Zagazig J. Pharm. Sci., June 1997
Vol.6. No. 1. pp 21-25

ISSN 1110-5089

ONE POT SYNTHESIS OF 2(1H)-QUINAZOLINONE DERIVATIVES

Zakaria K. Abd El-Samii

Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt.

ABSTRACT

Condensation of (3-methoxyphenyl)urea or guanidine derivatives (**1a-e**) with a variety of acyl chlorides in polyphosphoric acid leads to intramolecular cyclization with formation of the title compounds (**2a-j**). Attempted one pot preparation of new tricyclic pyrrolo[3,2,1-ij]-2(2H)-quinazolinone derivatives (**3**) using 1-carboxamidoindoline (**1f**) and acyl chlorides were carried out.

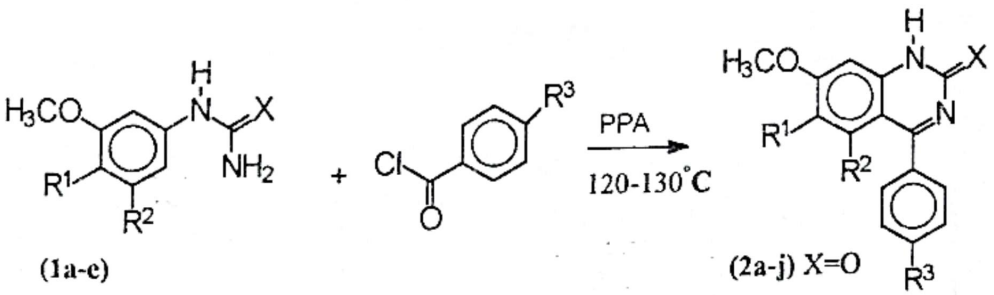
INTRODUCTION

Proquazone® and Fluproquazone® are 2(1H)-quinazolinone derivatives showed evident antiinflammatory activity.[1-5] Literature survey has revealed that the importance of establishing a general route to 2(1H)-quinazolinone is the need of a synthesis of more potant and safer non steroidal antiinflammatory agents. Obviously, most of the general methods[6-9] of preparation of 2(1H)-quinazolinones are often based on lengthy preparation of the corresponding substituted aromatic amino derivatives. Therefore, our attention has been paid to explore some new methods for the synthesis of 2(1H)-quinazolinone derivatives.

Recently,[10] in this connection we described two step synthesis of 2(1H)-quinazolinones and 2(1H)-quinazolinethiones as extention of the original Budesinsky and Lederer procedure[11]. We have found that polyphosphoric acid (PPA) can be efficiently used as cyclodehydrating agent. Moreover, it appears that this method provides a facile and covenient approach for prepartion of 2(1H)-quinazolinethiones. Herein, our investigations involved the direct condensation of (3-methoxy-phenyl)urea or guanidine derivatives (**1a-e**) or 1-carboxamidoindoline (**1f**) with acyl chlorides using polyphosphoric acid as cyclodehydrating agent. Thus, in our procedure, one pot synthesis of the title compounds has been acheived.

RESULTS AND DISCUSSION

By heating of (3-methoxy- and 3,4/ or 3,5-dimethoxyphenyl)ureas (**1a-c**) with acyl chlorides in presence of polyphosphoric acid, cyclization proceeded to form 2(1H)-quinazolinone derivatives (**2a-j**) (scheme 1).



