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SYNTHESIS OF NEW CONDENSED PYRIMIDO (1,6-a) INDOLE OF POTENTIAL PHARMACOLOGICAL INTREST

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ABSTRACT

Triethyloxonium tetrafluoroborate has been used as a selective o-alkalyting agent of lactam for preparation of the lactim ether of oxindole. The synthesis of new pyrimido [1,6 -a] indole derivatives is described. Addition of dicyanomethylidene indole (1) to varicous fluorophenyl isothiocyanates gave 2- fluorophenyl -3- imino -1- thioxo -1,2,3,5-tetrahydropyrimido, [1,6-a) indole -4- carbonitrile (2) . Reduction of these compounds with sodium borohydride gave the corresponding enaminonitriles 3- amino -2- fluorophenyl1-thioxo -1,2,4a , 50 tetrahydropyrimido [1,6-a] indole -4- carbonitrile (3) . Treatment of enaminonitriles with chloracetyl chloride afforded the N- chloroacetylamino derivatives (4) which underwent cyclization either by acid or base to the tetracyclic compounds 3- chloromethyl (or alkylaminomethyl) -1- oxo-6- thioxo-12-12a - dihydro- [2H,5H] - pyrimido [4, 5, 4, 5] pyrimido [1, 6-a) indoles (5) . Preliminary pharmacological screening of some compounds revealed analgesic and antiinflammatory activities.

INTRODUCTION

Selective O-alkylation of lactams has been achieved using tetiaryoxonium salts, particularly triethyloxonium tetrafluoroborate [1,2] . This reaction proceeds via cation formation (c.f the reaction with dialkyl sulfates) . Treatment of the salt with base leads to the lactim ether. The oxonium salts give better results than other alkylating agents and no N-alkyl derivatives could be isolated because of the high selectivity of oxonium salt in similar reactions. The alkylation of oxindole and its derivatives by triethyloxonium tetrafluoroborate is of special interest [3].

In previous work [4,5] we described the synthesis of pyrimido [1,6-a] indoles with potential pharmacological interest, this led to the realization of synthesis of some fluorophenyl pyrimido [1,6-a) indole that bear certain pharmacophores.

Gastric ulceration and haemorrhage are the major problems in therapy with antiinflammatory drugs [6] Thereby nonsteriodal, nonacidic antiinflammatory (NSAI) agents are enjoying great favour due to better gastrointestinal tolerability when compared with acidic agents [7] . As a part of our studies of nonacidic pyrimido [1,6-a] indole derivatives [4] , it was promising analgesic and antiinflammatory agents [5,8].

The titeled compounds were designed to study the influence of added heterocylic rings to the parent compound **1** and their relation to toxic and pharmacological effects. The approach utilized in the synthesis of the designed compounds is given in the schemes .

EXPERIMENTAL

All melting points were uncorrected and were determined using Gallenkamp apparatus Microanalyses were carried out at the Microanalytical Centre, University of Cairo. IR Spectra were determined as KBr discs on a Perkin Elmer 45, ^{1}H-NMR were carried out using S-6 (200 MHZ) Spectrometer TMS was used as internal standard.

0.1 M solution of triethyloxonuim tetrafluouoborate in CH_2Cl_2 (Aldrich) was used to prepare the lactim ether of oxindol, from which compound **1** was obtained .

1)General Method of preparation of 2-Fluorophenyl-3-imino-1 thioxo-1,2,3,5- tetrahydropyrimido (1,6-a) indole -4- carbonitrile 2a -d.

A mixture of 1 (0.03 m mol) and the appropriate fluoroisothiocyanate (0.06 mol) in methylene chloride (25 ml) was treated with with 1 mL of triethylamine. The mixture was refluxed for 6 hours, the solvent was removed under reduced pressur and the residue was triturated with ethanol, fillered and recrystallized from ethanol (Table 1).

