Chapter IIIB

Base Catalyzed Condensation of Thioglycolic Ester with β-chloropyrrolecarbaldehyde: One-pot Approach to Substituted Thieno[2,3-b]pyrroles

IIIB.1 Introduction :

Bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents. The concept of bioisosterism is often considered to be qualitative and intuitive.[1]

Blair *et al.*[2a] have shown that thiophene replacement of the annulated benzene ring in derivatives of piroxicam, amphetamine had no effect on activity. Many thieno-fused bicyclic compounds such as thienopyridines, thienopyrimidines and thienopyrroles have been recently prepared and tested for their biological properties. Among them thienopyrroles are of so important from both theoretical and synthetic point of view, as they are isosteric with indole with their six-π electrons. They are biologically active as sPLA2 inhibitors, MCP-1 inhibitors, glycogen phosphorylase inhibitors, gonadotropin releasing hormone antagonists, and antiviral agents.[2b] Moreover the variable position of the heteroatom in thienopyrrole derivatives increase the chance of suitable binding in biological system.

With the structure-activity relationships around the indole core evaluated, bioisosteric replacement of the indole arene ring with thiophene afforded a series of analogous thienopyrrole. The six isomeric ring structures, **(1)-(6)**, consisting of two heterocyclic five membered rings are of interest from both a theoretical and a synthetic point of view.[3]

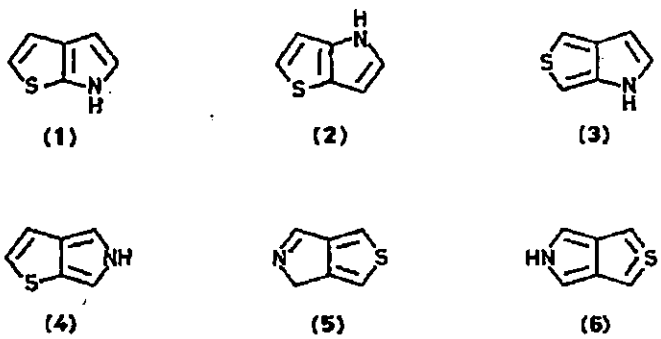


Figure 1

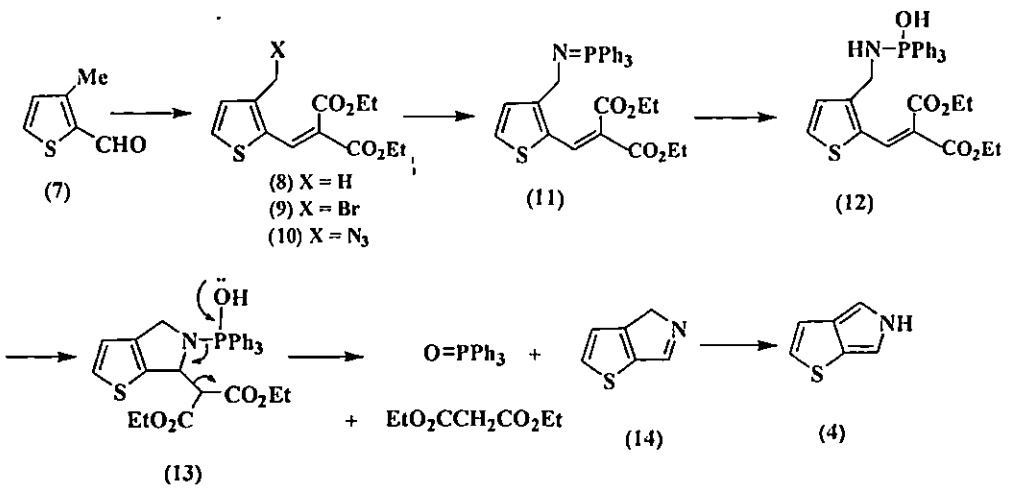
The synthesis of thienopyrroles has attracted much attention from organic chemists mainly because they are of pharmacological importance. However the existing methods

for the synthesis of thienopyrroles are laborious and have a number of limitations. Among the parent compounds of these isomeric thienopyrroles only **(1)** and **(2)** have been synthesized. The rest of the parent compounds **(3)-(6)** have not been synthesized owing to the lack of mild synthetic methods for the preparation of these highly labile ring systems.

The parent heterocycle **2** was synthesized in 1957 by the reductive cyclization of 3-nitro-2-thienylpyruvic acid, followed by decarboxylation of the product, namely, thieno[3,2-*b*]pyrrole-5-carboxylic acid, and also by the reduction of 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one obtained via cyclization of pyrrole-3-thioacetic acid.[4]

Most of the methods reported in literature[5] for the synthesis of thienopyrroles were by the condensation of the corresponding thiophenaldehydes with corresponding esters.

Sha *et al.*[3] reported the synthesis of 5H-thieno[2,3-c]pyrrole **(4)**, the parent compound of the ring system, by a novel phosphineimine-alkylidenemalonate cyclization reaction **(Scheme 1)**.

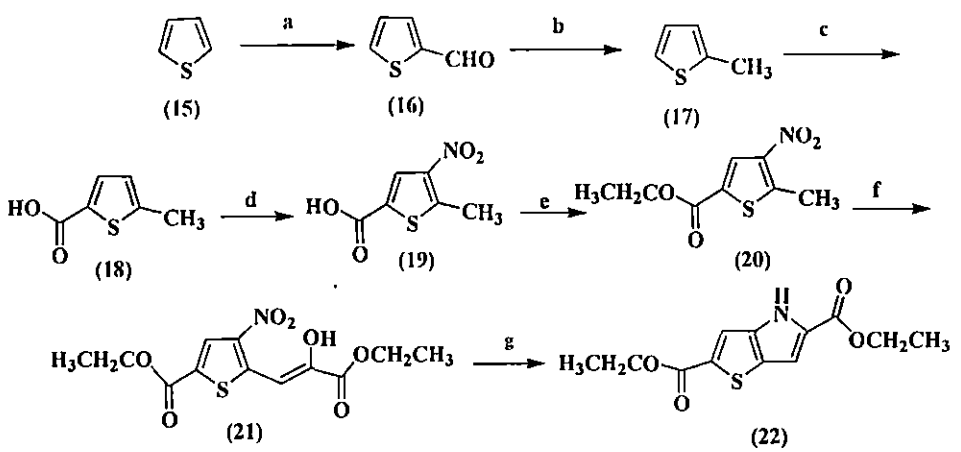


Scheme 1

Knoevenagel condensation of 3-methylthiophene-2-carboxaldehyde **7** with diethyl malonate gave compound **8** (98%). Bromination of compound **8** with N-bromosuccinimide-dibenzoyl peroxide afforded bromide **9** (80%). Treatment of **9** with sodium azide in aqueous ethanol at room temperature produced azido compound **10**

(92%). Treatment of azido compound **10** with triphenylphosphine in tetrahydrofuran followed by hydrolysis gave a mixture of compound **14**, diethyl malonate, and triphenylphosphine oxide. Upon silica gel chromatography compound **14** tautomerized into **4**, which was isolated in 78% yield.

