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SYNTHESIS AND PRELIMINARY TESTING OF CERTAIN NEW TRIAZOLOQUINAZOLINE DERIVATIVES ASANTIINFLAMMATORY , ANALGESIC AND ANTIPYRETIC AGENTS

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ABSTRACT

Several new triazoloquinazoline derivatives were prepared . The structures of the obtained compounds were established on the light of their elemental analysis and spectroscopic data. Two of the newly prepared compounds were screened for their antiinflammatory, analgesic and antipyretic activities compared to ibuprofen. Preliminary screeing of the selected compounds showed significant activities .

INTRODUCTION

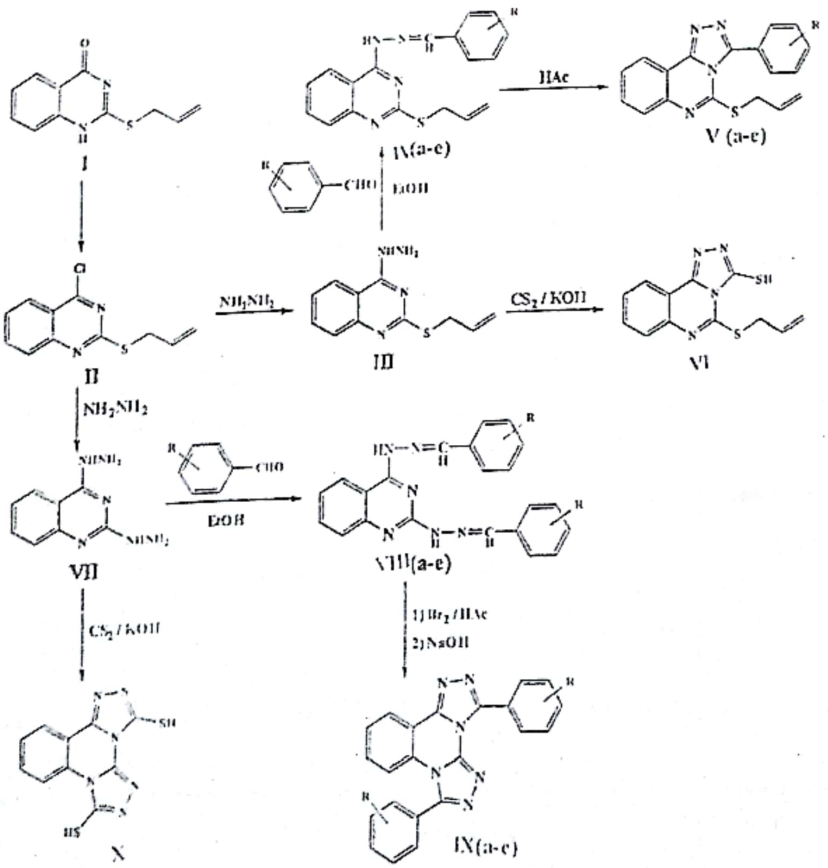
A versatile number of compounds having 4 (3H) quinazolinone ring system have been associated with diverse pharmacological activities.[1-5]Likewise many triazole[6] derivatives have shown interesting biological activities . Extensive structure activity relationships studies of great number of 4 (3 H) quinazolinones revealed that changing of substituents at positions 2 or 4 could affect the activity of these compounds.[7-10] Furthermore, it has been previously demonstrated that certain triazoloquinazoline derivatives would possess anticonvulsant and antiinflammatory activities[11-14] which might be due to selective antagonism of human A_3 receptor .[15]

Thus in view of these findings , the synthesis of some new modified triazoloquinazoline derivatives as potential antiinflammatory , analgesic and antipyretic agents has been considered in the present investigation

Chemistry

The sequence of reactions followed in the preparation of the target compounds is depicted in scheme 1.

The 2- allylthio - 4 (3H) quinazolinone (I) and 2-allylthio -4- chloroquinazoline (II) which were needed as substrates were prepared according to reported methods[16] .The hydrazinolysis of 2- allylthio - 4-chloroquinazoline (II) with hydrazine hydrate (98%) in ethanol for 12h at refluxing temperature yielded 2,4- dihydrazinoquinazoline (VII) which could result from the nucleophilic attack of hydrazine (in high concentration) on both electrophilic carbons at position 2 and 4 of II and subsequent replacement of allylthio and chloride moieties . Upon carrying out the reaction under milder conditions by heating an equimolecular mixture of II and hydrazine hydrate (50%) in ethanol for 6 h ; 2- allylthio- 4-hydrazinoquinazoline (III) was obtained . The structure of both III and VII were substantiated by elemental analysis , IR and NMR data. Refluxing III with certain aromatic aldehydes in ethanol for 1 h afforded $IV_{(a-e)}$ which were cyclised by heating in acetic acid and sodium acetate at refluxing temperature for 4 h to give triazoloquinazolines ($V_{(a-e)}$) .



