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SYNTHESIS AND PHARMACOLOGICAL SCREENING OF CERTAIN IMIDAZOQUINAZOLONE DERIVATIVES

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تشتمل هذه الدراسة على تشييد بعض مشتقات الإيميدازوكينازولين-٥-(٤هـ)أون وذلك باستبدال مجموعة ال٤-أمينو في المركب I بمجموعات فارماكوفورية مختلفة. وقد تم اختبار بعض المكبات المختارة لدراسة نشاطها ضد الالتهابات وكمسكن وخافض للحرارة ومضادة للتشنجات وقد أثبتت النتائج نشاط ملحوظ في هذه المجالات أكثر من الأدوية المستخدمة كمرجع للمقارنة.

Certain imidazoquinazolin-5(4H)-one derivatives have been synthesized by replacement of the 4-amino group compound I with different moieties of expected biological activity.

Representative example of the synthesized compounds were tested for their anti-inflammatory, analgesic, antipyretic and anticonvulsant activities. Certain derivatives showed activities higher than that of the reference drugs.

INTRODUCTION

Imidazoquinazolines either linear or angular are well known to exhibit various pharmacological activities, for example cardiovascular[1-6], bronchodilator[7&8], antitumor[9&10], anti-inflammatory[11-20] and anticonvulsant activities[21-26]. In a previous publication 4-amino-1(4-chlorophenyl) imidazo[1,5-a]quinazolin-5(4*H*)-one **I** has been synthesized and tested for several pharmacological activities[27]. It showed anti-inflammatory and anticonvulsant activities comparable to that of indomethacin and diazepam respectively which made this compound serves as a useful lead for further design of more active compounds.

The present investigation deals with the synthesis of certain new derivatives of compound **I** in which the amino group has been converted by different pharmacophoric groups so as further study the effect of these moieties on the pharmacological potencies. Anti-inflammatory, analgesic, antipyretic, and anticonvulsant activities of a number of the synthesized compounds were explored.

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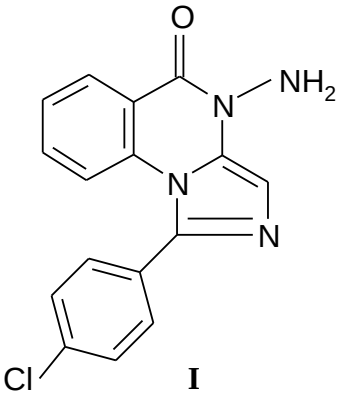


I

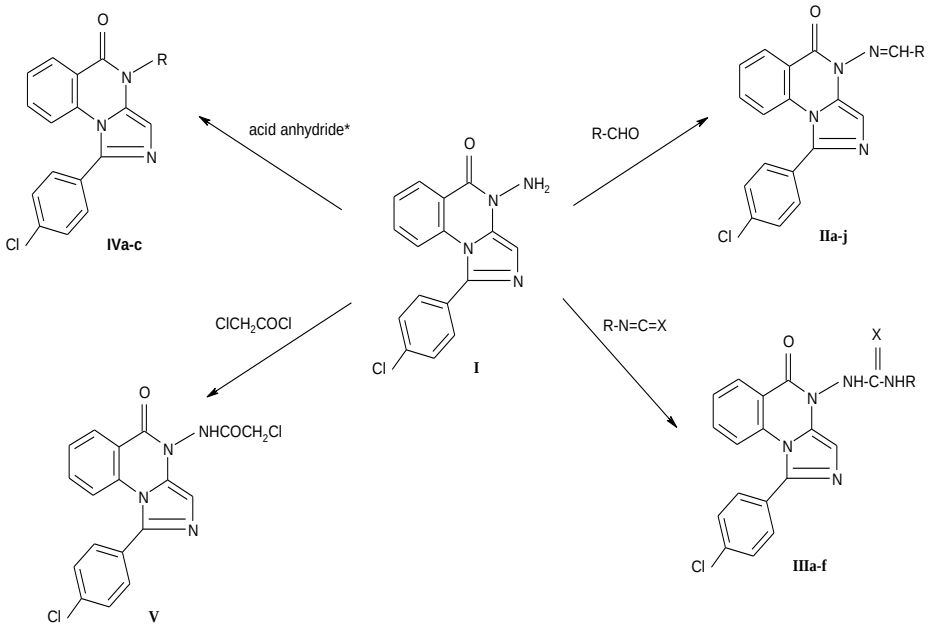
CHEMISTRY

The key starting compound 4-amino-1(4-chlorophenyl)imidazo[1,5-a]quinazolin-5(4*H*)-one **I** was prepared according to the reported procedure by refluxing methyl 2-[2-(4-chlorophenyl)-4-(substituted arylidene)-4,5-dihydro-5-oxo-imidazo-1-yl] benzoate with hydrazine hydrate in absolute ethanol[27&28]. The key compound **I** was reacted with different aromatic aldehydes, isocyanates or isothiocyanates, acid anhydride and chloroacetyl chloride to give the respected target derivatives **II, III, IV** and **V** respectively, Scheme 1. Compound **V** reacted with different secondary amines, potassium salt of substituted aromatic acids, phenytoin sodium or potassium phthalimide to produce the corresponding 4-(substituted aminometylcarbonyl-amino)-1-(4-chlorophenyl)imidazo [1,5-a]quinazolin-5(4*H*)-ones **VI**, 1-(4-chlorophenyl)-4,5-dihydro-5-oxo-imidazo[1,5-a]quinazolin-4-yl-amino-carbonylmethyl benzoates **VII**. 1-(4-chlorophenyl)-4-(4-oxo-5,5-diphenyl-imidazolin-2-yl)-oxymethylcarbonyl aminoimidazo[1,5-a]quinazolin-5(4*H*)-one **VIII** and 1-(4-chlorophenyl)-4-phthalimidomethyl carbonylamino-imidazo[1,5-a]quina-zolin-5(4*H*)-one **IX** respectively, Scheme 2. By reacting **I** with $NaNO_2$ / HCl, neither the hydroxamic acid derivative **X** nor the diazonium salt **XI** were obtained, instead the tetracyclic fused system **XIII** was obtained. A possible mechanism for the formation of the tetracyclic fused system is illustrated in Scheme 3.

