SYNTHESIS OF NEW [10H-SUBSTITUTED PHENOXAZINE-3- YL)-6-PYRIMIDIN-2-PHENYLTHIOL/OL/AMINE/THIOL] PYRROLES

Idries,M,Abeed AL-Mashkor*

ABSTRACT:

2-[4-hydroxy benz-1(propene-1-one)]Pyrrole II on treatment with phenyl thiourea, guanidine carbonate, urea and thiourea in alcoholic KOH yielded compounds III, IV, V, VI which on treatment with different aryl anilines gave compounds VII, VIII, IX, X which under goes cyclisation with sulphur and iodine to give 2-[4-(10H-substituted phenoxazine-3-yl)-6-pyrimidin-2-phenylthiol/-ol/-amine/-thiol] pyrrole XI (a-j), XII (a-j), XIII (aj) and XIV (a-j) respectively. The structural products were characterized by elemental analysis and spectral data.

INTRODUCTION

Heterocyclic compounds particularly five or six membered ring compounds have occupied the first place among various classes of organic compounds for their diverse biological activities[1]. A broad spectrum of biological activity is associated with both simple and fused pyrrole and a large number of natural and synthetic compounds containing such moieties find pharmaceutical applications[2-5]. Pyrimidine rings have received significant attention owing to their diverse range of biological properties. Pyrimidine nucleus is in clinical use such as antibacterial agents, anticancer agent, antiviral agents, antifungal agents and antimalarial agents. Pyrimidines have been used as therapeutic agents[6-7] possessing analgesics and anti-inflammatory activity[8-9]. Several important sulfa drugs are pyrimidine derivatives namely sulfadiazine, sulfamerazine and sulfadimidine. A variety of natural products such as alkaloids also contain the pyrimidine ring system, these include hypoxanthine and xanthine, which occur in tea, and caffeine and theophylline (the constituents of tea leaves). Phenoxazine derivatives possess diverse biological activities like antiparkinsonian[10-11], anticonvulsant [12], antihistaminic[13], antihelmatic[14], antiviral[15], antiparasitic [16] and CNS depressant[17].

Experimental & Materials

All the melting points were determined in open capillaries and are uncorrected. The IR spectra were run in KBr on a Perkin - Elmer infrared spectrophotometer. ^{1}H NMR spectra on Brucker AC – 300F (300 Hz) NMR spectrometer using DMSO as a solvent using tetramethyl silane as internal standard

General procedure for the preparation of the Compound (II a-m)

2-acetyl pyrrole (0.01mol) and 4-hydroxyhyde (0.01mol) was dissolved in 100ml ethanol. To this solution, NaOH (40%, 10ml) was added drop wise with constant stirring at room temperature till a dark yellow mass was obtained. The reaction mixture was kept 7-8 hr and acidified with dil HCl. The solid obtained was washed with cold water. It was filtered, dried and crystallized from

Department of Biochemistry, College of Medicine, University of Thi Qar

appropriate solvent. These compounds **(**II a-m**)** are synthesized by classical as well as microwave assisted reaction

General procedure for the preparation of the Compound III, IV, V and VI

A mixture of benzylidene acetyl pyrroles 2a (0.01mol) and phenylthiourea, guanidine carbonate, urea, thiourea (0.03mol) in alcoholic KOH was refluxed for 8 hr. The contents were evaporated to dryness and the product so obtained was washed with water repeatedly and then recrystallized from ethanol.

