



## Synthesis of certain fused pyrrolothieno[3, 2-e] pyrazine derivatives with possible anxiolytic activity

Mohga M.Badran, Samhia M.A.Roshdy, Mohammed K.Abd El-Hameid\*

Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo, (EGYPT)

E-mail: mohorganic@hotmail.com

### ABSTRACT

The work comprise the synthesis of some newly 4-substitutedopyrrolothienopyrazines (XIV) with possible anxiolytic effect by either cyclization of urea derivatives (XI) with phosphorus oxychloride or by reaction of 4-chloropyrrolothienopyrazine (XII) with morpholine. Also, 4-alkoxy pyrrolothienopyrazines (XIII) was prepared by heating of pyrrolothienopyrazin-4(5H)-one (VIII) with phosphorus oxychloride to afford 4-chloropyrrolothienopyrazine (XII) which upon reaction with certain alcohols in presence of sodium metal yielded alkoxy pyrrolothienopyrazines (XIII). Boiling of either compound (IV) or the azide (VII) with *o*-dichlorobenzene afforded pyrrolothienopyrazine-4(5H) one (VIII). in different yields Reaction of the acid hydrazide (VI) with sodium nitrite and concentrated hydrochloric acid afforded the new acyl azide (VII). Refluxing the acid (III) with thionyl chloride produced the intermediate 2-(pyrrol-1-yl)3-thiophene carbonyl chloride (V) which upon heating with hydrazine hydrate gave the desired acid hydrazide (VI). Reaction of 2-(pyrrol-1-yl)-3-thiophene carboxylic acid (III) with ethyl chloroformate, triethylamine and diphenyl phosphoryl azide (DPPA) afforded the unexpected urea derivative (IV). Open field test was done to determine changes of animal behaviors and as screening for antipsychotic activity for some of the prepared compounds, thus it can be concluded that some of the prepared compounds showed central sedative effects and possible anti-anxiety activity.

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### KEYWORDS

5-HT;  
Anxiolytic;  
Pyrrolothienopyrazine.

### INTRODUCTION

Serotonin (5-Hydroxytryptamine, 5-HT) is a major neurotransmitter in the brain and is also involved in a number of biological process at both the central and peripheral actions<sup>[1]</sup>. The potential therapeutic role of its agonist is based on their modulation of acetyl choline release in vivo which makes these compounds of value for the treatment of neurodegenerative and

neuropsychiatric disorders<sup>[2]</sup>. Very little is known about the possible therapeutic application of agonists, although some partial agonists possess an anxiolytic profile. The most frequently mentioned derivatives are indole alkylamine or tryptamine derivatives which bind at 5-HT<sub>3</sub> receptors in a non selective manner such as 2-methyl-5-hydroxytryptamine, the (m-chlorophenyl) biguanide (mCPBG) and the quipazine<sup>[3-6]</sup>. Quipazine was the first aryl piperazine shown to bind at 5-HT<sub>3</sub> receptors even

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though it is also a 5-HT<sub>2A</sub> agonist. Moreover, some new 5-HT<sub>3</sub> agonists which are structurally related to the quipazine have been published, among which are piperazinyl pyrroloquinoxaline (PPQ) derivatives<sup>[7]</sup>, these compounds have in common with the quipazine a polycyclic aromatic moiety linked to a piperazine via a "pseudoamidinic" bond as key pharmacophoric elements for high 5-HT<sub>3</sub> affinity. In 1996, a new family of piperazinopyrrolothienopyrazine (PPTP) derivatives was synthesized and this led to clearly establish Structure Activity Relationship (SAR) for selective and high affinity 5-HT<sub>3</sub> receptor agonist<sup>[8]</sup>. In contrast to the nu-

merous reports which have been appeared for the synthesis of pyrazine, few references are prevalent for the preparation of pyrrolo[1,2-a] quinoxaline<sup>[9-13]</sup> or its analogs pyrrolo[1,2-a] thieno [3,2-e] pyrazine<sup>[14-18]</sup> and pyrrolo [1,2-a] thieno [2,3-e] pyrazine<sup>[19-22]</sup>. These findings motivated us to synthesize certain pyrrolothienopyrazine derivatives aiming that the new compounds may find acceptable value as anxiolytic active agents, especially for binding with 5-HT<sub>3</sub> receptors ligands which may show more selectivity as central 5-HT<sub>3</sub> agonist