EXPERIMENTAL

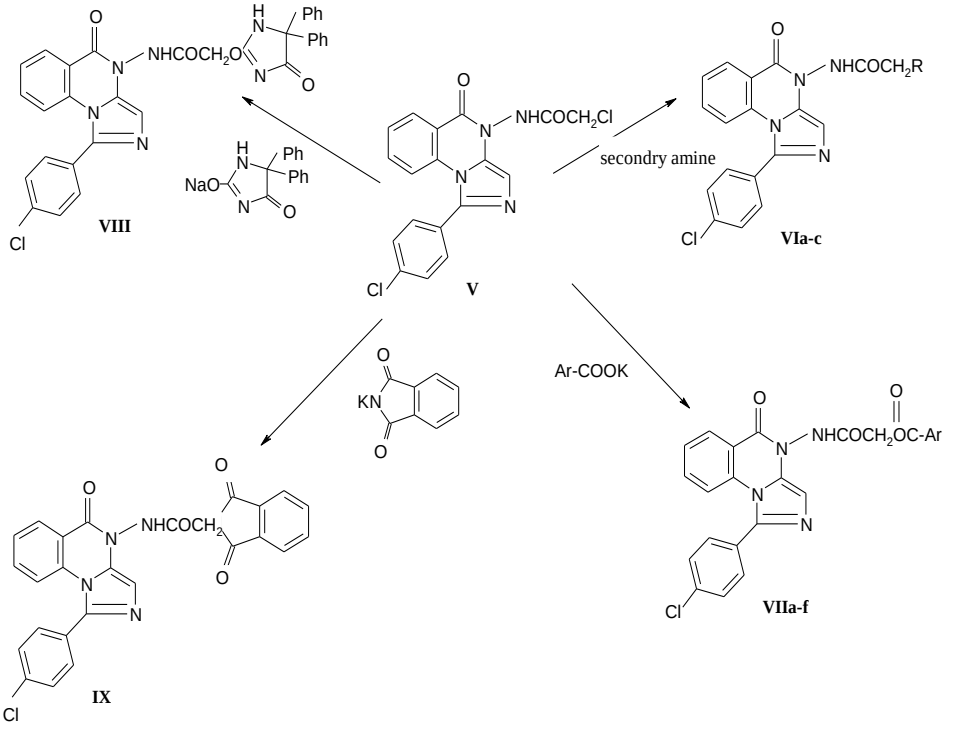
Melting points were carried out by the open capillary tube method using a Gallenkamp digital melting point apparatus and are uncorrected. Microanalyses were carried out at the microanalytical center, Cairo University. Infrared spectra were run on Shimadzu 435 IR spectro-photometer and Bruker Vector 22 FT IR (Fourier Transform Infrared Spectophotometer), and expressed in wave number (cm^{-1}), using potassium bromide pellets. Ultraviolet spectra were recorded in absolute ethanol on Shimadzu 265 UV- visible recording spectrophotometer. ^{1}H-NMR spectra were obtained on Varian Gemini 200, 200MHZ, the chemical shifts were expressed in δ ppm units using tetramethylsilane as the internal standard. Mass spectra were

performed on Hewlett Packard 5988, at 70 e V.



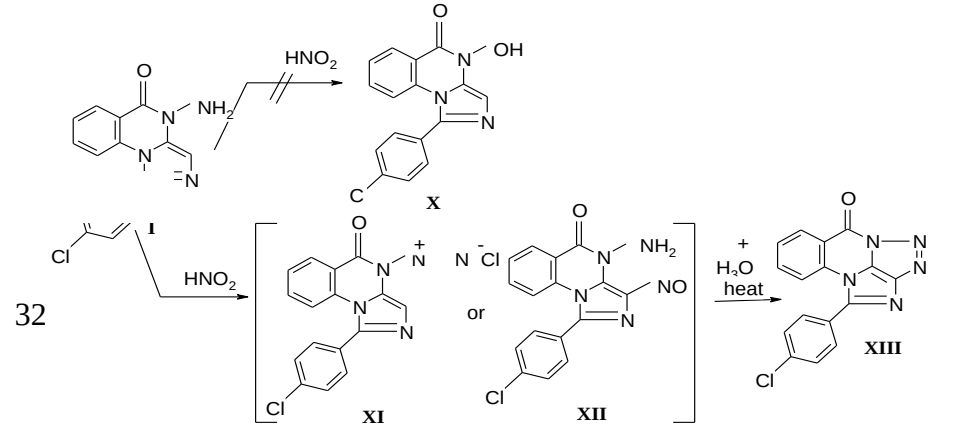
* Acid anhydride = acetic, succinic, or phthalic anhydride.

Scheme 1



Scheme 2

Scheme 3



1-(4-Chlorophenyl) 4-(substituted arylidenamino and 3-phenyl-2-propenylidenamino) -imidazo [1,5-a] quinazolin-5(4*H*)-ones IIa-j

A mixture of 4-amino-1-(4-chlorophenyl)imidazo[1,5-a]quinazolin-5(4*H*)-one **I** (0.01 mol; 3.10 g) and the appropriate aromatic aldehyde (0.01 mol) in absolute ethanol (20 ml) was refluxed for 8 hours. Then ethanol was removed under reduced pressure and the residue was triturated with ice water. The separated solid was filtered and crystallized from ethanol (Table 1). UV [$\lambda_{max.}$ (log ε)] of compound **IIb**: 300 (4.57), 226.4 (4.66). IR (cm^{-1}) of compound **IIa-IIj**: 3050 (CH aromatic), 2950-2850 (CH aliphatic), 1680 (C=O), 760 (C-Cl). ^{1}H NMR (δppm) ($CDCl_3$) of compound **IIb**: 3.86 (s, 3H, $OC\underline{H}_3$), 6.92-7.81 (m, 12H, aromatic), 8.35 (d, 1H, <u>H</u> C-6), 8.91 (s, 1H, C<u>H</u> of methine). MS m/z (rel.aband.%) of compound **IIc**: 415 (82.73), 339 (38.18), 313 (82.73), 281 (97.27), 237 (50.00), 171 (70.91), 118 (62.72), 60 (100.00).