In addition VI was obtained by refluxing III , with carbon disulphide and potassium hydroxide in ethanol for 3 h. On the other hand, refluxing VII with certain aromatic aldehydes in ethanol for 1h afforded $VIII_{(a-c)}$

The ditriazoloquinazolines ($IX_{(a-c)}$) were prepared from $VIII_{(a-c)}$ by treatment with an acetic acid solution of bromine in presence of sodium acetate followed by pouring the reaction mixture into excess sodium hydroxide . In addition; X was obtained by refluxing VII, with carbon disulphide and ethanol for 3 h .

Pharmacological Screening :

Two of the newly prepared compounds (V_a and IX_a) were screened for their antiinflammatory, analgesic and antipyretic activities .

1- Antinflammatory activity

The method explained by Alpermann[17] was used for studying the antiinflammatory activity of the tested compounds and ibuprofen as standard . For this purpose 24 albino rats of both sexes weighing 190-210 g were divided into 4 groups. Inflammation in rat paw was induced by injecting 0.1 ml of 20% Brewer's yeast suspension in pysiological saline solution into the paw skin of the hind limb . After 4 h the thickness of the paw was measured using a skin caliber to detect the inflammatory process achieved by 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 last two groups were i.p. injected with tested compounds in a dose of 20 mg / kg . The paw thickness was remeasured after 3 and 6 h post injection .

2- Analgesic activity

The hot plate method of jacob and Basovski[18] was adopted to evaluate the analgesic activity .

24 Mature Albino 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 ibuprofen (20mg / kg) as standard . The last two groups were i.p. injected with the tested compounds 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 licked or jumped was considered as reaction time and taken as a measure for the analgesic effect. Readings were taken 10, 20, 30, 60, 90 and 120 minutes post treatment.

3- Antipyretic activity

24 Mature Albino rats of both sexes weighing 190-210 g were divided into 4 groups . All animals were rendered hyperthermically using the method described by Teotiono[19] by subcutaneous injection of 20% aqueous susponsion of dry yeast in a dose of 0.1 ml / 100g . After 15 h, 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 ibuprofen (20 mg/kg). The tested compounds were given i.p. in a dose of 20 mg / kg for the last two groups . One hour following treatment , the rectal temperature was recorded every hour for a period of 3 h and the difference between the initial body temperature and that after treatment was calculated .

RESULTS

It was clear from (table 1) that i.p. injection of V_a induced a significant decrease ($p < 0.05$) in thickness of the paw skin after 3 and 6 h indicating antiinflammatory potency .

Concerning the analgesic activity of the tested compounds as shown in (table 2) the reaction time was significantly increased ($P< 0.001$) for 90 min by i.p. injection of V_a . A marked increase ($p<0.001$) in reaction time was also obtained for 2 h by i.p. injection of ibuprofen . It seemed that IXa showed less activity than that of ibuprofen . Equipotent activity was obtained by V_a after 30 min. Antipyretic effect of the tested compounds on rats was illustrated in (table 3) . The i.p. injection of the tested compounds (V_a or Ix_a) in a dose of 20 mg / kg was found to produce significant decrease ($P< 0.05$) in body temperature of rats .

Table 1: Antinflammatory activity of the tested compounds (Va & IX a) on rats , after i.p administration in a dose of 20 mg / kg

Group	Thickness of the paw skin(mm)		
	4 h after yeast administration	3 h after treatment	6 h after treatment
Control; without treatment	7. 46 ± 0. 34	6. 8 ±. 18	5. 91 ± 0.41
Control: treated with ibuprofen 20mg/ kg	7. 1 ±. 5	4. 8 ± 0. 47*	3. 80 ±. 35*
Treated with Va	7. 32 ± 02	5. 07 ±.0.54*	4. 35 ±0.38*
Treated with IX_a	7. 3 ± 0.07	6.7 ± 0.12	6.1± 0.2

* Significant difference from control at $P < 0.05$

Table2: Analgesic effect of the tested compounds(V_a & IX_a)on mice after i.p. administration in a dose of 20 mg / kg