(**1a**) $R^1 = R^2 = H$, X= O
(**1b**) $R^1 = OCH_3$, $R^2 = H$, X= O
(**1c**) $R^1 = H$, $R^2 = OCH_3$, X= O
(**1d**) $R^1 = R^2 = H$, X= NH
(**1e**) $R^1 = H$, $R^2 = OCH_3$, X= NH

(**2a**) $R^1 = R^2 = R^3 = H$
(**2b**) $R^1 = R^2 = H$, $R^3 = Cl$
(**2c**) $R^1 = R^2 = H$, $R^3 = Br$
(**2d**) $R^1 = R^2 = H$, $R^3 = CH_3$
(**2e**) $R^1 = R^2 = H$, $R^3 = OCH_3$
(**2f**) $R^1 = OCH_3$, $R^2 = H$, $R^3 = Cl$
(**2g**) $R^1 = OCH_3$, $R^2 = H$, $R^3 = Br$
(**2h**) $R^1 = H$, $R^2 = OCH_3$, $R^3 = Cl$
(**2i**) $R^1 = H$, $R^2 = OCH_3$, $R^3 = Br$
(**2j**) $R^1 = H$, $R^2 = OCH_3$, $R^3 = CH_3$
(**3**) $R^1 = R^2 = R^3 = H$, X=NH

Scheme 1

Reaction conditions were briefly examined using (3-methoxyphenyl)urea (**1a**) and 4-chlorobenzoyl chloride as starting materials and the results are summarized in table 1.

Table 1: Cyclization of **1a** with 4-chlorobenzoyl chloride under various conditions[a]

entry	time h	temp. °C	additive	2b yield[b] %
1	2	118	AcOH	7
2	5	118	AcOH	6
3	2	100	PPA	11
4	4	100	PPA	46
5	6	100	PPA	43
6	5	130	PPA	71

[a] Carried out by using **1a** (3 mmol) and 4-chlorobenzoyl chloride (3 mmol) in acetic acid (15 ml) or PPA (15g).
[b] Isolated yield after crystallization from DMF.

The yield of cyclization product was not satisfactory by the reaction of **1a** with 4-chlorobenzoyl chloride in glacial acetic acid (entry 1 and 2). After several trials (entries 3-5) using PPA as cyclodehydrating agent, we extended the reaction time to five hours at 120-130°C to obtain **2b** at 71% yield (entry 6). From the appropriate (3-methoxyphenyl)urea derivatives (**1a-c**) and acyl chlorides ten derivatives of 2(1H)-quinazolinone (**2a-j**) were prepared (table 2). Compounds **2a** and **2b** are known, but we obtained them in much higher yield (64 and 71% respectively) as compared with 53 and 16%[11]. Furthermore, loss of material during purification was less than mentioned in the literature[11].

All structures of the prepared 2(1H)-quinazolinone derivatives (**2a-j**) were characterized spectroscopically (UV, IR and ^{1}H NMR) and gave satisfactory elemental analyses (table 3).

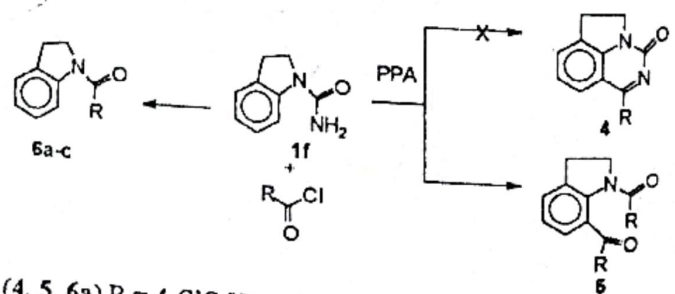
Table 2: One step synthesis of 2(1H)-quinazolinones **2a-j**.

start	product	solvent of crystallization	yield[a] %	m.p.°C
1a	**2a***	AcOEt/EtOH	64	276-278
1a	**2b#**	DMF	71	296-298
1a	**2c**	DMF	73	284-286
1a	**2d**	AcOEt/EtOH	66	280-282
1a	**2e**	AcOEt/EtOH	55	279-281
1b	**2f**	DMF	67	>303
1b	**2g**	DMF	64	303-305
1c	**2h**	DMF	98	299-301
1c	**2i**	DMF	95	306-308
1c	**2j**	AcOEt/EtOH	88	>303
1d	**2b**	DMF	61	296-298
1e	**2h**	DMF	72	299-303