1-(Alkyl or aryl)-3-[1-(4-chloro-phenyl)- 4,5-dihydro-5-oxo-imidazo[1,5-a]quinazolin-4-yl]carbamide or thiocarbamide (IIIa-IIIf)

A mixture of 4-amino-1-(4-chloro-phenyl)-imidazo[1,5-a] quinazolin-5(4*H*)-one **I** (0. 01 mole; 3.10 g), the appropriate aryl or alkyl isocyanate or isothiocyanate (0.01 mole) in methylene chloride (20 ml), and triethylamine (0.5 ml) was refluxed for 6 hours. The solid product separated on cooling was filtered, washed with water, and crystallized from benzene (Table 2). UV [$\lambda_{max.}$ (log ε)] of compound **IIIc**: 236.0 (4.30), for compound **IIIf**: 275.2 (4.34). IR (cm^{-1}) of compound **IIIb**: 3300, 3218 (2NH), 3092 (CH aromatic), 2957-2867 (CH aliphatic), 1664 (C=O), 1620 (NH bending), 767 (C-Cl). ^{1}H NMR (DMSO-d_6) of compound **IIIc**: 0.96-3.50 (m, 11H, cyclohexyl), 5.3 (s, 2H, 2NH disappeared by D_2O), 7.26-7.80 (m, 8H, C<u>H</u> aromatic), 8.3(d, 1H, <u>H</u>C-6). ^{1}H NMR($CDCl_3$) of compound **IIIe**: 0.8 (t, 3H, $CH_2C\underline{H}_3$), 1.25(q, 2H, $C\underline{H}_2CH_3$), 7.26-7.80 (m, 8H, C<u>H</u> aromatic), 8.3 (d, 1H, <u>H</u> C-6). MS m/z (rel.aband. %) of compound **IIIe**: 396.2 (3.17), 339.05 (4.56), 271.95 (75.00), 270.95 (100.00), 185.05 (9.92), 179 (7.34), 121.75 (16.87), 80.15 (7.14).

1-(4-Chlorophenyl)-4-Substituted (amido or imido)imidazo [1,5-a]quinazolin-5(4*H*)-ones (IVa-c)

Compound **IVa:** A mixture of **I** (0.01 mol; 3.10g) and acetic anhydride (10ml) was heated under reflux for one hour. The reaction mixture was poured onto ice water, filtered, washed with water, and crystallized from aqueous ethanol (Table 1).

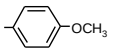
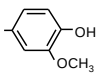
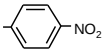
Compounds **IVb** and **IVc:** A mixture of **I** (0.01 mol; 3.10 g) and the appropriate acid anhydride (0.01 mol) in glacial acetic acid (10 ml) was refluxed for 6 hours. Excess

solvent was distilled under reduced pressure. The residue was triturated with ice water, filtered, washed with water, and crystallized from ethanol (Table 1). UV [$\lambda_{max.}$(log ε)]of compound **IVa**: 384.6 (4.39), 365.0 (4.54), 267.0 (4.18), 245.8 (4.04), 239.4 (4.03). For compound **IVb**: 236.4 (4.31). IR (cm^{-1}) of compound **IVa**: 3442 (NH), 3068 (CH aromatic), 2990-2926 (CH aliphatic), 1737, 1700 (C=O), 1620 (NH bending), 780 (C-Cl), for compound **IVb**: 3100 (CH aromatic), 2950-2850 (CH aliphatic), 1730, 1675 (C=O), 760 (C-Cl). ^{1}H NMR ($CDCl_3$) of compound **IVa:** 2.30(s, 3H, C<u>H</u>$_3$), 7.4-7.8 (m, 8H, C<u>H</u> aromatic), 8.3 (d, 1H, <u>H</u>C-6). MS m/z (rel.aband.%) of compound **IVa**: 355 (10.87), 296 (72.25), 271 (100.00), 242 (37.24), 178 (26.83), 139 (22.79), 90 (18.83), 76 (40.23).

4-Chloromethylcarbonylamino-1-(4-chlorophenyl)-imidazo[1,5-a]-quinazolin-5(4*H*)-oneV

A mixture of **I** (0.01 mol; 3.10 g) and chloroacetylchloride (0.01 mol; 1.129 g; 0.79 ml), dry benzene (20 ml) and triethylamine (1 ml) was refluxed for 6 hours. The excess solvent was distilled under reduced pressure. The residue was triturated with ice water, filtered, washed with water, and crystallized from ethanol. M.P. 202°C, Yield 70%. Microanalysis of $C_{18}H_{12}Cl_2N_4O_2$ (387.30) Cacld: C 55.81, H 3.12, N 14.47. Found C 56.10, H 3.40, N 14.90. UV [$\lambda_{max.}$ (log ε)]: 237.0 (4.49). IR (cm^{-1}): 3200 (NH), 3010 (CH aromatic), 2900-2845 (CH aliphatic), 1714 (C=O), 1674 (NH bending), 770 (C-Cl). ^{1}H NMR (DMSO-d_6): 4.20(s, 2H, COC<u>H</u>$_2$Cl), 7.56-7.96 (m, 8H, C<u>H</u> aromatic), 8.20-8.24 (d, 1H, <u>H</u> C-6), 11.6(s, 1H, N<u>H</u> disappeared by D_2O). MS m/z (rel. aband.%): 386.3 (44.39), 275.2 (42.93), 243.1 (66.83), 178.2 (74.63), 164.0 (22.79), 97.15 (49.27), 71.0 (100.00).

