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 NaN_3, leads to the formation of 3-azido-4-alkyl-aminothieno(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 martinellic 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) B_1 and B_2 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-1*H*-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.[12-14] More recently, others are synthesized as potent $\alpha_v\beta_3$ receptor antagonists.[15] 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,[16-21] 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.[22] 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.[23] As the preparation of novel tetracyclic systems is the main target of this synthetic program, the 3-azidothieno(or pyrrolo)quinoline derivatives **6a-g** 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),[16] in which C-4 chlorine atom is readily displaced by nucleophiles,[16,24,25] and reaction with ethyl mercaptoacetate (**2a**) led to ethyl 3-amino-4-chlorothieno[3,2-c]quinoline-2-carboxylate (**3a**).[21] 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-azidothieno-quinolines **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 H_2SO_4 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}.

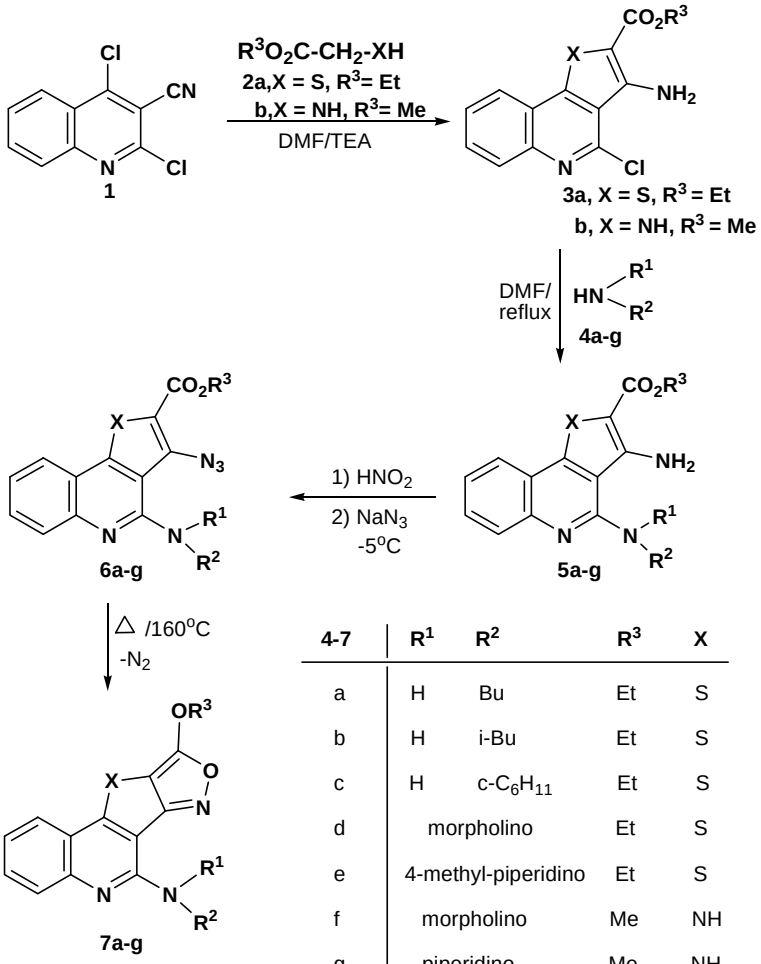
Thermolysis of azides with ortho-acyl substituents is known to afford the corresponding cyclization products,[22,26] in a 1,5-heteroelectrocyclic reaction *via* a pseudo-pericyclic process (without formation of a nitrene intermediate), by decomposition of the azido moiety; this reaction is of synthetic value.[27] 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}.[28] 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.