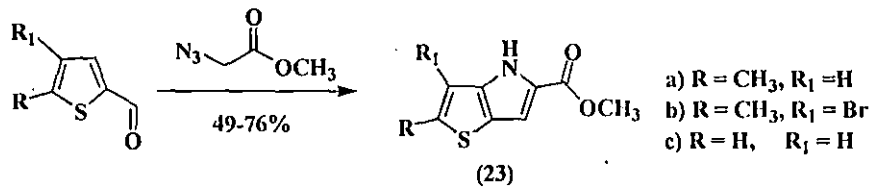
Reddy *et al.*[6] have synthesized a series of thiophene [3,2-b] pyrrole derivatives from thiophene carboxaldehyde. The thiophene [3,2-b] pyrrole was prepared starting from thiophene (**Scheme 2**). Thiophene **15** was converted into 2-formylthiophene **16** by formylation using standard procedure with DMF/$POCl_3$. The 2-formyl thiophene, thus obtained, was reduced to 2-methyl thiophene **17** with hydrazine hydrate. Frieder–Crafts alkylation reaction of **17** followed by oxidation with sodium perchlorate furnished 2-methylthiophenecarboxylic acid **18**, in good yields. The carboxylic acid **18**, on treatment with nitrating mixture gave nitro derivative **19**, which on esterification with ethanol furnished the corresponding ethylester **20**. The ester was treated with diethyloxalate to give the enol ester **21**. The enolester was converted into thieno-[3,2-b]-pyrrole moiety **22** using stannous chloride dihydrate in moderate yield.



Reagents and conditions: (a) DMF, $POCl_3$, 80 ^{0}C; (b) ethanediol, NH_2–$NH_2.H_2O$/KOH, 180 ^{0}C. (c) $AC_2O/AlCl_3$, DCE, 45–50 ^{0}C; (d) NaOCl, 70–80 ^{0}C; (e) HNO_3/H_2SO_4, 0–5 ^{0}C; (f) EtOH/H^+, reflux; (g) $(CO_2C_2H_5)_2$, NaOEt, ethanol, 50–60 ^{0}C; (h) $SnCl_2$ $2H_2O/H^+$, ethanol, reflux;

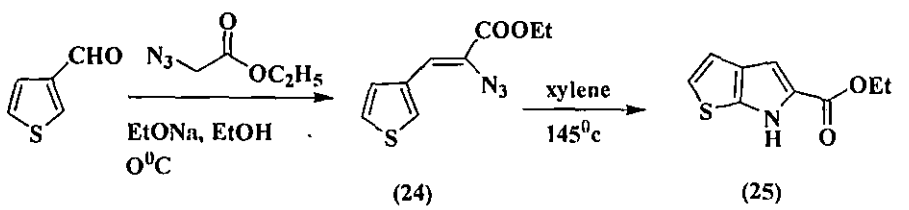
Scheme 2

Krayushkin *et al.* have synthesized thienopyrroles (**23a-c**) by the condensation of the corresponding thiophenaldehydes with esters of azidoacetic acid (Hemetsberger-Knittel reaction) (**Scheme 3**).[5c]



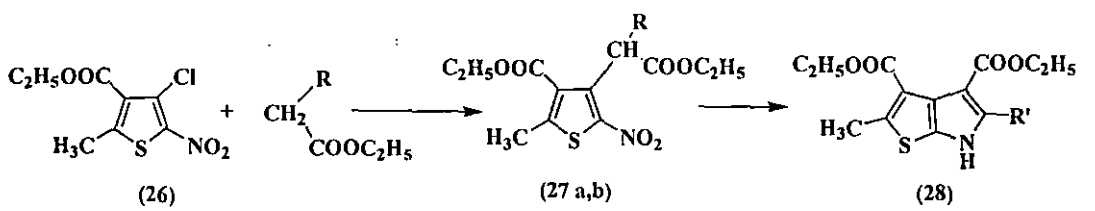
Scheme 3

The head-to-head thienopyrroles **25** were synthesized via Hemetsberger reaction of thiophene **24**, derived from the condensation of thiophene-3-carboxaldehyde and ethyl azidoacetate (**Scheme 4**).[5b]



Scheme 4

Shvedov *et al.* have found that thienopyrroles could be synthesized from *o*-halonitrothiophenes by the method known for the preparation of indole derivatives (**Scheme 5**).[7]

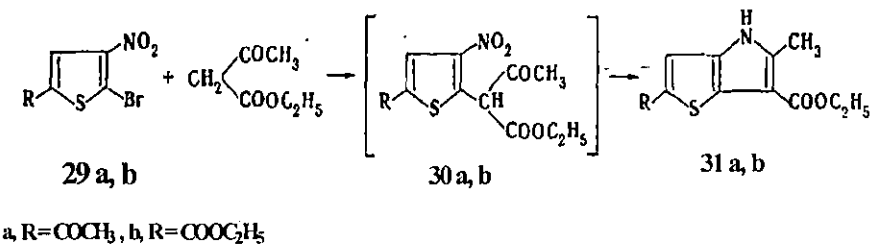


27a, R = CN. 27b, R = COCH3 28a, R' = NH2, 28b, R' = CH3

Scheme 5

The reaction of 2-methyl-3-carbethoxy-4-chloro-5-nitrothiophene **26** with the sodium derivative of cyanoacetic ester gave 2-methyl-3-carbethoxy-5-nitro-4-thienylcyanoacetic ester **27**, which was converted to thieno[2,3-b]pyrrole **28** under the conditions of reductive cyclization.

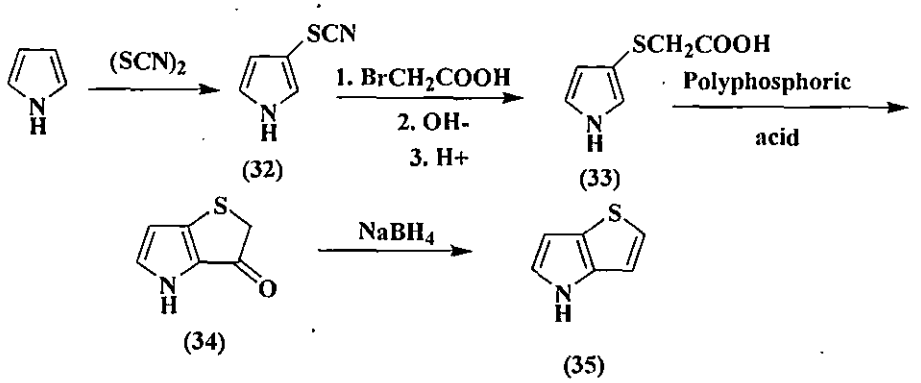
They also obtained the thieno[3,2-b]pyrroles (**31a, b**) from 2-bromo-3-nitrothiophenes (**29a, b**) and the sodium derivative of aceteacetic ester (**Scheme 6**).



Scheme 6

Pyrrole derivatives were also taken as a starting material for the thienopyrrole synthesis.

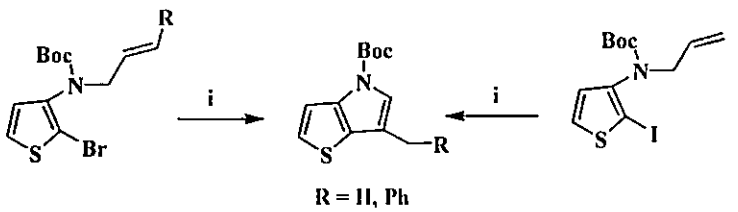
Methanolic solutions of pyrrole and thiocyanogen (prepared at – 60 ^{0}C from potassium thiocyanate and bromine) mixed rapidly at cold (-75^{0}C) condition furnished 3-thiocyanopyrrole **32** (50% yield) and was collected after pouring the reaction mixture onto ice and salt, and recrystallized from methylene chloride-methylcyclohexane.