Group	Duration of analgesic effect in sec.					
	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. 45	31.27 ± 2.36	31± 1.22	31.3 ± 1.62	29.8 ± 2.71	31.32 ± 3.86
Control, treated with ibuprufen 20 mg / kg	61 ± 6.72*	66 ± 2.04**	66.75±4.44**	67.25±5.01**	69 .±6.85**	67.7 ±5.32**
Treated with V_a	52 ±7. 76	61.75 ±9.8*	65.5 ± 3.98**	65.71±5.4**	69.5±10.51**	41.75± 3.8
Treated with IX_a	42.25 ± 5. 11	51.5 ± 6.1*	58.5 ± 9.23*	48.71±7.7 *	46 ± 5.68	42.5±3.62

* Significant difference from control at P < 0. 05 ** Highly significant difference from control at P< 0.001

Table 3 : Antipyretic activity of the tested compounds (V_a & IX_a) on rats , after i.p administration in a dose of 20 mg / kg

Group	Rectal temperature			
	15 h after yeast administration	1 h after treatment	2 h after treatment	3 h after treatment
Control; without treatment	38.8 ± 0.22	38.7 ± 0.20	38.1 ± 0.17	37.8 ± 0.51
Control; treated with ibuprofen 20mg/kg	38.3 ± 0.2	35.8 ± 0.32**	36.2 ± 0.32**	36.9 ± 0.9*
Treated with V_a	38.3 ± 0.42	37.4 ± 0.14*	37.7 ± 0.16**	37.8 ± 0.23
Treated with IX_a	38.2 ± 0.2	37.6 ± 0.17*	36.8 ± 0.34**	36.9 ± 0.48*

* Significant difference from control at P < 0. 05 ** Highly significant difference from control at P< 0.001

EXPERIMENTAL

All melting points were uncorrected . Microanalyses were performed at microanalytical center , cairo university . IR spectra were carried out using pye unicam sp 1100 spectrophotometer . The ^1H - NMR spectra were recorded on varian EM 390, 90 MHz spectrphotometer using DMSO-d_6 as a solvent and TMS as an internal standard.

2- Allylthio -4- hydrazinoquinazoline (III)

Hydrazine hydrate 50% (0.6 g , 0.01 mol) was added to a stirred solution of compound II (2.37 . g , 0.01 mol) in ethanol (50 ml) The reaction mixture was heated under reflux for 6 h. The solvent was concentrated under reduced pressure and poured into ice cold water . The separated solid was filtered , washed with water , dried and crystallized from dioxane . mp. 223 - 4 °c . Yield 65%.

Analysis for , $C_{11} H_{12} N_4 S$ (232)

	C	H	N
Calcd	56.89	5.17	24. 13
Found	57.0	5.2	24.0

^1H-NMR (ppm) 3.8 (d, 2H, S- CH_2),5.1 5.4 (m, 3H, CH = CH_2),7.7- 8.1 (m , 4 H , aromatic protons), 9.1(br, 2H, NH_2 D_20 exch.) 10.9 (br, 1H , NH , D_20 exch.) .

2-Allylthio -4- arylidenehydrazinoquinazolines (IV a-e)

A mixture of III (2.32 g , 0.01 mol) and the properly substituted benzaldehyde (0.01 mol) and absolute ethanol (30 ml) was heated under reflux for 1 h . The product was collected by filteration, dried and crystallized from dioxane / water . (Table 4).

5-Allylthio-3-aryl-1,2,4-triazolo[4,3 -c]quinazolines(Va-e)

A mixture of IV_{a-e} (0.01 mol), anhydrous sodium acetate (1g) and glacial acetic acid (30 ml) was heated under reflux for 4 h . The reaction mixture was cooled , poured into ice cold water (100 ml) and the separated solid was filtered, washed with water, dried and crystallized from dioxane .(Table 5) .

5- Allylthio- 3- mercapto- 1,2,4 - triazolo[4,3-c] quinazoline (VI)

A mixture of III (2.32 g. 0.01 mol), potassium hydroxide (0.8 g), carbon disulphide (1.5 g) and methanol (30 ml) was heated under reflux for 3 h. The solvent was removed under reduced pressure , the residue was dissolved in water (50 ml) and filtered. The filtrate was neutralized with dilute

