

SYNTHESIS OF SOME 1,3,4- OXADIAZOLES FROM ETHYL IMIDAZO [4,5-B] PYRIDINYL PROPIONATE AS POTENTIAL ANTIINFLAMMATORY AGENTS

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ABSTRACT

Synthesis of 2- [(6-bromo -2- imidazo [4,5-b] pyridinyl) ethyl] -5- (substituted) thio - 1,3,4 - Oxadiazole derivatives is described . The preparation of 1,3,4 - Oxadiazoles was achieved by cyclization of the corresponding acid hydrazide. Mannich reaction was applied on these new oxadiazoles giving the corresponding Mannich bases . Two of the prepared compounds were tested for their analgesic, antipyretic and antiinflammatory activities to show promising effects.

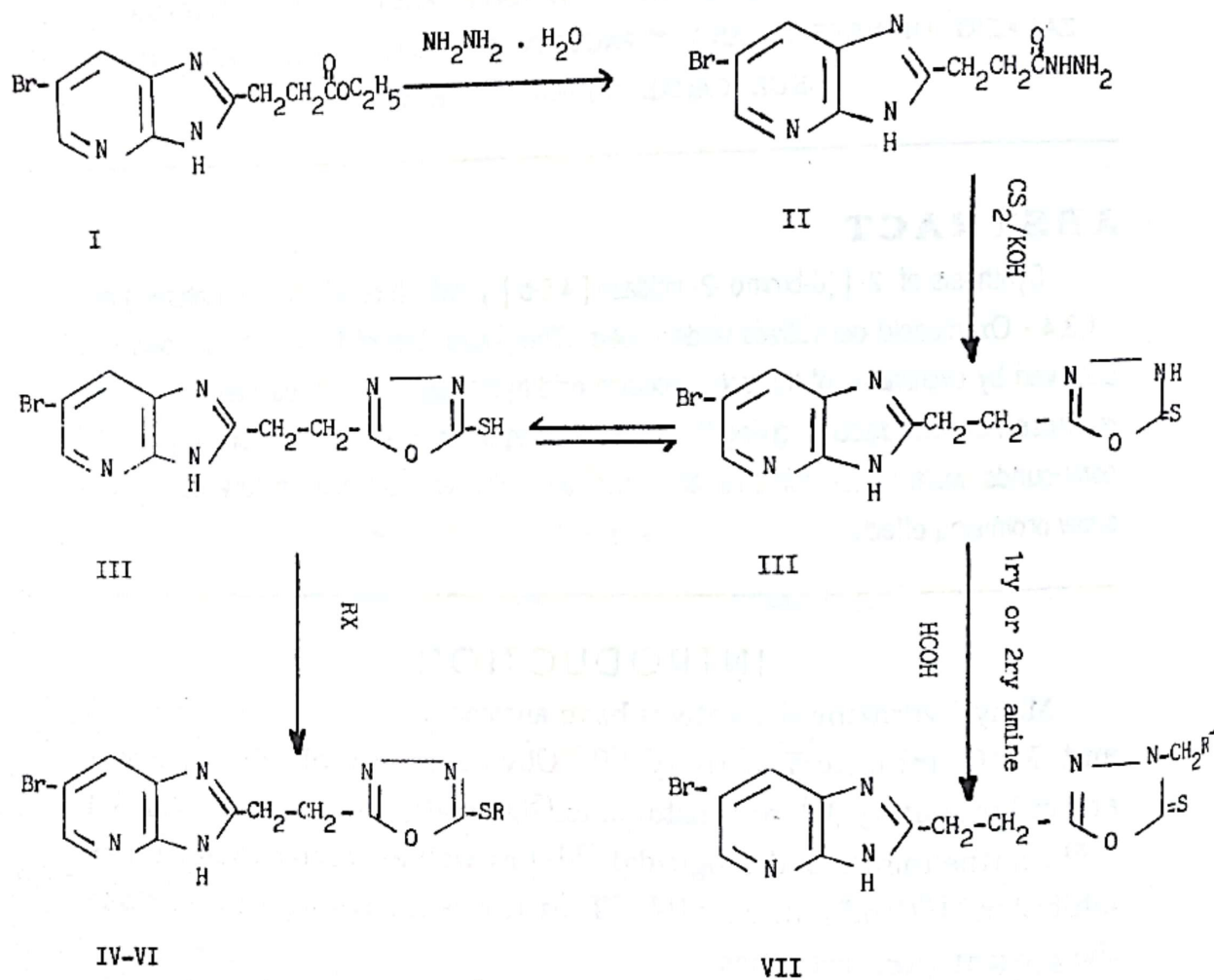
INTRODUCTION

Many hydrazine derivatives have anticonvulsant (1) psychotropic (2) and MAO inhibitory activity (3). Obviously, oxadiazoles possess antiinflammatory (4), antihistaminic (5), antidepressant (6), herbicidal (7,8) , anthelmintic and fungicidal (9,10) as well as, bactericidal , tumor inhibition (11) and antiulcer (12) . Thus it was interesting to undertake the present work activities.