General procedure for the preparation of the Compound VII, VIII, IX and X

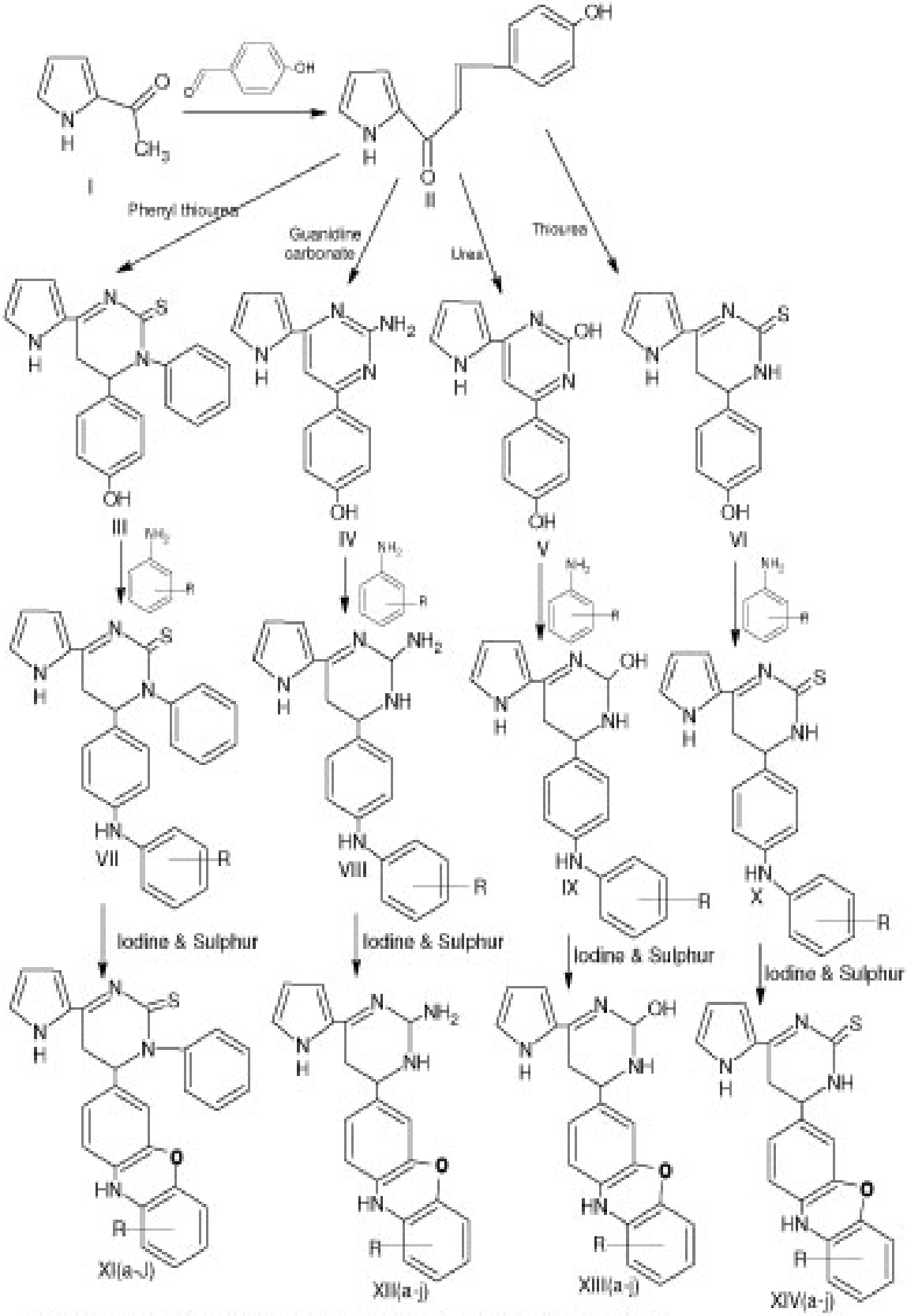
A mixture of **2** (0.05mole) and an aromatic primary amine (0.05mole) in absolute ethanol (50ml) was heated under reflux in the presence of anhyd. ZnCl2 (0.5g) for 6 hr. On cooling, a solid mass separated out which was washed with acidified water to remove inorganic materials, then it was filtered off to obtain the product and crystallized from ethanol.

General procedure for the preparation of compounds XI, XII, XIII and XIV

A mixture of **3** (0.01mole) sulphur (0.1 mole) and Iodine (0.5 g) was heated at 1200C in an oil bath for 2 hr. The hot melt was rapidly poured in to a mortar and crushed to a fine powder. It was washed with water dried and crystallized from ethanol.

Results & Discussion

The starting compound 2-acetyl pyrrole on reaction with 4-hydroxy benzaldehyde yielded 2-[4-hydroxy benz-1/(propene-1//-one)] Pyrrole II which on treatment with phenyl thiourea, guanidine carbonate, urea and thiourea in alcoholic KOH furnished compounds III, IV, V, VI. These then on treatment with different aromatic amines in appropriate solvent afforded VII, VIII, IX and X, which on treatment with iodine and sulphur in appropriate solvent gave the respective XI, XII, XIII and XIV.(Scheme-I). The structural products were characterized by elemental analysis and spectral data. (Tables 1-5).



