Fused quinoline heterocycles VII: synthesis of new isoxazolo[3',4':4,5]pyrrolo(or thieno)[2,3-c]quinolines

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† This paper is dedicated to the soul of my late friend Prof. Ahmed Khattab

Abstract
3-Amino-4-chlorothieno(or pyrrolo)[3,2-c]quinoline-2-carboxylates 3a,b react with alkylamines 4a-g to give the corresponding 4-alkylaminothieno(or pyrrolo)[3,2-c]quinoline-2-carboxylates 5a-g. Diazotization of 5a-g, followed by reaction with NaN₃, leads to the formation of 3-azido-4-alkylaminothieno(or pyrrolo)[3,2-c]quinoline-2-carboxylates 6a-g, a new heterocyclic ring system. Thermolysis of azido compounds 6a-g in bromobenzene at reflux temperature afforded the novel tetracyclic ring system isoxazolo[3',4':4,5]thieno[2,3-c]quinolines 7a-e and isoxazolo[3',4':4,5]-pyrrolo[2,3-c]quinolines 7f,g.

Keywords: Isoxazolo[3',4':4,5]thieno[2,3-c]quinolines, isoxazolo[3',4':4,5]pyrrolo[2,3-c]-quinolines, diazotization, thermolysis, cyclization, heterocycles

Introduction

The pyrrolo[3,2-c]quinoline skeleton can be found in Nature in the alkaloids martinelline and martinellonic acid, isolated from the roots of the tropical plant Martinella iquitosensis.¹⁻³ These compounds show unique biological activity, as they are the first naturally occurring nonpeptide bradykinin (BK) B₁ and B₂ receptor antagonists.⁴ They are also known for their antibiotic activity against both Gram-positive and Gram-negative bacteria.⁵ A number of synthetic analogues in a different oxidation states also have valuable biological properties, as an example 7-chloro-3-methyl-1H-pyrrolo[3,2-c]quinoline-4-carboxylic acid was found to be a relatively potent and selective inhibitor of kynurenine-3-hydroxylase.⁶ Moreover, some of the sulfur-containing fused quinolines and particularly thienoquinolines have recently drawn much attention due to their considerable biological and pharmacological activities.⁷⁻¹⁰

In addition, some of isoxazole derivatives show interesting pharmacological activity such as Gantricin, a sulfa drug from amino isoxazole,¹¹ Cycloserine and Oxamycin, simple derivative of
3-isoxazolidone as antibiotic. More recently, others are synthesized as potent α,β3 receptor antagonists. These features prompted us to design a specific program aimed at constructing novel tetracyclic ring systems containing both pyrrole or thiophene and isoxazole moieties condensed with a quinoline nucleus. The newly synthesized tetracyclic compounds, isoxazolothienoquinolines and isoxazolopyrroloquinolines, seem promising for biological-activity evaluation studies but to the best of our knowledge, these ring systems have remained totally unexplored.

In the course of a medicinal chemistry program directed at the synthesis of pharmacologically interesting new tetracyclic ring systems containing the quinoline moiety, we have succeeded in the synthesis of the first representatives of so far inaccessible tetracyclic systems, namely isoxazolo[3′,4′:4,5]thieno[2,3-c]quinoline and isoxazolo[3′,4′:4,5]pyrrolo[2,3-c]quinoline derivatives.

Organic azides with reactive ortho substituents are known to cyclize easily to heterocyclic compounds. The use of an ester group as the reactive ortho substituent in azido compounds should lead to isoxazoles having a functional group for further transformations. As the preparation of novel tetracyclic systems is the main target of this synthetic program, the 3-azidothieno(or pyrrolo)quinoline derivatives were selected as putative precursors for construction of hitherto unknown tetracyclic systems incorporating an isoxazole nucleus in addition to the thieno and/or pyrroloquinolines moiety.

**Results and Discussion**

We first investigated the synthesis of novel tetracyclic systems 7a-e. The reaction sequence to 3-azidothieno[3,2-c]quinoline derivatives 6a-e started with the conveniently available 2,4-dichloroquinoline-3-carbonitrile (1), in which C-4 chlorine atom is readily displaced by nucleophiles, and reaction with ethyl mercaptoacetate (2a) led to ethyl 3-amino-4-chlorothieno[3,2-c]quinoline-2-carboxylate (3a). Our first trials to convert 3-amino-4-chlorothienoquinolines 3a to the corresponding 3-azidothienoquinolines directly, were unsuccessful because in all cases we obtained several compounds as well as some colored byproducts that could not be isolated. This led us to investigate the replacement of the chloro atom at C-4 in thienoquinolines 3a with different aliphatic amines to obtain the corresponding amino-thienoquinolines 5a-e, as a good starting materials for preparation of the 3-azidothienoquinolines 6a-e. Additionally, this gave us the opportunity to synthesize some new derivatives of isoxazolothienoquinolines 7a-e.