4-7	R^1	R^2	R^3	X
a	H	Bu	Et	S
b	H	i-Bu	Et	S
c	H	c-C_6H_{11}	Et	S
d	morpholino		Et	S
e	4-methyl-piperidino		Et	S
f	morpholino		Me	NH
g	piperidino		Me	NH

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 withDMSO-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 Gc/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 (NH_2), 3000 (arom. CH), 2850 (aliph. CH), 1660 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 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, NH_2), 4.28 (q, 2H, *J* = 7 Hz, CH_2), 3.87 (br, 4H, $2OCH_2$), 3.42 (br, 4H, $2NCH_2$), 1.30 (t, 3H, *J* = 7 Hz, CH_3); Calcd. for $C_{18}H_{19}N_3O_3S$ (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 (NH_2), 2950, 2850 (aliph. CH), 1670 (CO) cm^{-1}; MS (EI): m/z 369 (M^+, 12), 340 (44), 324 (3), 322 (19), 287 (5), 252 (12), 224 (3), 200 (26), 172 (5), 154 (4), 153 (7), 128 (7), 98 (100), 56 (24); ^1H NMR (DMSO-d_6, 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, NH_2), 4.27 (q, 2H, *J* = 7 Hz, CH_2), 3.40 (br, 4H, $2NCH_2$), 1.78-1.44 (m, 5H, 5aliph-H), 1.30 (t, 3H, *J* = 7 Hz, CH_3), 0.99 (d, 3H, *J* = 6 Hz, CH_3); Calcd. for $C_{20}H_{23}N_3O_2S$ (369.48): C, 65.01; H, 6.27; N, 11.37; S, 8.68; Found: C, 65.20; H, 6.11; N, 11.43; S, 8.73.

Methyl 3-amino-4-morpholino-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (5f). Colorless crystals 0.450g, 85% yield; mp 259-260˚C, IR (KBr pellet): 3440-3300 (NH, NH_2), 3000 (arom. CH), 2970, 2830 (aliph. CH), 1660 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 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, NH_2), 3.88 (s, 3H, OCH_3), 3.84 (br, 4H, $2OCH_2$), 3.42 (br, 4H, $2NCH_2$); Calcd. for $C_{17}H_{18}N_4O_3$ (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-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (5g). Colorless crystals 0.420g, 80% yield; mp 240-241˚C, IR (KBr pellet): 3450-3248 (NH, NH_2), 3050 (arom. CH), 2950, 2850 (aliph. CH), 1660 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 400MHz): δ 12.31 (s, 1H, NH), 8.36 (d, 1H, *J* = 7 Hz, 1Ar-H), 7.63 (d, 1H, *J* = 8 Hz, 1Ar-H), 7.54 (t, 1H, *J* = 7 Hz, 1Ar-H), 7.40 (t, 1H, *J* = 7 Hz, 1Ar-H), 6.93 (s, 2H, NH_2), 3.86 (s, 3H, OCH_3), 3.45-3.31(m, 4H,

2NCH$_2$), 1.83-1.64 (m, 6H, 3CH$_2$); Calcd. for $C_{18}H_{20}N_4O_2$ (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-1*H*-pyrrolo[3,2-c]quinoline-2-carboxylates 6f,g

A solution of aminothieno(or pyrrolo)quinolines **5a-g** (0.73 mmol) in H_2SO_4 (4 ml, 70%) was cooled until the temperature of solution was -5^{o}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 H_2O (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 H_2O, 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 (N_3), 1650 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, 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, CH$_2$), 4.04 (q, 2H, *J* = 7 Hz, CH$_2$), 1.90-1.78 (m, 2H, CH$_2$), 1.47-1.39 (m, 2H, CH$_2$), 1.37 (t, 3H, *J* = 7 Hz, CH$_3$), 0.92 (t, 3H, *J* = 7 Hz, CH$_3$); Calcd. for $C_{18}H_{19}N_5O_2S$ (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 (N_3), 1670 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, 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, CH$_2$), 2.26 (t, 2H, *J* = 7 Hz, CH$_2$), 1.63 (m, 1H, CH), 1.32 (t, 3H, *J* = 7 Hz, CH$_3$), 1.06 (d, 6H, *J* = 7 Hz, 2CH$_3$); Calcd. for $C_{18}H_{19}N_5O_2S$ (369.45): C, 58.52; H, 5.18; N, 18.96; S, 8.68; Found: C, 58.61; H, 5.36; N, 18.87; 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), 2120 (N_3), 1690 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6, 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, 1aliph-H), 4.49 (q, 2H, *J* = 7 Hz, CH$_2$), 2.07-1.94 (m, 4H, 2CH$_2$), 1.79-1.57 (m, 6H, 3CH$_2$), 1.33 (t, 3H, *J* = 7 Hz, CH$_3$); Calcd. for $C_{20}H_{21}N_5O_2S$ (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 0.420 g, 81% yield; mp 139-140˚C, IR (KBr pellet): 2990, 2850 (aliph. CH), 2120 (N_3), 1705 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz): δ 8.24 (d, 1H, *J* = 8 Hz, 1Ar-H), 7.95 (d, 1H, *J* = 8 Hz, 1Ar-H), 7.70 (t, 1H, *J* = 8 Hz, 1Ar-H), 7.48 (t, 1H, *J* = 8 Hz, 1Ar-H), 4.51 (q, 2H, *J* = 7 Hz, CH$_2$), 4.03 (br, 4H, 2OCH$_2$), 3.50 (br, 4H, 2NCH$_2$), 1.40 (t, 3H, *J* = 7 Hz, CH$_3$);Calcd. for