Scheme 7

Treatment of a cold methanolic solution of **32** and bromoacetic acid with an excess of potassium hydroxide in aqueous methanol furnished (3-pyrrolylthio)-acetic acid **33** in 90% yields. Addition of a dilute methylene chloride solution of **33** over 1 hr. to vigorously stirred polyphosphoric acid at 125 ^{0}C, yielded 36% of 2H,3H-thieno [3,2-b]-pyrrol-3-one **34.** Treatment of **34** with sodium borohydride in methanol yielded 62% of sublimed thieno [3,2-b]-pyrrole **35** (**Scheme** 7).[8]

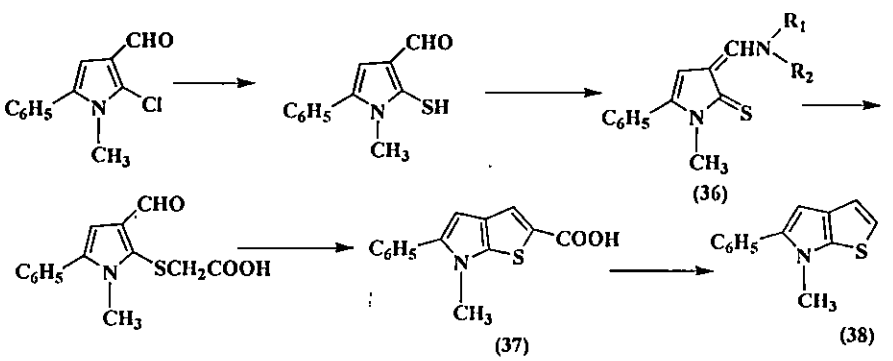
Paulmier *et al.* have synthesized thieno[3,2-*b*]-pyrrole derivative, via palladium-catalyzed cyclization (**Scheme 8**).[9]



Reagents and conditions: (i) $Pd(PPh_3)_4$, K_2CO_3, DMF, 60 °C.

Scheme 8

From literature survey we see that Kvitko *et al.* have synthesized thienopyrrole from pyrrole carboxaldehyde by the following method (**Scheme 9**).

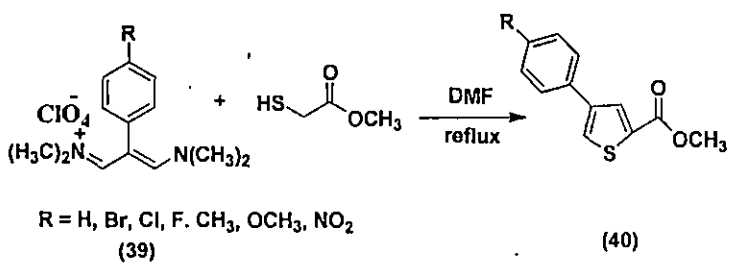


36a, $R_1 = R_2 = CH_3$; 36 b, $R_1 = H$, $R_2 = CH_3$

Scheme 9

An alcohol solution of 1-methyl-2-phenyl-4-formyl-5-chloropyrrole was treated with a threefold excess of an aqueous solution of potassium hydrosulfide, after which the mixture was poured into water and neutralized to pH 7. The mixture was then treated with a four-to fivefold excess of the hydrochloride of the appropriate amine and then refluxed in benzene with an equimolecular amount of chloroacetic acid for 2 h, after which it was cooled, and the reaction product was isolated and again refluxed with 20% NaOH for 3 h. Acidification of this mixture gave **37**. Compounds **37** were heated until CO_2 evolution ceased. Compound **38** was obtained in 60.5%.

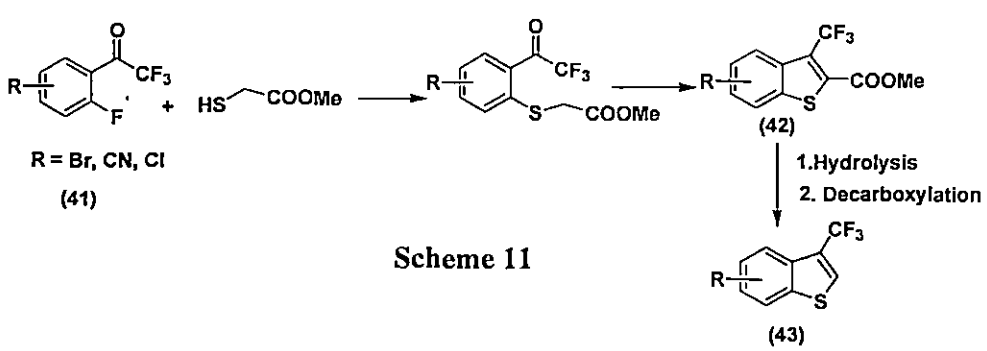
A number of research group have used the methyl thioglycolate for the construction of thiophene ring. Clemens *et al*[10] have synthesis of 2,4-disubstituted thiophenes by using the methyl thioglycolate with symmetrical vinamidinium salts.



Scheme 10

As shown in **Scheme 10**, the vinamidinium salts **39** were allowed to react with methyl thioglycolate in refluxing DMF overnight to give the 2,4-disubstituted thiophenes **40** in 41-95% yield. After workup the crude reaction mixture was analyzed by TLC, GC/MS.

Owton *et al.*[11] reported a straightforward method for the synthesis of 5/6-substituted 3-trifluoromethylbenzo[*b*]thiophenes by displacing fluorine from 2-fluoro-tri-fluoroacetophenones with thioglycolate.



Scheme 11

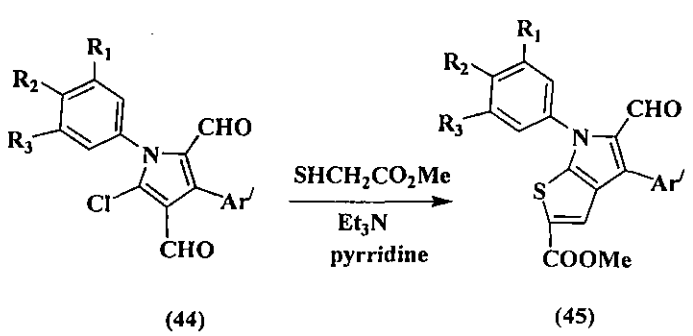
Thus 2-fluoro-2',2',2'-trifluoroacetophenone **41** was reacted with methylthio-glycolate in the presence of triethylamine. Work-up and chromatography gave the required methyl-3-trifluoromethylbenzo[*b*]thiophene-2-carboxylate **42** in 66% yield.

IIIB.2 Present Work :

Our success described in previous chapter prompted us to expand our methodology to other pyrrole core heterocyclic compounds and we see that the *N*-aryl-diformylated-pyrroles (chapter IIIA compound **36** and **38**) has a range of electrophilic centre and a range of sterically encumbered heteroaryl pyrroles can be synthesized from its reaction with nucleophiles.

We herein wish to report an efficient methodology for the synthesis of thienopyrroles by the reaction of methyl thioglycolate on *N*-aryl-diformylated-pyrroles.

Thus the *N*-aryl-5-chloro-3-aryl/heteroaryl-pyrrole-2,4-dicarbaldehyde derivatives **44** on treatment with thioglycolic ester and triethyl amine[12] in dry pyridine solution generated the head-to-head thienopyrrole derivatives **45** in good yield (**Scheme 12, Table 1**).



