

NEW POTENTIAL ANTI-INFLAMMATORY QUINAZOLINE-2,4(1H,3H)-DIONE DERIVATIVES

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ABSTRACT

A series of nucleophilic and condensation reactions were carried out to synthesize 1,3,4-triazolylmethoxyphenyl and 1,3,4-oxadiazolylmethoxyphenyl derivatives of quinazoline-2,4(1H,3H)-dione as potential antiinflammatory agents. Some of the new compounds showed promising results.

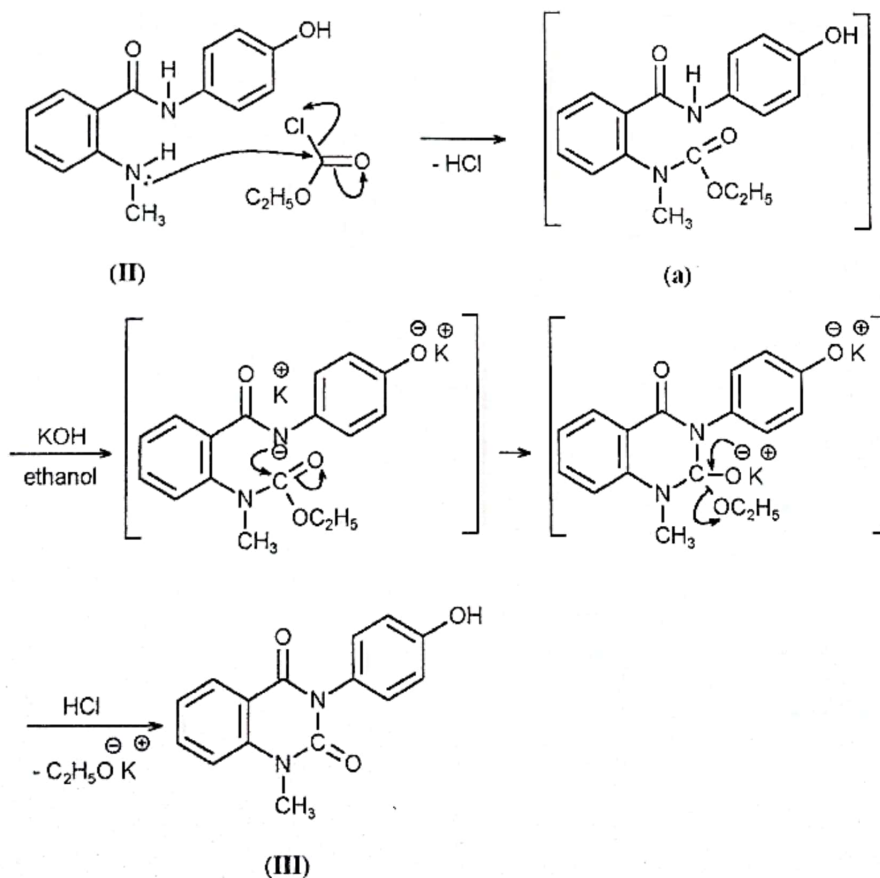
INTRODUCTION

3-Substituted quinazoline-2,4(1H,3H)-diones have been shown to possess diverse biological activities, as analgesic, antiinflammatory⁽¹⁾, hypnotic, anticonvulsant⁽²⁾, antimicrobial⁽³⁾ and antihypertensive⁽⁴⁾ as well as allergy inhibitors⁽⁵⁾. On the other hand, 1,3,4-triazoles and 1,3,4-oxadiazoles have been proved to be of pronounced interest^(6,7), since many of these derivatives were reported to act as antiinflammatory and analgesic antirheumatic agents^(8,9).

Derivatization of quinazoline-2,4(1H,3H)-dione analogs with 1,3,4-triazole or 1,3,4-oxadiazole moieties was the main aim of this investigation in

order to investigate their possible analgesic and antiinflammatory activity.