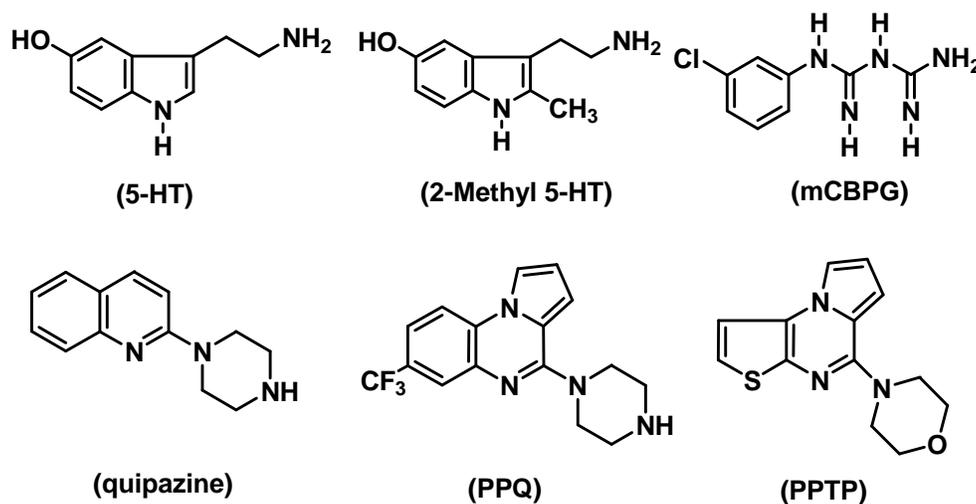


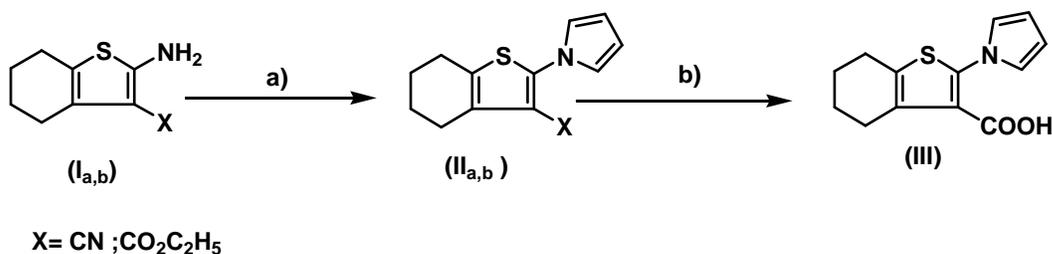
Figure 1 : Structures of some leads molecules with anxiolytic activity

## RESULTS AND DISCUSSION

### Chemistry

The required 2-(pyrrol-1-yl)-3-substituted thiophene derivatives (**II**<sub>a,b</sub>) were prepared by treatment of the 3-substituted-2-aminothiophene compounds (**I**<sub>a,b</sub>) with dimethoxy tetrahydrofuran (DMTHF) in boiling glacial acetic acid<sup>[23]</sup>. The IR spectrum of (**II**<sub>a,b</sub>)

which showed disappearance of absorption band of (NH<sub>2</sub>) function group originally present in the parent compound (**I**<sub>a,b</sub>) and signals at 6.51-7.36 ppm (pyrrolic protons) in the <sup>1</sup>H NMR spectrum of compound (**II**<sub>b</sub>). 2-(pyrrol-1-yl) thiophene-3-carboxylic acid (**III**) was obtained by basic hydrolysis of ester (**II**<sub>b</sub>). The <sup>1</sup>H NMR of compound (**III**) revealed the presence of one signal at 9.60 ppm exchangeable with D<sub>2</sub>O attributed to the acidic proton of the carboxylic group (figure 2).

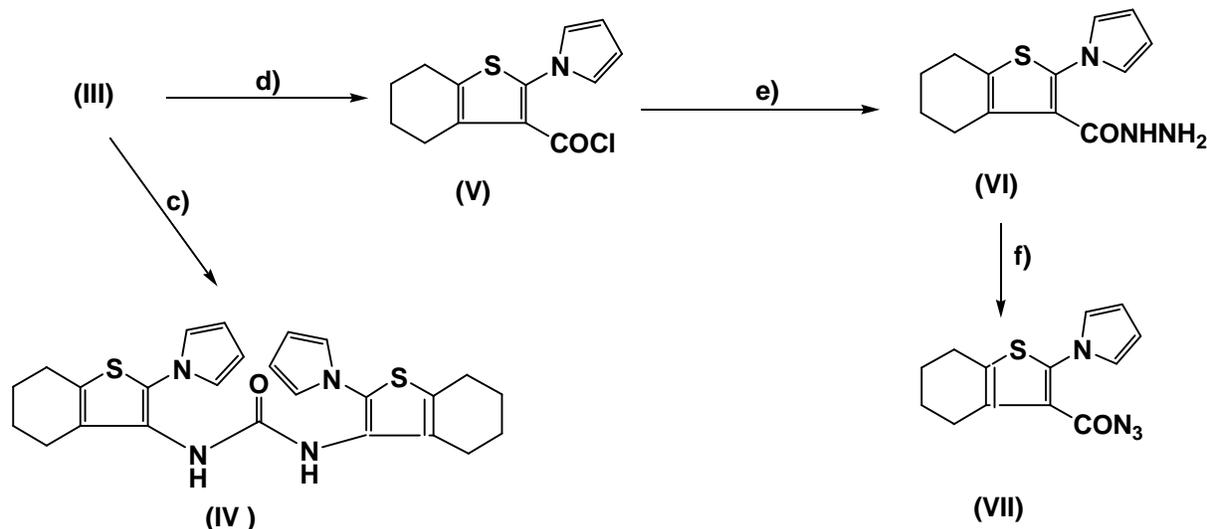


Reagents & conditions : a) DMTHF, AcOH, reflux; b) NaOH, EtOH, reflux

Figure 2 : Synthesis of starting compounds from (I-III)

In an attempt to prepare the target acid azide (VII) following Weinstocks method<sup>[24]</sup>, the parent thiophene carboxylic acid (III) was treated with ethyl

chloroformate and DPPA in presence of triethylamine, the product obtained was not the azide (VII) but the unexpected urea derivative (IV). (figure 3), as an evi-



**Reagents & conditions :** c)  $\text{ClCOOC}_2\text{H}_5$ , TEA, acetone, DPPA,  $0^\circ\text{C}$  d)  $\text{SOCl}_2$ , reflux, 2h; e)  $\text{NH}_2\text{NH}_2$ , reflux, 1h ; f)  $\text{NaNO}_2$ , HCl, stirr at  $0^\circ\text{C}$