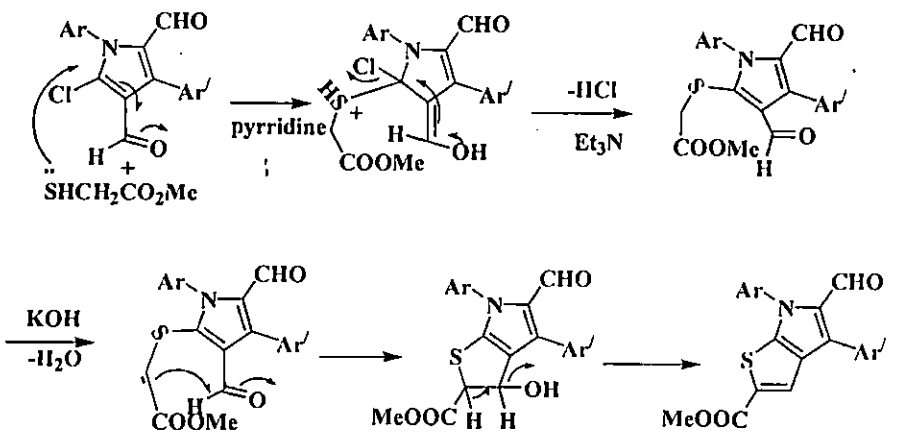
Scheme 12: Synthesis of thienopyrrole derivatives

Table 1. Synthesis of *N*-aryl- thienopyrrole derivatives (**45**) from *N*-aryl-diformylated pyrroles (**44**)

Substrate *N*-aryl-diformylated pyrrole		Ar'	Products *N*-aryl- thienopyrrole	Yield (%)
44a	R_1= R_3= H, R_2= Br	Phenyl	45a	60
44b	R_1= H, R_3= R_2= F	Phenyl	45b	52
44c	R_1= Cl, R_2= F, R_3= H	2-thienyl	45c	58
44d	R_1= H, R_3= R_2= Cl	Phenyl	45d	61
44e	R_1= R_3= H, R_2= Cl	Phenyl	45e	87
44f	R_1= R_3= R_2= H	Phenyl	45f	90
44g	R_1= R_2= Cl, R_3= H	2-thienyl	45g	76

Reagents and conditions: All the reactions were carried out with 2 equiv of methyl thioglycolate and 2 equiv of triethylamine in dry pyridine at O°C. Then it cooled to 10-15 °C and 50% KOH (aq.) soln was added to it.

However, the mechanism of the reaction is uncertain, and we were unable to isolate any intermediates, although a plausible mechanism[12] may be written as depicted in **Scheme 13.**



Scheme 13: Mechanistic study

The heteroarylpyrroles are less stable than their simple pyrrole counterparts and, in general, classical methods are not applicable for their synthesis so their preparation was of very much challenging to us.

In conclusion we can say that we have developed a new methodogy for the synthesis of thieno[2,3-b]pyrroles based on the use of active methylene thiol compounds and pyrrole-chloroaldehydes. The experimental simplicity of the reaction opens new opportunities for the use of this reaction in synthetic and industrial processes.

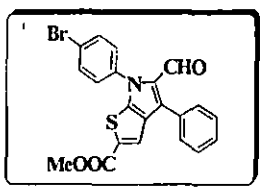
IIIB.3 Exprimental :

General procedure for the synthesis of thieno[2,3-b]pyrrole derivatives (45)

To a flask containing *N*-aryl-diformylated-pyrrole **44** (1 mmol) and methyl thioglycolate (2 mmol) in dry pyridine (3-5 mL) at O °C, triethylamine (2 mmol) was added dropwise. The reaction mixture was gradually allowed to attain the room temperature and then, stirred for additional 30 min at 45-50 °C. Then it cooled to 10-15 °C and 6 mL of 50% KOH (aq.) soln was added to it and stirred at that temp for 20 min. The reaction mixture was then poured into ice cold water and extracted with CH_2Cl_2. The combined organic layer was repeatedly washed with 10% HCl soln and brine. After drying the organic layer with Na_2SO_4, the solvent was evaporated under reduced pressure. The product thus obtained was purified by silica gel (60-120 mesh) column chromatography.

Physical properties and spectral data of representative compounds

Methyl-6-(4-bromo-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45a). Light yellow viscous dense liquid;

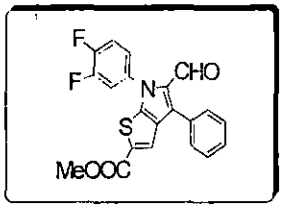


^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.89 (s, 3H), 7.37 (dd, J = 1.5, 6.6 Hz, 2H), 7.50-7.53 (m, 3H), 7.58-7.68 (m, 4H), 7.93 (s,1H), 9.71 (s, 1H),

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 52.36, 122.34, 125.53, 126.90 (2C), 128.78, 128.94 (2C), 129.44, 129.54, 129.67, 130.04 (2C), 131.00, 131.34, 132.56 (2C), 133.92, 137.61, 162.86, 179.91,

Anal. Calcd for $C_{21}H_{14}BrNO_3S$: C, 57.28; H, 3.20; N, 3.18%; Found: C, 57.54; H, 3.63; N, 3.47%.

Methyl-6-(3,4-difluoro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45b). Light yellow viscous semi solid;

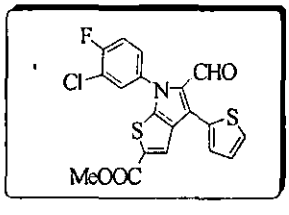


^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.93 (s, 3H), 7.29-7.37 (m, 2H), 7.47-7.55 (m, 4H), 7.60 (d, J = 6.8 Hz, 2H) 7.93 (s, 1H), 9.7 (s, 1H),

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 52.41, 115.45, 115.65, 117.78, 117.96, 121.80, 121.83, 125.54, 128.78, 128.87, 128.99 (2C), 129.49, 129.59, 130.02 (2C), 130.83, 131.18, 132.65, 133.96, 162.80, 179.87.

Anal. Calcd for $C_{21}H_{13}F_2NO_3S$: C, 63.47; H, 3.30; N, 3.52%; Found: C, 63.66; H, 3.83; N, 3.97%.

Methyl-6-(3-chloro-4-fluoro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45c). Light yellow viscous semi solid;

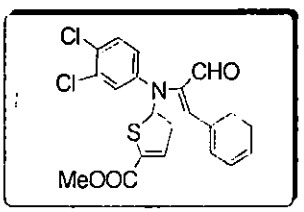


^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.90 (s, 3H), 7.20-7.32 (m, 2H), 7.35-7.39 (m, 2H), 7.53-7.56 (m, 2H), 8.03 (s, 1H), 9.92 (s, 1H),

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 52.46, 117.18, 117.41, 125.45, 125.53, 125.80, 127.93 (2C), 128.18, 128.78, 128.87, 129.20, 129.68, 130.83, 132.36, 132.64, 156.64, 159.14, 162.72, 179.36.

ESI-MS for $C_{19}H_{11}NO_3ClFS_2$ [M], [M+H$^+$] = 419.9525(^{35}Cl, ^{35}Cl), 421.9925 (^{37}Cl, ^{35}Cl).

