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SYNTHESIS OF 3 - SUBSTITUTED (6 - BROMO-2- IMIDAZO [4,5-B] PYRIDINYL) PROPIONIC ACID AS ANTIINFLAMMATORY, ANALGESIC, AND ANTIPYRETIC AGENTS

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ABSTRACT

A series of 3- substituted (6-bromo - 2 - imidazo [4,5 - b] -pyridinyl) propionic acid hydrazide (I) , thiosemicarbazide (II) and 1,2,4 - triaoles (III) were prepared. Some of the prepared compounds were tested for their antiinflammatory , analgesic and antipyretic activities.

INTRODUCTION

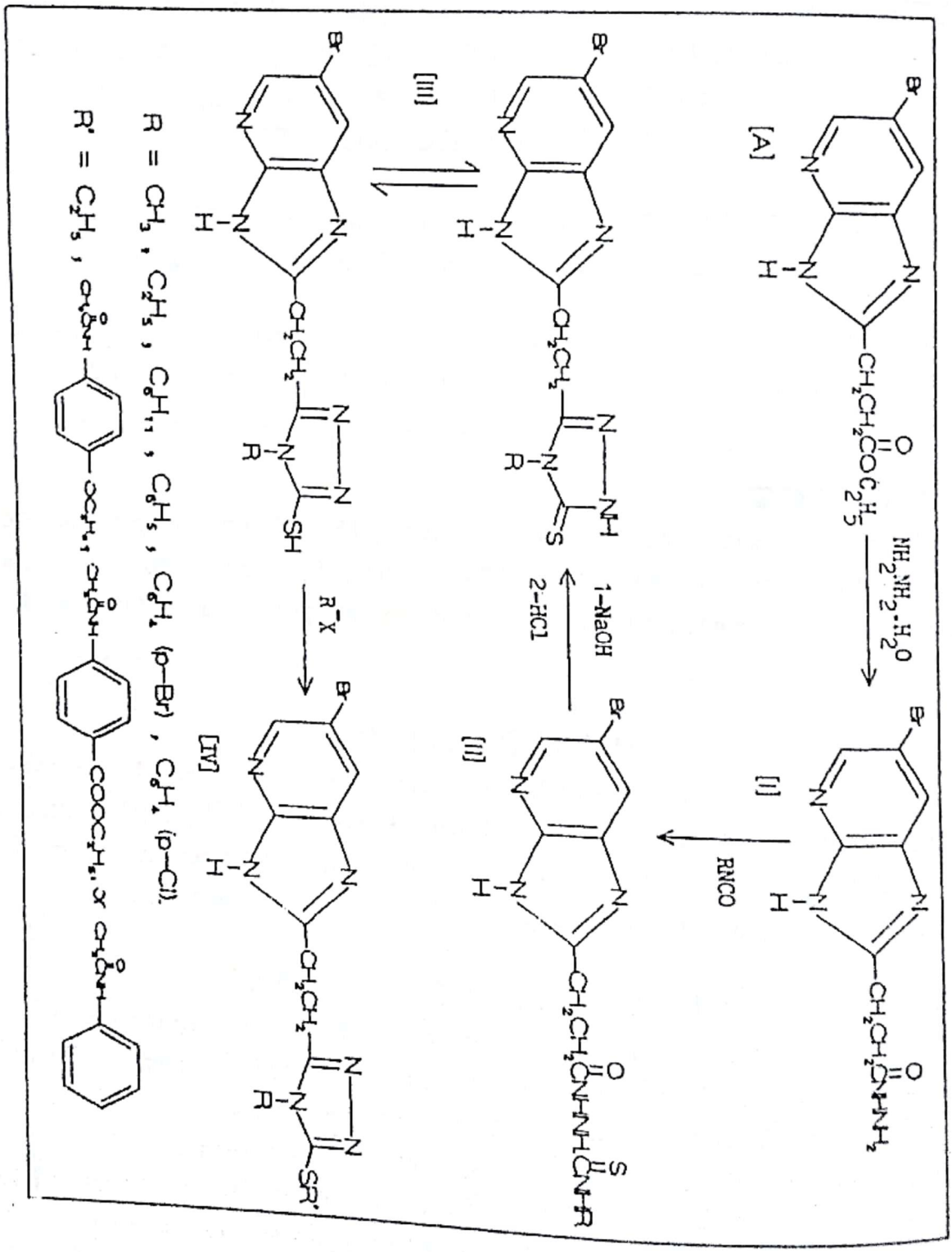
An interesting spectrum of biologicalactivities was shown by various imidazopyridines. Obviously, they showed herbicidal [1-3] , anthelmintic and fungicidal [4], antidepressant [5] bactericidal and tumer inhibitor [6] antihistaminic [7], antiinflammatory [8] and antiulcer [9] potentials .