Table 4 : Characterization data of compounds $IV_{(a-e)}$

NO	R	M.F&Mwt	M.P °C	Yield%	Elemental analysis %		
					Element	Calcd	Found
a	H	$C_{18}H_{16}N_4S$ (320)	178-9	84	C H N	67.5 0 5.00 17.50	67.6 5. 1 17. 4
b	4-OCH_3	$C_{19}H_{18}N_4OS$ (350)	165-6	88	C H N	65. 14 5. 14 16. 00	65.3 5.2 15.8
C	2,4- di Cl	$C_{18}H_{14}Cl_2N_4S$ (389)	201-2	90	C H N	55.52 3.59 14.39	55.4 3.4 14.5
d	2- OH	$C_{18}H_{16}N_4OS$ (336)	193-4	87	C H N	64. 28 4. 76 16.66	64.1 4.8 16.5
e	4- $(CH_3)_2N$	$C_{20}H_{21}N_5S$ (363)	181-2	78	C H N	66.11 5.78 19.28	66. 3 5 . 8 19. 3

^{1}**H-NMR** (ppm) for compound IV_b 3.6 (s, 3H, OCH_3) , 4.0 (d, 2H, S-CH_2) 5.1 - 5.4 (m, 3H , CH= CH_2) 6.8 - 7.4 (m, 4H aromatic protons) , 7.7- 8.6 (m, 5H, aromatic protons and Ar- CH = N) , 11.1 (br, 1H , NH) ; **IR** Cm^{-1} (KBr): 3250 (NH) 3075 (CH aromatic) , 2960 (CH aliphatic) .

Table 5 : Characterization data of compounds $V_{(a-e)}$

NO	R	M.F&Mwt	M.P °C	Yield%	Elemental analysis %		
						Calcd	Found
a	H	$C_{18}H_{14}N_4S$ (318)	210-1	75	C H N	67. 92 4. 40 17 . 61	68. 0 4. 2 17 .5
b	4 - OCH_3	$C_{19}H_{16}N_4OS$ (348)	195 - 6	82	C H N	65 . 51 4 . 59 16 . 09	65 . 6 4. 5 16. 0
c	2,4- di Cl	$C_{18}H_{12}Cl_2N_4S$ (387)	248 - 9	78	C H N	55. 81 3. 10 14. 47	55. 9 3. 2 14. 5
d	2 - OH	$C_{18}H_{14}N_4OS$ (334)	238 - 9	71	C H N	64. 67 4.19 16.76	64. 5 4. 2 16. 8
e	4- $(CH_3)_2N$	$C_{20}H_{19}N_5S$ (361)	225 - 6	70	C H N	66. 48 5.26 19. 39	66. 5 5. 1 19. 2

^{1}**H-NMR** (ppm) for compound V_b 3.7 (s , 3H, OCH_3) , 4.0 (d , 2H , S-CH_2) 5.1- 5.3 (m, 3H , CH= CH_2) , 6.8 - 7.4 (m, 4H , aromatic protons) , 7.7- 8.2 (m , 4H , aromatic protons) ; **IR** Cm^{-1} (KBr) ; 3050(CH aromatic) 2980 (CH aliphatic)

hydrochloric acid, the separated solid was filtered, washed. crystallized from ethanol m.p. 211- 2 °c . Yield 78% .

Analysis for $C_{12} H_{10} N_4 S_2$ (274)

	C	H	N
Calcd	52.55	3.64	20.47
Found	52.4	3.7	20.2

2,4- Dihydrazinoquinazoline (VII)

Hydrazine hydrate 98% (1.8 g , 0.03 mol) was added to a stirred solution of compound II (2.37 g, 0.01 mol) in ethanol (50ml). The reaction mixture was heated under reflux for 12 h . The separated solid was filtered , washed with water , dried and crystallized from dimethylformamide. m .p. 262-3 °c . Yield 82%

Analysis for $C_8 H_{10} N_6$ (190)

	C	H	N
Calcd	50.52	5.26	44.21
Found	50.4	5.3	44.4

2.4- Diarylidenehydrazinoquinazolines (VIII a-e)

A mixture of VII (1.90 g , 0.01 mol) and the properly substituted benzaldehyde (0.02 mol) in absolute ethanol (30 ml) was heated under reflux for 1 h . The product was collected by filteration , dried and crystallized from dioxane / water (Table 6)

3,8-Diaryl-di-1,2,4- triazolo [4,3 - c , 4,3 - a) quinazolines(IX a-e)

A solution of bromine (0.5 ml) in glacial acetic acid (1 ml) was added to a suspension of anhydrous sodium acetate (0.3 g) and the appropriate 2,4- diarylidenehy- drazinoquinazolines (VIII $_{a-e}$) (0.01 mol) in acetic acid (10 ml) . The reaction mixture was stirred at room temperature for 1 h , and poured into excess ice cold 0.5N sodium hydroxide . The product was collected by filteration , washed with water , dried and recrystallized from DMF/ water . (Table 7)