Figure 3 : Synthesis of intermediate compounds from IV-VII

dence for the formation of acyl azide during the during formation (IV), the acyl azide (VII) was prepared separately and stirred in dichloromethane for 1 hour at room temperature and the IR spectrum of the mixture produced showed strong band at  $3250\text{ cm}^{-1}$ ,  $2240$ ,  $2150\text{ cm}^{-1}$  and  $1650\text{ cm}^{-1}$  corresponding to (NH), (N=C=O), (N=N=N) and (C=O). The mass spectrum showed a peak at  $m/z$  462 (20 %) revealed that urea derivative (IV) was the sole product. The mechanism of formation is illustrated in (figure 4) 2-(Pyrrol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonyl chloride (V) was prepared by reaction of the parent acid (III) in benzene with freshly distilled thionyl chloride to afford the corresponding acid chloride (V) in (80 %) yield<sup>[25]</sup>. The structure of the newly prepared acid chloride (V) was confirmed by IR which showed the disappearance of OH of carboxylic acid in addition to a more strong (C=O) band at  $1800\text{ cm}^{-1}$ . The required hydrazide (VI) was prepared by reaction of the acid chloride (V) with hydrazine hydrate<sup>[25]</sup> to give (VI). The structure of the isolated hydrazide was confirmed by IR spectrum which showed the presence of absorption bands at  $3300$  ( $\text{NH}_2$ ),  $3250$  (NH) and  $1670$  (C=O). The acyl azide (VII) was prepared by nitrosation of the previously pre-

pared hydrazide (VI) with sodium nitrite and concentrated hydrochloric acid at  $0^\circ\text{C}$  and in a good yield. The IR spectrum showed the presence of absorption bands at  $2140\text{ cm}^{-1}$  and  $1650\text{ cm}^{-1}$  corresponding the (N=N=N) and (C=O) groups respectively (figure 5). Two pathways were used for preparation of the pyrrolothienopyrazin-4-one (VIII). The first pathway (A) involves heating of the acyl azide (VII) in *o*-dichlorobenzene to produce the isocyanate intermediate which undergoes spontaneous intramolecular cyclization to give the required compound (VIII) Moreover, the second pathway (B) involves pyrolysis of the previously prepared N,N-disubstituted urea derivative (IV) in *o*-dichlorobenzene to afford (VIII) and 2-(pyrrol-1-yl)-3-aminothiophene X. The separation of the two products was carried out by extraction with ethyl acetate. It is worth to mention that method (A) afforded higher yield than (B). The intermediates IX were prepared by refluxing a mixture of the acyl azide (VII) in the appropriate alcohol. The reaction sequence comprises the formation of the isocyanate intermediate previously formed during isolation of compound (VIII) which upon heating with alcohol yielded the target carbamates (IX). The IR spectrum of IX which showed disappearance of absorption

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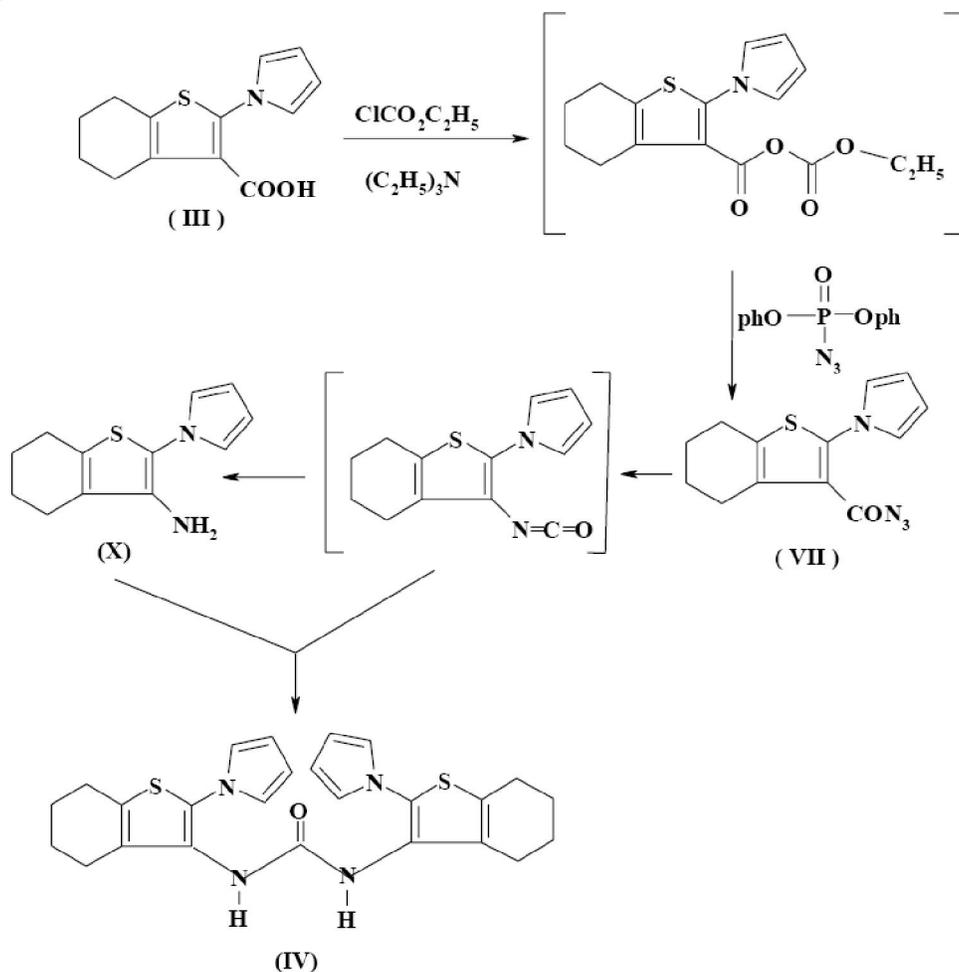
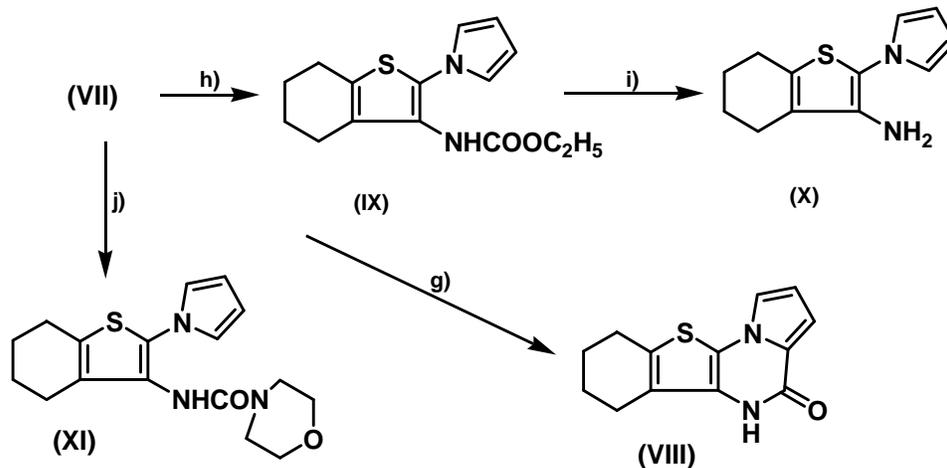