RESULTS AND DISCUSSIONS

The fact that many hydrazine derivatives have anticonvulsant [10] , psychotropic [11] and MAO inhibitory activities [12] urged the preparation of a hydrizide (I) from the ester [A] . This hydrazide (I) was considered as the key intermediate for the synthesis of several series of compounds .

In this work , to achieve a series of thiosemicarbazides, compound [I] was reacted with different alkyl and aryl isothiocyanates to give compounds [II a - h] .

1,2,4 - Triazoles display a wide range of pharmacological activities as anticonvulsant [13] , antiinflammatory [14] . On these bases a series of


[A]
[I]
[II]
[III]
[IV]
RNCO
1-NaOH
2-HCl
R'X
R = CH3 , C2H5 , C6H11 , C6H5 , C6H4 (p-Br) , C6H4 (p-Cl).
R' = C2H5 ,

Scheme 1

compounds [III a - h] and compounds [IVa - i] were prepared in order to investigate their chemical and pharmacological properties .

^{1}H- NMR (ppm) of compound (I) : δ 3.2 (t, 2H, CH_2 - 2) ; 3.7 (t, 2H, CH_2 - 3) ; 4.7 (br, 2H, NH_2) ; 7.2 (s ,CH aromatic at position 7) ; 7.6 (s , CH aromatic at position 5) ; 8.6 (s, 1H , NH - oxadiazole) and 8.8 (s , NH - imidazole) .

^{1}H- NMR (ppm) of compound IIIe : δ 3.43 (t, 2H, CH_2) ; 3.85 (t, 2H, CH_2); 7.3 (m, 3H , CH aromatic protons) ; 7.65 (d, 4H, CH_2 + CH_2 aromatic protons) ; 8.65 (s, 1H , NH) and 8.8 (s, 1H , NH).

Pharmacological Screening :

Compounds I, III were tested for their analgesic , antipyretic and antiinflammtory activities .

1- Analgesic activity

The hot plate method of Jacob and Basovski [15] was adopted to evaluate the analgesic activity .

20 Mature Albion mice of both sexes weighing 20 - 25 g were divided into 4 groups , the first group was left as control , while the second was i.p. injected with Brufen (20 mg / kg) as standard . The last groups were i.p. injected with compounds I and III in a dose 20 mg/ kg . Five minutes later, each mouse was placed in a two liter beaker immersed in water bath thermostatically controlled at 56° C. The time elapsed till the mouse liks or jumps was considered the reaction time and taken as a measure for the analgesic effect . Readings were taken 10 , 20 , 30 , 60 , 90 and 120 minutes post treatment.

2- Effect on body temperature

20 Mature Albino rats of both sexes weighing 200 -230 g were divided into 4 groups . All animals were rendered hyperthermically using the method described by Teotino [16] by subcutaneous injection of 20% aqueous suspension of dry yeast in a dose of 0.1 mL / 100 g . After 15 hours , the body temperature for each animal was taken rectally by a medical thermometer and recorded as the initial temperature. The first group was left as control , whereas , the second group was i.p. injected with Brufen (20 mg / kg). The tested compoun dsdissolved in propylene glycol were given i.p. in a dose of

Table (1): The Analgesic effect of the The Tested Compounds (I,III) On Mices After i.p. Administration in dose of 20 mg/Kg .