The synthetic approaches are outlined in Schemes 1 and 2. Refluxing of N-methylisatoic anhydride (I) with p-aminophenol in acetic acid afforded 2-methylamino-N-p-hydroxyphenylbenzamide (II) which was condensed with ethyl chloroformate followed by ring closure in ethanolic potassium hydroxide to give compound (III) which is the key intermediate in this synthetic strategy. Formation of 3-p-hydroxyphenyl-1-methylquinazoline-2,4(1H,3H)-dione (III) might be achieved according to the following suggested mechanistic pathway:

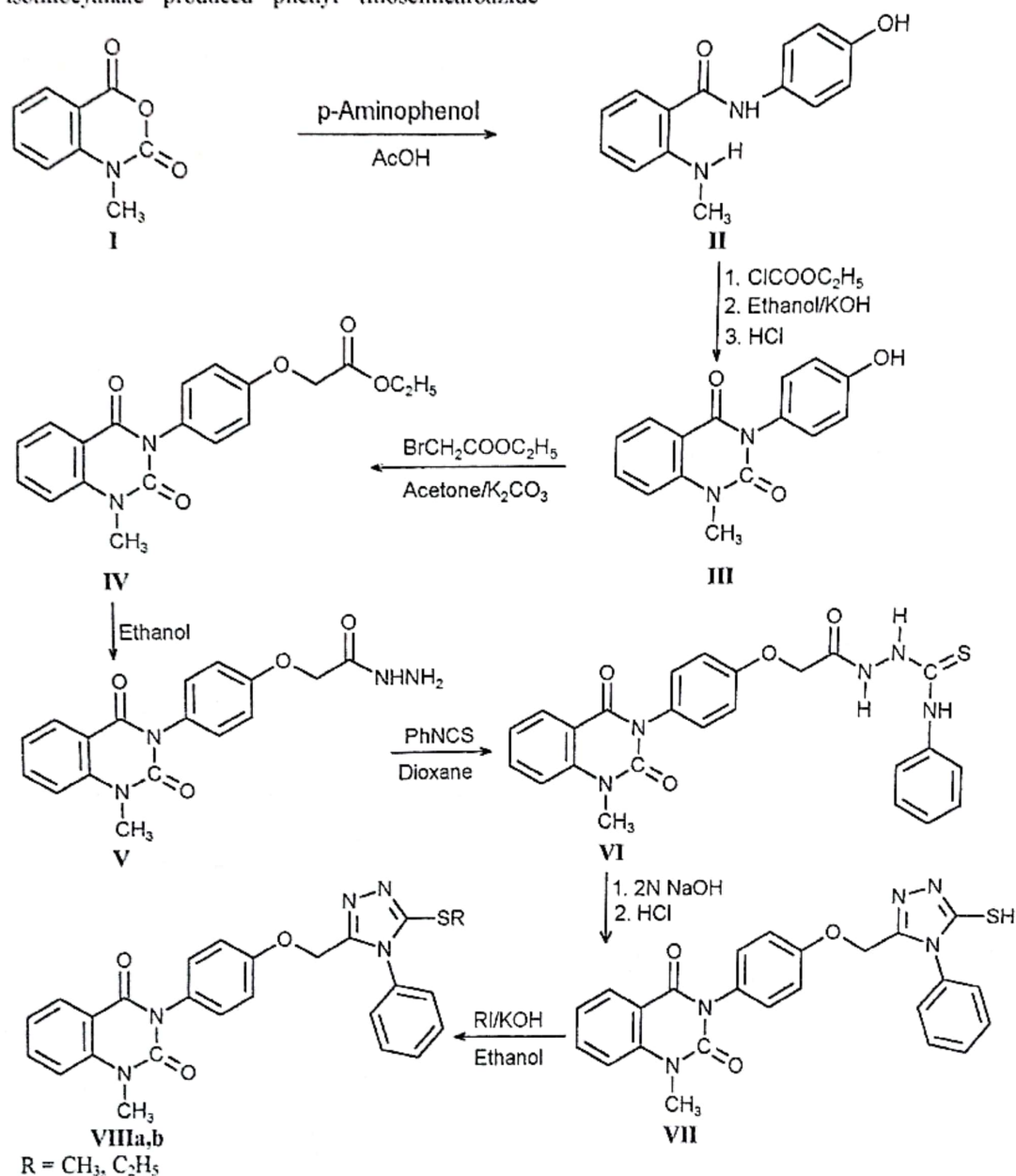


The reaction of 2-methylamino-N-p-hydroxyphenylbenzamide (II) with ethylchloroformate would proceed via nucleophilic attack of the secondary amino nitrogen rather than the phenolic hydroxyl group which should need a strong basic catalysis. The intermediate (a) could undergo cyclization at alkaline pH, which would potentiate the nucleophilicity of the amide nitrogen to afford compound (III). The latter was refluxed with ethyl bromoacetate in dry acetone in the presence of potassium carbonate to afford compound (IV) which in turn was refluxed in ethanolic hydrazine hydrate to produce the hydrazide derivative (V) which was the prime precursor for compounds (VI, IX, XI).