2) General method of preparation of 2-fluorophenyl-3-amino-1- thioxo-1,2 4a,5-tetrahydropyrimido (1,6-a) indole -4- carbonitrile 3a - d.

To compound **2** (0.1 mol) suspended in ethanol (20 mL) , sodium borohydride (0.06 mol) the was added in portions and the mixture was left over night . Few drops of water were added and the separated crystals were filtered washed with water and recrystallized from ethanol (Table 2).

3) Preparation of 3-chloroacetamido -1- thioxo -2- substituted - fluorophenyl -1,2 4a, 5-tetrahydropyrindo (1,6-a) indol -4- carbonitrile (4a-d) . A mixture of 3 (0.01 mol), chloroacetyl chloride (0.011 mol) and dry benzene (20 mL) was left overnight . The solvent was then refluxed with alcoholic HCL for 12 hours. The product was crystallized from ethanol (Table 3).

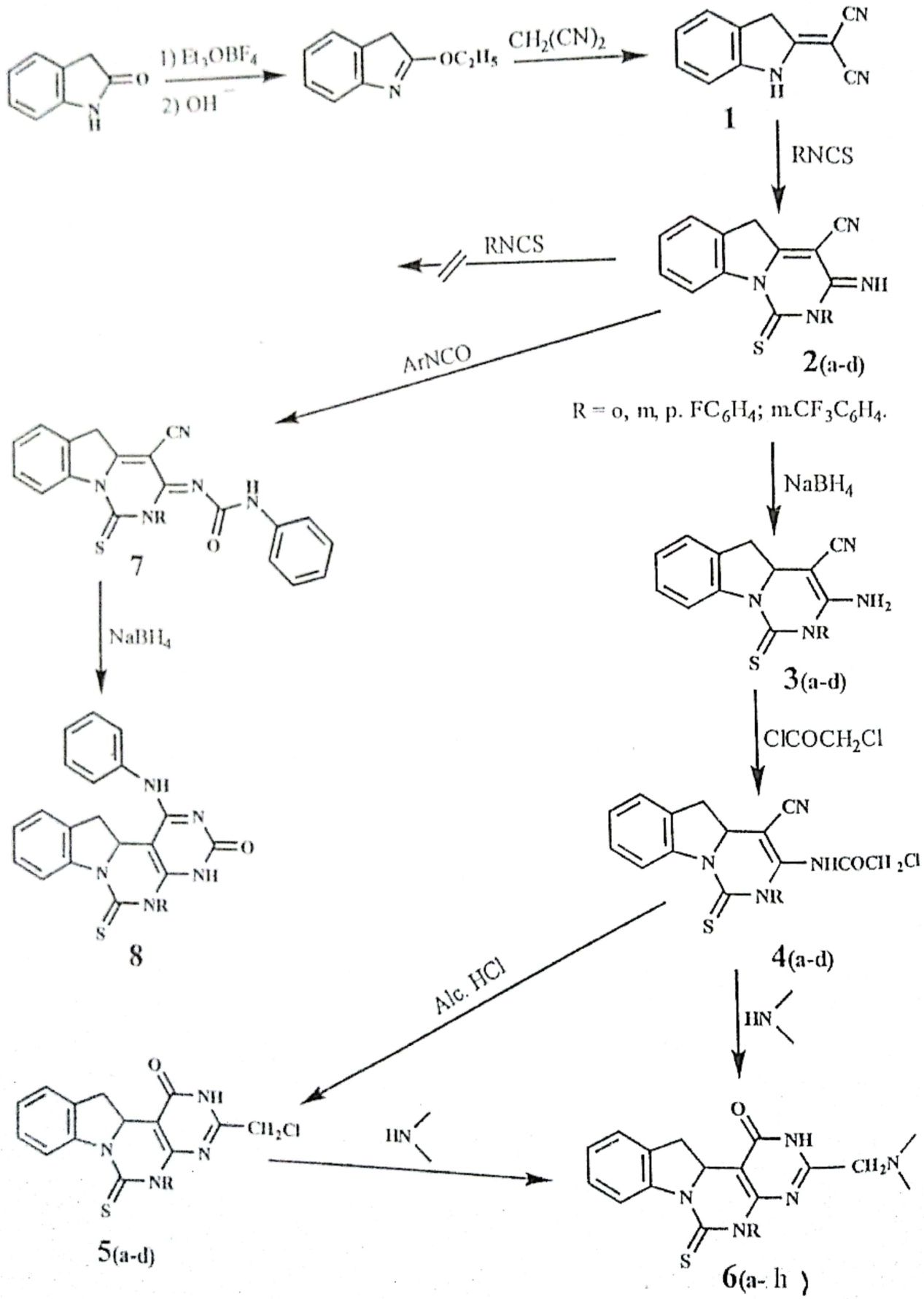
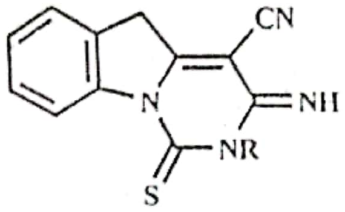