As the next step, ethyl 3-amino-4-chlorothieno[3,2-c]quinoline-2-carboxylate (3a) was reacted with an excess of the aliphatic amines 4a-e in DMF solution at reflux temperature, and we observed that the chloro atom in position 4 of the thienoquinoline nucleus had been exchanged by the alkylamino group to furnish the corresponding thieno[3,2-c]quinoline derivatives 5a-e, as stable crystalline solids. The 3-azidothienoquinolines required for our
investigation were prepared by diazotation of the respective 3-aminothienoquinolines 5a-e by adding sodium nitrite to a solution of the amine in sulfuric acid. Thus, when 5a-e were reacted with sodium nitrite in a 70% solution of H2SO4 at -5°C followed by reaction of the non-isolated thienoquinoline diazonium sulfate with an aqueous solution of sodium azide, the corresponding 3-azidothienoquinoline derivatives 6a-e were isolated as the only reaction products. The structures of these 3-azidothienoquinolines 6a-e were confirmed by infrared signals of the azido group at 2120-2140 cm⁻¹.

Thermolysis of azides with ortho-acyl substituents is known to afford the corresponding cyclization products, in a 1,5-heteroelctrocyclic reaction via a pseudo-pericyclic process (without formation of a nitrene intermediate), by decomposition of the azido moiety; this reaction is of synthetic value. Therefore, we investigated the thermal cyclization of 3-azidothienoquinolines 6a-e, with the hope of obtaining the interesting tetracyclic ring systems 7a-e. Thus, refluxing azido compounds 6a-e in bromobenzene for one hour afforded the hitherto unknown isoxazolo[3′,4′:4,5]thieno[2,3-c]quinolines 7a-e, in good yields (the reaction may be monitored by the evolution of nitrogen or by disappearance of the intense azide absorption at 2120-2140 cm⁻¹ in the IR spectra).

During the thermal decomposition of the azido compounds 6a-e, we have not generally observed any products which could be associated with arylnitrene formation, i.e. azo compounds and insertion products, indicating that the incipient nitrenes formed by the nitrogen extrusion may be bridged by the carbonyl group thus preventing the intrusion of other reaction mechanisms. The structures of 7a-e were substantiated by their elemental analyses and spectral data. The IR spectra revealed the absence of azido and ester carbonyl groups and the presence of the typical absorption bands due to the isoxazole ring frequency at 1550-1555 cm⁻¹. The ¹H NMR spectroscopic data of 7a-e showed only small differences to the precursors 6a-e, mainly with shifts of about 0.08 ppm for the ethoxy group. Furthermore, their structures were supported by correct mass spectra, which were compatible with assigned structures (see Experimental). Analytical data are in accordance with the proposed structures for compounds 7a-e. The same reaction sequence and preparative technique was applied also to the preparation of isoxazolo[3′,4′:4,5]pyrrolo[2,3-c]quinolines 7f,g (Scheme 1).

**Conclusions**

We have developed for the first time, a new, simple and general synthetic route for the construction of different substituted tetracyclic ring systems, otherwise obtainable only with difficulty. Furthermore, we have shown that the azido compounds 6a-g are useful precursors in the preparation of a wide variety of biologically important novel isoxazolo[3′,4′:4,5]-thieno[2,3-c]quinolines 7a-e and isoxazolo[3′,4′:4,5]pyrrolo[2,3-c]quinolines 7f,g. To the best of our knowledge, this is the first time that such syntheses of novel perianellated tetracyclic systems 7a-g have
been described. Further studies in our laboratory aimed at the synthesis of new tetracyclic ring systems are under investigation and will be published later.

