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Synthesis and Anti-inflammatory Activity of New 2,3-Dihydro-4(1H)-quinazolinone Derivatives

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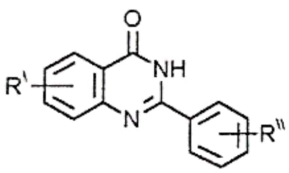
ABSTRACT

A new series of 2,3-dihydro-4(1H)-quinazolinones was synthesized by condensation of 2-methylamino-N-substituted benzamides (III) with either formaldehyde or aromatic aldehydes to produce 2,3-dihydro-1-methyl-3-(substituted phenyl)-4(1H)-quinazolinones (V) and 2,3-dihydro-2,3-di(substituted phenyl)-1-methyl-4(1H)-quinazolinones (VI) respectively.

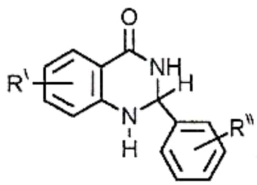
The anti-inflammatory study of some of the prepared compounds revealed that compound (VIa) showed significant activity in comparison with flufenamic acid.

INTRODUCTION

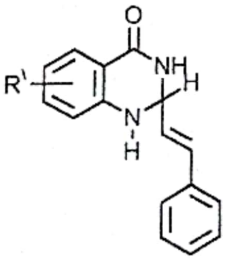
Phenylquinazolinones (PQZ), 2,3-dihydro-4(1H)-quinazolinones (DHPQZ) and 2-styrylquinazolin-4-ones (SQZ) are reported to be active as antitumer agents[1,2], where they are effective inhibitors of tubulin polymerization[3,4,5]. Also 4(1H)-quinazolinone derivatives are reported as anti-inflammatory agents[6], where 2-cyclopropyl-1-phenyl-4(1H)-quinazolinone (CPQZ) and 1-isopropyl-2-(2-fluorophenyl)-4(1H)-quinazolinone (IFPQZ) shown to be the most effective as anti-inflammatory agents. On the othe hand, 1-isopropyl-4-phenyl-7-methyl-2(1H)-quinazolinone (proquazone)[7] is advocated for clinical use as a non-steroidal anti-inflammatory agent (NSAID) in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, musculoskeletal disorders, and in acute inflammatory conditions such as dysmenorrhoea, postoperative pain and headache.



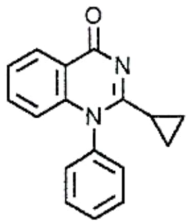
(PQZ)



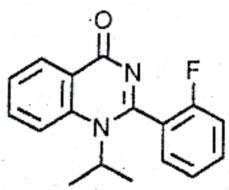
(DHPQZ)



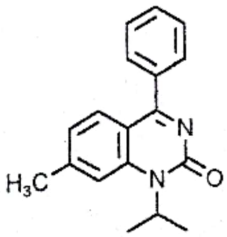
(SQZ)



(CPQZ)



(IFPQZ)