RESULTS AND DISCUSSION

The acid hydrazide (II) was considered the key - intermediate for the synthesis of 1,3,4-oxadiazole thione derivative (III) . This was accomplished by the reaction of the acid hydrazide (II) with carbon disulfide in ethanolic potassium hydroxide .The thioethers (IV,V,VI) were prepared by reacting the oxadiazole (III) with alkyl halides ,

substituted chloroacetanilide, appropriate acid chloride, chloroacetic acid and ethyl chloroacetate in dry acetone in the presence of anhydrous potassium carbonate. Since the thiol 1,3,4-oxadiazole (III) can be tautomerized, the mobile H allows the application of Mannich reaction. The bases (VIIa - e) were formed by reacting (III) with appropriate amines in absolute ethanol in the presence of formaline.



$\text{R} = \text{CH}_3, \text{C}_2\text{H}_5, \text{CH}_2\text{CH}=\text{CH}_2, \text{CH}_2\text{C}_6\text{H}_5, \text{CH}_2\text{C}_6\text{H}_4(\text{p.OH}), \text{CH}_2\text{C}_6\text{H}_4(\text{p.OCH}_3), \text{CH}_2\text{C}_6\text{H}_4(\text{p.NO}_2), \text{CH}_2\text{C}_6\text{H}_4(\text{p.CH}_3), \text{CH}_2\text{C}_6\text{H}_4(\text{p.Cl}), \text{CH}_2\text{C}_6\text{H}_4(\text{p.CH}_3), \text{CH}_2\text{C}_6\text{H}_4(\text{p.OH}), \text{CH}_2\text{C}_6\text{H}_4(\text{p.OCH}_3), \text{C}_2\text{H}_5, \text{C}_6\text{H}_5, \text{C}_6\text{H}_4(\text{p.NO}_2), \text{C}_6\text{H}_4(\text{p.CH}_3), \text{C}_6\text{H}_3(\text{OCH}_3)_2^{\text{o,p}}, \text{CH}_2\text{COOH}, \text{CH}_2\text{COOC}_2\text{H}_5.$

$\text{R}^+ = \text{N}(\text{CH}_3)_2, \text{N}(\text{C}_2\text{H}_5)_2, \text{N}(\text{C}_6\text{H}_5)_2, \text{NHC}_6\text{H}_{11}, \text{NHCH}_2\text{C}_6\text{H}_5.$

Pharmacological Screening :

Compounds IVg and Vb were tested for their analgesic, antipyretic and antiinflammatory activities:

1- Analgesic effect :

The hot plate method of Jacob and Basovski⁽¹⁴⁾ was adopted to evaluate the analgesic activity . 20 mature Albino mice of both sexes weighing 20-25 g were divided into 4 groups (5 mice each) . The first group was labelled as control, while the second was injected (i.p.) with the compounds IVg and Vb respectively , in a dose of 20 mg / kg . Five minutes later, each mouse was placed into a two litre-beaker immersed in water bath thermostatically controlled at 56° C. The time elapsed till the mouse licks or jumps was calculated as a measure for the analgesic effect. Readings were taken (10,20,30,60,90 and 120min) post treatment.

2- Antipyretic effect :

20 Mature Albino rats of both sexes (200-230 g) were divided into 4 groups (5 rats each) . All animals were rendered hyperthermic using the method described by Teotino ⁽¹⁵⁾ by subcutaneous injection of 20% aqueous suspension of dry yeast in a dose of 0.1 ml /100 g. After 15 hours , the animal temperature was taken rectally by a medical thermometer and recoded as the initial temperature. The first group was labelled as control , whereas the second group was i.p. injected with brufen (20 mg/ kg) . The tested compounds dissolved in propylene glycol were given i.p. in a dose of 20 mg/kg for the last two groups respectively. One hour following treatment, the rectal temperature was recorded for a period of 3 hours . The difference between the initial body temperature and that after treatment was calculated and compared with that of the control group which received an equivalent volume of the solvent.