![Scheme 1]

### Experimental Section

**General Procedures.** Melting points were determined on a Gallenkamp apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 plates, 0.25 mm thick with F-254 indicator. Visualization was accomplished by UV light. $^1$H NMR spectra were recorded with Bruker AM400 spectrometer at 400 MHz with DMSO-$d_6$ and CDCl$_3$ as solvents and TMS as an internal standard; Chemical shifts (δ) are reported in ppm. Mass spectra were measured on a Ge/Ms-QP1000EX (EI, 70 eV) mass spectrometer. IR spectra were recorded with a Schimadzu 470 spectrophotometer in KBr disks. Microanalyses were performed by the microanalytical Data Unit at Cairo University, and analytical values obtained
were within ±0.4% of the calculated values. All reagents were of commercial quality or were purified before use and the organic solvents were of analytical grade or purified by standard procedures. The preparation of 3-aminopyrroloquinolines 3b and 3-amino-thienoquinolines 5a-c has already been described by us in references 18 and 21, respectively.

**Ethyl 4-alkylamino-3-aminothieno[3,2-c]quinoline-2-carboxylates 5d,e and methyl 4-alkylamino-3-amino-1H-pyrrolo[3,2-c]quinoline-2-carboxylates 5f,g**

The appropriate sec. amine 4d-g (16.3 mmol) was added to a solution of 3a,b (1.63 mmol) in absolute ethanol (15 ml). The mixture was heated under reflux for 28-38 hrs. After concentration and cooling at room temperature, the resulting solid product was collected by filtration, washed with a small amount of ethanol, dried and recrystallized from EtOH to afford 5d-g.

**Ethyl 3-amino-4-morpholinothieno[3,2-c]quinoline-2-carboxylate (5d).** Colorless crystals 0.465g, 80% yield; mp 165-166°C, IR (KBr pellet): 3500, 3350 (NH2), 3000 (arom. CH), 2850 (aliph. CH), 1660 (CO) cm⁻¹; ¹H NMR (DMSO-d₆, 400MHz): δ 8.0 (d, 1H, J = 8 Hz, 1Ar-H), 7.85 (d, 1H, J = 8 Hz, 1Ar-H), 7.70 (t, 1H, J = 8 Hz, 1Ar-H), 7.51 (t, 1H, J = 8 Hz, 1Ar-H), 6.97 (s, 2H, NH₂), 4.28 (q, 2H, J = 7 Hz, CH₂), 3.87 (br, 4H, 2OCH₂), 3.42 (br, 4H, 2NCH₂), 1.30 (t, 3H, J = 7 Hz, CH₃); Calcd. for C₁₈H₁₉N₃O₃S (357.43): C, 60.49; H, 5.36; N, 11.76; S, 8.97; Found: C, 60.35; H, 5.49; N, 11.58; S, 9.08.

**Ethyl 3-amino-4-(4-methylpiperidino)thieno[3,2-c]quinoline-2-carboxylate (5e).** Colorless crystals 0.520g, 87% yield; mp 159-161°C, IR (KBr pellet): 3450, 3350 (NH₂), 2950, 2850 (aliph. CH), 1670 (CO) cm⁻¹; MS (EI): m/z 369 (M⁺, 12), 340 (44), 324 (3), 287 (5), 252 (12), 224 (3), 200 (26), 172 (5), 154 (4), 153 (7), 128 (7), 98 (100), 56 (24); ¹H NMR (DMSO-d₆, 400MHz): δ 8.00 (d, 1H, J = 8 Hz, 1Ar-H), 7.83 (d, 1H, J = 8 Hz, 1Ar-H), 7.69 (t, 1H, J = 8 Hz, 1Ar-H), 7.50 (t, 1H, J = 8 Hz, 1Ar-H), 7.0 (s, 2H, NH₂), 4.27 (q, 2H, J = 7 Hz, CH₂), 4.20 (q, 2H, J = 7 Hz, CH₂), 3.40 (br, 4H, 2NCH₂), 1.78-1.44 (m, 5H, 5aliph-H), 1.30 (t, 3H, J = 7 Hz, CH₃), 0.99 (d, 3H, J = 6 Hz, CH₃); Calcd. for C₂₀H₂₃N₃O₂S (369.48): C, 65.01; H, 6.27; N, 11.37; Found: C, 65.20; H, 6.11; N, 11.43; S, 8.73.