Figure 4 : Proposed mechanism for formation of intermediate (IV)

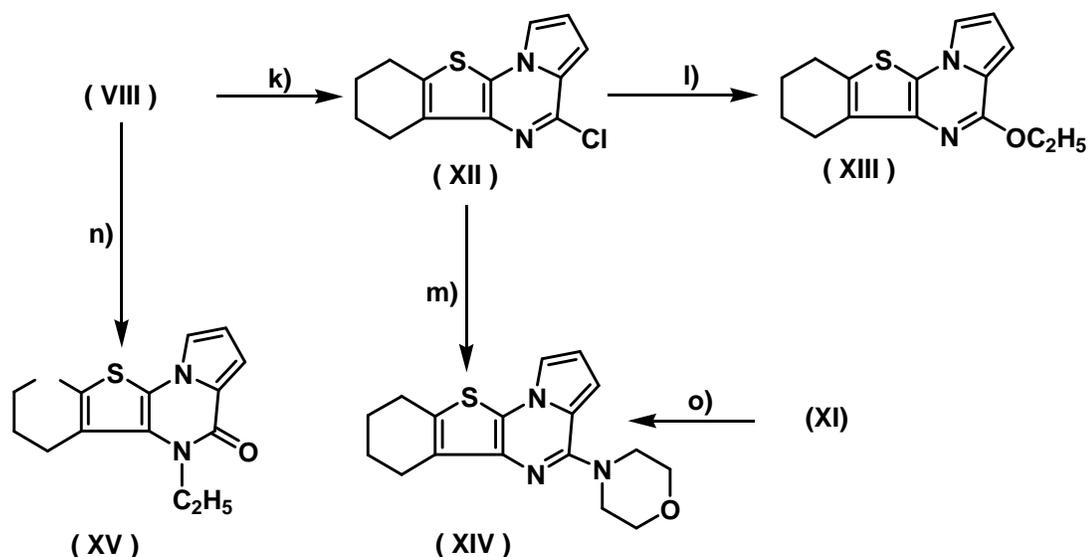


Reagents & conditions : h)  $C_2H_5OH$ , reflux, 1h; i)  $NaOH$ , reflux; j) morpholine, reflux, 2h ; g) *o*-dichlorobenzene, reflux, 3h

Figure 5: Synthesis of intermediate compounds from (VIII-XI)

band of (N=N=N) function originally present in the parent compound (VII), also showed the appearance of NH absorption band at  $3250\text{ cm}^{-1}$ . Two methods were

adopted for the preparation of (X). The first method involved hydrolysis of ethyl carbamate IX using sodium hydroxide to yield 2-(pyrrol-1-yl)-3-amino-5,6,7,8-



Reagents & conditions : k)  $\text{POCl}_3$ , reflux; 3h l) Na, EtOH, reflux 2h; m) morpholine, DMF,  $\text{K}_2\text{CO}_3$ , reflux; n)  $\text{C}_2\text{H}_5\text{-Cl}$ ,  $\text{K}_2\text{CO}_3$ , heat at  $100^\circ\text{C}$  for 1 hr; o)  $\text{POCl}_3$ , reflux, 2h.

Figure 6 : Synthesis of target synthetic molecules from XIII-XV

tetrahydro-1-benzothiophene X in 65 % yield. Moreover, in the second method 2-(pyrrol-1-yl)-3-amino-5,6,7,8-tetrahydro-1-benzothiophene X was obtained by boiling the urea derivative (IV) in *o*-dichlorobenzene in 30 % yield. The newly N,N-disubstituted ureas (XI) were prepared when the acyl azide (VII) underwent Curtius rearrangement in benzene with the secondary amine (figure 5).

The preparation of compound (XII) involves chlorination of the respective pyrrolo-thienopyrazin-4-one (VIII) in phosphorus oxychloride and catalytic amount of pyridine<sup>(26,27)</sup> (VIII) was heated under reflux to produce the target compound (XII). The compounds (XII) were successfully obtained in a relatively low yield<sup>[28]</sup> when a solution of the alkoxide in the corresponding alcohol was allowed to react with the 4-chloropyrrolo-thienopyrazine (XII). Two pathways were adopted for the preparation of (XIV). The first pathway (A) was achieved by treatment of the 4-chloropyrrolo-thienopyrazine (XII) with an equivalent amount of the amine in boiling DMF in the presence of potassium carbonate to produce the required derivatives (XIV) in low yield. The low reactivity of chlorine towards nucleophilic substitution in 4-chloropyrrolo-thienopyrazine (XII) prompted us to search in the literature for a better route to prepare

the target compounds (XIV) in a better yield. Accordingly, a second method was used in which cyclodehydration of ureas (XI) was affected by boiling with phosphorus oxychloride<sup>[29,30]</sup> and leads to the formation of the 4-substituted aminopyrrolo-thienopyrazine (XIV) in a better yield. Additionally, the compounds XV were prepared by heating a mixture of pyrrolo-thienopyrazin-4-one (VIII), alkyl halide and anhydrous potassium carbonate in DMF<sup>[31]</sup> (figure 6).