3- Antiinflammatory effect :

The method explained by Alpermann (16) was followed for studying the tested compounds using brufen as standard. 20 Albino rats of both sexes (210-230 g) were divided into 4 groups (5 rats each). Inflammation in rats was induced by injecting 0.1 ml of 20 % Brewer's yeast suspension (in physiological saline) in the paw skin of the hind limb. After 4 hours, the thickness of the paw was measured using a skin caliber to detect the inflammatory process achieved by the yeast. The first group was labelled as control, while the second group was injected (i.p.) with brufen in a dose of 20 mg/kg . The tested compounds were injected i.p. to the tested groups in a dose of 20 mg/kg. The paw thickness was measured after 3 and 6 hours post injection .

RESULTS

Table (1) demonstrates the analgesic activity of the test compounds. It seems that IVg showed less activity to that of brufen, while i.p. injection of Vb exhibited no significant analgesic activity.

The antipyretic effect of the tested compounds was illustrated in table (2) . The i.p. injection of Vb in a dose of 20 mg/kg was found to produce significant decrease ($p < 0.05$) in body temperature of rats, while IVg caused highly significant decrease ($p < 0.001$) for only one hour .

It is evident from table (3) that an effect nearly equal to that produced by brufen was induced by IVg for 3 hours only. On the contrary , Compound Vb expressed no antiinflammatory activity .

EXPERIMENTAL

All melting points were uncorrected .Microanalyses were carried out by the Microanalytical Center, Faculty of Science Cairo University. IR spectra were determined on Perkin- Elmer PE- 298 Spectrophotometer using KBr disc . $^1\text{H-NMR}$ was carried out on Varian A - 60 Spectrophotometer.

Table 1 : The Analgesic Affect of Compounds IVg and Vb on Mice (20 mgr/kg)

Group	Duration of analgesic effect in seconds					
	10min	20 min	30min	60min	90min	120min
control	32.5±3.95	31.27±2.36	31.0±1.22	31.3±1.62	29.8±2.71	31.32±3.86
Brufen	61.0±6.72*	66.0±2.04**	66.75±4.44**	67.25±5.78**	69.0±6.87**	67.75±5.41**
IVg	39.25±2.1	39.75±2.96	41.0±4.58	49.75±5.97*	51.75±7.89*	49.25±4.95*
Vb	42.25±4.48	47.25±6.78	47.75±8.55	37.0±3.14	32.5±2.63	30.75±4.52

* Significant difference from the control at P< 0.05

** Highly significant difference from the control P<0.001

Table 2 : The Antipyretic Effect of Compounds IVg and Vb on Rats (20 mg /kg).

group	The rectal temperature			
	15 h after yeast admin .	1 h after	2 h after	3 h after
Control	38.8±0.21	38.7±0.3	38.1±0.17	37.8±0.51
Brufen	38.3±0.2	35.8±0.32**	36.4±0.32**	36.9±0.4
IVg	37.9±0.21	36.9±0.23**	37.3±0.32	37.5±0.61
Vb	38.5±0.26	37.1±0.24*	37.6±0.21	37.8±0.56

* Significant difference from the control at P< 0 . 05

** Highly significant different from the control at P < 0.001

Table 3:The Antiinflammatory Effect of Compounds IVg and Vb on Rats (20mg/kg).

group	Thickness of the paw skin (mm)		
	4 h after yeast admin .	3 h after treat .	6 h after treat .
control	7.53±0.32	6.8±0.19	5.93±0.45
Brufen	7.10±0.5	4.8±0.49*	3.81±0.37*
IVg	6.92±0.15	4.9±0.45*	3.95±0.51
Vb	6.49±0.71	5.61±0.57*	4.7±0.59

* Significant difference from the control at P< 0.05

3 - (6 - Bromo -2- imidazo (4,5 - b) pyridinyl) propionic acid hydrazide II :

A mixture of (I) 1.5 g (0.005 mole) and 98% hydrazine hydrate 0.5 ml (0.01mole) in 30 ml absolute ethanol was heated at reflux for 8 hours. The solvent was removed by distillation under vacuum and the residue was crystallized from ethanol (m.p 240° C). In yield 91 %

Microanalysis	C ₉ H ₁₀ BrN ₅ O	Calcd.	Found
	C	38.02	38.2
	H	3.52	3.9
	N	24.64	24.2

¹H nmr (ppm) : δ 3.2 (t, 2H , CH₂ - 2) ; 3.7 (t, 2H, CH₂ - 3) ; 4.7 (br, 2H, NH₂) ; 7.2 (s, 1H, CH aromatic at position 7) ; 7.6 (s, 1H, CH aromatic at position 5) ; 8.8 (s, 1H, NH - imidazole) and 9.3 (br, 1H, - CO - NH) .