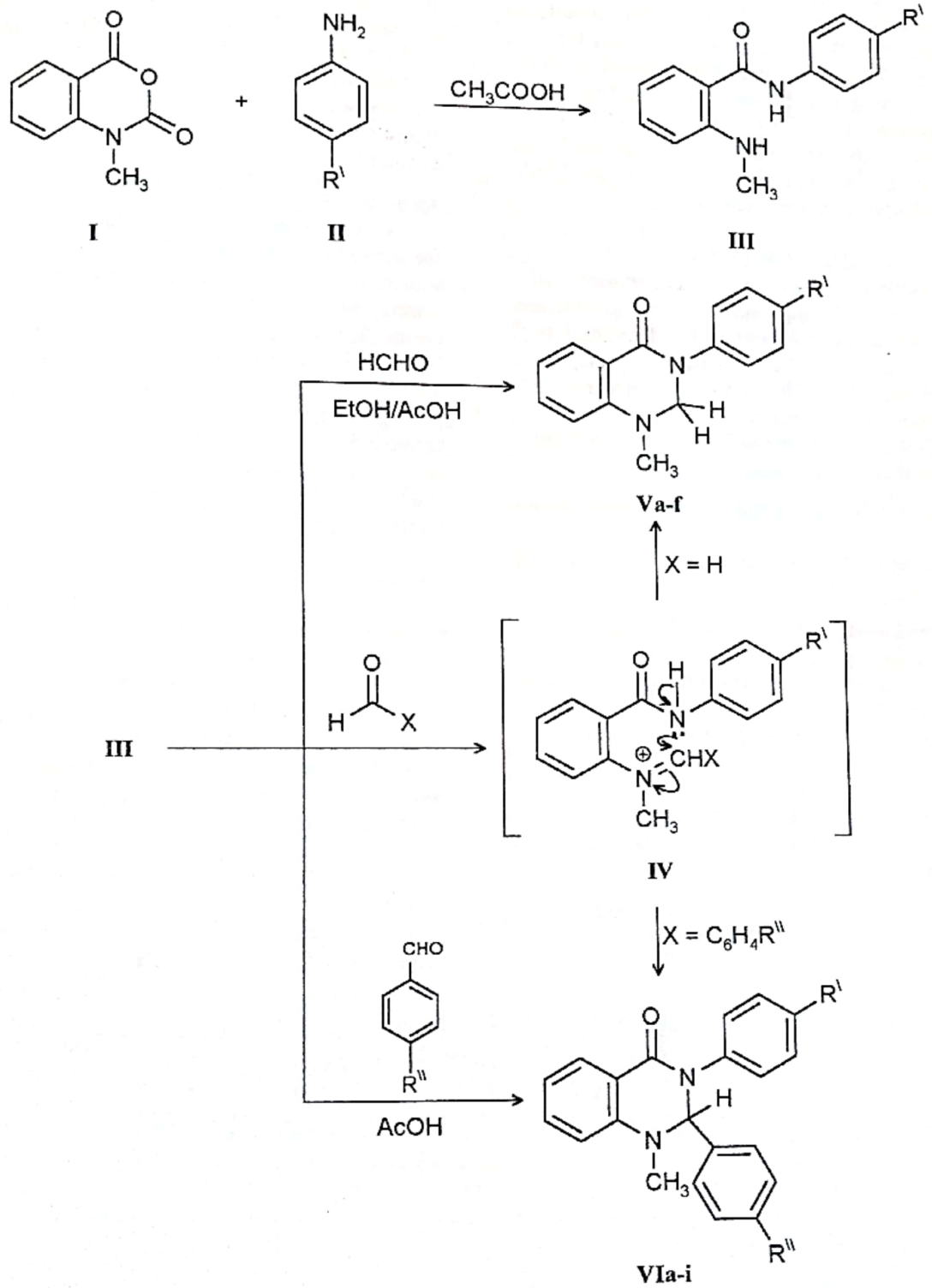
(Proquazone)

In the present work 2,3-dihydro-1-methyl-3-(substituted phenyl)-4(1H)-quinazoloinones **(Va-f)** and 2,3-dihydro-2,3-di(substituted phenyl)-1-methyl-4(1H)-quinazolinones **(VIa-i)** were synthesised to be evaluated as anti-inflammatory agents.

CHEMISTRY

Starting 2-methylamino-N-substitutedphenylbenzamides **(III)** were prepared using standard procedure[7] from N-methylisatoic anhydride **(I)** by reaction with different aromatic amines **(II)** as shown in the general reaction sequence in scheme 1. The starting benzamides **(III)** were subjected to two pathways, the first, the reaction of benzamides **(III)** with formaldehyde in ethanol acidified with few drops of glacial acetic acid to produce 2,3-dihydro-1-methyl-3-substituted phenyl-4(1H)-quinazolinones **(Va-f)** in good yields. And the second pathway is the reaction of benzamides **(III)** with different aromatic aldehydes in glacial acetic acid to afford 2,3-dihydro-2,3-di(substituted phenyl)-1-methyl-4(1H)-quinazolinones **(VIa-i)** as shown in Scheme 1.