### Biological screening

The results of the tested compounds in open field test were shown in TABLE 1. All the test compounds as well as the reference compound chlorpromazine produced a parallel reduction in both behavioral variables (ambulation and rearing) compared with the con-

TABLE 1 : Acute effect of test compound on ambulation and rearing of mice in an "open field test"

Treatment	Ambulation	Rearing
Control	26 ± 1.8	11.25 ± 0.55
Chlorpromazine	114.3 ± 8.2	30 ± 6.8
XIV	97.66 ± 6.76	25.6 ± 0.89
XIII	93.6 ± 4.17	21.3 ± 4.2
XV	59.33 ± 3.73	17. ± 3.11
VIII	37.38 ± 3.8	16.6 ± 1.6

Each value is the mean of 12 experiments

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trol group. (XIV) seemed to be more potent than other compounds. Thus it can be concluded that some compounds such as ((XIV) and (XIII)) have central sedative effects and possible anti-anxiety properties.

### EXPERIMENTAL

#### General

Melting points were determined using a Griffin apparatus and were uncorrected. IR spectra were recorded on Shimadzu IR 435 spectrophotometer and values were represented in  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR were carried out on Varian Gemini 200 MHz spectrophotometer, Cairo University, Cairo, Egypt, using TMS as an internal standard and chemical shifts were recorded in ppm on  $\delta$  scale and coupling constants (J) are given in Hz. The electron impact (EI) mass spectra were recorded on Hewlett Packard 5988 spectrometer Microanalytical center, Cairo University, Cairo, Egypt. Elemental microanalyses were performed at Microanalytical center, Cairo University, The results within  $\pm 0.4\%$ . Analytical thin layer chromatography (TLC) on silica gel plates containing UV indicator was employed routinely to follow the course of reactions and to check the purity of products. All reagents and solvents were purified and dried by standard techniques. Compounds Ia and Ib are prepared according to literature procedure<sup>[32]</sup>

#### 2-(Pyrrol-1-yl)-3-substituted-4,5,6,7-tetrahydro-1-benzo- thiophenes (II<sub>a,b</sub>)

A mixture of (DMTHF) (81.84 g, 0.62 mol) and glacial acetic (50 ml) was stirred for 10 minutes, then I<sub>a</sub> or I<sub>b</sub> (0.62 mol) was added. The solution was heated under reflux for specific reaction time 1-2 h.. The excess acid was removed under reduced pressure and the residue obtained was rendered alkaline with solution of sodium bicarbonate (10 %, 20ml) then extracted with diethyl ether (2 $\times$  20ml). The ethereal layer was dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), evaporated to dryness and the residue was crystallized from a suitable ethanol to furnish II<sub>a</sub> or II<sub>b</sub>

#### 2-(Pyrrol-1-yl)-3-substituted-4,5,6,7-tetrahydro-1-benzo- thiophenes-3-carbonitrile (II<sub>a</sub>)

Yield: 40 %; mp: 63-65 °C; Anal. % Calcd. For C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>S (228) :C, 68.42; H, 5.26; N, 12.28, Found:

C, 68.31; H, 5.60; N, 12.30; IR, KBr, ( $\text{cm}^{-1}$ ): 3250 (NH<sub>2</sub>), 2965- 2840 (CH-aliphatic) 2200 (CN);  $^1\text{H}$  NMR (DMSO-d<sub>6</sub>) : $\delta$ =1.50-1.72(m,4H,C-5,6),2.32-2.60(m,4H,C-4,7),6.62-7.20 (m, 4H, pyrrole).:MS:m /z 228 (M<sup>+</sup>,73 %)

#### Ethyl (-2-(Pyrrol-1-yl)-3-substituted-4,5,6,7-tetrahydro-1-benzo- thiophenes-3-)carboxylate (II<sub>b</sub>)

Yield: 30 %; mp: 50-52 °C; Anal. % calcd. For C<sub>15</sub>H<sub>17</sub>NO<sub>2</sub>S (275) :C, 65.45; H, 6.18; N, 5.09; Found: C, 65.50; H, 6.20; N, 5.30 ; IR, KBr, ( $\text{cm}^{-1}$ ): 3250 (NH<sub>2</sub>), 2911- 2824 (CH-aliphatic), 1720 (C=O).,  $^1\text{H}$  NMR (DMSO-d<sub>6</sub>) : $\delta$ =1.60-1.80 (m,4H,C-5,6),2.40-2.70,(m,4H,C-4,7) 2.87-2.92 (t,3H,CH<sub>3</sub>), 3.40-3.55 (q, 2H,CH<sub>2</sub>), 6.51-7.36 (m, 4H, pyrrole); MS: m/z 275 (M<sup>+</sup>,15.68 %).

#### 2-(Pyrrol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid (III)

A mixture of the ester II<sub>b</sub> (27.5g, 0.1 mol) and an ethanolic solution of sodium hydroxide (prepared from 10.5g. Na OH and 200 ml ethanol) was heated for 5 h on a steam bath. Then ethanol was removed under reduced pressure and the residue formed was dissolved in ice cold water (100ml). The solution was acidified with concentrated hydrochloric acid and separated solid was filtered then washed with chloroform. Yield: 0.13g 60 %; mp: 120-122 °C; Anal. % calcd. For C<sub>13</sub>H<sub>13</sub>N O<sub>2</sub>S (247) :C, 63.15; H, :5.26; N, 5.66; Found: C, 63.12; H, 5.25; N, 5.30; IR KBr  $\text{cm}^{-1}$ : 3150-2650 (OH carboxylic), 2946- 2864 (CH-aliphatic) and 1700 (C=O);  $^1\text{H}$ -NMR (DMSO-d<sub>6</sub>):  $\delta$ =1.80-1.91(m, 4H, C-5,6),2.64-2.73(m,4H,C 4,7),6.93-7.35(m,4H, pyrrole),9.60(br s,1H, OH acid,D<sub>2</sub>O exchangeable); MS: m/z 247(M<sup>+</sup>, 65.23 %)