[a] Isolated yield after crystallization. * Lit[11] m.p. 276-278°C. # Lit[11] m.p. 295-297°C

Alternatively, the cyclization of 1-(3-methoxyphenyl)guanidine (**1d**) with 4-chlorobenzoyl chloride offers the possibility of formation of 2(1H)-quinazolinimine derivative (**3**). Instead 2(1H)-quinazolinone (**2b**) was isolated. This result is consistent with the initial formation of the 2-quinazolinimine derivative **3** which undergoes in situ acid hydrolysis to give **2b**. Similarly formed was 5,7-dimethoxy-2(1H)-quinazolinone derivative (**2h**) from the reaction of 1-(3,5-dimethoxyphenyl)guanidine (**1e**) and 4-chlorobenzoyl chloride. Although our report of the direct formation of 2(1H)-quinazolinones from alkoxyphenylureas is novel, the in situ acid hydrolysis of the imine derivative (**3**) to the corresponding ketone has a good literature precedent[12-14].

The possibility of cyclization of 1-carboxamidoindoline (**1f**) with acyl chlorides to give the tricyclic pyrrolo[3,2,1-ij]-quinazolin-2-ones (**4**) was also investigated (scheme 2). Heating of **1f** with 4-chlorobenzoyl chloride in presence of polyphosphoric acid, under conditions similar to those employed for formation of the 2(1H)-quinazolinones (**2**), afforded 1,7-bis(4-chlorobenzoyl)indoline (**5**) and no sign of ring closure had taken place. Also, a mixture of **1f** and 4-chlorobenzoyl chloride was heated in glacial acetic acid over a steam bath for up to 24 hours. No cyclization occurred and the product was identified as 1-(4-chlorobenzoyl)indoline (**6a**). Moreover, heating under reflux, a mixture of **1f** and 4-chlorobenzoyl chloride in dioxane for five hours gave **6a**. Similarly obtained were 1-(4-methoxybenzoyl)indoline (**6b**) and 1-cinnamoylindoline (**6c**) from the reaction of **1f** with 4-methoxybenzoyl chloride and cinnamoyl chloride, respectively.



(4, 5, 6a) R = 4-ClC$_6$H$_4$
(6b) R = 4-CH$_3$OC$_6$H$_4$
(6c) R = C$_6$H$_4$CH=CH

Scheme 2

In conclusion, the methodology described above appears to be convenient and efficient route to produce the 2(2H)-quinazolinone derivatives. Direct synthesis of new tricyclic derivatives of 2(2H)-quinazolinone remains to be studied.

Zagazig J Pharm Sci., June 1997
Vol 6, No 1, pp 21-25

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. Elemental analyses were carried out in the microanalytical center, Cairo University. IR spectra were recorded as mulls in Nujol (ν_{max} cm^{-1}) using Shimadzu IR 435. UV spectra (ethanol) were recorded on Shimadzu UV-260 spectrophotometer. ^1H NMR spectra were obtained on Jeol Fx 90 Q spectrometer using DMSO-d_6 as the solvent and TMS as an internal reference (chemical shift is measured in δ ppm).

The alkoxyphenylureas **(1a-e)** were prepared from the appropriate 3-methoxyaniline and aqueous potassium cyanate by standard procedure[15]. Similarly, 1-carboxamidoindoline **(1f)** was prepared from the reaction of indoline with potassium cyanate. The alkoxyphenylguanidines **(1d,e)** were prepared from the appropriate alkoxyaniline with dicyandiamide in glacial acetic acid by a standard procedure[16].