This reaction is suggested to proceed via internal Mannich reaction through the postulated intermediate **(IV)** illustrated in Scheme 1, where the rate of the reaction is affected by the electronic effect of the substituent in 2-methylamino-N-substituted phenylbenzamides **(III)**. So, the electron donating groups **(Vc & Vd)** in the p-substituted phenylbenzamides **(III)** make the reaction with formaldehyde proceeds faster than that containing electron withdrawing ones **(Va, Vb & Vf)**. Moreover, the reaction of benzamides **(III)** and aromatic aldehydes is relatively dependent on the electronic effect of substituents in both the benzamide **(III)** and the aromatic aldehyde used. When R` is either electron donating or electron withdrawing groups, the reaction proceeds faster with the electron withdrawing R`` rather than the electron donating R``. TLC check analysis was used to determine the reaction time in each case (Table 1 & 2).



Scheme 1

The structural elucidation of the final targets (**V**, **VI**) was confirmed by the disappearance of the two NH- absorption bands, in the IR spectrum, which are present in that of the corresponding starting benzamide at (3392 cm^{-1} for CONH and 3285 cm^{-1} for NHMe), and the shifting of the carbonyl absorption band from 1640 cm^{-1} of the open benzamide to 1654 cm^{-1} of the cyclic quinazolinone (**Va**). It is noted also in the 2,3-dihydro-2,3-di(substituted phenyl)-1-methyl-4(1H)-quinoazolinone series (**VI**), where the shifting of the carbonyl absorption band occur from 1630 cm^{-1} (of the open benzamide) to 1660 cm^{-1} of the cyclic target (**VIf**) with the disapperance of NH-absorption bands of the starting banzamide at (3415 cm^{-1} for CONH and 3253 cm^{-1} for NHMe). Another evidence for the formation of the final targets (**V**, **VI**) is the lacking of NH- signals in ^{1}H-NMR spectra of compounds (**Vb**, **Vf**, **VIa**, **VIe**). In addition, the

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^{1}H-NMR of (Vb) and (Vf) showed a singlet signal integrating two protons of the methylene protons at 4.982 δ ppm for (Vb) and at 4.659 δ ppm for (Vf) while ^{1}H-NMR of (VIa) and (VIe) showed a singlet signal integrating one proton corrosponding to the benzylic proton at 6.4347 δ ppm and 6.1772 δ ppm respectively. All spectral data confirmed our assignment of compounds (V) and (VI) as 2,3-dihydro-4(1H)-quinazolinones derivatives.

EXPERIMENTAL

All melting points were determined with GALLENKAMP-UK apparatus and are uncorrected. Microanalysis was carried out in the microanalytical center, Cairo University. IR spectra (KBr disc) were determined on BRUKER vector 22 Germany. ^{1}H-NMR spectra were carried out using VARIAN GEMINI 200-200 MHz using DMSO-d_6 as a solvent and TMS as an internal standard.

2-Methylamino-N-substituted phenylbenzamides (III) :

Were synthesized according to the reported methods[8]:

2,3-Dihydro-1-methyl-3-(substituted phenyl)-4(1H)-quinazolinones (Va-f):

To a solution of the 2-methylamino-N-substituted phenylbenzamide (III) (10 mmol) in absolute ethanol (50 ml), add formaldehyde 40% (1 ml) and few drops of glacial acetic acid. The reaction mixture was heated under reflux with stirring for 3-8 hrs, then concentrated to half volume and the crystallized solid was filtered after cooling and recrystallized from ethanol (Table 1).

2,3-Dihydro-2,3-di(substituted phenyl)-1-methyl-4(1H)-quinazol-inones (VIa-i):

A solution of the appropriate aromatic aldehyde (10 mmol) in glacial acetic acid (5 ml) was added to the appropriate 2-methylamino-N-substitutedphenyl-benzamide III (10 mmol) dissolved in glacial acetic acid (50 ml). The reaction mixture was refluxed with stirring for 3-12 hrs. After cooling the reaction mixture was poured into cold water (100 ml) and the separated solid was filtered and recrystallized from ethanol (Table 2).

Anti-inflamatory evaluation:

The compounds **IVa, IVd, Va and Vf** were tested for anti-inflammatory activity using flufenamic acid as standard. Mature male albino rats weighing 180 - 200 g were used and classified into six groups each of six : Group 1, rats were left as a control group. Groups from 2 to 6, rats were injected compounds **Va, Vd, VIa, VIf** and flufenamic acid I.p at a dose of 4.5 mg/Kg b.wt. respectively. The human doses were converted to rate doses according to the surface area according to Paget and Barnes[9]. One hour later oedema in the rat right hind paw was induced by injection of 0.1 ml of 10% carragenin according to the method of Winter et al[10], the thickness of the paw was measured using skin caliber at 1, 2, 3, 4 h., after carragenin injection to determine the antiinflammatory effect of the tested compounds.

