EI-MS: m/z (%) = 412 (M+1, 11), 411 (M⁺, 100), 446 (M⁺-CH₃, 45), 431 (M⁺-CH₃, 92), 397 (M⁺-C₆H₄, 11), 375 (M⁺-morpholine, 21.6), 366 (M⁺-CH₂N⁺, 46.6), 338 (M⁺-C₆H₄N⁺, 15), 252 (M⁺-C₅H₅N⁺, 9).

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

A mixture of carbohydrazide compound 3 (1.0 g, 2.2 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°C. Anal. Calcd. For: C₂₀H₂₃N₂O₂S₂ (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=O). ¹H-NMR (CDCl₃): 2.00 (m, 4H, 2 x CH₂ cyclohexeno), 2.80 (m, 4H, 2 x CH₂ cyclohexeno), 3.65 (m, 4H, 2 x CH₂-N morpholine), 4.20 (m, 4H, 2 x CH₂-O morpholine), 6.70 (s, 2H, 2CH=C pyrrole), 7.05 (s, 2H, 2CH-N pyrrole).

Ethyl[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°C. Anal. Calcd. For: C₂₃H₂₅N₂O₃S (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=O). ¹H-NMR (CDCl₃): 1.30 (t, J= 7.50 Hz, 3H, CH₃ ester), 1.70 (m, 4H, 2 x CH₂ cyclohexeno), 2.70 (m, 4H, 2 x CH₂ cyclohexeno), 3.20 (m, 4H, 2 x CH₂-N morpholine), 3.80 (m, 4H, 2 x CH₂-O morpholine), 4.10 (s, 2H, SCHR₂), 4.20 (q, J= 6.00 Hz, 2H, CH₂ ester), 6.30 (s, 2H, 2CH=C pyrrole), 6.90 (s, 2H, 2CH-N pyrrole).

Morpholin-4-yl-(1H-pyrrol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carbazide (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°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°C. Anal. Calcd. For: C₂₅H₂₇N₂O₃S (408.49) C, 58.81; H, 4.94; N, 20.57; S, 7.85%. IR ν (cm⁻¹): 2950, 2850 (CH aliphatic), 2150 (N=O), 1665 (CO azide), 1580 (C=O).
Alky1-5-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). ¹H-NMR (CDCl₃): 1.30 (t, J= 7.5 Hz, 3H, CH₃), 1.70 (m, 4H, 2 x CH₂ cyclohexeno), 2.75 (m, 4H, 2 x CH₂ cyclohexeno), 3.20 (m, 4H, 2 x CH₂-N morpholine), 3.80 (m, 4H, 2 x CH₂-O morpholine), 4.20 (q, J= 6.0 Hz, 2H, CH₂ 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). ¹H-NMR (CDCl₃): 1.50 (m, 4H, 2 x CH₂ cyclohexeno), 2.60 (m, 4H, 2 x CH₂ cyclohexeno), 3.00 (m, 4H, 2 x CH₂-N morpholine), 3.70 (m, 4H, 2 x CH₂-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 (CDCl₃): 1.30,1.35 (δ, 6H, 2CH₃ isopropyl), 1.70 (m, 4H, 2 x CH₂ cyclohexeno), 2.70 (m, 4H, 2 x CH₂ cyclohexeno), 3.15 (m, 4H, 2 x CH₂-N morpholine), 3.80 (m, 4H, 2 x CH₂-O morpholine), 5.00 (s, 1H, CH isopropyl), 6.30 (s, 2H, 2CH=C pyrrolyl), 6.70 (s, 2H, 2CH-N pyrrolyl), 9.55 (s, 1H, NH). El-MS: m/z (%) = 440 (M+, 100), 412 (M+ -C₂H₄, 12), 397 (M⁻-C₆H₅, 15), 381 (M⁻-C₃H₇O, 3), 354 (M⁻-C₄H₈O₂, 21), 338 (M⁻-C₅H₆NO₃).