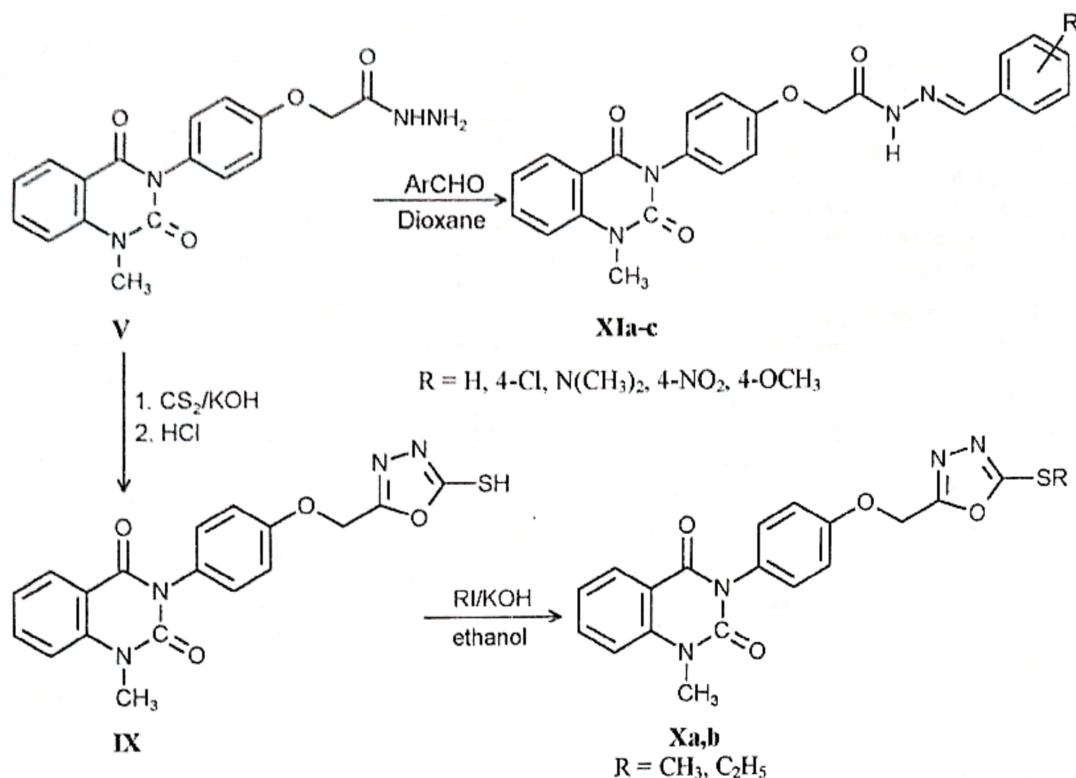
Condensation of compound (V) with phenyl isothiocyanate produced phenyl thiosemicarbazide

(VI) which cyclized in 2 N sodium hydroxide for 2 h. to produce 1,3,4-triazolethiole derivative (VII) followed by S-alkylation using alkyl halide in alcoholic potassium hydroxide to afford the target compounds (VIIIa,b). While refluxing of compound (V) in ethanol containing carbon disulphide and potassium hydroxide for 12 h. afforded 1,3,4-oxadiazolethiole (IX) which was confirmed by the formation of its alkyl derivatives (Xa,b). Otherwise reaction of compound (V) with aromatic aldehydes produced arylidene hydrazino derivatives (XIa-e).

The structures of the new compounds were confirmed by elemental analyses and the main absorption bands in IR-spectra as well as the signals in the $^1\text{H-NMR}$.