General procedure for preparation of 2(1H)-quinazolinones 2a-j :

The mixture of **1a-e** (0.015 mol) and polyphosphoric acid (35g) was stirred in an oil bath at 90°C. The acyl chloride (0.02 mol) was added to the warm mixture dropwise during 10-15 min.. Heating at 120-130°C was continued for 5 h. The melt was cooled to 50 °C and added to ice water. The solution was weakly alkalized with conc. NH_3, and the precipitate was washed with water, dried and crystallized from the proper solvent to give **2a-j**. Melting points and yield (%) are listed in table 2. Elemental analyses, and UV, IR and ^1H NMR spectral data are shown in table 3.

Attempted preparation of 8,9-dihydro-4-substituted pyrrolo[3,2,1,-ij]-quinazolin-2(2H)-one (4) :

a) Formation of 1,7-bis(4-chlorobenzoyl)indoline (5):

A mixture of **1f** (0.015 mol), 4-chlorobenzoyl chloride (0.02 mol) and PPA (30 g) was reacted under

Table 3: 4-Aryl-1,2-dihydro-7-methoxy-or (6,7 and 5,7-dimethoxy)-2(1H)-quinazolinones **2a-j** .

Compd.	Molecular Formula	Analysis % Calcd./Found C	H	N	UV(EtOH) λmax (log ε) nm	IR ν_{max} (cm^{-1})
2a	$C_{15}H_{12}N_2O_2$ (252.3)	71.4 71.5	4.8 4.8	11.1 11.2	217 (4.44),232 (4.20) 253 (4.14),322 (3.50)	1665 (C=O), 1620 (C=N) 1590 (C=C)
2b	$C_{15}H_{11}ClN_2O_2$ (286.7)	62.8 62.7	3.9 3.8	9.8 9.9	214 (4.40),234 (4.20) 261 (4.64),294 (3.90 312 (4.20)	1680 (C=O), 1625 (C=N) 1595 (C=C)
2c	$C_{15}H_{11}BrN_2O_2$ (331.2)	54.4 54.4	3.3 3.4	8.5 8.4	216 (4.60),236 (4.41) 266 (4.10),294 (3.90) 327 (4.20)	1685 (C=O), 1620 (C=N) 1595 (C=C)
2d	$C_{15}H_{14}N_2O_2$ (266.3)	72.2 72.0	5.3 5.1	10.5 10.4	213 (3.95),236 (4.40) 262 (4.15),297 (4.20) 334 (3.94)	1680 (C=O), 1620 (C=N) 1595 (C=C)
2e	$C_{16}H_{14}N_2O_3$ (282.3)	68.1 68.0	5.0 4.8	9.9 9.8	216 (4.60),232 (4.41) 266 (4.10),294 (3.85) 327 (4.20)	1675 (C=O), 1615 (C=N) 1590 (C=C)
2f	$C_{16}H_{13}ClN_2O_3$ (316.7)	60.7 60.6	4.1 4.1	8.8 8.6	213 (4.49),242 (4.41) 265 (4.01),293 (4.94) 363 (3.94)	1680 (C=O), 1620 (C=N) 1590 (C=C)
2g	$C_{16}H_{13}BrN_2O_3$ (361.2)	53.2 53.0	3.6 3.5	7.8 7.9	214 (4.60),244 (4.20) 262 (4.10),295 (4.45) 355 (4.40)	1680 (C=O), 1620 (C=N) 1590 (C=C)
2h	$C_{16}H_{13}ClN_2O_3$ (316.7)	60.7 60.7	4.1 4.1	8.8 8.9	218 (4.60),233 (4.40) 257 (4.14),292 (3.98) 327 (4.26)	1665 (C=O), 1620 (C=N) 1590 (C=C)
2i	$C_{16}H_{13}BrN_2O_3$ (361.2)	53.2 53.1	3.6 3.7	7.8 7.6	216 (4.45),234 (4.20) 261 (4.34),294 (3.75) 352 (4.24)	1675 (C=O), 1620 (C=N) 1590 (C=C)
2j	$C_{17}H_{16}N_2O_3$ (296.3)	68.9 70.0	5.4 5.4	9.5 9.4	213 (4.35),238 (4.50) 266 (3.90),284 (4.20) 334 (4.35)	1675 (C=O), 1615 (C=N) 1590 (C=C)