GROUP	Duration of analgesic effect in seconds					
	10 min after treatment	20 min.after treatment	30 min after treatment	60 min after treatment	90 min after treatment	120 min after treatment
control "without treatment"	32.5±3.95	31.27±2.36	31±1.22	31.3±1.62	29.8±2.71	31.32±3.86
control treated with Brufen 20 mg/kg "standard"	61±6.72*	66±2.04**	66.75±4.44 **	67.25±4.98 **	69±6.87**	67.75±5.41 **
treated with compound no.I	52.5±7.71	61.75±9.5*	65.5±3.97* *	65.75±6.01 **	69.5±10.51* *	41.75±3.47
treated with compound no. III	42.25±5.01	51.5±6.3*	58.5±9.13	48.75±7.89 *	46±5.68	42.5±3.76

*siginificant difference from the control at $p<0.05$
**highly siginificant difference from the control at $p<0.001$

20 mg / kg for the last two groups. One hour following treatment, the rectal temperature was recorded for a period of 3 hours and the difference between the initial body temperature and that after treatment was calculated and compound with that of control group that received equivalent volume of solvent.

3- Antiinflammatory effect

The method explained by Alpermann [17] was used for studying the antiinflammatory activity of the tested compounds and Brufen as standard. For this purpose , 20 Albino rats of both sexes weighing 210-230 g were divided 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 inflammatory process achieved by the yeast. The first group was left as control , while the second group was i.p. injected with Brufen in adose of 20 mg / kg. The last group were i.p. injected with the tested compounds in a dose of 20 mg / kg. The paw thickness was remeasured after 3 and 6 hours post injection.

RESULTS

Concerning the Analgesic activity of the tsted compounds as shown in table (1) the reaction time was significantly increased ($p < 0.001$) for 90 minutes by i.p. injection of compound I . A marked increase ($p < 0.001$) in the reaction time was also obtained for 2 hours by i.p. injection of Brufen. It seems that compound III showed less equipotant activity to that of Brufen , yet , the maximum analgesic activity was obtained by compound I after 30 minutes .

The antipyretic effect of the tested compounds on rats was illustrated in table (2) . The i.p. injection of the tested compounds I and III in a dose of 20 mg / kg was found to produced significant decrease ($p < 0.05$) body temperature of rats.

It was clearly evident from table (3) that i.p. injection of compound III induced a significant decrease ($p<0.05$) in the thickness of the paw skin after 3 and 6 h as ameasure of the antiinflammatory effect .

Table(2): The Antipyretic Activity of The Tested Compounds (I,III) On Rats, After Their Administration i.p in a dose of 20 mg/Kg.

GROUP	The rectal temperature			
	15 hs after yeast administ.	1h after treatment	2h after treatment	3h after treatment
control without treatment	38.8±0.21	38.7±0.3	38.1±.17	37.8±.51
control treated with Brufen 20 mg/kg.	38.3±.2	35.8±.32**	36.4±.32**	36.9±.4
treated with compound no.1	38.3±.44	37.4±.19*	37.7±.16	37.8±.23
treated with compound no.111	38.2±.2	37.6±.17*	36.8±.34*	36.9±.48

* significant differant from control at p<.05
** highly siginificant different from control at p<.001

Table (3): The Anti inflammatory Activity of The Tested Compounds (1,111) On Rats After Their Administration i.p In a Dose Of 20 mg/Kg.