1) Et3OBF4
2) OH⁻
CH2(CN)2
1
RNCS
RNCS
2(a-d)
R = o, m, p. FC6H4; m.CF3C6H4.
ArNCO
7
NaBH4
3(a-d)
NaBH4
ClCOCH2Cl
8
4(a-d)
Alc. HCl
HN
5(a-d)
6(a-h)

Table (1) : Phyical data for 2- Substituted -3- imino -1- thioxo -1,2,3,5- tetahydropyrimido (1,6-a) indole -4- cabonitrile.



Comp	R	M.P.	Yield %	M. F. & M.Wt.	Microanalysis	
					Calc.	Found
2a	o FC_6H_4	182 3	79	$C_{18}H_{11}FN_4S$ (334)	C= 64.67 H=3.29 N=16.77	64.7 3.3 16.8
2b	m FC_6H_4	176-7	81	$C_{18}H_{11}FN_4S$ (334)	C=64.67 H=3.29 N=16.77	64.7 3.3 16.7
2c	p FC_6H_4	198 9	83	$C_{18}H_{11}FN_4S$ (334)	C=64.67 H= 3.29 N= 16.77	64.8 3.3 16.7
2d	m $C_3FC_6H_4$	132 3	86	$C_{19}H_{11}F_3N_4S$ (384)	C=59.38 H= 2.86 N= 14.58	59.5 2.9 14.6

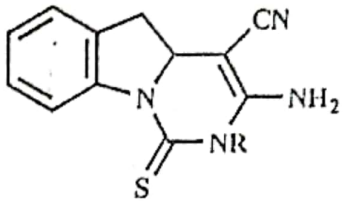
General IR (KBr) cm^{-1} : 3290 (NH), 2210 (CN), 1650 - 1680 (C= 0) , 1610 (NH) , ^{1}H-NMR (ppm) of compound 2a 4.1 (S, 2H, CH_2 at position 5) ; 6 - 35 (br, S, 1H , NH) ; 6.95 - 7.9 (M, 8H, aromatic protons).

4) 3-Chloromethyl -5- substituted - fluorophenyl-1-oxo-6- thioxo-2H, 5H, 12, 12a - dihydropyrimido (4,5, : 4,5) pyrimido (1,6-a) indole 5a -d.

Compound 4 (0.01mol) was refluxed with alcoholic HCl for 12, hours . The product was crystallized from ethanol (Table 4).

5) 3-Alkylaminomethyl -5- substituted- fluorophenyl -1-oxo-6- thioxo-52H, 5H - dihydropyrimido [4,5,: 4,5] pyrimido [1,6-a] indol (6a -h) . A mixture of 4 (0.01 mol) , Secondary amine (1.5 mL) and ethanol (30 mL) was refluxed for 12 hours. The solvent was removed under reduced pressure and the separated crystals were washed with water, then recrystallized from ethanol to gave the product (Table 5).