$C_{18}H_{17}N_5O_3S$ (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 ($CDCl_3$, 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), 7.44 (t, 1H, *J* = 8 Hz, 1Ar-H), 4.36 (q, 2H, *J* = 7 Hz, CH_2), 3.88 (m, 2H, CH_2), 3.50 (m, 2H, CH_2), 1.86-1.43 (m, 5H, 5 aliph-H), 1.35 (t, 3H, *J* = 7 Hz, CH_3), 1.03 (d, 3H, *J* = 6 Hz, CH_3); Calcd. for $C_{20}H_{21}N_5O_2S$ (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-1*H*-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), 2120 (N_3), 1715 (CO) cm^{-1}; ^1H NMR: (DMSO-d_6, 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), 7.74 (t, 1H, *J* = 8 Hz, 1Ar-H), 7.59 (t, 1H, *J* = 8 Hz, 1Ar-H), 4.02 (br, 4H, $2OCH_2$), 3.89 (s, 3H, OCH_3), 3.78 (br, 4H, $2NCH_2$); Calcd. for $C_{17}H_{16}N_6O_3$ (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-1*H*-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), 2120 (N_3), 1715 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 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), 7.33 (t, 1H, *J* = 8 Hz, 1Ar-H), 3.96 (s, 3H, OCH_3), 3.39-3.33 (m, 4H, $2NCH_2$), 2.16-1.64 (m, 6H, $3CH_2$); Calcd. for $C_{18}H_{18}N_6O_2$ (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), 2950, 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), 106 (34), 240 (10), 224 (10), 215 (96), 155 (11), 72 (5); ^1H NMR ($CDCl_3$, 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), 7.45(t, 1H, *J* = 8 Hz, 1Ar-H), 6.94 (br, 1H, NH), 4.32 (q, 2H, *J* = 7 Hz, CH_2), 4.20 (q, 2H, *J* = 7 Hz, CH_2), 1.88 (m, 2H, CH_2), 1.56 (m, 2H, CH_2), 1.42 (t, 3H, *J* = 7 Hz, CH_3), 0.96 (t, 3H, *J* = 7 Hz, CH_3); Calcd. for $C_{18}H_{19}N_3O_2S$ (341.44): C, 63.32; H, 5.61; N, 12.31; S, 9.39; Found: C, 63.44; H, 5.71; N, 12.29; S, 9.43.

6-*Iso*-Butylamino-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), 2990 (aliph.