GROUP	Thickness of the paw skin (mm)		
	4 hs after yeast administration	3hs after treatment	6hs after treatment
control "without treatment"	7.53 ± 0.32	6.8±.19	5.93±.45
control treated with Brufen 20mg/kg	7.1±.5	4.8±.49*	3.81±.37*
treated with compound no.I	7.32±.07	5.07±.56*	4.36±.43*
treated with compound no.III	7.3±		

*Significant different from control at p<0.05

EXPERIMENTAL

All melting points are uncorrected and determined by open capillary method. Microanalysis was carried in the Microanalyticai Centre, Cairo University. IR spectra were determined on Perkin-Elmer PE-298 Spectrophotometer using KBr discs. ^{1}H - NMR was carried on Varian - A - 60 spectr.

3 - N - substituted (6 - bromo -2- imidazo (4 , 5 - b) pyridinyl) propionic acid hydrazide Ia - b :

To a solution of 3- (6 bromo -2- imidzo [4,5-b] pyridingyl propionate ester [A] 1.5 gm (0.005 mole) in 20 ml absolute ethanol , hydrazine hydrate 99% 0.5 ml (0.01 mole) in 20 ml absolute ethanol was added and the reaction mixture was refluxed for 8 hours. The solvent was removed by distitllation under vacuum and the residue crystallized from ethanol (Table4) .

N - Substituted -3- (6-bromo -2- imidazo (4,5-b) pyridinyl) propionyl hydrazine carbothioamide II a - h :

A mixture of (I) 2.7 gm (0.01 mole) and alkyl or aryl isothiocyanate (0.01 mole) in 30 ml of dioxan was refluxed for 6 hours.The solvent was removed by distillation under vacuum and the obtained residue was washed with water , then with ether, dried and crystallied from the appropriate solvent (Table 5) .

((4-Alkyl or aryl - 5-mercapto - 1,2,4 - triazol -3- yl) ethyl) - 6 - bromo -2- imidazo (4,5-b) pyridine IIIa - h :

A solution of (II) 0.002 mole in 6 ml of 2n sodium hydroxide was refluxed for 2 hours . The reaction mixture was cooled and acidified with dilute hydrochloric acid . The separated solid was filtered , washed with water , dried and crystallized from the appropriate solvent (Table 6) .

{(4-Alkyl or aryl -5- (substituted thio) -1,2,4- triazolo -3- yl) ethyl } 6 - bromo -2- imidazo (4,5-b) pyridine IV a - i

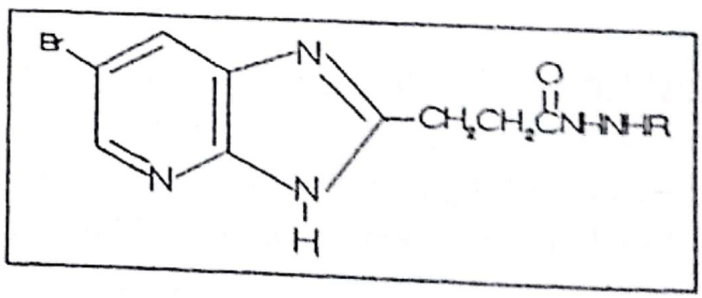
A mixture of (III a,b,e) 0.003 mole, anhydrous potassium carbonate 0.8 gm (0.006 mole) and ethyl iodide or 2-chloroacetanilide derivative (0.003

mole) in 50 ml of dry acetone was refluxed for 10 hours. The reaction mixture was filtered and the solvent was removed by distillation under vacuum. The residue obtained was crystallized from the appropriate solvent (Table 7).

^{1}H- NMR (ppm) of compound (I) : δ 3.2 (t, 2H, CH_2 - 2) ; 3.7 (t, 2H, CH_2 - 3) ; 4.7 (br, 2H, NH_2) ; 7.2 (s ,CH aromatic at position 7) ; 7.6 (s , CH aromatic at position 5) ; 8.6 (s, 1H , NH - oxadiazole) and 8.8 (s , NH - imidazole) .