Table (2) : Phyical data for 2- Substituted -3- imino -1- thioxo -1,24a,5- tetahydropyrimido (1,6-a) indole -4- cabonitrile.



Comp	R	M.P.	Yield %	M. F. & M.Wt.	Microanalysis	
					Calc.	Found
3a	o FC_6H_4	127-8	85	$C_{18}H_{13}FN_4S$ (336)	C=64.29 H=3.87 N=16.67	64.3 3.8 16.8
3b	m FC_6H_4	189-90	76	$C_{18}H_{13}FN_4S$ (336)	C=64.29 H=3.87 N=16.67	64.3 3.7 16.8
3c	p FC_6H_4	191-2	81	$C_{18}H_{13}FN_4S$ (336)	C=64.29 H=3.87 N= 16.67	64.3 3.8 16.8
3d	m $C_3FC_6H_4$	109-10	82	$C_{19}H_{13}F_3N_4S$ (386)	C=59.07 H=3.37 N= 14.51	59.1 3.3 14.6

^{1}HNMR (ppm) of Compound 3b :
3.50 - 3.52 (d , 2H, Ch2 at position 5) , 4.9 (br, 2H , 2H, NH2) , 6.40 - 7.10 (m, 7H, aromatic protons), 7.20 - 7.25 (t, 1 H, CH at position 4a), 7.4 -7.45 (t, 1H, one aromatic proton at position 7 or the aromatic ponton at position 5 of fluorophenylring).

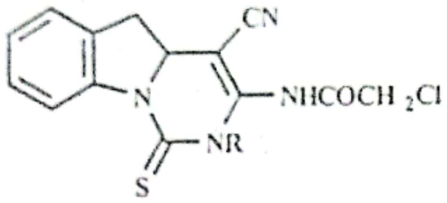
6) 3-phenylureido -2- fluorophenyl -1- thioxo-1,2,3,5-tetrahydro pyrimido [1,6-a] indole -4- carbonitrile 7. To a mixture of 2a (0.01 mol) and methylene chloride (30 mL), phenyl isocyanate (0.011 mol) was added , followed by triethylamine (0.5 mL). The mixture was refluxed for 3 hours . The separaed crystals were filtered , washed with water and recrystallized from ethanol.

m.p. 192 °C **Yield** 86%

M.F. $C_{25}H_{16}FN_5OS$ **M. wt** 453

Microanalysis	**C**	**H**	**N**
Calc.	66.23	3.53	15.45
Found	66.10	3.50	15.40

Table (3): Phyical data for 2- substituted -3- imino -1- thioxo -1,2 , 4a, 5- tetahydropyrimido (1,6-a) indole -4- cabonitrile.



Comp	R	M.P.	Yield %	M. F. & M.Wt.	Microanalysis	
					Calc.	Found
4a	o FC_6H_4	192 3	86	$C_{20}H_{14}ClFN_4OS$ (412.5)	C= 58.18 H= 3.39 N=13.58	58.2 3.3 14.0
4b	m FC_6H_4	201 2	89	$C_{20}H_{14}ClFN_4OS$ (412.5)	C=58.18 H=3.39 N=13.58	58.2 3.3 13.7
4c	p FC_6H_4	204 5	90	$C_{20}H_{14}ClFN_4OS$ (412.5)	C=58.18 H= 3.39 N= 13.58	58.2 3.3 13.7
4d	m $C_3FC_6H_4$	146 7	93	$C_{21}H_{14}ClF_3N_4OS$ (462.5)	C=54.49 H=3.03 N=12.11	54.6 3.0 12.2