**t-Butyl-(5-Morpholino-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). ¹H-NMR (CDCl₃): 1.50 (s, 9H, 3CH₃), 1.70 (m, 4H, 2 x CH₂ cyclohexeno), 2.70 (m, 4H, 2 x CH₂ cyclohexeno), 3.10 (m, 4H, 2 x CH₂-N morpholine), 3.85 (m, 4H, 2 x CH₂-O morpholine), 6.30 (s, 2H, 2CH=C pyrrolyl), 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]-isoquinolin-2-yl substituted-4-carboxamide (10a-g)**

**General procedure:**
A mixture of pyrrol-1-ylcarboazide 8 (0.5 g, 1.2 mmol) and primary (secondary) amine (1.25 mmol) was refluxed in dry toluene for 2 hrs. The solid product which formed during reflux 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). ¹H-NMR (CDCl₃): 1.80 (m, 4H, 2 x CH₂ cyclohexeno), 2.75 (m, 4H, 2 x CH₂ cyclohexeno), 3.20 (m, 8H, 4CH₂-N morpholine), 3.90 (m, 8H, 4CH₂-O morpholine), 6.30 (s, 2H, 2CH=C pyrrolyl), 6.75 (s, 2H, 2CH-N pyrrolyl), 9.50 (s, 1H, NH). ¹³C-NMR (CDCl₃): 21.93, 22.27, 23.33, 26.45 (C16-C19 cyclohexeno), 50.31 (C12, C15, C21, C24 ; 2 x (CH₂)₂-N morpholine), 66.52, 66.96 (C13, C14, C22, C23; 2 x (CH₂)₂-O morpholine), 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). El-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) pyrazine-4-carboxamide (10b)**

Obtained from carboazide 8 and pyrazine. 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). ¹H-NMR (DMSO-d₆): 1.90 (m, 4H, 2x CH₂ cyclohexeno), 2.80 (m, 4H, 2 x CH₂ cyclohexeno), 2.90 (m, 4H, 2CH₂-N pyrazine), 3.20 (m, 8H, (CH₂)₂-N pyrazine + (CH₂)₂-N morpholine), 3.80 (m, 4H, (CH₂)₂-O morpholine), 6.70 (s, 2H, 2CH=C pyrrolyl), 6.95 (s, 2H, 2CH-N pyrrolyl), 7.40 (s, 1H, NH pyrazine), 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). ¹H-NMR (CDCl₃): 1.50 (m, 4H, 2 x CH₂ C₂, C4
piperidine), 1.60 (m, 2H, CH2 C3 piperidine), 1.75 (m, 4H, 2 x CH2 cyclohexeno), 2.70 (m, 4H, 2 x CH2 cyclohexeno), 3.20 (m, 4H, 2 x CH2-N morpholine), 3.40 (m, 4H, 2 x CH2 C1, C5 piperidine), 3.80 (m, 4H, 2 x CH2-O morpholine), 6.30 (s, 2H, 2CH=N 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), 1680 (CO), 1590 (C=N). ¹H-NMR (DMSO-d6): 1.70 (m, 4H, 2 x CH2 cyclohexeno), 2.65 (m, 4H, 2 x CH2 cyclohexeno), 3.25 (m, 4H, 2 x CH2-N morpholine), 3.70 (m, 4H, 2 x CH2-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]isoquinolin-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). ¹H-NMR (CDCl₃): 1.70 (m, 4H, 2 x CH2 cyclohexeno), 2.70 (m, 4H, 2 x CH2 cyclohexeno), 3.20 (m, 4H, 2 x CH2-N morpholine ), 3.90(m, 4H, 2 x CH2-O morpholine), 4.30 (s, 2H, CH2ph), 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, NHbenzyl), 9.60 (s, 1H, NHCO).