Table 1: Physical and microanalytical data of compounds **IIa-j, IVa-c, VIa-d** and **VIIa-f**.

No.	R	M.P. °C	Yield %	M.F. M.Wt.	Microanalysis	
					Calc. %	Found %
IIa		186	75	$C_{23}H_{15}ClN_4O$ 398.87	C 69.25 H 3.79 N 14.04	69.10 4.00 14.00
IIb		181	78	$C_{24}H_{17}ClN_4O_2$ 428.90	C 67.20 H 3.99 N 13.06	67.50 4.20 13.00
IIc		229	73	$C_{23}H_{15}ClN_4O_2$ 414.87	C 66.58 H 3.64 N 13.50	66.30 4.00 13.60
IId		201	77	$C_{24}H_{17}ClN_4O_3$ 444.90	C 64.78 H 3.85 N 12.59	64.60 3.70 12.60
IIe		188	71	$C_{23}H_{14}ClN_5O_3$ 443.87	C 62.23 H 3.17 N 15.77	61.80 3.20 15.70

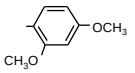
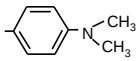
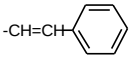
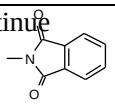
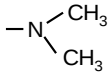
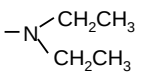
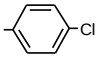
No.	R	M.P. °C	Yield %	M.F. M.Wt.	Microanalysis	
					Calc. %	Found %
IIf		241	69	$C_{23}H_{14}Cl_2N_4O$ 433.36	C 63.74 H 3.25 N 12.92	63.90 3.20 12.50
IIg		204	81	$C_{25}H_{19}ClN_4O_3$ 458.92	C 65.42 H 4.17 N 12.20	65.80 3.80 12.10
IIh		181	80	$C_{25}H_{20}ClN_5O$ 441.94	C 67.93 H 4.56 N 15.84	68.00 4.10 15.90
IIi		216	72	$C_{23}H_{14}Cl_2N_4O$ 433.36	C 63.74 H 3.25 N 12.92	63.50 3.50 12.50
IIj		179	69	$C_{25}H_{17}ClN_4O$ 424.91	C 70.66 H 4.03 N 13.18	71.00 4.30 13.10
IVa	-NHCOCH$_3$	153	82	$C_{18}H_{13}ClN_4O_2$ 352.80	C 61.27 H 3.71 N 15.87	60.90 4.00 15.50
IVb		196	78	$C_{20}H_{13}ClN_4O_3$ 392.82	C 61.14 H 3.33 N 14.26	61.20 3.50 13.90
IVc		256	80	$C_{24}H_{13}ClN_4O_3$ 440.86	C 65.38 H 2.97 N 12.70	65.00 3.30 12.50
VIa		206	80	$C_{20}H_{18}ClN_5O_2$ 395.87	C 60.68 H 4.57 N 17.69	61.00 4.80 18.00
VIb		163	82	$C_{22}H_{22}ClN_5O_2$ 423.92	C 62.32 H 5.23 N 16.50	62.60 5.40 15.90
VIc		206	80	$C_{20}H_{18}ClN_5O_2$ 395.87	C 60.68 H 4.57 N 17.69	61.00 4.80 18.00
VId		164	75	$C_{22}H_{20}ClN_5O_2$ 421.91	C 62.62 H 4.77 N 16.59	62.40 4.60 16.30
VIIa		146	81	$C_{25}H_{17}ClN_4O_4$ 472.91	C 63.48 H 3.62 N 11.84	63.40 4.00 12.00
VIIb		142	83	$C_{25}H_{17}ClN_4O_5$ 488.91	C 61.41 H 3.50 N 11.45	61.80 3.80 11.30
VIIc		228	93	$C_{25}H_{16}Cl_2N_4O_4$ 507.40	C 59.17 H 3.17 N 11.04	59.50 2.80 11.00

Table 1: continue

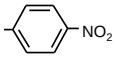
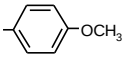
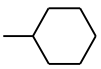
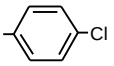
No.	R	M.P. °C	Yield %	M.F. M.Wt.	Microanalysis	
					Calc. %	Found %
VIId		248	94	$C_{25}H_{16}ClN_5O_6$ 517.90	C 57.97 H 3.11 N 13.52	58.20 3.50 13.10
VIIe		170	71	$C_{26}H_{19}ClN_4O_5$ 502.93	C 62.08 H 3.80 N 11.13	62.30 4.20 11.10
VIIf		124	63	$C_{25}H_{16}Cl_2N_4O_4$ 507.40	C 59.17 H 3.17 N 11.04	59.40 3.50 11.10

Table 2: Physical and microanalytical data of compound **IIIa-f**.

No.	R	*X*	*M.P.* ^oC	*Yield %*	M.F. M.Wt.	*Microanalysis*	
						Calc. %	*Found %*
IIIa	$-CH_2CH_2CH_3$	O	144	89	$C_{20}H_{18}ClN_5O_2$ 395.87	C 60.68 H 4.57 N 17.69	60.40 4.80 17.50
IIIb	$-CH_2CH_2CH_2CH_3$	O	220	67	$C_{21}H_{20}ClN_5O_2$ 409.90	C 61.52 H 4.91 N 17.08	61.20 5.00 17.10
IIIc		O	232	90	$C_{23}H_{22}ClN_5O_2$ 435.93	C 63.36 H 5.08 N 16.06	63.70 4.70 15.80
IIId		O	194	83	$C_{23}H_{15}Cl_2N_5O_2$ 464.38	C 59.48 H 3.25 N 15.08	60.00 3.60 15.10
IIIe	$-CH_2CH_3$	S	136	93	$C_{19}H_{16}ClN_5OS$ 397.84	C 57.35 H 4.05 N 17.60	57.60 4.30 17.70
IIIf		S	234	80	$C_{23}H_{16}ClN_5OS$ 445.88	C 61.95 H 3.61 N 15.70	62.30 4.00 15.80