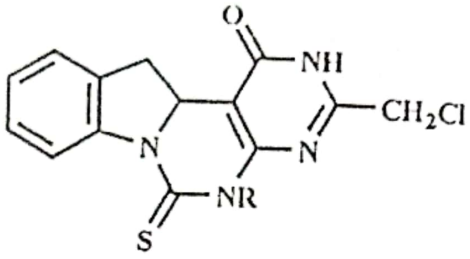
^{1}HNMR (ppm) of Compound **4b** :
3.36 - 3.57 (d, 2H, CH_2 at position 5) ; 4.40 (S, 2H, CH2 Cl); 6.5 - 7.3 (M, 8H, aromatic protons), 7.42 - 7.45 (t, lH, CH at position 4a) ; 12.7 (S, 1H, NH)

^{1}HNMR (ppm) of compound **7**

4.1 (s, 2H Ch_2 at position 5) ; 6.2 (s, lh, NH); 7.2 - 7.4 (m. 13H, aromatic protons).

7) 1-phenylamino -5-flurophenyl. 3- oxo-6- thioxo -12 , 12a dihydro-2H, 5H - pyrimido (4, 5 : 4,5) pyrimido [1,6-a] indole **8** . A mixture of **7** (0.01mol) , ethanol (20 mL) and sodium borohydride (0.005 mol) added in portions was left over night , the separated crystals were filtered, washed with water and recrystallized from ethanol.

Table (4) : Phyical data for 5- Substituted -3- chloromethyl - 1 oxo -6- thioxo - 2H, 5H- 12, 12 a- dihydro- (4`, 5` : 4,5) Pyrimido (1.6 - a) indole.



Comp	R	M.P.	Yield %	M. F. & M.Wt.	Microanalysis	
					Calc.	Found
5a	o FC_6H_4	188 9	79	$C_{20}H_{14}ClFN_4OS$ (412.5)	C=58.18 H=3.39 N=13.58	58.2 3.3 13.6
5b	m FC_6H_4	202-3	86	$C_{20}H_{14}ClFN_4OS$ (412.5)	C=58.18 H=3.39 N=13.58	58.3 3.3 13.7
5c	p FC_6H_4	206-7	90	$C_{20}H_{14}ClFN_4OS$ (412.5)	C=58.18 H=3.39 N= 13.58	58.3 3.3 13.8
5d	m $C_3FC_6H_4$	143-4	92	$C_{21}H_{14}ClF_3N_4OS$ (462.5)	C=54.49 H=3.03 N=12.11	54.6 3.1 12.3

^{1}HNMR (ppm) of Compound **5c** :
3.4-3.43 (d, 2H , CH_2 at position 12) ' 4.0 (S, 2H, CH_2 Cl) ; 6.15 - 6.20 (t, 1H, CH at position 12a) ; 7.0 - 7.5 (mg 8 H, aromatic protons) ; 10.6 (S, 1H, NH).

m. p. 221 °C **Yield** 83%

M.F. ($C_{25}H_{16}FN_5OS$) **M. wt** 453

Microanalysis	**C**	**H**	**N**
Calc.	66.23	3.53	15.45
Found	66.0	3.9	15.4

^{1}HNMR (ppm) of compound **8**

3.5-3.7 (d, 2H, CH2 at position 12) ; 6.2-6.25 (t, 1H, CH at position 12 a) 6.8 (s, 1H , NH - ph) ; 7.2-7.35 (m, 13H, aromatic protons) ; 8.2 (s, 1H , NH at position 4).

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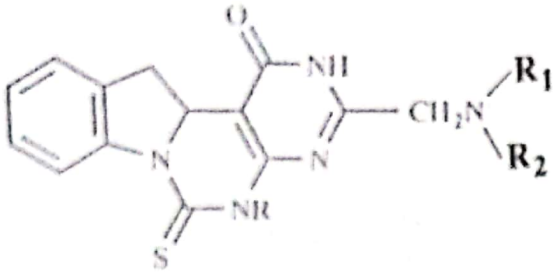
Table (5) : Phyical data for 5- substituted -3- alkylaminomethyl -1- oxo - 6- thioxo - 2H, 5H- 12, 12 a dihydropyrimido (4`, 5` : 4, 5) pyrimido (1,6 - a) indole.