**Methyl 3-amino-4-morpholino-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (5f).** Colorless crystals 0.450g, 85% yield; mp 259-260°C, IR (KBr pellet): 3450, 3350 (NH₂), 2950, 2850 (aliph. CH), 1670 (CO) cm⁻¹; MS (EI): m/z 340 (M⁺, 12), 311 (44), 295 (3), 278 (5), 252 (12), 224 (3), 200 (26), 172 (5), 154 (4), 153 (7), 128 (7), 98 (100), 56 (24); ¹H NMR (DMSO-d₆, 400MHz): δ 12.34 (s, 1H, NH), 8.02 (d, 1H, J = 8 Hz, 1Ar-H), 7.87 (d, 1H, J = 8 Hz, 1Ar-H), 7.68 (t, 1H, J = 8 Hz, 1Ar-H), 7.63 (t, 1H, J = 8 Hz, 1Ar-H), 6.95 (s, 2H, NH₂), 3.88 (s, 3H, OCH₃), 3.84 (br, 4H, 2OCH₂), 3.42 (br, 4H, 2NCH₂); Calcd. for C₁₇H₁₈N₄O₃ (326.35): C, 62.57; H, 5.56; N, 17.17; Found: C, 62.63; H, 5.47; N, 17.21.

**Methyl 3-amino-4-piperidino-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (5g).** Colorless crystals 0.420g, 80% yield; mp 240-241°C, IR (KBr pellet): 3450-3300 (NH, NH₂), 3000 (arom. CH), 2970, 2830 (aliph. CH), 1660 (CO) cm⁻¹; ¹H NMR (DMSO-d₆, 400MHz): δ 12.34 (s, 1H, NH), 8.02 (d, 1H, J = 8 Hz, 1Ar-H), 7.87 (d, 1H, J = 8 Hz, 1Ar-H), 7.68 (t, 1H, J = 8 Hz, 1Ar-H), 7.53 (t, 1H, J = 8 Hz, 1Ar-H), 6.95 (s, 2H, NH₂), 3.88 (s, 3H, OCH₃), 3.84 (br, 4H, 2OCH₂), 3.42 (br, 4H, 2NCH₂); Calcd. for C₁₇H₁₈N₄O₃ (326.35): C, 62.57; H, 5.56; N, 17.17; Found: C, 62.63; H, 5.47; N, 17.21.
2NCH₂), 1.83-1.64 (m, 6H, 3CH₂); Calcd. for C₁₈H₂₀N₄O₂ (324.38): C, 66.65; H, 6.21; N, 17.27; Found: C, 66.53; H, 6.04; N, 17.35.

**Ethyl 4-alkylamino-3-azidothieno[3,2-c]quinoline-2-carboxylates 6a-e and methyl 4-alkylamino-3-azido-1H-pyrrolo[3,2-c]quinoline-2-carboxylates 6f,g**

A solution of aminothieno(or pyrrolo)quinolines 5a-g (0.73 mmol) in H₂SO₄ (4 ml, 70%) was cooled until the temperature of solution was -5°C and treated with sodium nitrite (0.151g, 2.19 mmol) in water (1 ml). To the resulting solution of the diazonium ion was added sodium azide (0.142g, 2.19 mmol) in H₂O (1 ml) and maintained at 0–(-5)°C. Stirring was then continued for 2 hrs. at room temperature (25°C). The resulting solid products were collected by filtration, washed well with H₂O, dried and recrystallized from EtOH to afford compounds 6a-g.

**Ethyl 3-azido-4-butylaminothieno[3,2-c]quinoline-2-carboxylate (6a).** Yellow crystals 0.20g, 74% yield; mp 150-152°C, IR (KBr pellet): 3400 (NH), 3100 (arom. CH), 2950 (aliph. CH), 2140 (N₃), 1670 (CO) cm⁻¹; H NMR (CDCl₃, 400MHz): δ 8.34 (d, 1H, J = 8 Hz, 1Ar-H), 7.51 (d, 1H, J = 8 Hz, 1Ar-H), 7.41 (t, 1H, J = 8 Hz, 1Ar-H), 7.19 (t, 1H, J = 8 Hz, 1Ar-H), 6.73 (br, 1H, NH), 4.34 (q, 2H, J = 7 Hz, CH₂), 4.04 (q, 2H, J = 7 Hz, CH₂), 1.90-1.78 (m, 2H, CH₂), 1.47-1.39 (m, 2H, CH₂), 1.37 (t, 3H, J = 7 Hz, CH₃), 0.92 (t, 3H, J = 7 Hz, CH₃); Calcd. for C₁₈H₁₉N₅O₂S (369.45): C, 58.52; H, 5.18; N, 18.96; S, 8.68; Found: C, 58.43; H, 4.98; N, 18.85; S, 8.59.