2- ((5 - Thioxo - 1,3,4- oxadiazol - 2-yl) ethyl) - 6- bromo -2 - imidazo (4 ,5-b) pyridine III :

A mixture of (II) 1.4 g (0.005 mole) , potassium hydroxide 0.28 g (0.005 mole) and carbon disulfide 0.076 g (0.01 mole) in 30 absolute ethanol was heated at reflux for 8 hrs. The solvent was evaporated under reduced pressure, the residue was diluted with water ml and acidified with dilute hydrochloric acid a solid was separated. The separated solid was filtered, washed with water and recrystallized from absolute ethanol and dimethylformamide, m.p. 255° C, yield 66%

Microanalysis	C ₁₀ H ₈ Br N ₅ OS	Calcd.	Found
	C	36.80	36.9
	H	2.45	2.6
	N	21.147	21.4

¹H nmr (ppm) : δ 3.25 (t , 2H , CH₂) ; 3.7 (t , 2H, CH₂) ; 7.3 (d, 2 H , CH + CH aromatic) ; 8.6 (s, 1 H , NH - oxadiazole) and 8.8 (s , 1 H , NH - imidazole) .

2 - ((5- (substituted thio) - 1,3,4,- oxadiazol - 2- yl) ethyl) - 6- bromo - 2- imidazo (4,5,- b) pyridine IV a - i

A mixture of (III) 0.66 g (0.002 mole) , anhydrous potassium carbonate 0.55 g (0.004 mole) and alkyl halide or appropriate 2-chloroacetanilide (0.01 mole) in 50 ml dry acetone was heated at reflux for 12 hours . The mixture was filtered while hot and the solvent was evaporated under reduced pressure. The residue was washed with water , filtered , dried and recrystallized from the appropriate solvent (table 4) .

2 - ((5- (substituted thio) - 1,3,4,- oxadiazol - 2- yl) ethyl) - 6- bromo - 2- imidazo (4,5- b) pyridine IV a - i .

A mixture of (III) 0.66 g (0.002 mole), anhydrous potassium carbonate 0.55 g (0.004 mole) and the appropriate acid chloride (0.0022 mole) in 50 ml dry benzene was heated reflux for 10 hours . The mixture was filtered while hot and solvent was at the removed by distillation under reduced pressure. The residue was recrystallized from the appropriate solvent (table 5) .

5 - (2- (6- Bromo - 2- imidazo (4,5 - b) pyridinyl) ethyl - 1,3,4- oxadiazol - 2- yl) thioglycolic acid or its ethyl ester VIa - b :

A mixture of (III) 0.66 g (0.002 mole) , potassium hydroxide 0.22 g (0.004 mole) and chloroacetic acid or ethyl chloroacetate (0.002 mole) in 30 ml absolute ethanol was heated at reflux for 8 hours . The reaction mixture was cooled, filtered and the solvent was evaporated under reduced pressure. The solid residue was filtered, washed with water, dried and recrystallized from the appropriate solvent (table 6) .

¹H nmr (ppm) of compound (VIa) showed : δ 3.2 (t, 2H, CH₂) ; 3.6 (t, 2H, CH₂) ; 4.8 (s, 2H, CH₂ of thioglycolic acid) ; 7.6 (d, 2H, CH + CH aromatic) ; 8.7 (s, 1H, NH - imidazole) and 8.9 (s, 1H, OH of thioglycolic acid) .