CH), 1550 cm^{-1}, MS (EI): m/z 342 (M^{+1}, 5), 341 (M^{+}, 30), 287 (100), 254 (72), 199 (11), 155 (11), 72 (2); ^{1}H NMR (DMSO-d_6, 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, CH_2), 3.65 (t, 2H, *J* = 6 Hz, CH_2), 2.16 (m, 1H, CH), 1.42 (t, 3H, *J* = 7 Hz, CH_3), 1.01 (d, 6H, *J* = 6 Hz, $2CH_3$); Calcd. for $C_{18}H_{19}N_3O_2S$ (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^{+1}, 3), 367 (M^{+}, 10), 322 (7), 287 (100), 268 (3), 224 (2), 215 (53), 98 (9); ^{1}H NMR (DMSO-d_6, 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, $2CH_2$), 1.64-1.45 (m, 6H, $3CH_2$), 1.45 (t, 3H, *J* = 7 Hz, CH_3); Calcd. for $C_{20}H_{21}N_3O_2S$ (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^{+1}, 8), 355 (M^{+}, 36), 324 (26), 296 (99), 281 (8), 251 (100), 224 (13), 196 (39), 86 (9); ^{1}H NMR ($CDCl_3$, 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, CH_2), 4.07 (br, 4H, $2OCH_2$), 3.12 (br, 4H, $2NCH_2$), 1.51 (t, 3H, *J* = 7 Hz, CH_3); Calcd. for $C_{18}H_{17}N_3O_3S$ (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^{+1}, 46), 367 (M^{+}, 100), 352 (6), 222 (9), 220 (63), 279 (43), 278 (28), 251 (46), 196 (19), 98 (1); ^{1}H NMR ($CDCl_3$, 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), 7.42 (t, 1H, *J* = 8 Hz, 1Ar-H), 4.31 (q, 2H, *J* = 7 Hz, CH_2), 3.89 (m, 2H, CH_2), 3.52 (m, 2H, CH_2), 2.06-1.57 (m, 5H, 5 aliph-H), 1.39 (t, 3H, *J* = 7 Hz, CH_3), 0.99 (d, 3H, *J* = 6 Hz, CH_3); Calcd. for $C_{20}H_{21}N_3O_2S$ (367.47): C, 65.37; H, 5.76; N, 11.43; S, 8.73; Found: C, 65.29; H, 5.67; N, 11.33; S, 8.68.

8-Methoxy-6-morpholino-7*H*-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 326 (M^{+2}, 100), 325 (M^{+1}, 10), 324 (M^{+}, 15), 291 (4), 238 (8), 205 (7), 154 (32), 84 (3); ^{1}H NMR (DMSO-d_6, 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), 7.39 (t, 1H, *J* = 8 Hz, 1Ar-H), 3.89 (br, 4H, $2OCH_2$), 3.85 (s, 3H, OCH_3), 3.44 (br, 4H, $2NCH_2$); Calcd. for $C_{17}H_{16}N_4O_3$ (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-7*H*-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^{+2}, 100), 323 (M^{+1}, 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 $C_{18}H_{18}N_4O_2$ (322.37): C, 67.07; H, 5.63; N, 17.38; Found: C, 67.13; H, 5.56; N, 17.43.