**Ethyl 3-azido-4-iso-butylaminothieno[3,2-c]quinoline-2-carboxylate (6b).** Yellow crystals 0.210g, 78% yield; mp 141-142°C, IR (KBr pellet): 3350 (NH), 3050 (arom. CH), 2950 (aliph. CH), 2140 (N₃), 1670 (CO) cm⁻¹; H NMR (CDCl₃, 400MHz): δ 8.49 (d, 1H, J = 8 Hz, 1Ar-H), 7.46 (d, 1H, J = 8 Hz, 1Ar-H), 7.36 (t, 1H, J = 8 Hz, 1Ar-H), 7.17 (t, 1H, J = 8 Hz, 1Ar-H), 6.94 (br, 1H, NH), 4.35 (q, 2H, J = 7 Hz, CH₂), 2.26 (t, 2H, J = 7 Hz, CH₂), 1.63 (m, 1H, CH), 1.32 (t, 3H, J = 7 Hz, CH₃), 0.92 (d, 6H, J = 7 Hz, 2CH₃); Calcd. for C₁₈H₁₉N₅O₂S (369.45): C, 58.52; H, 5.18; N, 18.96; S, 8.74.

**Ethyl 3-azido-4-cyclohexylaminothieno[3,2-c]quinoline-2-carboxylate (6c).** Yellow crystals 0.270g, 93% yield; mp (decomposed at 160, melted at 240°C); IR (KBr pellet): 3424 (NH), 3100 (arom. CH), 2980 (aliph. CH), 2140 (N₃), 1670 (CO) cm⁻¹; H NMR (DMSO-d₆, 400MHz): δ 7.89 (d, 1H, J = 8 Hz, 1Ar-H), 7.81 (d, 1H, J = 8 Hz, 1Ar-H), 7.63 (t, 1H, J = 8 Hz, 1Ar-H), 7.39 (t, 1H, J = 8 Hz, 1Ar-H), 6.86 (br, 1H, NH), 5.13 (m, 1H, aliph-H), 4.49 (q, 2H, J = 7 Hz, CH₂), 2.07-1.94 (m, 4H, 2CH₂), 1.79-1.57 (m, 6H, 3CH₂), 1.33 (t, 3H, J = 7 Hz, CH₃); Calcd. for C₂₀H₂₁N₅O₂S (395.49): C, 60.74; H, 5.35; N, 17.71; S, 8.11; Found: C, 60.81; H, 5.54; N, 17.61; S, 8.19.

**Ethyl 3-azido-4-morpholinothieno[3,2-c]quinoline-2-carboxylate (6d).** Yellow crystals 0.420g, 81% yield; mp (decomposed at 160, melted at 240°C); IR (KBr pellet): 3242 (NH), 3100 (arom. CH), 2980 (aliph. CH), 2120 (N₃), 1690 (CO) cm⁻¹; H NMR (DMSO-d₆, 400MHz): δ 7.89 (d, 1H, J = 8 Hz, 1Ar-H), 7.81 (d, 1H, J = 8 Hz, 1Ar-H), 7.63 (t, 1H, J = 8 Hz, 1Ar-H), 7.39 (t, 1H, J = 8 Hz, 1Ar-H), 6.86 (br, 1H, NH), 5.13 (m, 1H, aliph-H), 4.49 (q, 2H, J = 7 Hz, CH₂), 2.07-1.94 (m, 4H, 2CH₂), 1.79-1.57 (m, 6H, 3CH₂), 1.33 (t, 3H, J = 7 Hz, CH₃); Calcd. for C₂₀H₂₁N₅O₂S (395.49): C, 60.74; H, 5.35; N, 17.71; S, 8.11; Found: C, 60.81; H, 5.54; N, 17.61; S, 8.19.
C_{18}H_{17}N_{5}O_{3}S (383.43): C, 56.39; H, 4.47; N, 18.26; S, 8.36; Found: C, 56.43; H, 4.59; N, 18.34; S, 8.29.