4-(Substituted aminomethy-carbonylamino)-1-(4-chlorophenyl) imidazo[1,5-a]quinaolin-5(4*H*)-ones VIa-c

A mixture of 4-chloromethyl-carbonylamino-1-(4-chlorophenyl)-imidazo[1,5-a]quinazolin-5(4H)-one **IX** (0.01 mol; 3.87g.) and the appropriate amine (0.015 mol) in absolute ethanol(20 ml) was refluxed for 12 hours. The resulting solution was distilled under reduced pressure. The residue was triturated with ice water. The separated solid was filtered, washed with water and crystallized from ethanol (Table 1). UV [$\lambda_{max.}$ (log ε)] of compound **VIc**: 277.2 (4.23), 230.0 (4.60). IR (cm^{-1}) of compound **VIc**: 3211 (NH), 3067 (CH aromatic), 2981-2830 (CH aliphatic), 1720, (C=O), 1692 (NH bending), 780 (C-Cl). ^{1}H NMR ($CDCl_3$) of compound **VIb**: 0.94-1.01 (t, 6H, 2 x $CH_2C\underline{H}_3$), 2.44-2.60 (q, 4H, 2 x $C\underline{H}_2CH_3$), 3.29 (s, 2H, $COC\underline{H}_2$-), 7.3-7.8 (m, 8H, C<u>H</u> aromatic), 8.29 (d, 1H, <u>H</u>C-6). MS m/z (rel. aband.%): of compound **VIc:** 438 (7.35), 368 (8.53), 298 (9.12), 257 (22.35), 197 (14.12), 158 (30.00), 100 (100.00).

1-(4-Chlorophenyl)-4,5-dihydro-5-oxo-imidazo[1,5-a] quinazolin -4-aminocarbonyl methyl benzoates VIIa-f

A mixture of 4-chloromethyl-carbonylamino-1-(4-chlorophenyl)-imidazo[1,5-a]quinazolin-5(4H)-one **V** (0.01mol; 3.87 g) and the appropriate substituted potassium benzoate (0.01 mol) in dimethyl-formamide (5ml) was heated in a boiling water bath for 3 hours. The

resulting solution was cooled, poured on ice water. The solid product was filtered, washed with water, and crystallized from ethanol (Table 1). UV [$\lambda_{max.}$ (log ε)] of compound **VIb**: 3062. (4.07), 240.2 (4.50), 223.6 (4.60). IR (cm^{-1}) of compound **VIb**: 3450 (OH), 3250 (NH), 3050 (CH aromatic), 2950 (CH aliphatic), 1700, (C=O), 1680 (NH bending), 750 (C-Cl). ^{1}H NMR (DMSO-d_6) of compound **VIb:** 5.01 (s, 2H,-COC<u>H</u>$_2$O-, 7.3-8.18 (m, 12H, aromatic), 8.44 (d, 1H, H C-6), 10.34 s, 1H, OH disappeared by D_2O), 11.26 (s, 1H, NH disappeared by D_2O). MS m/z (rel. aband. %) of compound **VIb**: 488.6 (2.20), 404.8 (3.30), 329.2 (77.66), 298.0 (15.75), 256.0 (73.99), 178.0 (100.00), 139.95 (21.61), 76.0 (36.26).

1-(4-Chlorophenyl)-4-[(4-oxo-5,5-diphenylimidazolin-2-yl)oxymethyl-carbonyl amino]imidazo[1,5-a] quinazolin-5(4*H*)-one VIII

A mixture of 4-chloromethyl-carbonylamino-1-(4-chlorophenyl)-imidazo[1,5-a]quinazo-lin-5(4*H*)-one **V** (0.01 mol; 3.87 g) and phenytoin sodium (0.01 mol 2.74 g) in dimethyl formamide (5 ml) was heated in a boiling water bath for 3 hours. The resulting solution was cooled, poured onto ice water. The solid product was filtered, washed with water, and crystallized from ethanol. M.P. 204ºC, Yield 83%. Microanalysis of $C_{33}H_{23}ClN_6O_4$ (603.05) calcd.: C 65.71, H 3.84, N 13.94. Found: C 65.20, H 4.30, N 13.70. UV [$\lambda_{max.}$ (log ε)]: 304.8 (3.65). IR (cm^{-1}): 3300-3200 (NH), 3050 (CH aromatic), 2900-2850 (CH aliphatic), 1780 (C=O), 1620 (NH bending), 750 (C-Cl). ^{1}H NMR (DMSO-d_6): 4.40(s, 2H, -COC<u>H</u>$_2$O-), 7.30-7.94 (m, 18H, C<u>H</u> aromatic), 8.09 (d, 1H, <u>H</u>C-6), 9.77 (s, 1H, NH disappeared by D_2O), 10.77 (s, 1H, N<u>H</u> disappeared by D_2O). MS m/z (rel. aband. %): 603.1 (1.22), 576.9 (1.63), 523.6 (1.32), 446.5 (2.95), 369.2 (2.34), 327.2 (2.85), 257.3 (4.48), 198.0 (2.85), 81.2 (100.00).