4-(3-(5-Morpholin-4-yl-1-(1H-pyrrol-1-yl)-6,8,9-tetrahydrothieno[2,3-c]isoquinolin -2-yl)ureido)benzensulfonamide (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, NH2), 3030 (CH aromatic), 2920, 2850 (CH aliphatic), 1695 (CO). ¹H-NMR (DMSO-d6): 1.70 (m, 4H, 2 x CH2 cyclohexeno), 2.70 (m, 4H, 2 x CH2 cyclohexeno), 3.20 (m, 4H, 2 x CH2-N morpholine), 3.80 (m, 4H, 2 x CH2-O morpholine), 5.90 (s, 2H, NH2), 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-tetrahydrothieno[2,3-c]isoquinolin -2-yl)ureido)-N-(thiazol-2-yl)benzensulfonamide (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). ¹H-NMR (DMSO-d6): 1.70 (m, 4H, 2 x CH2 cyclohexeno), 2.60 (m,4H, 2 x CH2 cyclohexeno), 3.20 (m, 4H, 2 x CH2-N morpholine), 3.85 (m, 4H, 2 x CH2-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 caboozide 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°C. Anal. Calcd. For: C26H28N6O4S (592.94) C, 63.14; H, 5.10; 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). ¹H-NMR (CF₃COCD₃): 1.80 (m, 4H, 2 x CH2 cyclohexeno), 2.50 (m, 4H, 2 x CH2 cyclohexeno), 3.65 (m, 4H, 2CH2-N morpholine), 4.20 (m, 4H, 2 x CH2-O morpholine), 6.20 (s, 1H, CH C2 pyrrole), 6.50 (s, 1H, CH C1 pyrrole), 7.30 (s, 1H, CH C3 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] isoquinolin-12 (12)

A solution of pyrrolypyrrolopyrroloisoquinolinoisoquinoline 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°C. Anal. Calcd. For: C26H26N2O2S (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). ¹H-NMR (DMSO-d6): 1.70 (m, 4H, 2 x CH2 cyclohexeno), 2.60 (m, 4H, 2 x CH2 cyclohexeno), 3.25 (m, 4H, 2 x CH2-N morpholine), 3.80 (m, 4H, 2 x CH2-O morpholine), 6.35 (s, 1H, CH C2 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 refluxed 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°C. Anal. Calcd. For: C35H26ClN2O2S (671.92) C, 78.60; H, 4.93; N, 11.25; S, 3.75%. Found: C, 78.60; H, 4.92; N, 11.25; S, 3.75%.
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 during reflux was filtered off, dried and recrystallized from ethanol into white crystals in 52% yield, m.p. 242-244°C. Anal. Calcd. For: C_{22}H_{23}N_3OS (394.50) C, 60.97; H, 5.58; N, 21.38; S, 8.15%. Found: C, 60.97; H, 5.50; N, 21.30; S, 8.13%. IR ν (cm⁻¹): 3350, 3300, 3250 (NH), 2920, 2850 (CH aliphatic), 1640 (C=N). ¹H-NMR (CDCl₃): 1.80 (m, 4H, 2 x CH₂ cyclohexeno), 2.70 (m, 4H, 2 x CH₂ cyclohexeno), 3.25 (m, 4H, 2 x CH₂-N morpholine), 3.85 (m, 4H, 2 x CH₂-O morpholine), 6.35 (s, 1H, CH C:2 pyrrole), 6.50 (s, 2H, NH₂), 6.85 (s, 1H, CH C:3 pyrrole), 7.20 (s, 1H, CH C:1 pyrrole), 7.90 (s, 1H, NH).

Benzyldiene-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 benaldehyde (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_{24}H_{25}N_4OS (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 ν (cm⁻¹): 3030 (CH aromatic), 1640 (C≡N). ¹H-NMR (CF₃COOD): 1.80 (m, 4H, 2 x CH₂ cyclohexeno), 2.75 (m, 4H, 2 x CH₂ cyclohexeno), 3.20 (m, 4H, 2 x CH₂-N morpholine), 3.85 (m, 4H, 2 x CH₂-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 + CHp + 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 hydrazine compound 15 (0.5 g, 1 mmol) and triethylthio 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°C. Anal. Calcd. For: C_{22}H_{23}N_3OS (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 ν (cm⁻¹): 2950, 2850 (CH aliphatic), 1640 (C≡N). ¹H-NMR (CF₃COOD): 1.80 (m, 4H, 2 x CH₂ cyclohexeno), 2.75 (m, 4H, 2 x CH₂ cyclohexeno), 3.30 (m, 4H, 2 x CH₂-N morpholine), 3.95 (m, 4H, 2 x CH₂-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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