Methyl-6-(3,4--Dichloro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45d). Light yellow viscous semi solid;

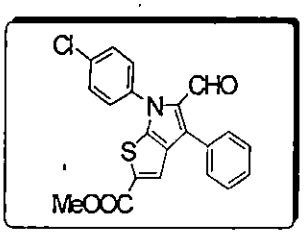


^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.90 (s, 3H), 7.51-7.63 (m, 7H), 7.93 (s, 1H), 8.10 (s,1H), 9.7 (s, 1H),

^{13}C NMR ($CDCl_3$, 50 MHz) δ: 52.40, 114.34, 125.60, 126.72 (2C), 128.84, 129.01 (2C), 129.70 (2C), 129.84, 130.12 (2C), 131.47, 131.99, 132.72, 133.89, 135.62, 136.48, 162.89, 179.95.

ESI-MS for $C_{21}H_{13}NO_3Cl_2S$ [M], $[M+H^+]$ = 430.0994 (^{35}Cl, ^{35}Cl), 432.0977 (^{37}Cl, ^{35}Cl).

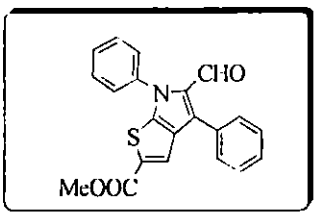
Methyl-6-(4-chloro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45e). Light yellow viscous dense liquid;



^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.86 (s, 3H), 6.97 (d, J = 8.6 Hz, 1H), 7.42-7.50 (m, 8H), 7.81 (d, J = 8.8 Hz, 1H), 9.67 (s, 1H),

^{13}C NMR ($CDCl_3$, 50 MHz) δ: 52.54, 122.64, 124.53, 126.89 (2C), 128.72, 128.94 (2C), 129.44, 129.54, 129.67, 130.04 (2C), 131.00, 131.34, 132.88 (2C), 133.92, 137.71, 162.86, 179.89.

Methyl-5-formyl-4,6-diphenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45f) Light yellow viscous dense liquid;

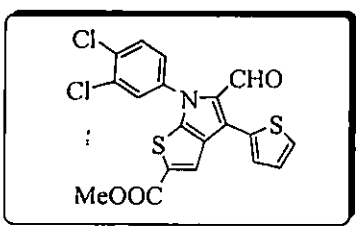


^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.88 (s, 3H), 7.47-7.54 (m, 8H), 7.63 (d, J = 6.8 Hz, 2H), 7.94 (s, 1H), 9.73 (s, 1H),

^{13}C NMR ($CDCl_3$, 50 MHz, *tertiary carbon not appeared*) δ: 52.30, 125.27 (2C), 125.55, 128.59, 128.86 (2C), 129.43 (2C), 130.07 (2C), 152.54, 179.94.

Anal. Calcd for $C_{21}H_{15}NO_3S$: C, 69.79; H, 4.14; N, 3.88%; Found: C, 69.46; H, 3.83; N, 4.27%.

Methyl-6-(3,4--Dichloro-phenyl)-5-formyl-4-thiophen-2-yl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45g). Dense yellow viscous liquid;



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.86 (s, 3H), 7.32-7.40 (m, 2H), 7.52-7.54 (m, 2H), 7.59-7.61 (m, 2H), 8.03(s, 1H), 9.73 (s, 1H),

ESI-MS for $C_{19}H_{11}NO_3Cl_2S_2$ [M], [M+H$^+$] = 436.0611 (^{35}Cl, ^{35}Cl), 438.2875 (^{37}Cl, ^{35}Cl).

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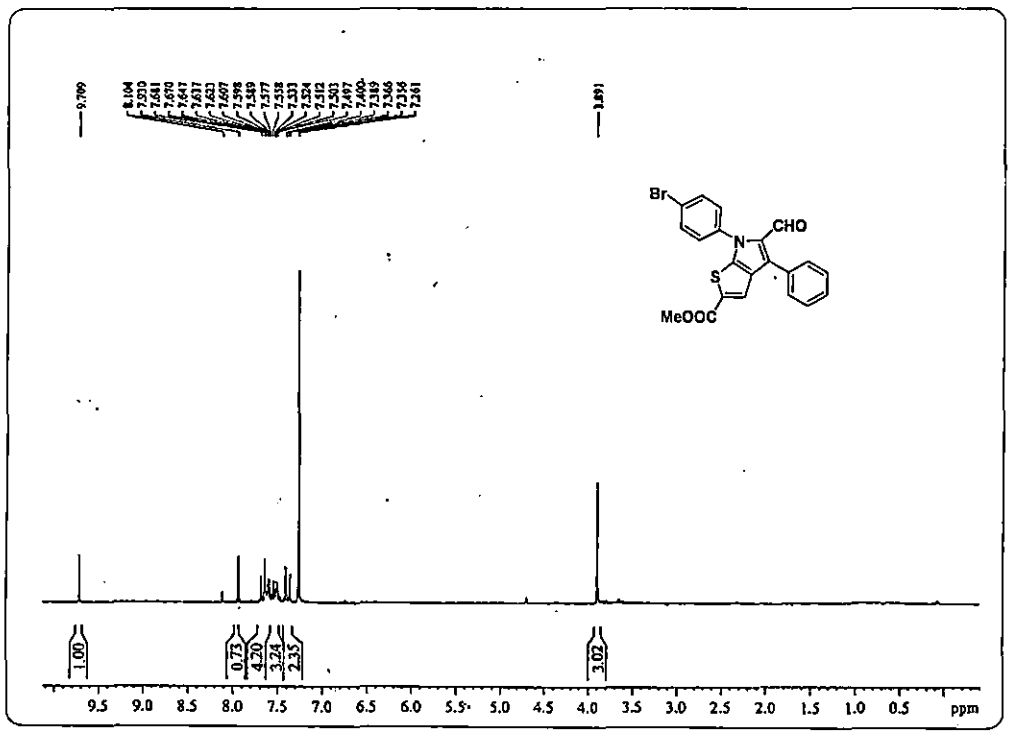
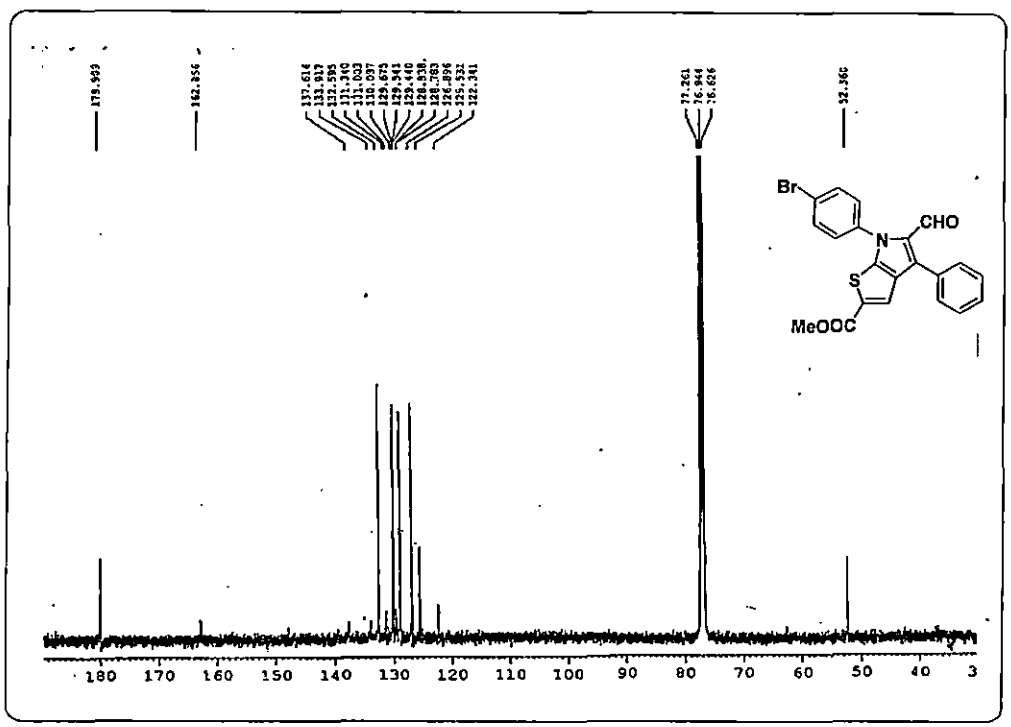
Selected spectra