Comp	R	R_1, R_2	M.P.	Yield %	M. F. & M.Wt.	Microanalysis	
						Calc.	Found
6a	o FC_6H_4	$N(CH_3)_2$	261-2	88	$C_{22}H_{20}FN_5OS$ (421)	C= 62.71 H= 4.75 N=16.63	62.8 4.7 16.8
6b	o FC_6H_4	$N(C_2H_5)_2$	252-3	86	$C_{24}H_{24}FN_5OS$ (449)	C=64.14 H=5.35 N=15.59	64.1 5.4 15.6
6c	m FC_6H_4		218-9	78	$C_{24}H_{22}FN_5OS$ (447)	C=64.43 H= 4.92 N= 15.66	64.5 4.9 15.7
6d	m $C_3FC_6H_4$		220-1	92	$C_{24}H_{22}FN_5O_2S$ (421)	C=62.20 H= 4.75 N= 15.12	62.4 4.6 15.3
6e	p FC_6H_4	$N(CH_3)_2$	247-8	86	$C_{22}H_{20}FN_5OS$ (421)	C=62.71 H= 4.75 N= 16.63	62.7 4.7 16.7
6f	p FC_6H_4		227-8	91	$C_{25}H_{24}FN_5OS$ (461)	C= 65.07 H= 5.21 N=15.18	65.1 5.2 15.2
6g	m $CF_3C_6H_4$		117-8	76	$C_{25}H_{22}F_3N_5OS$ (497)	C=60.36 H=4.43 N=14.08	60.3 4.4 14.0
6h	m $CF_3C_6H_4$		108-9	88	$C_{25}H_{22}F_3N_5O_2S$ (513)	C=58.48 H= 4.29 N= 13.65	58.5 4.3 13.8

^{1}HNMR (ppm) of Compound **6e** :
2.7 (s, 6H, $(CH_3)_2$) ; 2.4 (d, 2H, CH2 at position 12) ; 3.75 (S 2H, CH_2 N) ; 6.15 - 6.17 (d, 1H, CH at position 12 a) ; 6.9 - 7.5 (m, 8H aromatic protons); 10.15 (s, 1H, NH).

PHARMACOLOGICAL SCREENING

Compounds **5a** and **6f** were tested for their analgesic and antiinflammatory activities.

Analgsic activity :

The hot plate method of **Jacob and Basovski** [9] was adopted to evaluate the analgesic activity. 24 Mature Albino mice of both sexes weighing 20-25 g were devided into 4 groups , the first group was left as a control , while the second was i.p. injected with Ibuprofen (20 mg/kg) as standard. The last groups were i.p. injected with compound **5a** , **6f** in a dose 20 mg/kg. Fifteen minutes later, each mouse was placed in a two liters capacity beaker immersed in water bath thermostatically controlled at 56°C . The time elapsed till the mouse liks its feet or jumps was considered the reaction time and taken as a measure for analgesic activity. The process was continued at the following time intervals : 15, 30 , 60, 90, 120 minutes post treatment.

Antiinflammatory activity:

The method explained by **Alpermann** [10] was used for studying the the antiinflammatory activity of the tested compounds and Ibuprofen as standard. For this purpuse, 24 Albino rats of both sexes weighing 210 -230 g were devided into 4 groups. Inflammation in the rat paw was induced by injecting 0.1 ml of 20% Brewer's yeast suspension in physiological saline solution in the paw skin of the hind limb. After 4 hours the thickness of the paw was measured using a skin calibre to detect the inflammation process achieved by the yeast . The first group was left as control, while the second group was i.p. injected with Ibuprofen in a dose of 20 mg/kg. The paw thickness was measured after 3 and 6 hours post injection. The last group was I.P. injected with compounds **5a** and **6f.** in a dose of 20 mg/kg .