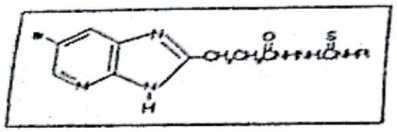
^{1}H- NMR (ppm) of compound IIIe : δ 3.43 (t, 2H, CH_2) ; 3.85 (t, 2H, CH_2); 7.3 (m, 3H , CH aromatic protons) ; 7.65 (d, 4H, CH_2 + CH_2 aromatic protons) ; 8.65 (s, 1H , NH) and 8.8 (s, 1H , NH).

Table (4)



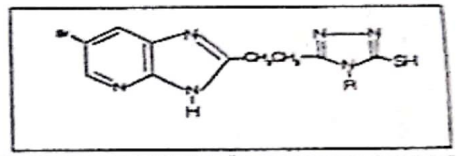
No	R	M.f & M.wt.	Yield	M.p	Microanalysis Calcd	Found
Ia	H	$C_9H_{10}BrN_5O$ (284)	88%	240	C 38.02	38.2
					H 3.52	3.9
					N 24.64	24.3
Ib	C_6H_5	$C_{15}H_{14}BrN_5O$ (360)	86%	261	C 50.02	49.8
					H 3.88	4.00
					N 19.44	19.2

Table.(5)



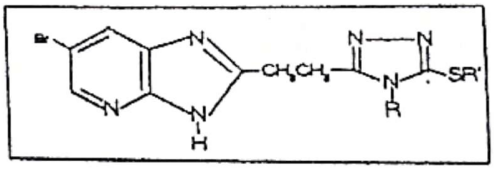
No	R	M.f & M.wt.	yield	M.p	Microanalysis Calcd	Found
IIa	CH_3	$C_{11}H_{13}BrN_6OS$ (357)	70%	>300	C 36.97	36.8
					H 3.64	3.4
					N 23.52	23.3
IIb	C_2H_5	$C_{12}H_{15}BrN_6OS$ (371)	74%	>300	C 38.81	39.0
					H 4.04	4.2
					N 22.64	22.4
IIc	C_6H_{11}	$C_{16}H_{21}BrN_6OS$ (425)	65%	>300	C 45.17	45.3
					H 4.94	5.1
					N 19.76	19.6
IId	C_6H_5	$C_{16}H_{15}BrN_6OS$ (419)	80%	>300	C 45.82	45.6
					H 3.57	3.7
					N 20.04	19.8
IIe	C_6H_4 (p.Br)	$C_{16}H_{14}BrN_6OS$ (498)	82%	>300	C 38.55	38.4
					H 2.81	3.0
					N 16.86	16.6
IIf	C_6H_4 (p.Cl)	$C_{16}H_{14}BrClN_6OS$ (454)	85%	>300	C 42.29	42.4
					H 3.08	3.3
					N 18.50	18.3
IIg	CH_2CH_2Cl	$C_{13}H_{15}BrN_6OS$ (383)	70%	225	C 40.73	40.5
					H 3.91	4.1
					N 21.93	21.8
IIh	C_6H_4 (p.CH_3)	$C_{17}H_{17}BrN_6OS$ (433)	62%	>300	C 47.11	47.3
					H 3.92	4.2
					N 19.40	19.1

Table.(6)