1-(4-Chlorophenyl)-4-(phthalimido-methylcarbonylamino)imidazo[1,5-a]quinazolin-5(4H)-one IX

A mixture of 4-chloromethyl-carbonylamino-1-(4-chlorophenyl)-imidazo[1,5-a] quinazolin-5(4*H*)-one **V** (0.01 mol; 3.87 g) and potassium phthalimide (0.01 moI; 1.85 g) in dimethylformamide (5 ml) was heated in a boiling water bath for 3 hours. The resulting solution was cooled, poured onto ice water. The solid product was filtered, washed with water, and crystallized from ethanol. M.P. 266ºC, Yield. Microanalysis of $C_{26}H_{16}ClN_5O_4$ (497.91): Calcd: C 62.71, H 3.23, N 14.06. Found: C 63.10, H 3.50, N 13.70. UV [$\lambda_{max.}$ (log ε)]: 292.6 (3.95), 236.8 (4.65). IR (cm^{-1}): 3242 (NH), 3061 (CH aromatic), 2925-2854 (CH aliphatic), 1726, 1650 (C=O), 1614(NH bending), 750 (C-Cl). ^{1}H NMR (DMSO-d_6): 4.86 (s, 2H, -NHCOC<u>H</u>$_2$-), 7.22-7.94 (m, 12H, aromatic), 8.07 (d, 1H, H C-6). MS m/z (rel. aband. %): 497 (13.95), 466 (15.12), 356 (26.74), 342 (32.56), 263 (25.58), 211 (45.35), 160 (46.51),114 (100.00).

4-(4-Chlorophenyl) imidazo[5,4,3-c] 1,2,3-triazolo [4,3-b] quinazolin-10(10*H*)-one XIII

To a solution of **I** (0.01 mol; 3.1 g) in 1N hydrochloric acid (20 ml) sodium nitrite solution (10%; 10 ml) was added while stirring in ice bath. The mixture was stirred for one hour. The mixture was boiled for 5 minutes, cooled, and extracted with methylene chloride (3x5 ml). The combined organic layer was collected, dried on anhydrous sodium sulphate. The excess solvent was removed under vacuum. The separated solid was crystallized from ethanol. M.P.: 242ºC, Yield 68%. Microanalysis of $C_{16}H_8ClN_5O$ (321.75): Calcd.: C 59.72, H 2.50, N 21.76. Found: C 59.50, H 2.80, N 22.00.UV [$\lambda_{max.}$ (log ε)]: 235.2(4.44). IR (cm^{-1}): 3050(CH aromatic), 1680 (C=O), 760 (C-Cl). ^{1}H NMR (DMSO-d_6): 7.12-7.91 (m, 8H, aromatic). MS m/z (rel. aband.%): 323 (68.65), 321 (42.70), 285 (42.70), 211 (32.43), 162 (71.36), 132 (64.86), 115 (100.00), 62 (98.92).

PHARMACOLOGICAL SCREENING

General behaviour of acute toxicity

Mice of both sexes weighing 20-25 g were used to study the toxicological effect of the chosen compounds. Animals were observed within 24 hours for any mortality. It was found that all compounds are safe up to the highest chosen dose**.**

Anti-inflammatory activity

The anti-inflammatory activity of **I** and the new imidazo[1,5-a]quinazolin-5(4H)-one derivatives **IIc**, **IIIa**, **IIIf**, **IVa**, **V**, **VIc**, **VIIb**, and **XIII** were tested using indomethacin as reference. The tested compounds and indomethacin were prepared as a suspension in 2% Tween 80. The method of carrageenan- induced paw edema of Winter et al[29&30] was used to induce inflammation in this study. The percentage inhibition of inflammation was calculated according to the following equation:

$$\% \text{ Inhibition} = \frac{\left[\text{Wt. of paw edema of control} - \text{wt of paw edema of treated}\right]}{\text{Wt. of paw edema of control}} \times 100$$

Result and discussion

Results are recorded in Table 3 and illustrated by Figures 1 and 2. It is obvious from the dose response curve that there is a direct relationship between the dose and the anti-inflammatory activity. Compound **I** showed in a previous work[11] higher anti-inflammatory than the reference drug flufenamic acid in a dose of 50 mg/kg. Replacement of the amino group by hydroxybenzylidene **IIc**, urea **IIIa**, thiourea **IIIf**, acetamide **IVa**, chloroacetamide **V** or substituted aminomethycarbonylamino **VIc** groups increases the activity than the parent amino derivative **I**. The percentage inhibition of compounds **IIc**, **IIIa**, **IIIf**, **IVa**, **V**, and **VIc** in a dose of 50 mg/kg was 84.84, 54.54, 56.06, 54.54, 74.24, 69.62 respectively. The tetracyclic derivative **XIII** showed a marked decrease in the anti-inflammatory activity than the tricyclic amino derivative **I**.

The most active compound was **IIc** that has 4-hydroxybenzylidene group. Its percentage inhibition was 84.84 in a dose of 50 mg/kg.

The chloroacetyl derivative **V** was much more active than the acetyl derivative **IVa** where their percentage inhibition was 75.24 and 54.54 respectively.

The aminomethycarbonylamino derivative **VIc** was more active than the acetamide derivative **IVa** but less active than the chloroacetyl derivative and its percentage of inhibition was 69.62 in a dose of 200 mg/kg.

Carbamide and thiocarbamide formation **IIIa** and **IIIf** slightly increases the anti-inflammatory activity than the parent amine **I**, where their percentage inhibition was 54.54 and 56.05 respective.

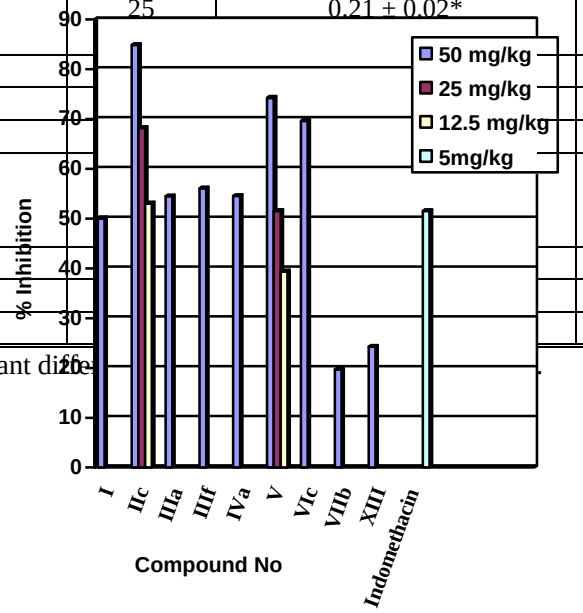
The tetracyclic derivative **XIII** showed a marked decrease in the anti-inflammatory activity than the tricyclic amine derivative **I** and its percentage inhibition was 24.24 in a dose of 200 mg/kg. Moreover, esterification of compound **V** led to inactive derivative.