References

1. Snider, B. B.; Ahn, Y.; Foxman, B. M. *Tetrahedron Lett*. **1999**, *40*, 3339.
2. Hadden, M.; Stevenson, P. J. *Tetrahedron Lett*. **1999**, *40*, 1215.
3. Nyerges, M.; Fejes, I.; Töke, L. *Tetrahedron Lett*. **2000**, *41*, 7951.
4. Witherup, K.; Ranson, R. W.; Graham, A. C.; Barnard, A. M.; Salvatore, M. J.; Limma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc*. **1995**, *117*, 6682.
5. Ho, T. C. T., Jones, K. *Tetrahedron* **1997**, *53,* 8287.
6. Heidempergher, F.; Pevarello, P.; Pillan, A.; Pinciroli, V.; Della Torre, A.; Speciale, C.; Marconi, M.; Cini, M.; Toma, S.; Greco, F.; Varasi, M. *II Farmaco* **1999**, *54*, 152.
7. Wagner, G.; Vieweg, H.; Leistner, S. *Pharmazie* **1993**, *48,* 576.
8. Kinji, H.; Makoto, I.; Takahiro, T.; Takuji, K.; Yukio, S.; Toshiko, K. Jap. Patent, 0692963, 1994; *Chem. Abstr.* **1994**, *121*, 157630v.
9. Peter, Z.; Rainer, B.; Volker, G.; Wolfgang, I.; Hildegard, B.; Wolf-Rudiger, U.; Thomas, B.; PCT Int. Appl. WO 9728166, 1997, *Chem. Abstr*. **1997**, *127,* 205562x.
10. Geies, A. A.; Bakhite, E. A.; El-Kashef, H. S. *Pharmazie* **1998**, *53*, 686.
11. Schnitzer, F.; Ercoli, S. H.; Mangieri, J. *Pharmacol*. **1946**, *88*, 47.
12. Hidy Phil, H.; Hodge, E. B.; Young, V. V.; Harned, L. R.; Brewer, A. G.; Philips, W. F.; Runge, W. F.; Stavely, E. H.; Pohland, A.; Boaz, H.; Sullivan, H. R. *J. Am. Chem. Soc.* **1955**, *77*, 2345.
13. Kuehl, A. F.; Wolf, J. F.; Trenner, R. N.; Peck, L. R.; Buhs, P. R.; Howe, E.; Putter, I.; Hunnewell, D. B.; Ormond, R.; Downing, G.; Lyons, E. J.; Newstead, E.; Chaiet, L.; Folkers, K. *J. Am. Chem. Soc*. **1955**, *77*, 2344.
14. Stammer, H. C.; Wilson, N. A.; Holly, W. F.; Folkers, K. *J. Am. Chem. Soc*. **1955**, *77*, 2346.
15. Penning, T. D.; Khilevich, A.; Chen, B. B.; Russell, M. A.; Boys, M. L.; Wang, Y.; Duffin, T.; Engleman, V. W.; Finn, M. B.; Freeman, S. K.; Hanneke, M. L.; Keene, J. L.; Klover, J. A.; Nickols, G. A.; Nickols, M. A.; Rader, R. K.; Settle, S. L.; Shannon, K. E.; Steininger, C. N.; Westlin, M. M.; Westlin, W. F.; *Bioorg. Med. Chem. L*ett. **2006**, *16*, 3156.
16. Mekheimer, R. A. *J. Chem. Soc. Perkin Trans 1* **1999**, 2183 is considered part 1 of this Series.
17. Mekheimer, R. A. *Synth. Commun*. **2001**, *31*, 1971 is considered part 2 of this Series.
18. Mekheimer, R. A. *Synthesis* **2000**, 2078 is considered part 3 of this Series.

19. 19. Mekheimer, R. A.; Ahmed, E. Kh.; EL-Fahham, H. A.; Kamel, L. H. *Synthesis* **2001**, 97 is considered part 4 of this Series.
20. Mekheimer, R. A.; Ahmed, E-Kh.; El-Fahham, H. A.; Kamel, L. H.; Döpp, D. *J. Chem. Res. (S),* **2003**, 388 is considered part 5 of this Series.
21. Mekheimer, R. A.; Sadek, K. U.; Abd El-Nabi, H. A.; Mohamed, A. Abd El-H.; Ebraheem, E. A.; Smith, M. B. *J. Heterocyclic Chem*., **2005**, *42*, 567 is considered part 6 of this Series.
22. (a) Smith, P. A. S., In *Azides and Nitrenes*, Scriven, E. F. V. Ed., Academic Press: New York, 1984. (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev*. **1988**, *88*, 297.
23. Stadlbauer, W.; Prattes, S.; Fiala, W. *J. Heterocyclic Chem*. **1998**, *35*, 627.
24. Mekheimer, R. A.; Kappe, T. *Heterocyclic Commun*. **1998**, *4*, 131.
25. Steinschifter, W.; Stadlbauer, W. *J. Prakt. Chem*. **1994**, *336*, 311.
26. Bakulev, V. A.; Kappe, C. O.; Padwa, A., *In Organic Synthesis: Theory and Applica-tions*, *Vol. 3*, 149, Hudlicky, Ed., JAI Press Inc.: Greenwich/USA-London, 1996.
27. Hojas, G.; Fiala, W.; Stadlbauer, W. *J. Heterocyclic Chem*. **2000**, *37*, 1559.
28. Sutter, P.; Weis, C. D. *J. Heterocyclic Chem*. **1982**, *19*, 997.