Scheme 1



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 were determined as KBr discs on BRUKER vector 22 Germany. ¹H-NMR spectra were carried out using VARIAN GEMINI 200-200 MHz using DMSO-d₆ as a solvent and TMS as an internal standard.

2-Methylamino-N-p-hydroxyphenylbenzamide (II):

A mixture of N-methylisatoic anhydride I (1.77 g, 0.01 mol) and p-minophenol (1.09 g, 0.01 mol) was refluxed in glacial acetic acid (50 ml) for 2 h. The cold reaction mixture was poured with stirring into cold water (150 ml) and the separated solid was filtered and crystallized from aqueous ethanol (Table I). IR (cm⁻¹) 3400 (OH), 3306 (NH), and 1632 (C=O).

3-(p-Hydroxyphenyl)-1-methyl-quinazoline-2,4(1H,3H)-dione (III):

A mixture of II (2.42 g, 0.01 mol) and ethyl chloroformate (10 ml) was heated in an oil bath at 85-110°C for 2 h, and then dissolved in absolute ethanol. The reaction mixture was concentrated, 50 ml of ethanol and 2 g of KOH were added, and the mixture was refluxed with stirring for 3 h, and again concentrated. The cold reaction mixture was poured into cold water (100 ml) and filtered, the clear filtrate was acidified with dil HCl and the separated solid was filtered, dried and crystallized from aqueous dioxane (Table I). IR (cm⁻¹) 3312 (OH), 1701 and 1646 (4

C=O, 2 C=O). ¹H-NMR (DMSO-d₆, δ ppm) of compound (III) 3.5 (s, 3H, CH₃), 6.81-8.09 (m, 8 H, aromatic protons) and 9.64 (s, 1H, -OH, exchangeable by adding D₂O).

3-(p-Ethoxycarbonylmethoxyphenyl)-1-methyl-quinazoline-2,4(1H,3H)-dione (IV)

A mixture of III (2.68 g, 0.01 mol) and ethyl bromoacetate (1.67 g, 0.01 mol) was heated for 12 h in dry acetone (50 ml) in the presence of anhydrous K₂CO₃ (2.76 g, 0.02 mol). The reaction mixture was concentrated, poured into cold water (150 ml) and the separated solid was filtered, dried and crystallized from ethanol (Table I). IR (cm⁻¹): 1740, 1710 and 1650 (ester C=O), 4 C=O and 2 C=O).

3-(p-Hydrazinocarbonylmethoxyphenyl)-1-methyl-quinazoline-2,4(1H,3H)-dione (V):

A mixture of IV (3.54 g, 0.01 mol) and hydrazine hydrate (2 g, 0.04 mol) was refluxed in absolute ethanol (100 ml) for 5 h. The reaction mixture was concentrated, cooled and the separated crystalline solid was filtered, dried and recrystallized from dioxane (Table I). IR (cm⁻¹) showed a stretching band at the range of 3533-3307 for (NH-NH₂), 1715, 1706, 1672 (three carbonyls).

1-Methyl-3-[p-(4-phenylthiosemicarbazinocarbonylmethoxy)-phenyl]-quinazoline-2,4(1H,3H)-dione (VI):

A mixture of V (1.7 g, 0.005 mol) and phenyl isothiocyanate (0.68 g, 0.005 mol) was refluxed in dioxane (50 ml) for 3 h. The reaction mixture was concentrated, cooled and treated with cold water (100 ml) while stirring. The separated solid was filtered, dried and crystallized from aqueous dioxane (Table I).

1-Methyl-3-[p-(1-phenyl-5-mercapto-1H-1,3,4-triazol-2-yl)-methoxyphenyl]-quinazoline-2,4(1H,3H)-dione (VII):

A solution of VI (1.5 g, 0.003 mol) in 2 N NaOH (50 ml) was heated to reflux for 2 h. The reaction mixture was filtered while hot, the filtrate was acidified with HCl and the separated solid was filtered, dried and crystallized from aqueous dioxane (Table I).