From the dose-response curves (Fig. 2), it is obvious that there is a direct relationship between the dose and the percentage inhibition.

Table 3: Effect of new imidazo[1,5-a]quinazolin-5(4*H*)-one derivatives, and indomethacin on carrageenan-induced paw edema in rats.

No	Dose mg /kg	Paw edema (g) ±S.E	% inhibition
Control	0	0.66 ± 0.05	0
Indomethacin	5	0.32 ± 0.02*	51.51
I	50	0.33 ± 0.03*	50.00
IIc	50	0.10 ± 0.01*	84.84
	25	0.21 ± 0.02*	68.18
	12.5	0.31 ± 0.03*	53.03
IIIa	50	0.30 ± 0.02*	54.54
IIIf	50	0.29 ± 0.02*	56.06
IVa	50	0.30 ± 0.02*	54.54
V	50	0.17 ± 0.01*	74.24
	25	0.32 ± 0.02*	51.51
	12.5	0.40 ± 0.03*	39.39
VIc	200	0.20 ± 0.02*	69.62
VIIb	200	0.53 ± 0.03*	19.69
XIII	200	0.50 ± 0.03*	24.24

* = Significant diffe



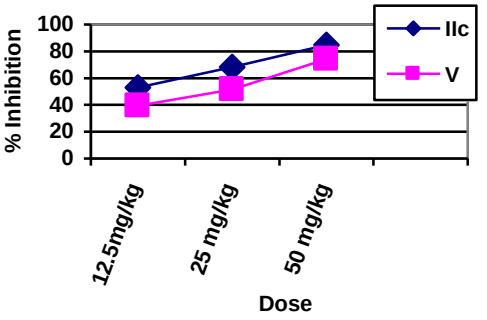


Fig. 2: Dose-response curve for compounds **IIc** and **V**.

Analgesic activity

Compounds showed higher anti-inflammatory activity **IIc**, and **V** were chosen to study their analgetic activity.

Adult male albino mice weighing 20 - 25 g were used in this study. The new tested compounds and the reference drug indomethacin were prepared as a suspension in 2% Tween 80. The method of Okun et al[31] was used to induce writhing in this study.

$$\% \text{ Protection} = \frac{\text{Number of protected animals} \times 100}{\text{Total number of animals}}$$

Results and discussion

Results are recorded in Table 4 and illustrated by Figure 3. Compounds **IIc** and V in a dose of 25 mg/kg showed higher analgesic activity than the reference drug indomethacin in a dose of 5mg/kg. The percentage protection of **IIc**, Vand indomethacin was 83.33, 100.00, and 66.66 respectively. Moreover, compound **VI** was proved to be equipotent to the reference drug in a dose of 12.5 mg/kg.

Table 4: Analgesic activity of new imidazo[1,5-a] quinazolin-5(4*H*)-one derivatives and indomethacin using p-benzoquinone induced writhing in mice.

No	Dose mg /kg	No. of animals	No of protected animals	% protection
Control	0	6	0	0
Indomethacin	5	6	4	66.66
IIc	25 12.5	6 6	5 3	83.33 50.00
V	25 12.5	6 6	6 4	100.00 66.66

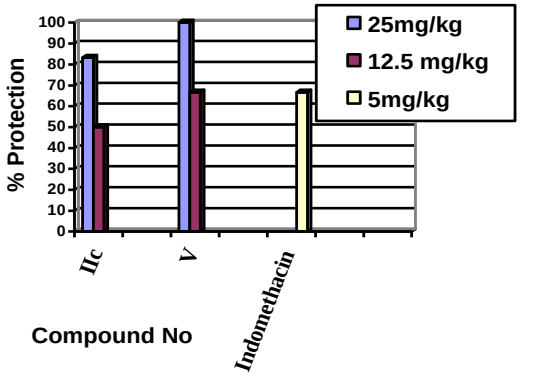


Fig. 3: Analgesic activity of imidazo[1,5-a] quinazolin-5(4*H*)-one derivatives and indomethacin using p-benzoquinone induced writhing method.

Antipyretic activity

Compounds which were tested for their analgesic activity **IIc**, and Vwere also chosen to study their antipyretic activity. Male albino mice weighing 20-25 g were chosen for this study according to Loux *et al* method[32]. Rectal body temperature of the animals was measured after one and two hours from drug administration.

Results and discussion

Results are recorded in Table 5 and illustrated by Figure 4. Compound **V** was more active as antipyretic than compound IIc in a dose of 50 mg/kg after two hours of drug administration (the difference in body temperature was 1.54 and 1.36^{o}C respectively).

Table 5: Effect of imidazo[1,5-a]quinazolin-5(4*H*)-one derivatives and indomethacin on yeast induced hyperthermia in mice.