#### N, N-Di [2-(pyrrol-1-yl)- 4,5,6,7-tetrahydro-1-benzothiophen-3-yl] urea (IV)

A solution of the acid III (24.7 g, 0.1 mol), ethyl chloroformate (11.9 g 0.11 mol.) and triethylamine (5.0 g, 0.5 mol) in acetone (50 ml) was stirred at 0 °C for 1 h then (DPPA) (50 g, 0.2 mol) was added at 0 °C during a period of 1 hour and the solution was stirred for 1 h more at room temperature. The reaction mixture was poured onto water (300 ml) and the formed precipitate was crystallized from toluene to produce (IV)

as yellow solid. Yield: 0.13g 80 %; mp: 200-202 °C; Anal.% calcd. For  $C_{25}H_{26}N_4OS_2$  (462): C, 64.93; H, : 5.62; N, 12.12; Found: C, 64.35 ; H, 5.30; N, 12.20; IR, KBr, ( $cm^{-1}$ ): 3250 (NH), 2916-2854 (CH-aliphatic) and 1680(C=O); MS: m/z 462( $M^+$ , 20 %).

### 2-(Pyrrol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonyl chloride (V)

To a solution of the acid III (148.2g, .60 mol) in benzene (500ml), thionyl chloride (66 g, 0.9 mol) was added and the reaction mixture was heated under reflux for 1 h. The reaction mixture was evaporated under reduced pressure and the residue obtained was crystallized from petroleum ether (60-80) to give (V) as brown solid. Yield:82 %; mp: 85 -87°C; Anal.% calcd. For  $C_{13}H_{12}ClNO_2S$  (265.5):C, 58.75 ; H, 4.51; N, 5.27 ; Found: C, 58.70 ; H, 4.50; N, 5.30; IR, KBr, ( $cm^{-1}$ ): : 2950- 2824 (CH-aliphatic),1800 (C=O).;MS: m/z 265( $M^+$ , 5 %), m/z 267,( $M+2$ , 2 %).

### 2-(Pyrrol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid hydrazide (VI)

A mixture of the acid chloride (V) (0.531g, 0.002 mol) and hydrazine hydrate 100 % (5 g, 0.1 mol) in ethanol (20ml) was refluxed for 1 h..After cooling, the formed precipitate was filtered and crystallized from DMF to give (VI) as brown. Yield: 0.13g (38 %); mp: 250-255 °C; Anal.% calcd. For  $C_{13}H_{15}N_3OS$  (261) :C, 59.77 ; H, 5.74; N, 16.09; Found: C, 59.80; H, 5.75; N, 16.05; IR,KBr, ( $cm^{-1}$ ): (NH<sub>2</sub>) forked, 3300-3250 (NH), 2986-2864 (CH-aliphatic)and 1670 (C=O).; <sup>1</sup>H NMR (DMSO- $d_6$ ) : $\delta$ =1.43-1.81(m,4H,C-5,6),2.22-2.60(m,4H,C-4,7),4.23(brs,1H, NH, D<sub>2</sub>O exchangeable), 5.10(brs, 2H,NH<sub>2</sub>, D<sub>2</sub>O exchangeable),6.71-7.31 (m, 4H, pyrrole) ;MS: m/z 261( $M^+$ ,10 %).

### 2-(Pyrrol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonyl azide (VII)

A suspension of the hydrazide (VI) (0.52g,0.002 mol) in concentrated hydrochloric acid (10 ml) was cooled to 0 °C and a cold solution of sodium nitrite (3.88g, 0.056 mol) in water (5 ml) was added dropwise during stirring within 15 minutes. The reaction mixture was stirred for one hour at 0°C then left in the refrigerator overnight. Upon dilution with water (750 ml) a brown precipitate was formed, filtered, washed several times with water (30ml) followed by ethanol (30

ml) and dried to afford azide (VII) as yellowish brown solid.. Yield: 65 %; mp: 230-232 °C; Anal.% calcd. For  $C_{13}H_{12}N_4OS$  (272) :C, 57.35; H, 4.41; N, 20.58; Found: C, 57.21; H, 4.35; N, 20.60 ; IR,KBr, ( $cm^{-1}$ ): 2922-2814 (CH-aliphatic), 2140 (N=N=N) and 1650(C=O). MS: m/z 272( $M^+$ , 5 %), m/z 244 (100 %).

### 6,7,8,9-Tetrahydropyrrolo[1,2-a]-1-benzothieno [3,2-e] pyrazin-4(5H) -one (VIII)

Two methods were adopted for preparation of the title compound.

#### Method A

A suspension of (IV) (4.62 g, 0.01mol) in o-dichlorobenzene (150 ml) was refluxed for 1 h. After cooling, the solid formed was filtered and extracted with ethyl acetate (3×25 ml). The residue left after extraction was crystallized from petroleum ether (60-80 °C) to gave brown solid, yield: (35 %).