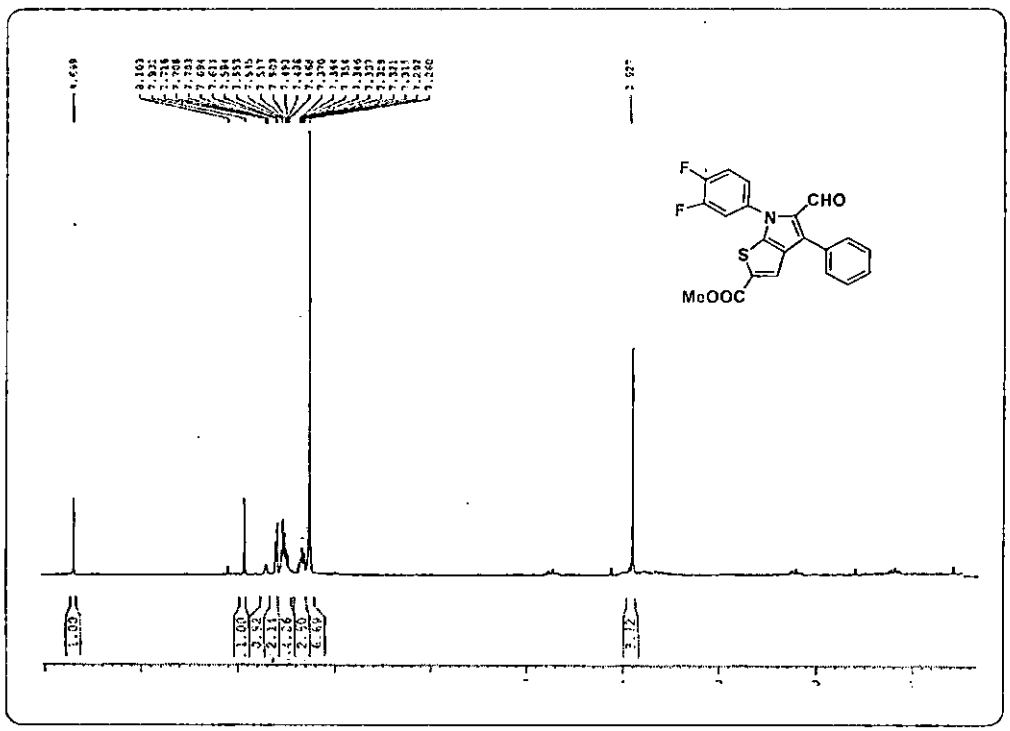
^{1}H NMR (200 MHz, $CDCl_3$) of Methyl-6-(4-bromo-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45a).



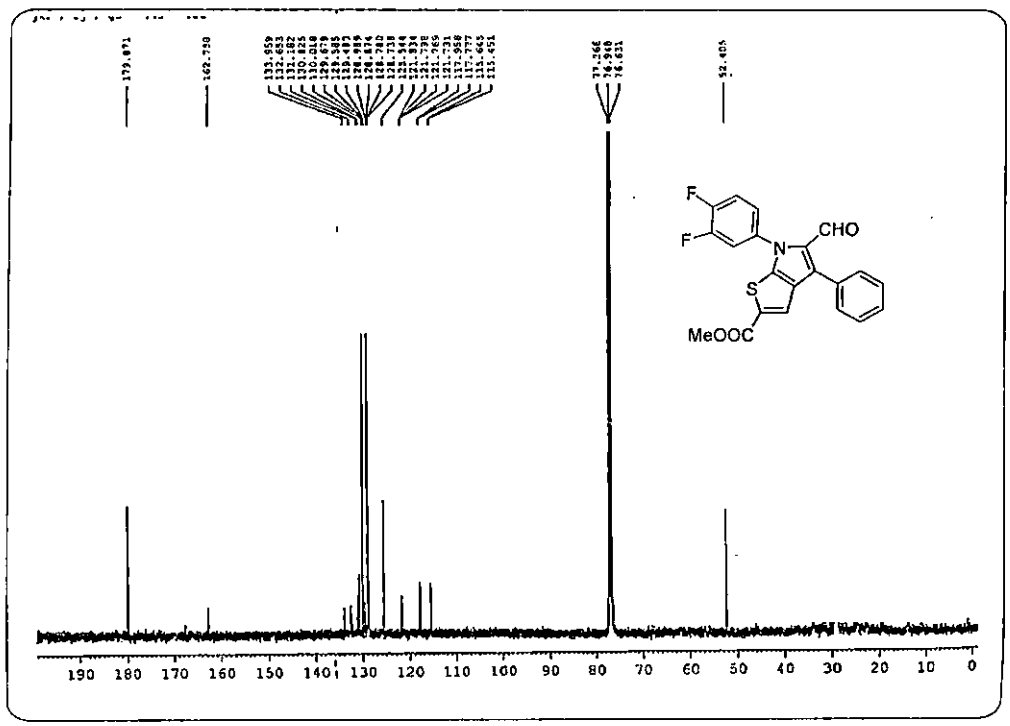
^{13}C NMR (100 MHz, $CDCl_3$) of Methyl-6-(4-bromo-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45a).



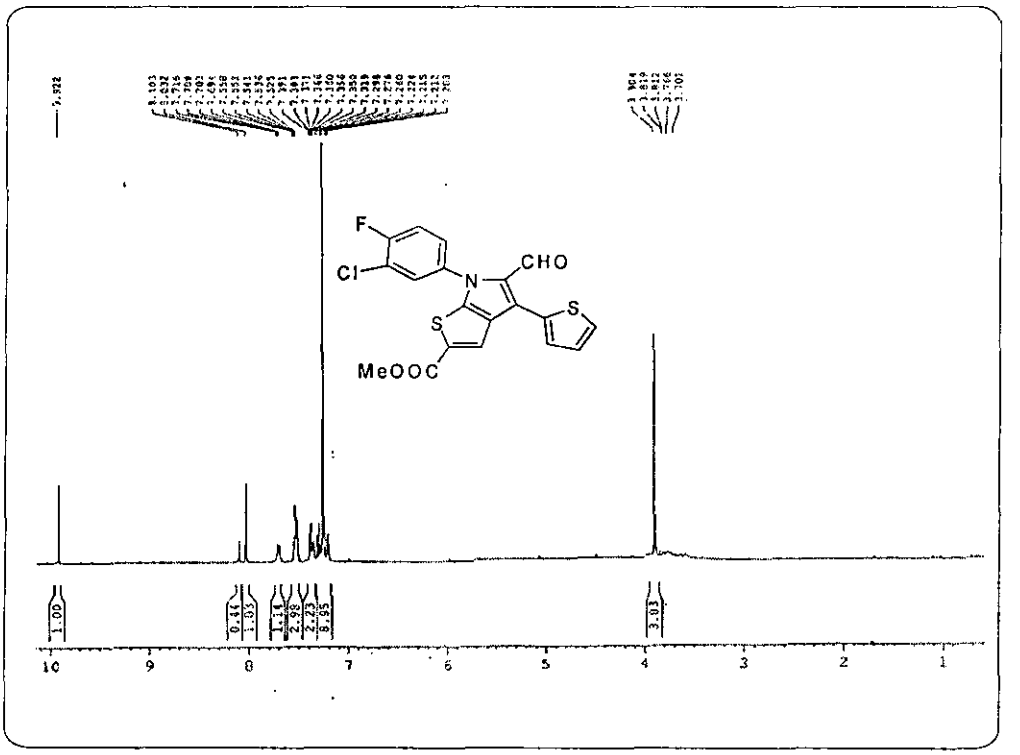
^{1}H NMR (400 MHz, $CDCl_3$) of Methyl-6-(3,4-difluoro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45b).