3,8-Dimercapto-di-1,2,4-triazolo [4,3-c, 4, 3- a] quinazoline (X)

A mixture of VII, potassium hydroxide (1.9 g) , carbon disulphide (3g) and methanol (30 ml) was heated under reflux for 3h . The solvent was removed under reduced pressure , the residue was dissolved in water (50 ml) , and filtered .The filtrate was neutralized with dilute hydrochloric acid , the separated solid was filtered , washed and recrystalized from ethanol mp. 281-2 °c . Yield 85% .

Analysis for $C_{10} H_6 N_6 S_2$ (274) C HN Calcd 43. 79 2.18 30. 65 Found 43.9 2.3 30.5

Table 6 : Characterization data of compounds VIII$_{(a-e)}$

NO	R	M.F&Mwt	M.P °C	Yield%	Elemental analysis %		
						Calcd	Found
a	H	$C_{22} H_{18} N_6$ (366)	290-1	87	C H N	72.13 4. 91 22. 95	72.2 5.0 22.7
b	4 - OCH_3	$C_{24} H_{22} N_6 O_2$ (426)	284 -5	90	C H N	67.60 5. 16 19. 71	67.5 5.2 19.8
c	2,4- di Cl	$C_{22} H_{14} Cl_4 N_6$ (504)	298 - 9	91	C H N	52. 38 2. 77 16. 66	52.5 2.6 16.6
d	2 -.OH	$C_{22} H_{18} N_6 O_2$ (398)	296-7	88	C H N	66.33 4.52 21.10	66.5 4.6 21.0
e	4- ($CH_3)_2N$	$C_{26} H_{28} N_8$ (452)	>300	82	C H N	69.02 6.19 24.77	69.2 6.1 24.6

^{1}H-NMR (ppm) for compound VIII $_b$ 3.7 [s , 6H, 2(OCH_3)],6.6-7.4 (m, 8H aromatic protons) , 7.7 - 8.6 (m, 8H , aromatic protons and 2(Ar- CH=N) , 10.5 (s 1H , NH) 10.8 (br, 1H , NH). **IR** cm^{-1} (KBr) 3250(NH) 3075 (CH- aromatic) 2970 (CH - aliphatic)

Table 7 : Characterization data of compounds $IX_{(a-e)}$

NO	R	M.F&Mwt	M.P °C	Yield%	Elemental analysis %		
						calcd	found
a	H	$C_{22}H_{14}N_6$ (362)	>300	75	C	72.92	73.1
					H	3.86	3.8
					N	23.20	23.0
b	4 - OCH_3	$C_{24}H_{18}N_6O_2$ (422)	>300	77	C	68.24	68.1
					H	4.26	4.3
					N	19.90	20.0
c	2,4- di Cl	$C_{22}H_{10}Cl_4N_6$ (500)	>300	72	C	52.8	53.0
					H	2.00	2.1
					N	16.8	16.6
d	2 - OH	$C_{22}H_{14}N_6O_2$ (394)	>300	70	C	67.00	67.1
					H	3.55	3.4
					N	21.31	21.2
e	4- $(CH_3)_2N$	$C_{26}H_{24}N_8$ (448)	>300	68	C	69.64	69.8
					H	5.35	5.2
					N	25.00	24.9

^{1}H-NMR (ppm) for compound Ixb 3.7 [s , 6H, $2(OCH_3)$],6.6 -7.4(m, 8H, aromatic protons), 7.7 - 8.2 (m, 4H, aromatic protons)

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التشييد و الفحص المبدئي لبعض مشتقات ترايازولوكينازولين الجديدة كمضادات للالتهابات ومسكنات للألم و مخفضات للحرارة .

منصور السيد أبو كل

قسم الكيمياء الطبية – كلية الصيدلة – جامعة الزقازيق – الزقازيق – مصر .

لقد تم في هذا البحث تحضير العديد من مركبات ترايازولوكينازولين . و قد تم إثبات التركيب البنائي لهذه المركبات بالتحليل الكمي و الأشعة تحت الحمراء و الترددد النووي المغناطيسي و قد تم إجراء اختبارات اقربازينية أولية لمركبين و وجد أن لهما تأثير ملموس كمضادات للالتهابات و مسكنات للألم و مخفضات للحرارة بالمقارنة بالأيبوبروفين .