**Ethyl 3-azido-4-(4-methylpiperidino)thieno[3,2-c]quinoline-2-carboxylate (6e).** Yellow crystals 0.410g, 75% yield; mp 130-132°C, IR (KBr pellet): 2950 (aliph. CH), 2120 (N 3), 1670 (CO) cm\(^{-1}\); ¹H NMR (CDCl₃, 400MHz): δ 8.18 (d, 1H, J = 8 Hz, 1Ar-H). 7.92 (d, 1H, J = 8 Hz, 1Ar-H), 7.63 (t, 1H, J = 8 Hz, 1Ar-H), 4.36 (q, 2H, J = 7 Hz, CH₂), 3.88 (m, 2H, CH₂), 3.50 (m, 2H, CH₂), 1.86-1.43 (m, 5H, 5 aliph-H), 1.35 (t, 3H, J = 7 Hz, CH₃), 1.03 (d, 3H, J = 6 Hz, CH₃); Calcd. for C_{20}H_{21}N_{5}O_{2}S (395.49): C, 60.74; H, 5.35; N, 17.71; S, 8.11; Found: C, 60.67; H, 5.28; N, 17.83; S, 8.23.

**Methyl 3-azido-4-morpholino-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (6f).** Colorless crystals 0.260g 80% yield; mp 154-155°C, IR (KBr pellet): 3400 (NH), 3050 (arom. CH), 2980, 2850 (aliph. CH), 1715 (CO) cm\(^{-1}\); ¹H NMR (DMSO-d₆, 400MHz): δ 13.73 (s, 1H, NH), 8.21 (d, 1H, J = 8 Hz, 1Ar-H), 8.04 (d, 1H, J = 8 Hz, 1Ar-H), 7.59 (t, 1H, J = 8 Hz, 1Ar-H), 4.02 (br, 4H, 2OCH₂), 3.89 (s, 3H, OCH₃), 3.78 (br, 4H, 2NCH₂); Calcd. for C_{17}H_{16}N_{6}O_{3} (352.36): C, 57.95; H, 4.58; N, 23.85; Found: C, 57.87; H, 4.49; N, 23.78.

**Methyl 3-azido-4-piperidino-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (6g).** Colorless crystals 0.250g, 77% yield; mp 179-180°C, IR (KBr pellet): 3400 (NH), 3050 (arom. CH), 2940, 2850 (aliph. CH), 1715 (CO) cm\(^{-1}\); ¹H NMR (DMSO-d₆, 400MHz): δ 13.65 (s, 1H, NH), 8.15 (d, 1H, J = 8 Hz, 1Ar-H), 7.79 (d, 1H, J = 8 Hz, 1Ar-H), 7.59 (t, 1H, J = 8 Hz, 1Ar-H), 3.96 (s, 3H, OCH₃), 3.39-3.33 (m, 4H, 2NCH₂), 2.16-1.64 (m, 6H, 3CH₂); Calcd. for C_{18}H_{18}N_{6}O_{2} (350.38): C, 61.70; H, 5.18; N, 23.99; Found: C, 61.81; H, 4.89; N, 23.87.

**Isoxazolo[3′,4′:4,5]thieno[2,3-c]quinolines 7a-e and isoxazolo[3′,4′:4,5]pyrrolo[2,3-c]-quinolines 7f,g**

A solution of 6a-g (1.26 mmol) in bromobenzene (10 ml) was refluxed for 1h. After concentration and cooling to room temperature, the resulting solid product was collected by filtration, dried and recrystallized from EtOH to give compounds 7a-g.

**6-Butylamino-8-ethoxy-isoxazolo[3′,4′:4,5]thieno[2,3-c]quinoline (7a).** Yellow crystals 0.350g, 81% yield; mp 224-226°C, IR (KBr pellet): 3350 (NH), 3100 (arom. CH), 2980, 2900 (aliph. CH), 1550 cm\(^{-1}\); MS (EI): m/z 342 (M +1, 12), 341 (M +, 12), 327 (6), 314 (48), 301(60), 287 (94), 272 (28), 254 (100), 166 (34), 240 (10), 224 (10), 215 (96), 155 (11), 72 (5); ¹H NMR (CDCl₃, 400MHz): δ 8.13 (d, 1H, J = 8 Hz, 1Ar-H). 8.05 (d, 1H, J = 8 Hz, 1Ar-H), 7.70 (t, 1H, J = 8 Hz, 1Ar-H), 6.94 (br, 1H, NH), 4.32 (q, 2H, J = 7 Hz, CH₂), 4.20 (q, 2H, J = 7 Hz, CH₂), 1.88 (m, 2H, CH₂), 1.56 (m, 2H, CH₂), 1.42 (t, 3H, J = 7 Hz, CH₃), 0.96 (t, 3H, J = 7 Hz, CH₃); Calcd. for C_{18}H_{18}N_{6}O_{2}S (341.44): C, 63.32; H, 5.18; N, 12.31; S, 9.39; Found: C, 63.44; H, 5.71; N, 12.29; S, 9.43.