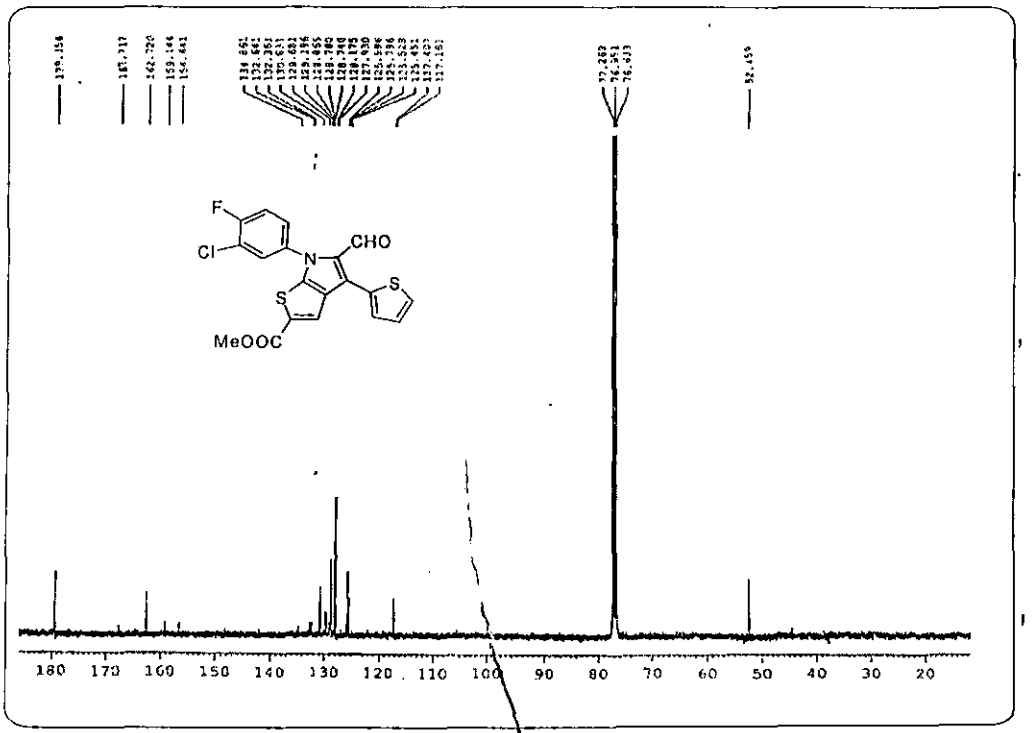
^{13}C NMR (100 MHz, $CDCl_3$) of Methyl-6-(3,4-difluoro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45b).



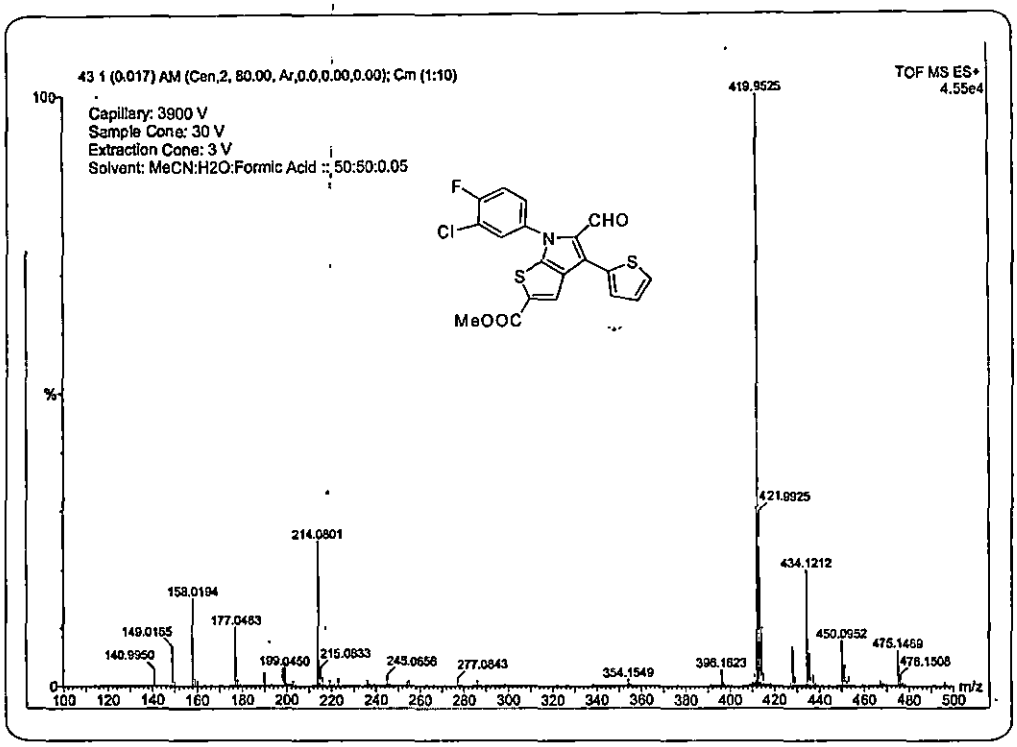
^{1}H NMR (400 MHz, $CDCl_3$) of Methyl-6-(3-chloro-4-fluoro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45c).