No	Dose mg /kg	Average rectal body temperature ^{o}C ± S.E.		
		Pre-administration	One hour post administration	Two hours post administration
Control	0	38.28 ± 0.21	38.25± 0.17	38.36 ± 0.17

Indomethacin	5	38.26 ± 0.18	36.72* ± 0.22	36.58* ± 0.20
IIc	25	38.13 ± 0.25	37.76 ± 0.29	37.58 ± 0.55
	50	38.10 ± 0.16	36.46* ± 0.49	36.74* ± 0.40
V	25	37.94 ± 0.07	37.92 ± 0.24	37.18* ± 0.25
	50	38.02 ± 0.21	36.54* ± 0.17	36.60* ± 0.18

* = Significant difference from the control value at $p < 0.05$

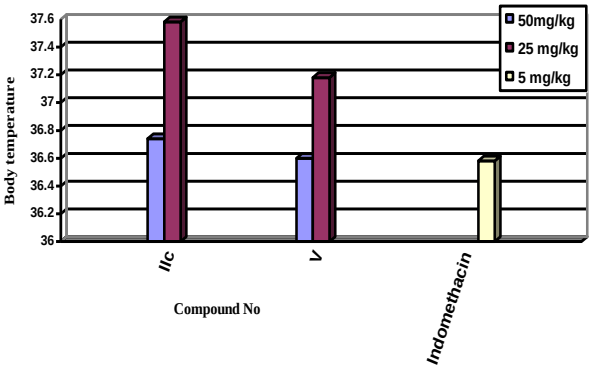


Fig. 4: Antipyretic activity of imidazo[1,5-a] quinazolin-5(4*H*)-one derivatives and indomethacin.

Ulcerogenic effect

Compounds **IIc** and **V** were subjected to further study for their ulcerogenic effect. Adult male albino rats weighing 120 –150 g were used in this study. Animals were fasted eighteen hours before the drug administration[33]. The ulcer index was calculated according to the method of Robert et al[34]. The degree of ulcerogenic effect was expressed in term of:

I- Percentage incidence of ulcers in each group of animals divided by 10

II- The average number of ulcers per stomach.

III- The average severity of ulcers by visual observation.

The ulcer index is the value that result from the sum of the above three values.

Results and discussion

Results are recorded in Table 6 and illustrated by Figure 5. Result revealed that indomethacin in a dose of 5 mg/kg showed an ulcer index of 17.60. Both compounds **IIc** and **V** in a dose of 50 mg/kg showed slight decrease in their ulcer indices than the indomethacin. Their ulcer indices were 17.14 and 16.25 respectively.

Table 6: Ulcerogenic effect of the new anthranilate analogs, imidazo[1,5-a] quinazolin-5(4*H*)-one derivatives, flufenamic acid, and indomethacin.

No	Dose mg/kg	Rats No	% Incidence divided by 10	Average No of ulcer	Average severity	Ulcer index
Control	0	5	0	0	0	0
Indomethacin	5	5	10	6.0	1.60	17.60
IIc	50	5	10	5.6	1.54	17.14
V	50	5	10	4.8	1.45	16.25

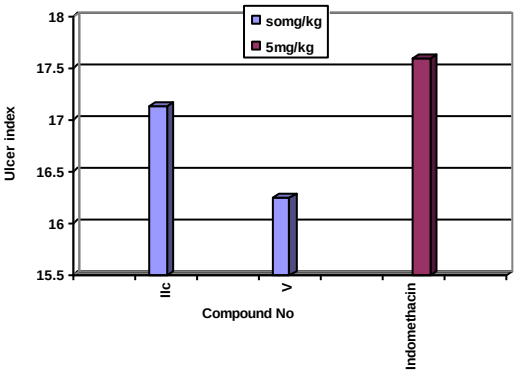


Fig. 5: Ulcerogenic effect imidazo[1,5-a] quinazolin-5(4*H*)-one derivatives and indomethacin.

Anticonvulsant activity

Compounds **I**, **IIIc**, **VIc** and **VIII** which contain ureido or hydantoin function were chosen for this study using diazepam as a reference drug. Mice of both sexes weighing 20-25 g were used for this study. Animals were stimulated through ear electrode of 50 mA as a single stimulator for 0.2 sec.[35&36]. The anticonvulsant activity was expressed as the percentage protection according to the following equation:

$$\% \text{ Protection} = \frac{\text{Number of protected animals} \times 100}{\text{Total number of animals}}$$

Results and discussion

Results were recorded in Table 7, and illustrated by Figure 6. All the chosen compounds **I**, **IIIc**, **VIc**, and **VIII** exhibited anticonvulsant activity and their PD_{50} were 50, 25, 25, and 50 mg/kg respectively. Replacement of the amino group of I by ureido **IIIc** or aminomethycarbonylamino **VIc** led to increase in the anticonvulsant activity. The phenytoin derivative VIII did not change the efficacy of the parent amine **I**.

Table 7: Anticonvulsant activity of imidazo[1,5-a]quinazolin-5(4*H*)-one derivatives and diazepam.

No	Dose mg /kg	No of animals did not convulse	% Protection
Control	0	0 / 6	0
Diazepam	5	3 / 6	50.00
I	25	2 / 6	33.33
	50	3 / 6	50.00
IIc	25	3 / 6	50.00
	50	5 / 6	83.33
Vic	25	3 / 6	50.00
	50	5 / 6	83.33
VIII	25	2 / 6	33.33
	50	3 / 6	50.00

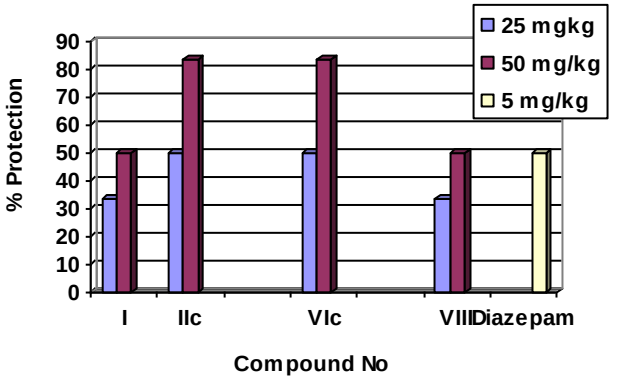


Fig. 6: Anticonvulsant activity of imidazo[1,5-a]quinazolin-5(4H)-one derivatives and diazepam.

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