2 - ((4- (substituted amino) methyl) - 5- thioxo- 1,3,4,- oxadiazol - 2- yl) ethyl) - 6- bromo - 2- imidazo (4,5,- b) pyridine VII a - e :

A mixture of (III) 0.66 g (0.002 mole) , formaldehyde solution 40 % (0.006 mole) and the suitable primary or secondary amine (0.002 mole) in 30 ml absolute ethanol was stirred for 3 hours at room temperature. The reaction mixture was allowed to

stand in a refrigerator over night. The formed solid was filtered, washed with water and recrystallized from the appropriate solvent (table 7).
 The ^1H nmr (ppm) of compound (VIIe) showed : δ 3.1(t, 2H, CH_2); 3.3 (t, 2H, CH_2); 4.3 (d, 2H, CH_2 of benylamine moiety); 7.3 (m, 5 H, aromatic protons); 7.8 (d, 2H, CH + CH aromatic); 8.5 (s, 1H, NH - imidazole).
 IR general characters : NH (sharp) 3400 cm^{-1} ; OH $3400 - 3200$ (br) cm^{-1} ; C = O $1670, 1710\text{ cm}^{-1}$.

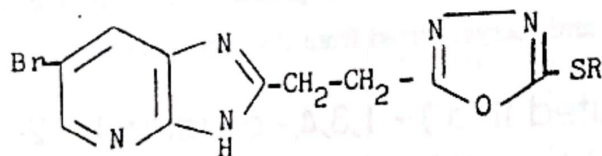


Table (4)

No.	R	M.L & M.wt.	Yield	M.P. $^{\circ}\text{C}$	Microanalysis	
					Calcd.	Found
IVa	CH_3	$\text{C}_{11}\text{H}_{10}\text{BrN}_5\text{OS}$ (340)	63%	265	C 38.82	38.6
					H 2.94	3.1
					N 20.58	20.4
IVb	C_2H_5	$\text{C}_{12}\text{H}_{12}\text{BrN}_5\text{OS}$ (354)	66%	>300	C 40.67	40.6
					H 3.38	3.5
					N 19.77	19.7
IVc	$\text{CH}_2\text{CH}=\text{CH}_2$	$\text{C}_{13}\text{H}_{12}\text{BrN}_5\text{OS}$ (366)	67%	165	C 42.62	42.5
					H 3.27	3.4
					N 19.12	19.0
IVd	$\text{CH}_2-\text{C}_6\text{H}_5$	$\text{C}_{17}\text{H}_{14}\text{BrN}_5\text{OS}$ (316)	75%	275	C 49.03	49.0
					H 3.36	3.5
					N 16.82	16.8
IVe	$\text{CH}_2\overset{\text{O}}{\parallel}\text{CNH}-\text{C}_6\text{H}_5$	$\text{C}_{18}\text{H}_{15}\text{BrN}_6\text{O}_2\text{S}$ (459)	73%	285	C 47.05	47.2
					H 3.26	3.3
					N 18.30	18.5
IVf	$\text{CH}_2\overset{\text{O}}{\parallel}\text{CNHC}_6\text{H}_4(\text{p.Cl})$	$\text{C}_{18}\text{H}_{14}\text{BrClN}_6\text{O}_2\text{S}$ (493.5)	65%	295	C 43.76	43.8
					H 2.83	2.7
					N 17.02	17.2
IVg	$\text{CH}_2\overset{\text{O}}{\parallel}\text{CNHC}_6\text{H}_4(\text{p.CH}_3)$	$\text{C}_{19}\text{H}_{17}\text{BrN}_6\text{O}_2\text{S}$ (473)	72%	291	C 48.20	48.4
					H 3.59	3.5
					N 17.75	17.9
IVh	$\text{CH}_2\overset{\text{O}}{\parallel}\text{CNHC}_6\text{H}_4(\text{p.OH})$	$\text{C}_{18}\text{H}_{15}\text{BrN}_6\text{O}_3\text{S}$ (475)	69%	>300	C 45.47	45.6
					H 3.15	3.2
					N 17.68	17.8
IVi	$\text{CH}_2\overset{\text{O}}{\parallel}\text{CNHC}_6\text{H}_4(\text{p.OCH}_3)$	$\text{C}_{19}\text{H}_{17}\text{BrN}_6\text{O}_3\text{S}$ (489)	71%	280	C 46.62	46.8
					H 3.47	3.4
					N 17.17	17.9

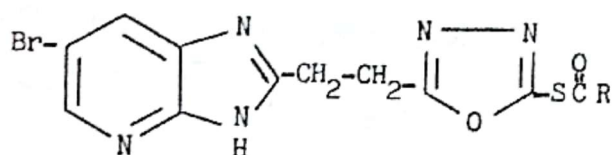


Table (5)