RESULTS

The intradermal injection of carragenin 10% at a dose of 0.1 ml in the rat paw of the hind limb significantly increased its thickness after 1, 2, 3, 4 h, post injection. Likewise, the I.p injection of the test compounds by the dose of 4.5 mg/kg b.wt., significantly decreased the thickness of rat paw after two h., till the end of the experiment (table 3). The rank order of potency as anti-inflammatory was as follow: compound **VIa** > standard > compound **VIf** > compound **Vd** > compound **Va** .

Table 1 : Physiochemical parameters of compounds **Va-f**:

Comp. No.	R^1	R.T (hrs)	m.p. (°C)	Yield (%)	Mol. Form. (M.W.)	Analysis (% Calcd/Found)		
						C	H	N
Va	p-COOH	8	232-5	80	$C_{16}H_{14}N_2O_3$ (282)	68.08 68.13	4.96 5.00	9.92 10.05
Vb	p-$COOC_2H_5$	8	180-2	80	$C_{18}H_{18}N_2O_3$ (310)	69.67 –	5.80 5.50	9.03 9.16
Vc	p-OH	4	212-14	75	$C_{15}H_{14}N_2O_2$ (254)	70.86 71.04	5.51 5.65	11.02 11.05
Vd	p-CH_3	3	95-7	82	$C_{16}H_{16}N_2O$ (252)	76.19 76.54	6.34 6.50	11.11 10.82
Ve	p-$COCH_3$	5	150-2	75	$C_{17}H_{16}N_2O_2$ (280)	72.85 72.86	5.71 5.83	10.00 –
Vf	p-Cl	6	145-7	85	$C_{15}H_{13}ClN_2O$ (272.5)	66.05 66.12	4.77 4.96	10.27 10.12

IR (cm^{-1}) for compound (**Va**): 3073 – 2545 (broad O-H stretch), 1692 (C=O of COOH) and 1654 (C=O of CON).
IR (cm^{-1}) for compound (**Vb**): 1705 (C=O of COOEt) and 1655 (C=O of CON).
^{1}H-NMR (DMSO-d_6-δ ppm) of compound (**Vb**): 1.3099 - 1.3862 (t, 3H, CH_2-$\underline{CH_3}$), 2.9646 (s, 3H, N-CH_3), 4.3214 - 4.3626 (Q, 2H, $\underline{CH_2}$-CH_3), 4.9822 (s, 2H, N-$\underline{CH_2}$-N) and 6.9131 - 8.0330 (m, 8H, aromatic protons).
^{1}H-NMR ($CDCl_3$- δ ppm) of compound (**Vf**): 2.835 (s, 3H, N-CH_3), 4.659 (s, 2H, N-$\underline{CH_2}$-N) and 6.6520-7.8793 (m, 8H, aromatic protons).

Table 2: Physiochemical parameters of compounds **VIa-i** .

Comp. No.	R`	R``	R.T (hrs)	m.p. (°C)	Yield (%)	Mol. Form. (M.W.)	Analysis (% Calcd/Found)		
							C	H	N
VIa	p-CH_3	p-NO_2	4	182-4	90	$C_{22}H_{19}N_3O_3$ (373)	70.77 70.35	5.09 4.77	11.26 11.30
VIb	p-Cl	p-OH	8	221-3	75	$C_{21}H_{17}ClN_2O_2$ (364.5)	69.13 69.10	4.66 5.33	7.68 7.51
VIc	p-$COOC_2H_5$	p-NO_2	12	245-7	80	$C_{24}H_{21}N_3O_5$ (431)	66.82 66.43	4.87 4.70	9.74 9.65
VId	p-OH	p-NO_2	3	260-2	70	$C_{21}H_{17}N_3O_4$ (375)	67.20 66.99	4.53 4.22	11.20 --
VIe	p-OMe	p-Cl	4	185-7	80	$C_{22}H_{19}ClN_2O_2$ (378.5)	69.74 69.10	5.01 4.89	7.39 7.27
VIf	H	p-Cl	6	143-5	80	$C_{21}H_{17}ClN_2O$ (348.5)	72.30 72.11	4.87 4.81	8.03 7.97
VIg	p-OH	p-Cl	4	253-5	75	$C_{21}H_{17}ClN_2O_2$ (364.5)	69.13 69.11	4.66 --	7.68 7.69
VIh	H	p-NO_2	5	165-7	75	$C_{21}H_{17}N_3O_3$ (359)	70.19 70.26	4.73 5.10	11.69 11.25
VIi	H	p-OH	8	213-15	75	$C_{21}H_{18}N_2O_2$ (330)	76.36 76.33	5.45 5.32	8.48 8.85