No	R	M.f & M.wt.	Yield	M.p	Microanalysis Calcd	Found
IIIa	CH_3	$C_{11}H_{11}BrN_6S$ (339)	71%	>300	C 38.93	38.7
					H 3.24	3.4
					N 24.77	24.5
IIIb	C_2H_5	$C_{12}H_{13}BrN_6S$ (353)	74%	>300	C 40.79	41.0
					H 3.68	3.9
					N 23.79	23.6
IIIc	C_6H_{11}	$C_{16}H_{19}BrN_6S$ (407)	65%	>300	C 47.17	47.5
					H 4.67	4.9
					N 20.63	20.4
IIId	$CH_2CH=CH_2$	$C_{13}H_{13}BrN_6S$ (365)	73%	260	C 42.73	42.5
					H 3.55	3.8
					N 23.01	22.8
IIIe	C_6H_5	$C_{16}H_{13}BrN_6S$ (401)	75%	>300	C 47.88	47.6
					H 3.24	3.5
					N 20.94	20.6
IIIf	C_6H_4 (p.Br)	$C_{16}H_{12}BrN_6S$ (480)	79%	>300	C 40.0	40.1
					H 2.50	2.8
					N 17.50	17.2
IIIg	C_6H_4 (p.Cl)	$C_{16}H_{12}BrClN_6S$ (436)	81%	>300	C 44.03	44.3
					H 2.75	3.0
					N 19.26	20.1
IIIh	C_6H_4 (p.CH_3)	$C_{17}H_{15}BrN_6S$ (415)	63%	>300	C 49.15	48.9
					H 3.61	3.9
					N 20.24	20.1

Table (7)



No	R	R_1	M.f & M.wt.	Yield	M.p	Microanalysis Calcd	Found
IVa	CH_3	C_2H_5	$C_{13}H_{15}BrN_6S$ (367)	78%	>300	C 42.50	42.5
						H 4.08	5.1
						N 22.88	22.6
IVb	C_2H_5	C_2H_5	$C_{14}H_{17}BrN_6S$ (381)	74%	>300	C 40.09	40.3
						H 4.46	4.7
						N 22.04	22.8
IVc	C_6H_5	C_2H_5	$C_{18}H_{17}BrN_6S$ (429)	70%	297	C 50.34	50.1
						H 3.96	4.2
						N 19.58	19.8
IVd	CH_3	$CH_2\overset{O}{C}NH\,C_6H_5$	$C_{19}H_{18}BrN_7OS$ (472)	88%	295	C 48.30	48.4
						H 3.81	3.6
						N 20.76	20.9
IVe	C_2H_5	$CH_2\overset{O}{C}NH\,C_6H_5$	$C_{20}H_{20}BrN_7OS$ (486)	79%	299	C 49.38	49.1
						H 4.11	4.3
						N 20.16	20.5
IVf	C_6H_5	$CH_2\overset{O}{C}NH\,C_6H_5$	$C_{24}H_{20}BrN_7OS$ (534)	81%	280	C 53.93	54.0
						H 3.74	3.9
						N 18.35	18.1
IVg	CH_3	$CH_2\overset{O}{C}NH\,(p\text{-}CH_3)C_6H_4$	$C_{20}H_{20}BrN_7OS$ (486)	80%	296	C 49.38	49.5
						H 4.11	4.3
						N 20.16	20.3
IVh	C_2H_5	$CH_2\overset{O}{C}NH\,(p\text{-}CH_3)C_6H_4$	$C_{21}H_{22}BrN_7OS$ (500)	85%	>300	C 50.40	50.6
						H 4.40	4.7
						N 19.60	19.7
IVi	C_6H_5	$CH_2\overset{O}{C}NH\,(p\text{-}CH_3)C_6H_4$	$C_{25}H_{22}BrN_7OS$ (548)	80%	294	C 54.74	54.9
						H 4.01	4.2
						N 17.88	17.6

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تخليق -٣- مشتقات (٦- بروم -٢-أميدازو(٤ ، ٥ - ب) بيريدينيل

حامض البروبيونيك كمضادات للإلتهابات ومسكنات ومخفضات للحرارة

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في هذا البحث تم تخليق سلسلة من ٣- مشتقات - (٦- بروم -٢- اميدازو ٤ ، ٥- ب) بيردينيل هيدارازيد حمض البروبيونيك ثيوسمي كاريازيد ، ١ ، ٢ ، ٤ تراي ازول .وقد تم اختيار بعض هذه المركبات كمضادات للالتهابات ومسكنات ومخفضات للحرارة .