No.	R	M.F & M.wt.	Yield	M.P.	Microanalysis		
					Calcd.	Found	
Va	C ₂ H ₅	C ₁₃ H ₁₂ BrN ₅ O ₂ S (382)	64%	180	C	40.83	40.9
					H	3.14	3.1
					N	18.32	18.5
Vb	C ₆ H ₅	C ₁₇ H ₁₂ BrN ₅ O ₂ S (430)	67%	225	C	47.44	47.6
					H	2.79	2.7
					N	16.27	16.3
Vc	C ₆ H ₄ (p.NO ₂)	C ₁₇ H ₁₁ BrN ₅ O ₄ S (475)	71%	245	C	42.94	43.1
					H	2.31	2.4
					N	17.68	17.8
Vd	C ₆ H ₄ (p.CH ₃)	C ₁₈ H ₁₄ BrN ₅ O ₂ S (444)	69%	270	C	48.64	48.7
					H	3.15	3.3
					N	15.76	15.9
Ve	C ₆ H ₃ (OCH ₃) ₂ ^{o,p}	C ₁₉ H ₁₆ BrN ₅ O ₄ S (490)	65%	280	C	46.53	46.6
					H	3.26	3.3
					N	14.28	14.4

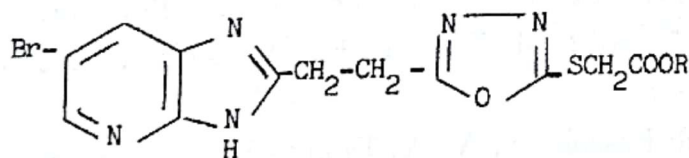


Table (6)

No.	R	M.f & M.wt	Yield	M.P.	Microanalysis		
					Calcd.	Found	
VIa	H	C ₁₂ H ₁₀ BrN ₅ O ₃ S (384)	61%	235	C	37.5	37.6
					H	2.60	2.8
					N	18.22	18.4
VIb	C ₂ H ₅	C ₁₄ H ₁₄ BrN ₅ O ₃ S (412)	71%	265	C	40.77	40.9
					H	3.39	3.5
					N	16.99	17.1

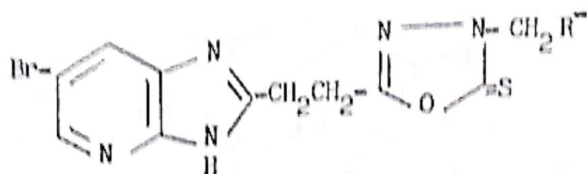



Table (7)

No	R ⁻	M.f & M.wt.	Yield	M. P.	Microanalysis		
					Calcd	Found	
VIIa	N(CH ₃) ₂	C ₁₃ H ₁₅ BrN ₆ OS (383)	72%	250	C	40.73	40.8
					H	3.91	3.8
					N	21.93	21.9
VIIb	N(C ₂ H ₅) ₂	C ₁₅ H ₁₉ BrN ₆ OS (411)	79%	235	C	43.79	43.9
					H	4.62	4.6
					N	20.43	20.4
VIIc		C ₁₅ H ₁₇ BrN ₆ O ₂ S (425)	72%	240	C	42.35	42.5
					H	4.0	4.2
					N	19.76	19.8
VII d	NHC ₆ H ₁₁	C ₁₇ H ₂₁ BrN ₆ OS (437)	81%	266	C	46.68	46.6
					H	4.80	4.6
					N	19.22	19.3
VIIe	NHCH ₂ C ₆ H ₅	C ₁₈ H ₁₇ BrN ₆ OS (445)	79%	270	C	48.53	48.7
					H	3.82	3.7
					N	18.87	18.9

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تحضير بعض مركبات ١ و ٣ و ٤ - أوكساديازول من إيثيل إيميدازول -
(٤ و ٥ - ب) بيريدينيل حامض البروبيونيك كمسكنات للألم
ومخفضات للحرارة ومضادات للإلتهابات

محمد عبيد* - السيد لاشين - ناجح أبو طالب - لبنى عبد العزيز -

مجدى عامر**

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جامعة قناة السويس

تم فى هذا البحث تحضير ١ و ٣ و ٤ أوكساديازول المشتق من إيميدازوبيريدينيل إستر لحمض البروبيونيك . كما تم تشييد بعض الإثيرات الكبريتية وكذلك تم تطبيق قاعدة مانج على ١ و ٣ و ٤ أوكساديازول .

وقد تم إجراء إختبارات إقربازينية أولية على مركبين من هذه المركبات قد ظهر لها تأثير مسكن للألم وخافض للحرارة ومضاد للإلتهاب بالمقارنة بعقار البروفين .