#### Method B

A suspension of (VII) (2.72 g, 0.01mol) in o-dichlorobenzene (150 ml) was heated under reflux for 1 h. The mixture was cooled, filtered and the precipitate formed was crystallized from petroleum ether (60-80 °C) to Yield: (80 %) mp: 225-257 °C; Anal.% calcd. For  $C_{15}H_{12}N_2OS$  (244) :C, 63.93; H, 4.91; N, 11.47; Found: C, 63.71; H, 4.80; N, 11.38; IR,KBr, ( $cm^{-1}$ ): 3100(NH), 2916- 2854 (CH-aliphatic) and 1690(C=O), <sup>1</sup>H NMR (DMSO- $d_6$ ):  $\delta$ =1.55-1.75 (m, 4H, C-7,8),2.80-2.30 (m,4H, C-6,9) 6.90-7.31(m, 3H,C-1-3 pyrrole), 9.21 (brs, 1H,NH,D<sub>2</sub>O exchangeable); MS: m/z 244( $M^+$ , 100 %);

### 3-(Ethoxycarbonylamino)-2-(pyrrol-1-yl)-4,5,6,7-tetrahydro-1-benzo thiophenes (IX)

A mixture of the azide (VII) (0.27g, 0.001mol) and the respective alcohol (5 ml) was refluxed for 2 h. The excess alcohol was removed by distillation under reduced pressure and the solid formed was crystallized from acetone Yield: (40 %); mp: 120-122 °C; Anal.% calcd. For  $C_{15}H_{18}N_2O_2S$  (290) :C, 62.06; H, 6.20; N, 9.65; Found: C, 62.10; H, 6.30 ; N, 9.70; IR,KBr, ( $cm^{-1}$ ): 3250(NH) 2916- 2854 (CH-aliphatic) and 1740 (C=O); <sup>1</sup>H. NMR (DMSO- $d_6$ ):  $\delta$ = 1.49-1.72 (m, 4H,C-5,6), 2.55-2.75 (m,4H,C-4,7), 2.90-3.21

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(t,3H,CH<sub>3</sub>), 3.31-3.43 (q,2H,CH<sub>2</sub>), 5.10 (brs,H, NH, D<sub>2</sub>O exchangeable), 6.89-7.20 (m, 4H, pyrrole); MS: m/z 290(M<sup>+</sup>, 6 %), m/z 218 (100 %).

### 3-Amino-2-(pyrrol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophene (X)

Two methods were adopted for preparation of the title compound.

#### Method A

A mixture of ethyl carbamate IX (2.9 g, 0.01 mol) and sodium hydroxide solution (50 ml, 6 N) was refluxed for 4 h. The reaction mixture was cooled and the precipitate formed was filtered and crystallized from benzene to give as white crystals, yield : 65 %.

#### Method B

A suspension of (IV) (4.62g.0.01 mol) in o-dichlorobenzene (150 ml) was refluxed for 1 h. After cooling the precipitate formed was filtered and extracted with ethyl acetate (3×25 ml). The combined extracts were evaporated under reduced pressure to produce X. yield:20 %, mp: 160-163 °C; Anal.% calcd. For C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>S (218) :C, 66.05; H, 6.42; N, 12.84; Found: C, 66.30; H, 6.50; N, 12.80 ; I R,KBr, (cm<sup>-1</sup>): 3200(NH<sub>2</sub>); 2960-2823 (CH-aliphatic);<sup>1</sup>H. NMR (DMSO-d<sub>6</sub>): δ= 1.49-1.72 (m, 4H,C-5,6),2.55-2.75(m,4H,C-4,7), 5.21 (brs,2H,NH<sub>2</sub>,D<sub>2</sub>O exchangeable), 6.91-7.37 (m, 4H, pyrrole); MS: m/z 218(M<sup>+</sup>, 17 %).

### 3-[Morpholinocarbonylamino]-2-(pyrrol-1-yl)-4,5,6,7-tetrahydro-1-benzothiophenes (XI)

A mixture of the azide (VII) (3.80 g, 0.014 mol) and the appropriate secondary amine (0.014 mol) was refluxed in benzene (50 ml) for 2 h. After cooling, the formed precipitate was filtered, washed with petroleum ether (40-60 °C) and crystallized from toluene to give (XI). Yield 55 %; mp: 96-99 °C; Anal.% calcd. For C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S (331):C, 61.63; H, 6.34; N, 12.68; Found: C, 61.60; H, 6.35 ; N, 12.60; I R,KBr, (cm<sup>-1</sup>): 3250(NH), 2980-2812 (CH-aliphatic) and 1670(C=O);<sup>1</sup>H. NMR (DMSO-d<sub>6</sub>): δ= 1.49-1.72 (m, 4H,C-5,6),2.55-2.75 (m, 4H,C-4,7),3.35-3.45(m,4H,2CH<sub>2</sub>),3.50-3.65(m,4H,2CH<sub>2</sub>), 5.51 (brs, H, NH,D<sub>2</sub>O exchangeable), 6.91-7.37 (m, 4H, pyrrole);MS: m/z 331(M<sup>+</sup>, 17 %).

### 4-Chloro-6,7,8,9-tetrahydropyrrolo[1,2-a]-1-benzothieno[3,2-e] pyrazine (XII)

A mixture of (VIII) (5.4 g,0.02 mol), phosphorus oxychloride (7.35 ml,0.08 mol) and pyridine (0.05 mol) was heated under reflux for 4 h, The mixture was allowed to cool then poured onto crushed ice. The precipitated product was filtered, crystallized from acetone to afford (XII) as yellowish brown. Yield: 65 %; mp: 205-207 °C; Anal.% calcd. For C<sub>13</sub>H<sub>11</sub>Cl N<sub>2</sub>S : (262.5):C, 59.42 ; H, 4.19 ; N, 10.66; Found: C, 59.31 ; H, 4.10; N, 10.50 ; I R,KBr, (cm<sup>-1</sup>): 2976, 2861 (CH-aliphatic), 1650(C=N).<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ=1.51-1.67 (m, 4H, C-7,8),2.75-2.81 (m,4H, C-6,9) 6.80-7.21(m, 3H,C-1-3 pyrrole) MS: m/z 262(M<sup>+</sup>, 11 %), 264(M+2,5%).