Ibuprofen, comp. 5 a and 6f significantly increased the normal reaction time of mice on the hot plate. In Table (6) results showed that, all the injected compounds in addition to Ibuprofen significantly increased the total area under the reaction time curve . The percentage increase in the area under the curve were 120 % 105 % and 88.6% of control value in case of Ibuprofen and compound **5a** and **6f** respectively. These compounds can be arranged in descending order according to their analgesic activities into Ibuprofen > compound **5a** > compound **6f**. In respect to the antiinflammatory activity of these compounds. Table (7) showed that Ibuprofen compound **5a** and **6f** significantly reduced the thickness of the hind paw odema. The percentage reduction in thickness were 27.18% , 20.55% and 19.39% of the values before administration. After 3 hours treatment this effect was extended for 6 hours, since compound **5a** and **6f** as well as Ibuprofen significantly reduced the thickness of the hind paw odema. The recorded percentage reductions were 25.46% , 28.75% and 31.72% of the values before treatment in case of Ibuprofen, compound **5a** and **6f** respectively. The antiinflammatory effect of compound 5a and **6f** was more pronounced than that of Ibuprofen. The relative potency of these compounds was 1.13 and 1,25 incase of compounds **5a** and **6f** respectively related to that of Ibuprofen. Accordingly, these compounds can be arranged in a descending order in respect to their antiinflammatory activities into compound **6f** > compound **5a** > Ibuprofen. From these results it could be concluted that.

a) Compound **5a** and **6f** are less potent than Ibuprofen as analgesic and antiinflammatory especially in the first 3 hours of treatment.

b) The activity of these compounds were changed when the test was extended for 6 hours especially for antiinflammatory activity. Since compound **6f** was more potent than compound **5a** > Ibuprofen.

c) There was coincidence between both the analgesic and antiinflammatory activities of compound **5a** and **6f** in relation to Ibuprofen , especially in the first 3 hours of treatment.

Table (6) : The total area under curves of the reaction time of adult mice to hot plate after pretreatment with Ibuprofen, compounds **5a** and **6f.**

Treatment	Total area under the reaction time curve (sec. Min. 0 ~ 120 min.)	The increase in the area under the curve compared to control (sec. Min.)	% increase in the area under the curve from the control value	Relative potency in relation to Ibprufen in respect to the area under the curve
Control	3222.2 ± 231.12	-------	------	------
Ibuprofen	7099.8 ± 411.16***	3877.6	120	1
Comp. **5a**	6623.6 ± 339.86***	3401.4	105	0.87
Comp. **6f**	6076.3 ± 228.54***	2854.1	88.6	0.74

**Significantly different from the total area under the reaction time curve of control at $P < 0.001$

Table (7) : Changes in the thickeness of the hind paw odema of rats before and after treatment with Ibuprofen, compounds **5a** and **6f.**

Treatment	Thickness of hind paw Odema before treatment (mm) (X ± S.E.)	Thickness of hind paw odema after treatment									
		After 3 hours					After 6 hours				
		Thickness of hind paw (mm) (X ± S.E.)	Reduction in thickness of hind paw (mm) (X ± S.E.)	Absolute reduction in thickness of hind paw (mm)	% reduction of thickness of hind paw from before treatment	Relative potency to Ibuprofen	Thickness of hind paw (mm) (X ± S.E.)	Reduction in thickness of hind paw (mm) (X ± S.E.)	Absolute reduction in thickness of hind paw (mm)	% reduction in thickness of hind paw from before treatment	Relative potency to Ibuprofen
Control	7.32 ± 0.44	6.6 ± 0.16	0.7 ± 0.051	------	------	------	5.75 ± 0.33	1.57 ± 0.13	------	------	------
Ibuprofen	7.11± 0.4	4.4 ± 0.33**	2.71 ± 0.21	1.99	27.18	1	3.73 ± 0.32**	3.38 ± 0.25	1.81	25.46	1
Comp. 5a	7 2 ± 0.6	5.0 ± 0.39**	2.2 ± 0.198	1.48	20.55	0.756	3.56 ± 0.24***	3.64 ± 0.22	2 07	28.75	1.13
Comp. 6f	7.22 ± 0.5	5.1 ± 0.23***	2.12±0.201	1.4	19.39	0.714	3.36 ± 0.14***	3.86 ± 0.11	2.29	31.72	1.25

**Significantly different from control value at $P < 0.01$
***Significantly different from control value at $P < 0.001$

d)We are expecting that, if the duration of the test for analgesia was extended for 6 hours, it might be as the same the antiinflammatory activity.