R=H, 2-OH, 3-OH, 4-OH, 2-NO_2, 3-NO_2, 4-NO_2, -$N(CH_3)_2$, 2-Cl, 4-OCH_3

Scheme-I

Table 1. Characterization data of compounds (XI a-j)

Compd	IR cm^{-1}	^1H NMR
XI a	3532(NH-pyrrole), 3369(NH- phenoxazine), 3344(NH- pyrimidine), 1630(ArH), 1443(C=N), 814(C-N), 657(C-O)	δ 8.20 (1H,s,NH-pyrrol),7.8 (1H,s,NH-phenoxazine), 6.8(5H, m, ArH). 6.8 (s, 1H, CH-pyrrole), 5.48 (1H,s,NH-pyrimidine)
XI b	3430(-OH), 3332 (NH-pyrrole), 32269(NHphenoxazine),3234(NH pyrimidine), 1640(ArH), 1446(C=N), 834(C-N), 659(C-O);	δ 8.22 (1H,s,NH-pyrrol),7.3 (1H,s,NH-phenoxazine),6.7(5H, m, ArH). 6.2(s,1H,CH-pyrrole), 5.28 (1H,s,NH- pyrimidine)
XI e	3532 (NH-pyrrole), 34269(NHphenoxazine), 3344 (NH- pyrimidine), 1630(ArH), 1443(C=N), 814(C-N), 655(C-O), 732(C-NO2);	δ 8.6 (1H,s,NH-pyrrol),7.8 (1H,s,NH-phenoxazine),6.8(5H, m, ArH), 6.5 (s, 1H, CH-pyrrole). 5.36 (1H,s,NH- pyrimidine)
XII a	3532 (NH-pyrrole), 34269(NHphenoxazine), 3344 (NH- pyrimidine), 1630(ArH),1443(C=N814(C-N), 657(C-O);	δ 8.20 (1H,s,NH-pyrrol),7.8 (1H,s,NH-phenoxazine),6.8(5H, m, ArH). 6.3 (s, 1H, CH-pyrrole), 5.68 (1H,s,NH- pyrimidine)
XII b	3430(-OH), 3532 (NH-pyrrole), 34269(NH-phenoxazine), 3344(NH- pyrimidine), 1630(ArH), 1443(C=N814(C-N), 657(C-O);	δ 8.7 (1H,s,NH-pyrrol),7.6 (1H,s,NH-phenoxazine),6.8(5H, m, ArH). 6.8 (s, 1H, CH-pyrrole), 5.38 (1H,s,NH-pyrazole)
XII i	3532 (NH-pyrrole), 34269(NHphenoxazine), 3344 (NH- pyrimidine), 1630(ArH), 1443(C=N)814(C-N), 657(C-O), 770(C-Cl);	δ 8.20 (1H,s,NH-pyrrol),7.8 (1H,s,NH-phenoxazine),6.8(5H, m, ArH). 6.8 (s, 1H, CH-pyrrole), 28 (1H,s,NH- pyrimidine)
XIII a	3532 (NH-pyrrole), 34269(NHphenoxazine), 3344 (NH- pyrimidine), 1630(ArH),1443(C=N814(C-N),657(C-O);	δ8.7 (1H,s,NH-pyrrol),7.9 (1H,s,NH-phenoxazine),6.8(5H, m, ArH). 6.8 (s, 1H, CH-pyrrole), 5.78 (1H,s,NH- pyrimidine)
XIII b	3532 (NH-pyrrole), 34269(NHphenoxazine), 3344 (NH- pyrimidine), 1630(ArH),1443(C=N814(C-N),657(C-O);	δ 8.5 (1H,s,NH-pyrrol),7.6 (1H,s,NH-phenoxazine),6.8(5H, m, ArH). 6.7 (s, 1H, CH-pyrrole), 5.34(1H,s,NH- pyrimidine)
XIII j	3532 (NH-pyrrole), 34269(NH- phenoxazine), 3344 (NH- pyrimidine), 1630(ArH),1443(C=N814(C-N),657(C-O);	δ8.4 (1H,s,NH-pyrrol),7.5 (1H,s,NH-phenoxazine),6.4(5H, m, ArH). 6.7 (s, 1H, CH-pyrrole), 5.58 (1H,s,NH- pyrimidine)
XIV a	3532 (NH-pyrrole), 34269(NHphenoxazine), 3344 (NH- pyrimidine), 1630(ArH),1443(C=N814(C-N),657(C-O).	δ 8.3 (1H,s,NH-pyrrol),7.5 (1H,s,NH-phenoxazine),6.4(5H, m, ArH). 6.7 (s, 1H, CH-pyrrole), 5.48 (1H,s,NH- pyrimidine)
XIII i	3532 (NH-pyrrole), 34269(NHphenoxazine), 3344 (NH- pyrimidine), 1630(ArH), 1443(C=N814(C-N), 657(C-O) 767(C-Cl).	δ 8.26 (1H,s,NH-pyrrol),7.4 (1H,s,NH-phenoxazine),6.8(5H, m, ArH). 6.7 (s, 1H, CH-pyrrole), 5.68 (1H,s,NH- pyrimidine