**6-Isobutylamino-8-ethoxy-isoxazolo[3′,4′:4,5]thieno[2,3-c]quinoline (7b).** Yellow crystals 0.330g, 77% yield; mp 243-244°C, IR (KBr pellet): 3350 (NH), 3100 (arom. CH), 2980 (aliph.
CH), 1550 cm⁻¹, MS (EI): m/z 342 (M⁺, 5), 341 (M⁺, 30), 287 (100), 254 (72), 199 (11), 155 (11), 72 (2); ¹H NMR (DMSO-d₆, 400MHz): δ 8.16 (d, 1H, J = 8 Hz, 1Ar-H), 8.06 (d, 1H, J = 8 Hz, 1Ar-H), 7.75 (t, 1H, J = 8 Hz, 1Ar-H), 7.47 (t, 1H, J = 8 Hz, 1Ar-H), 6.95 (br, 1H, NH), 4.34 (q, 2H, J = 7 Hz, CH₂), 3.65 (t, 2H, J = 6 Hz, CH₂), 2.16 (m, 1H, CH), 1.42 (t, 3H, J = 7 Hz, CH₃), 1.01 (d, 6H, J = 6 Hz, 2CH₃); Calcd. for C₁₈H₁₉N₃O₂S (341.44): C, 63.32; H, 5.61; N, 12.31; S, 9.39; Found: C, 63.44; H, 5.49; N, 12.23; S, 9.56.

6-Cyclohexylamino-8-ethoxy-isoxazolo[3',4':4,5]thieno[2,3-c]quinoline (7c). Yellow crystals 0.280g, 61% yield; mp 279-280°C, IR (KBr pellet): 3424 (NH), 3100 (arom. CH), 2950, 2850 (aliph. CH), 1550 cm⁻¹, MS (EI): m/z 368 (M⁺, 3), 367 (M⁺, 10), 322 (7), 287 (100), 268 (3), 224 (2), 215 (53), 98 (9); ¹H NMR (DMSO-d₆, 400MHz): δ 8.11 (d, 1H, J = 8 Hz, 1Ar-H), 8.01 (d, 1H, J = 8 Hz, 1Ar-H), 7.77 (t, 1H, J = 8 Hz, 1Ar-H), 7.52 (t, 1H, J = 8 Hz, 1Ar-H), 6.80 (br, 1H, NH), 5.20 (m, 1H, 1 aliph-H), 4.45 (q, 2H, J = 7 Hz, CH₂), 2.04-1.76 (m, 4H, 2CH₂), 1.64-1.45 (m, 6H, 3CH₂), 1.45 (t, 3H, J = 7 Hz, CH₃); Calcd. for C₂₀H₂₁N₃O₂S (367.47): C, 65.37; H, 5.76; N, 11.43; S, 8.73; Found: C, 65.43; H, 5.82; N, 11.51; S, 8.81.

8-Ethoxy-6-morpholino-isoxazolo[3',4':4,5]thieno[2,3-c]quinoline (7d). Yellow crystals 0.350g, 78% yield; mp 211-212°C, IR (KBr pellet): 2950, 2850 (aliph. CH), 1555 cm⁻¹, MS (EI): m/z 356 (M⁺, 8), 355 (M⁺, 36), 324 (26), 296 (99), 281 (8), 251 (100), 224 (13), 196 (39), 86 (9); ¹H NMR (CDCl₃, 400MHz): δ 7.89 (d, 1H, J = 8 Hz, 1Ar-H), 7.78 (d, 1H, J = 8 Hz, 1Ar-H), 7.58 (t, 1H, J = 8 Hz, 1Ar-H), 7.29 (t, 1H, J = 8 Hz, 1Ar-H), 4.36 (q, 2H, J = 7 Hz, CH₂), 4.07 (br, 4H, 2OCH₂), 3.12 (br, 4H, 2NCH₂), 1.51 (t, 3H, J = 7 Hz, CH₃); Calcd. for C₁₈H₁₇N₃O₃S (355.42): C, 60.83; H, 4.82; N, 11.82; S, 9.02; Found: C, 60.74; H, 4.91; N, 11.94; S, 8.93.