RESULTS AND DISCUSSION

Adopting the general procedure, Dinitrile [11] **1** smoothly added to various fluorphenyl isothiocyanates to give the corresponding iminonitriles 2-fluorophenyl-3- imino-1- thioxo- 1,2,3,5 - tetrahydropyrimido [1,6-a] indole -4- carbonitrile **2** . The IR spectra of **2** have revealed the disapperrance of the bands corresponding to the geminal dinitriles and appearance of sharp bands at 3290 cm^{-1} (CN) . These obtained thioxo compounds **2** did not react with excess isothiocyanates used and no arylthioureido derivatives were separated . However, these compounds remain reactive towards ary but not alkylisocyanates, thus when compound 2 a reacted with phenylisocyanate it afforded 3- phenylureida derivative **7** , which upon treatment with sodium borohydride underwent interamolecular cycliazation to give tetracyclic compound **8**. The vanishing of the nitrile absorption at 2210 cm^{-1} IR spectrum of compound **8** , was taken as a confirmation for tetracyclic structure pyrimido [4,5,: 4,5] pyrimido [1,6-a] indole, which confirmed **Dimorth** rearrangement [4,12] . Reduction of compound **2** was achieved by sodium borohydride to the corresponding enaminonitriles 3-amino -4-cyano-2-fluorophenyl -1- 2, 4a, 5-tetrahydropyrimido [1,6-a] indole (3) . The IR spectra of which have revealed two bands at 3200, 3400 cm^{-1} (NH2) and 2185 cm^{-1} (CN).

Because of the presence of the free amino group at position 3 of compound **3**, therefore when **3** reacted with chloroacetyl chloride it afforded the N-chloroacetylamino derivative **4**, which underwent cyclization either by acid or base to the tetracyclic compound 3-chloromethyl (or 3- alklaminomethyl) -1-oxo-6-thioxo -12, 12a - dihydro-[2H,5H]- pyrimido [4`, 5` : 4, 5] pyrimido [1,6-a] indoles . These reactions were followed up by the IR spectra which revealed the disappearance of the nitrile bands. The reaction takes place through 4-imino-m-oxazine formation [8,13].

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تشييد مركبات مكثفة جديدة لمشتقات بيريميدو (١ر٦ – أ) انترول ذات أهمية دوائية

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فى هذا البحث تم وصف طريقة تشييد لبعض مشتقات البريميدو (١ر٦-أ) اندول وذلك بإظافة ثنائى سيانوميثيليدين اندول إلى مركبات الفلوروايزوثيوسيانات المختلفة للحصول على ٢ – فلوروفينيل -٣- ايمنو -١- نيواكسو – ١ر٢ر٣ر٥ – رباعى هيدوبيريميدو (١ر٦-أ) اندول-٤- كاربونيتريل وقد تم تحضير مركبات الاينامينونيتريل المقابلة بالاختزال باتسخدام بوروهيدريد الصوديوم . وبمعالجة الإينامونيونيتريل بكلوريد اسيتيل الكلوريد تم الحصول على مركبات ن – كلورواسيتيل الأمين والتى تم تحويلها إلى مركبات رباعية الحلقات الأحماض أو القلويات. وقد أظهرت الدراسة الفارماكولوجية لاثنين من المركبات المحضرة أن لهما نشاط كمضات للإلتهابات ومسكنات بالمقارنه بمركب الإيبروفين.