3-[p-(5-Alkylthio-1-phenyl-1H-1,3,4-triazol-2-yl)-methoxyphen-yl]-1-methyl-quinazoline-2,4(1H,3H)-dione (VIIIa,b):

A solution of VII (1 g, 0.0022 mol) in absolute ethanol (25 ml) containing KOH (0.12 g, 0.0022 mol) was added dropwise to the appropriate alkyl iodide (0.0022 mol) in ethanol (25 ml). The reaction mixture was refluxed for 1 h, then cooled and treated with cold water (50 ml). The obtained solid was filtered, dried and crystallized from ethanol (Table I). ¹H-NMR (DMSO-d₆, δ ppm) of compound (VIIIa) 2.8 (s, 3 H, S-CH₃), 3.36 (s, 3 H, N-CH₃), 5.08 (s, 2 H, O-CH₂) and 6.63-7.67 (m, 13 H, aromatic protons).

3-[p-(5-Mercapto-1,3,4-oxadiazol-2-yl)methoxyphenyl]-1-methylquinazoline-2,4(1H,3H)-dione (IX):

A mixture of V (1.7 g, 0.005 mol) and CS₂ (20 ml) in 95% ethanol (75 ml) containing KOH (0.39 g, 0.007 mol) was refluxed for 12 h. The reaction mixture was concentrated to 25 ml and diluted with 100 ml cold water, filtered. The filtrate was acidified with dil. HCl and the precipitated solid was filtered, dried and crystallized from ethanol (Table I). IR (cm⁻¹) 2610 (weak -S-H stretching), 1709, 1649 (two carbonyl groups).

3-[p-(5-Alkylthio-1,3,4-oxadiazol-2-yl)methoxyphenyl]-1-methyl quinazoline-2,4(1H,3H)-dione (Xa,b):

A solution of IX (1 g, 0.0026 mol) in absolute ethanol (25 ml) containing KOH (0.15 g, 0.0026 mol) was added dropwise to the appropriate alkyl iodide (0.0026 mol) in ethanol (25 ml). The reaction mixture

was refluxed for 1 h, then cooled and treated with cold water (50 ml). The obtained solid was filtered, dried and crystallized from ethanol (Table I). ¹H-NMR (DMSO-d₆, δ ppm) of compound (Xa) 2.74 (s, 3H, S-CH₃), 3.55 (s, 3H, N-CH₃), 5.47 (s, 2H, O-CH₂), 7.14-8.09 (m, 8H, aromatic protons).

1-Methyl-3-[p-(substitutedbenzylidenehydrazinocarbonyl)methoxyphenyl]quinazoline-2,4(1H,3H)-dione (XIa-e):

A mixture of V (1 g, 0.003 mol) and the appropriate aldehyde (0.003 mol) in dioxane (30 ml) was refluxed with stirring for 1 h, on cooling the separated product was filtered, dried and crystallized from DMF. (Table I) IR (cm⁻¹) for compound (XIa): 1710, 1685, 1664 (three carbonyl), 1517, 1342 (asymmetrical and symmetrical stretching of the NO₂ group).

Anti-inflammatory testing:

The compounds VII, IX and Xa were tested for antiinflammatory activity using flufenamic acid as standard. Mature male albino rats weighing 180-200 g were used and classified into five equal groups each of six: Group 1, rats were left as a control group. Group 2, rats were injected compound (VII) I.p at a dose of 4.5 mg/kg b.wt. Group 3, rats were injected compound (IX) I.p at a dose of 4.5 mg/kg b.wt. Group 4, rats were injected compound (Xa) I.p at a dose of 4.5 mg/kg b.wt. Group 5, rats were injected flufenamic acid I.p at dose of 4.5 mg/kg b.wt. The human doses were converted to rat doses according to the surface area according to Paget and Barnes⁽¹⁰⁾. 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⁽¹¹⁾, 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 2). The rank order of potency as antiinflammatory was as follow: compound VII > standard > compound Xa > compound IX.