8-Ethoxy-6-(4-methylpiperidino)-isoxazolo[3',4':4,5]thieno[2,3-c]quinoline (7e). Yellow crystals 0.375g, 81% yield; mp 203-204°C, IR (KBr pellet): 3050 (arom. CH), 2950, 2870 (aliph. CH), 1555 cm⁻¹; MS (EI): m/z 368 (M⁺, 46), 367 (M⁺, 100), 352 (6), 222 (9), 220 (63), 279 (43), 278 (28), 251 (46), 196 (19), 98 (1); ¹H NMR (CDCl₃, 400MHz): δ 7.87 (d, 1H, J = 8 Hz, 1Ar-H), 7.73 (d, 1H, J = 8 Hz, 1Ar-H), 7.66 (t, 1H, J = 8 Hz, 1Ar-H), 7.41 (q, 2H, J = 7 Hz, CH₂), 3.89 (m, 2H, CH₂), 3.52 (m, 2H, CH₂), 2.06-1.57 (m, 5H, 5 aliph-H), 1.39 (t, 3H, J = 7 Hz, CH₃), 0.99 (d, 3H, J = 6 Hz, CH₃); Calcd. for C₂₀H₂₁N₃O₂S (367.47): C, 65.37; H, 5.76; N, 11.43; S, 8.73; Found: C, 65.43; H, 5.82; N, 11.51; S, 8.81.

8-Methoxy-6-morpholino-7H-isoxazolo[3',4':4,5]pyrrolo[2,3-c]quinoline (7f). Colorless crystals 0.330g, 81% yield; mp 289-290°C, IR (KBr pellet): 3320 (NH), 3050 (arom. CH), 2980, 2850 (aliph. CH), 1555 cm⁻¹; MS (EI): m/z 356 (M⁺, 8), 355 (M⁺, 36), 324 (26), 296 (99), 281 (8), 251 (100), 224 (13), 196 (39), 86 (9); ¹H NMR (CDCl₃, 400MHz): δ 12.97 (s, 1H, NH), 8.01 (d, 1H, J = 8 Hz, 1Ar-H), 7.80 (d, 1H, J = 8 Hz, 1Ar-H), 7.61 (t, 1H, J = 8 Hz, 1Ar-H), 4.36 (q, 2H, J = 7 Hz, CH₂), 4.07 (br, 4H, 2OCH₂), 3.12 (br, 4H, 2NCH₂), 1.51 (t, 3H, J = 7 Hz, CH₃); Calcd. for C₁₇H₁₇N₄O₃ (324.34): C, 62.95; H, 4.97; N, 17.27; Found: C, 62.85; H, 4.84; N, 17.34.

8-Methoxy-6-piperidino-7H-isoxazolo[3',4':4,5]pyrrolo[2,3-c]quinoline (7g). Yellow crystals 0.310g, 76% yield; mp 260-262°C, IR (KBr pellet): 3400 (NH), 3100 (arom. CH), 2950 (aliph. CH), 1555 cm⁻¹; MS (EI): m/z 324 (M⁺, 100), 323 (M⁺, 10), 322 (M⁺, 4), 291 (25), 238...
(3), 207 (10), 179 (4), 154 (31), 84 (65); 

$^1$H NMR (DMSO-$d_6$, 400MHz): δ 12.95 (s, 1H, NH), 7.98 (d, 1H, $J = 8$ Hz, 1Ar-H), 7.78 (d, 1H, $J = 8$ Hz, 1Ar-H), 7.59 (t, 1H, $J = 8$ Hz, 1Ar-H), 7.34 (t, 1H, $J = 8$ Hz, 1Ar-H), 3.87 (s, 3H, OCH$_3$), 3.43-3.29 (m, 4H, 2NCH$_2$) 1.74-1.60 (m, 6H, 3CH$_2$); Calcd. for C$_{18}$H$_{18}$N$_4$O$_2$ (322.37): C, 67.07; H, 5.63; N, 17.38; Found: C, 67.13; H, 5.56; N, 17.43.

References

18. Mekheimer, R. A. Synthesis 2000, 2078 is considered part 3 of this Series.