Table 2. Characterization data of newly synthesized compounds (XI a-j)

Comp	R	Mol Formula	M.P. °C	Yield %	Analysis formulacalcd %		
					C	H	N
XIa	-H	$C_{26}H_{19}ON_4S$	195	71	69.16 69.11	4.21 4.20	12.41 12.40
XIb	2-OH	$C_{26}H_{19}O_2N_4S$	174	67	66.79 66.70	4.06 4.00	11.98 11.91
XIc	3-OH	$C_{26}H_{19}O_2N_4S$	176	65	66.79 66.70	4.06 4.00	11.98 11.91
XId	4-OH	$C_{26}H_{19}O_2N_4S$	179	58	66.79 66.70	4.06 4.00	11.98 11.91
XIe	2-NO_2	$C_{26}H_{18}O_3N_5S$	191	78	62.89 62.80	3.62 3.60	14.11 14.10
XIf	3-NO_2	$C_{26}H_{18}O_3N_5S$	192	68	62.89 62.80	3.62 3.60	14.11 14.10
XIg	4-NO_2	$C_{26}H_{18}O_3N_5S$	194	64	62.89 62.80	3.62 3.60	14.11 14.10
XIh	$N(CH_3)_2$	$C_{28}H_{24}ON_5S$	196	81	68.00 68.01	4.85 4.80	14.16 14.15
XIi	-Cl	$C_{26}H_{18}$ ON_4ClS	163	66	64.25 64.24	3.70 3.71	11.53 11.52
XIJ	-OCH_3	$C_{27}H_{21}O_2N_4S$	193	77	67.34 67.30	4.36 4.34	11.63 11.62

Table 3. Characterization data of newly synthesized compounds (XII a-j)

Comp	R	Mol Formula	M.P. °C	Yield %	Analysis formulacalcd %		
					C	H	N
XIIa	-H	$C_{20}H_{16}ON_5$	197	71	67.02 67.00	4.46 4.40	19.54 19.52
XIb	2-OH	$C_{20}H1_6O_2N_5$	184	67	64.16 64.16	4.27 4.0	18.71 18.70
XIIc	3-OH	$C_{20}H_{16}O_2N_5$	183	65	64.16 64.16	4.27 4.00	18.71 18.70
XIId	4-OH	$C_{20}H_{16}O_2N_5$	182	58	64.16 64.16	4.27 4.00	18.71 18.70
XIIe	2-NO_2	$C_{20}H_{15}O_3N_6$	190	78	59.54 59.49	3.72 3.70	20.84 20.80
XIIf	3-NO_2	$C_{20}H_{15}O_3N_6$	194	68	59.54 59.49	3.72 3.70	20.84 20.80
XIIg	4-NO_2	$C_{20}H_{15}O_3N_6$	191	64	59.54 59.49	3.72 3.70	20.84 20.80
XIIh	$N(CH_3)_2$	$C_{22}H_{21}ON_6$	212	81	65.82 65.81	5.23 5.21	20.94 20.92
XIIi	-Cl	$C_{20}H_{15}ON_5Cl$	123	66	61.14 61.10	3.82 3.80	17.83 17.82
XIIJ	-OCH_3	$C_{21}H_{18}O_2N_5$	223	77	63.82 63.80	4.78 4.78	18.61 18.64

Table 4. Characterization data of newly synthesized compounds (XIII a-j)