IR (cm^{-1}) for compound (**VIa**) : 1646 (C=O of CON), 1517 (asymmetric NO_2 stretch) and 1345 (symmetric NO_2- stretch).

IR (cm^{-1}) for compound (**VId**): 3237 (broad O-H stretch), 1643 (C=O of CON). 1517 (asymmetric NO_2- stretch) and 1344 (symmetric NO_2- stretch).

IR (cm^{-1}) for compound (**VIf**) : 1660 (C=O of CON).

^{1}H-NMR (DMSO-d_6-δ ppm) of compound (**VIa**): 2.2931 (s, 3H, N-C_6H_4-$\underline{CH_3}$), 3.0180 (s, 3H, N-$\underline{CH_3}$), 6.4347 (s, 1H, Benzylic proton) and 6.6976 - 8.2070 (m, 12H, aromatic protons).

^{1}H-NMR (DMSO-d_6-δ ppm) of compound (**VIe**): 2.9200 (s, 3H, N-CH_3), 3.7475 (s, 3H, o-CH_3), 6.1772 (s, 1H, benzylic proton), and 6.6567 - 7.8609 (m, 12H, aromatic protons).

Table 3: The anti-inflammatory activity of the tested compounds:

Group	Initial volume	Thickness of paw skin in mm after			
		1 hour	2 hour	3 hour	4 hour
Control	0.35 ± 0.063	0.59 ±0.012	0.95 ±0.075	1.22 ±0.075	1.45 ± 0.088
Va	0.36 ± 0.03	0.5* ±0.013	0.71** ±0.06	0.82** ±0.07	0.95** ±0.045
Vd	0.38 ±0.016	0.49* ±0.012	0.58** ±0.03	0.72** ±0.03	0.81** ±0.06
VIa	0.37 ± 0.033	0.39* ±0.028	0.45** ±0.025	0.55** ±0.057	0.58** ±0.041
VIf	0.36 ±0.029	0.45* ±0.015	0.54** ±0.019	0.69** ±0.025	0.75** ±0.03
(Flufenamic acid)	0.38 ±0.027	0.4* ±0.03	0.46** ±0.038	0.60** ±0.07	0.68** ±0.05

Mean ± S.E.; * $P < 0.01$, ** $P < 0.001$

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تشييد والفاعلية ضد الإلتهابات لمشتقات ٣،٢-ثنائى الهيدروجين -٤(١يد)-كينازولينون الجديدة

سامى مجاهد صقر

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

تم فى هذا البحث تحضير سلسلة جديدة منن مشتقات ٣،٢-ثنائى الهيدروجين -٤(١يد)-كينازولينون بتفاعل ٢-أمينوميثيل – ن- مشتق البنزاميد (**III**) سواء مع الفورمالدهيد أو الألدهيدات الأروماتية وتم الحصول على مركبات ٣،٢-ثنائى الهيدروجين -١-ميثيل-٣-(مشتق الفينيل)-٤(١يد)-كينازولينون (**V**) و٣،٢-ثنائى الهيدروجين -٣،٢-ثنائى (مشتق الفينيل)-١-ميثيل-٤(١يد)-كينازولينون (**VI**) على الترتيب.

وتمت دراسة التأثير المضاد للإلتهابات لبعض المركبات المشيدة وعكست النتائج فاعلية المركب (**VIa**) الكبيرة بالقياس لحمض الفلوفيناميك.