### 4-Ethoxy-6,7,8,9-tetrahydropyrrolo [1,2-a]-1-benzothieno[3, 2-e] pyrazines (XIII)

Compound XII (5.25 g, 0.02 mol) was dissolved in ethanol or methanol (10 ml) by gentle heating. The resulting solution was added portionwise to sodium alkoxide solution [prepared by addition of sodium metal (1g) to the corresponding alcohol (20 ml)]. The resulting mixture was refluxed for 4 h. then kept overnight at room temperature. The excess alcohol was removed under reduced pressure and the solid formed was crystallized from DMF to yield (XIII). Yield:35 %; mp: 196-198 °C; Anal.% calcd. For C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>OS (272) :C, 66.18; H, 5.88; N, 10.29; Found: C, 66.20; H, 5.86; N, 10.35; I R,KBr, (cm<sup>-1</sup>): 2926-2814 (CH-aliphatic),1640 (C=N).; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ =1.55-1.75 (m, 4H, C-7,8),2.22-2.53 (m,4H, C-6,9), 2.90-3.21(t,3H,CH<sub>3</sub>),3.41-3.50(q,2H,CH<sub>2</sub>), 6.90-7.31(m, 3H,C-1-3 pyrrole);MS: m/z 272(M<sup>+</sup>, 25 %).

### 4-(Morpholino)-6,7,8,9-tetrahydropyrrolo[1,2-a]-1-benzothieno[3,2-e]pyrazines (XIV)

Two methods were adopted for preparation of title compounds.

#### Method A

The 4-chloropyrrolothienopyrazine (XII) (2.62 g, 0.01 mol) was added to the corresponding secondary amine (0.01 mol) and anhydrous potassium carbonate (2.8 g, 0.02 mol) in DMF (10 ml). The solution was heated under reflux for 2 h, cooled, and added to 100 ml of water. The suspension was extracted with diethyl

ether (4×50 ml). The ethereal layer was washed three times with water (10ml). The ether was evaporated under reduced pressure and the solid formed was re-crystallized from DMF to give (XIV).

### Method B

Compounds (XI) (0.01 mol.) were heated in presence of phosphorus oxychloride (30 ml) for 2 h. After cooling, the solution was treated with a sodium bicarbonate solution (10 %, 50 ml) while stirring and extracted with ethyl acetate (2×50 ml). The organic layer was evaporated under reduced pressure and the residue obtained was crystallized from DMF to give (XIV).

Yield: (25 %); mp: 250-252 °C; Anal.% calcd. For C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>OS (313) :C, 65.17; H, 6.07; N, 13.41; Found: C, 65.50 ; H, 6.40; N, 13.35 ; IR,KBr, (cm<sup>-1</sup>): 2916-2854 (CH-aliphatic), 1650(C=N); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ =1.55-1.75 (m, 4H, C-7,8), 2.80-2.30 (m, 4H, C-6,9), 3.35-3.45 (m, 4H, 2CH<sub>2</sub>), 3.50-3.65(m, 4H, 2CH<sub>2</sub>), 6.90-7.31(m, 3H, C-1-3 pyrrole), MS: m/z 313(M<sup>+</sup>, 5 %).

### 5-Ethyl-6,7,8,9-tetrahydropyrrolo[1,2-a]-1-benzothieno [3,2-e]pyrazin-4(5H)-ones (XV)

A mixture of pyrrolothienopyrazin-4-one (VIII) (2.44 g, 0.01 mol), the corresponding alkyl halide (0.01 mol) and anhydrous potassium carbonate (1.4 g, 0.01 mol) in DMF (30 ml) was heated at 100 °C for 1 h. The reaction mixture was poured onto ice-cold water (50 ml) and the solid separated was filtered and crystallized from DMF. Yield: 30 %; mp: 214-216 °C; Anal.% calcd. For C<sub>16</sub>H<sub>16</sub>N<sub>2</sub>OS (284) :C, 67.60 ; H, 5.63; N, 9.85; Found: C, 67.70; H, 5.82; N, 9.90; IR,KBr, (cm<sup>-1</sup>): 2997-2840 (CH-aliphatic), 1670(C=O). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ =1.49-1.68 (m, 4H, C-7,8), 2.26-2.61 (m, 4H, C-6,9), 2.90-3.21(t, 3H, CH<sub>3</sub>), 3.31-3.43(q, 2H, CH<sub>2</sub>), 6.80-7.22(m, 3H, C-1-3 pyrrole); MS: m/z 284(M<sup>+</sup>, 12 %).

### Preliminary pharmacological testing

The open field test<sup>[33]</sup> in mice is method used as screening method for anxiolytic properties

### Material and methods

A natural wooden box (60x60x30cm) divided into 6 squares (10x10cm) was used. Each animal was tested only once to prevent habituation. All tests were run in a

room shielded from laboratory surrounds. The mice were housed in groups of 12 in plastic cage; they were permitted free access to food and water. All animals were allowed to acclimatize for 24 h. period to the start of the experimental under standard laboratory conditions. The test compounds were suspended in 2 % tween 80 and administered orally in groups of 12 mice at a dose of 10mg /1 Kg. After the administration of the test compound or the reference compound chlorpromazine, the animals were tested in the open field apparatus. Each mouse was placed singly in the test box for 3 min. two behavioral parameters were measured: ambulation and rearing. Ambulation was defined as the number of squares the animal crossed in the 3 min observations period, Rearing was defined as the numbers of times the animal stand and hind feet in the 3 min. observation period. A control group (n=12) received orally saline which run parallel with the treated group. The means of each group were statistically compared for significant rearing

### CONCLUSION

In summary, a series of new 4-alkoxyopyrrolothienopyrazines and 4-morpholino pyrrolothienopyrazines was synthesized. Open field test was done to determine changes of animal behaviors and as screening for antipsychotic activity for some of the prepared compounds, thus it can be concluded that some of the prepared compounds showed central sedative effects and possible anti-anxiety activity.

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