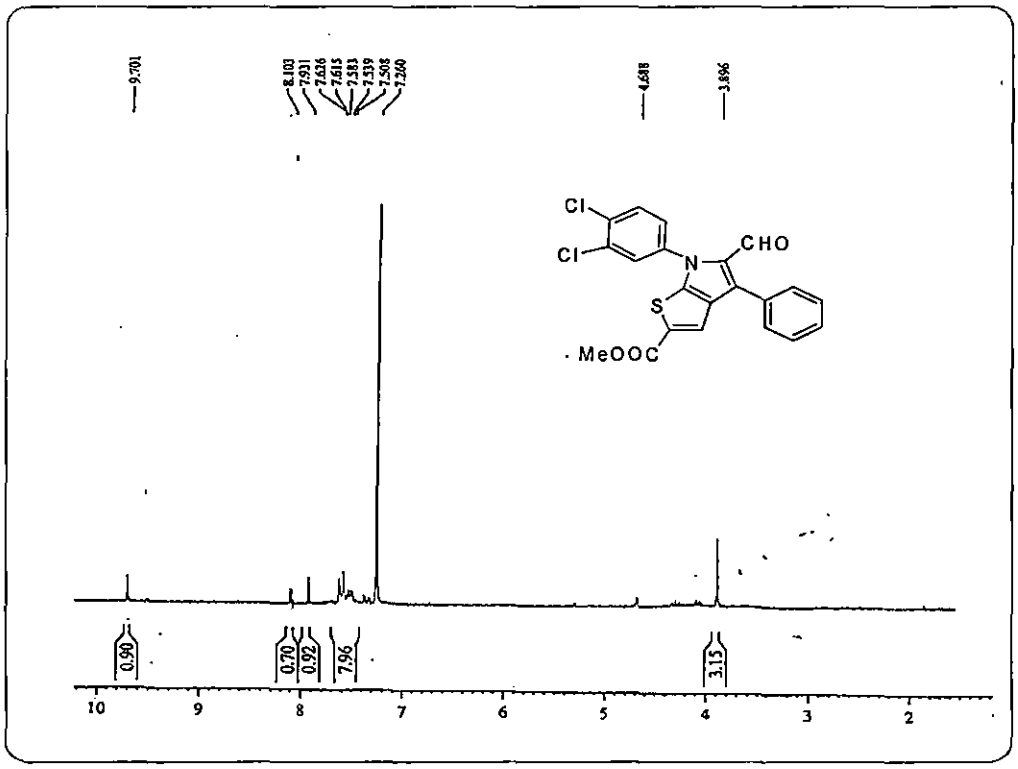
^{13}C NMR (100 MHz, $CDCl_3$) of Methyl-6-(3-chloro-4-fluoro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45c).



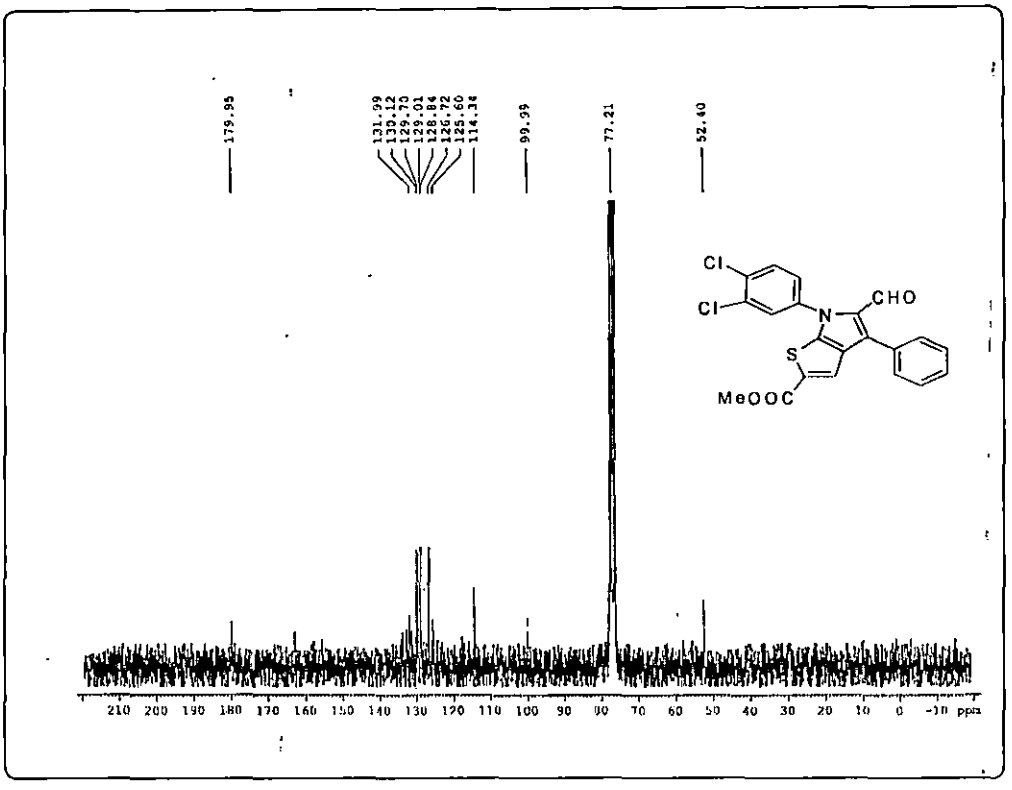
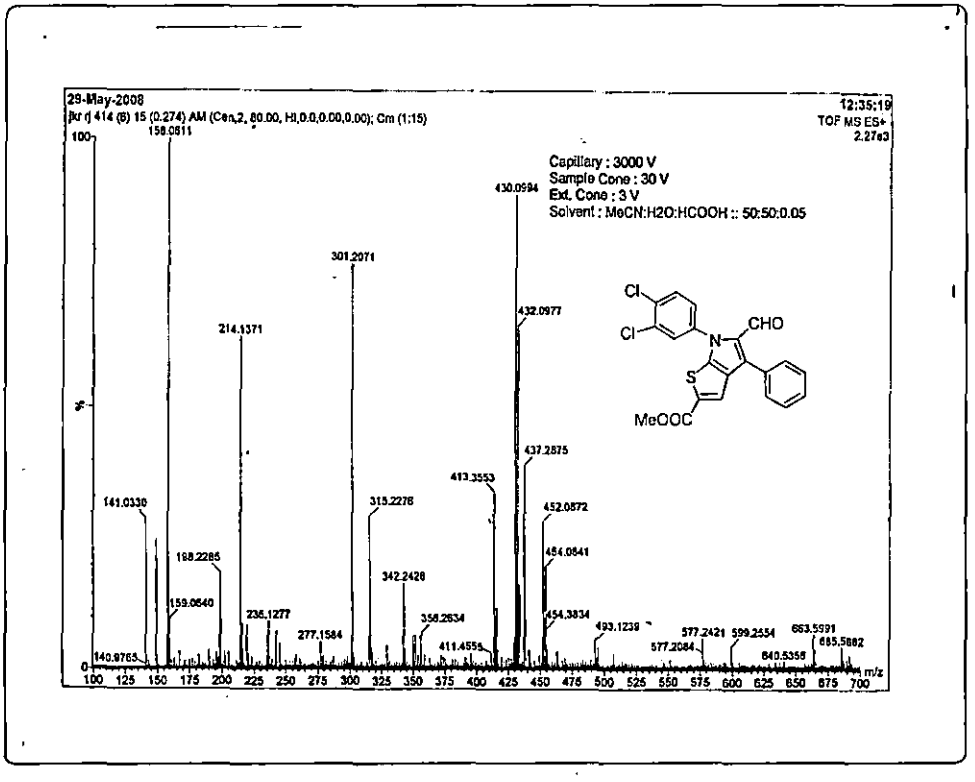
ESI-MS of Methyl-6-(3-chloro-4-fluoro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45c).



^{1}H NMR (400 MHz, $CDCl_3$) of Methyl-6-(3,4--Dichloro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45d).



^{13}C NMR (100 MHz, $CDCl_3$) of Methyl-6-(3,4--Dichloro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45d).



ESI-MS of Methyl-6-(3,4--Dichloro-phenyl)-5-formyl-4-phenyl-6H-thieno[2,3-b]pyrrole-2-carboxylate (IIIB.45d).