Comp	R	Mol Formula	M.P. °C	Yield %	Analysis formulacalcd %		
					C	H	N
XIIIa	-H	$C_{20}H_{16}O_2N_4$	176	71	66.65 66.62	4.43 4.41	15.55 15.52
XIIIb	2-OH	$C_{20}H_{16}O_3N_4$	167	67	63.82 63.82	4.25 4.00	14.89 14.87
XIIIc	3-OH	$C_{20}H_{16}O_3N_4$	167	65	63.82 63.82	4.25 4.00	14.89 14.87
XIIId	4-OH	$C_{20}H_{16}O_2N_4$	174	58	63.82 63.82	4.25 4.00	14.89 14.87
XIIIe	2-NO_2	$C_{20}H_{15}O_4N_5$	184	78	59.25 59.21	3.70 3.60	17.28 17.20
XIIIf	3-NO_2	$C_{19}H_{13}O_4N_5$	165	68	59.25 59.21	3.70 3.60	17.28 17.20
XIIIg	4-NO_2	$C_{19}H_{13}O_4N_5$	169	64	59.25 59.21	3.70 3.60	17.28 17.20
XIIIh	$N(CH_3)_2$	$C_{22}H_{21}O_2N_5$	210	81	65.50 65.49	5.21 5.20	17.36 17.35
XIIIi	-Cl	$C_{20}H_{15}O_2N_4Cl$	123	66	60.83 60.56	3.80 3.77	14.19 14.10
XIIIJ	-OCH_3	$C_{21}H_{18}O_3N_4$	225	77	64.60 64.59	4.61 4.60	14.35 14.34

Table 5.Characterization data of newly synthesized compounds (XIV a-j)

Comp	R	Mol Formula	M.P. °C	Yield %	Analysis formulacalcd %		
					C	H	N
XIVa	-H	$C_{20}H_{15}ON_4S$	156	71	63.96 63.91	3.99 3.94	14.92 14.90
XIVb	2-OH	$C_{20}H_{15}O_2N_4S$	167	67	61.36 61.34	3.83 3.80	14.31 14.30
XIVc	3-OH	$C_{20}H_{15}O_2N_4S$	161	65	61.36 61.34	3.83 3.80	14.31 14.30
XIVd	4-OH	$C_{20}H_{15}O_2N_4S$	180	58	61.36 61.34	3.83 3.80	14.31 14.30
XIVe	2-NO_2	$C_{20}H_{14}O_3N_5S$	174	78	57.12 57.10	3.33 3.30	16.66 16.52
XIVf	3-NO_2	$C_{20}H_{14}O_3N_5S$	164	68	57.12 57.10	3.33 3.30	16.66 16.52
XIVg	4-NO_2	$C_{20}H_{14}O_3N_5S$	189	64	57.12 57.10	3.33 3.30	16.66 16.52
XIVh	$N(CH_3)_2$	$C_{22}H_{20}ON_5S$	226	81	63.13 63.12	4.71 4.70	16.74 16.74
XIVi	-Cl	$C_{20}H_{14}ON_4ClS$	128	66	58.65 58.60	3.42 3.40	13.68 13.62
XIVJ	-OCH_3	$C_{21}H_{17}O_2N_4S$	227	77	63.29 63.26	4.07 4.00	13.42 13.40

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تحضير مركبات جديدة مشتقة من المركب
[(H10 – فينوكسازين – 3 – يل)- 6- بيرميدين – 2- فنيل ثايول/اول/امين/ثايول] بيرولات

أدريس محسن عبيد المشكور*

الخلاصة

عند معاملة المركب ٢-(٤-هايدروكسي بنز –(بروبين -١-اون) بيرول مع فنيل ثايو يوريا ، كربونات الكوندين ،يوريا وثا يويوريا في محيط قاعدي كحولي من KOH ينتج عدد من المركبات التي لها القابلية على التآصر مع مركبات الانلين بتكثيف تكوين حلقات من مشتقات الفينوكسازين البرميدينية بوجود اليود والكبريت كعوامل محفزه ينتج مركبات ٢-(٤-(١٠-فينوكسازين -٣-يل) -٦- بيرمدين -٢- فنيل ثايول /امين / اول /ثايول) بيرولات ذات الفعالية البايلوجية العالية .

تم تشخيص تلك المركبات من خلال بيانات المطيافية (IR, ^{1}HNMR, C.H.N Mass)

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* قسم الكيمياء الحياتية، كلية الطب، جامعة ذي قار