Table (1): Characterization data of compounds (II-XIe)

No.	R	M.F & M.W	M.P. °C	Yield %	Elemental analysis		
					%	Calcd.	found
II	-	C ₁₄ H ₁₄ N ₂ O ₂ (242)	216-17	85	C H N	69.42 5.78 11.57	69.2 5.6 11.6
III	--	C ₁₅ H ₁₂ N ₂ O ₃ (268)	289-90	75	C H N	67.16 4.47 10.44	67.0 4.5 10.5
IV	--	C ₁₉ H ₁₈ N ₂ O ₅ (354)	174-5	80	C H N	64.40 5.08 7.90	64.2 5.1 7.8
V	--	C ₁₇ H ₁₆ N ₄ O ₄ (340)	186-7	78	C H N	60.00 4.70 16.47	60.2 4.5 16.5
VI	--	C ₂₄ H ₂₁ N ₅ O ₄ S (475)	144-5	80	C H N	60.63 4.42 14.73	60.4 4.5 14.6
VII	--	C ₂₄ H ₁₉ N ₅ O ₃ S (457)	244-4	60	C H N	63.01 4.15 15.31	62.9 4.3 15.4
VIIIa	CH ₃	C ₂₅ H ₂₁ N ₅ O ₃ S (471)	204-5	75	C H N	63.69 4.45 14.86	63.5 4.4 14.9
VIIIb	C ₂ H ₅	C ₂₆ H ₂₃ N ₅ O ₃ S (485)	214-15	75	C H N	64.32 4.74 14.43	64.2 4.8 14.5
IX	--	C ₁₈ H ₁₄ N ₄ O ₄ S (382)	239-40	65	C H N	56.54 3.66 14.65	56.4 3.5 14.7
Xa	CH ₃	C ₁₉ H ₁₆ N ₄ O ₄ S (396)	179-80	70	C H N	57.57 4.04 14.14	57.6 4.1 14.2
Xb	C ₂ H ₅	C ₂₀ H ₁₈ N ₄ O ₄ S (410)	195-6	70	C H N	58.53 4.39 13.65	58.4 4.4 13.7
XIa	H	C ₂₄ H ₂₀ N ₄ O ₄ (428)	248-9	95	C H N	67.28 4.67 13.08	67.1 4.7 13.0
XIb	4-Cl	C ₂₄ H ₁₉ ClN ₄ O ₄ (462.5)	274-5	95	C H N	62.27 4.10 12.10	62.3 4.2 12.2
XIc	4-N(CH ₃) ₂	C ₂₆ H ₂₅ N ₅ O ₄ (471)	230-1	95	C H N	66.24 5.30 14.86	66.3 5.4 14.8
XId	4-NO ₂	C ₂₄ H ₁₉ N ₅ O ₆ (473)	>300	95	C H N	60.88 4.01 14.79	60.8 4.1 14.9
XIe	4-OCH ₃	C ₂₅ H ₂₂ N ₄ O ₅ (458)	222-3	95	C H N	65.50 4.80 12.22	65.6 4.9 12.1

Table 2: The antiinflammatory activity of the tested compounds.

Group	Initial volume	Thickness of paw skin in mm after			
		1 hour	2 hours	3 hours	4 hours
Control	0.35 ± 0.063	0.59 ± 0.012	0.95 ± 0.075	1.23 ± 0.075	1.42 ± 0.088
VII	0.37 ± 0.033	0.39* ± 0.028	0.45** ± 0.025	0.55** ± 0.057	0.58** ± 0.041
IX	0.36 ± 0.03	0.5 ± 0.013	0.71* ± 0.06	0.82** ± 0.077	0.95** ± 0.048
Xa	0.4 ± 0.015	0.49* ± 0.012	0.58** ± 0.03	0.69** ± 0.03	0.75** ± 0.06
(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 مركبات جديدة محملة الفعالية كمضادات للإلتهابات عبارة عن مشتقات من كينازولين -٤،٢- (أيد، ٣، ١، ٢، ٣)

دايون

سامى مجاهد صقر

قسم الكيمياء الصيدلانية - كلية الصيدلة - جامعة الزقازيق - مصر

تم عمل مجموعة من التفاعلات التكميلية لتشييد مشتقات ٤،٣،١- ترايازول و ٤،٣،١- أوكسادايازول لمركبات كينازولين -٤،٢- (أيد، ٣، ١، ٢، ٣) دايون وتم إثبات التركيب البنائى للمركبات التى تم تحضيرها بواسطة الطرق الطيفية والكيميائية وكذلك بالتحليل العنصرى الدقيق. وباختبار بعض المركبات الجديدة وجد أن لها تأثير فعال كمواد مضادة للإلتهابات.