Table 3. Continued

Compd.	^{1}H NMR• (δ ppm)
2a	3.95 (s, 3H, OCH_3), 7.0 (m, 5H, Ar-H), 7.25 (m, 2H,Ar-H), 7.95 (d, J=9 Hz, 1H,Ar-H.), 10.60 (s,1H, NH)
2b	3.92 (s, 3H, OCH_3), 6.70 (d, J=9 Hz, 2H, Ar-H), 6.88 (d, J=9 Hz, 1H, Ar-H), 7.20 (d, J=9 Hz, 1H, Ar-H), 7.70 (d, J=9 Hz, 2H, Ar-H), 7.90 (s,1H, Ar-H), 10.80(s,1H, NH)
2c	4.0 (s, 3H, OCH_3), 6.65 (d, J=9 Hz, 2H, Ar-H), 6.75 (d, J=9 Hz, 1H, Ar-H), 7.15 (d, J=9 Hz, 1H, Ar-H), 7.66 (d, J=9 Hz, 2H, Ar-H), 7.95 (s,1H, Ar-H), 11.10 (s, 1H, NH).
2d	2.30 (s, 3H, CH_3), 4.0 (s, 3H, OCH_3), 6.60 (d, J=9 Hz, 2H, Ar-H), 6.72 (d,J=9Hz,1H,Ar-H), 7.23 (d, J=9 Hz, 1H, Ar-H),7.75 (d, J=9 Hz, 2H, Ar-H), 7.98 (s, 1H, Ar-H),10.9 (s, 1H, NH)..
2e	3.95 [s, 6H,$(OCH_3)_2$], 6.72 (d, J=9 Hz, 2H, Ar-H), 6.78 (d, J=9 Hz, 1H, Ar-H), 7.20 (d, J=9 Hz, 1H, Ar-H), 7.65 (d, J=9 Hz, 2H, Ar-H), 7.90 (s, 1H, Ar-H), 10.70 (s, 1H, NH).
2f	4.0 (s, 3H, OCH_3), 4.30 (s, 3H, OCH_3), 7.34 (d, 2H, Ar-H), 7.85 (m, 4 H,Ar-H), 10.90 (s, 1H, NH).
2g	3.95 (s, 3H, OCH_3), 4.17 (s, 3H, OCH_3), 7.30 (d, 2H, Ar-H), 7.64 (m, 4H, Ar-H), 10.70 (s, 1H, NH).
2h	3.78 (s, 3H, OCH_3), 4.17 (s, 3H, OCH_3), 6.65 (d, J =9 Hz, 1H, Ar-H),, 7.60 (m, 4H, Ar-H), 10.70 (s, 1H, NH).
2i	3.89 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 6.75 (d, J =9 Hz, 1H, Ar-H), 7.75 (m, 4 arom. H), 10.90 (s,1 H, NH)
2J	2.30 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 6.58 (d, 1H, Ar-H), 6.64 (d, 1H, Ar-H), 7.55 (m, 4H, Ar-H), 10.45 (s, 1H, NH).

• solvent DMSO-d_6

the same above reaction conditions. Work up of the reaction mixture as mentioned above gave **5** in 47% yield; crystallized from ethyl acetate.; m.p:174-176°C. Analysis: $C_{22}H_{15}Cl_2NO_2$ (395.3); Calcd.: %C, 66.5, %H, 3.8, %N, 3.6; Found: %C, 66.4, %H, 3.7, %N,3.5. IR(cm^{-1}): 1645 (C=O), 1585 (C=C). ^{1}H NMR (δ ppm): 3.15 (t, 2H, CH_2), 4.13 (t, 2H, CH_2), 7.10-7.80 (m, 11H, Ar-H).

b) Formation of 1-(4-chlorobenzoyl)indoline (6a):

Method 1:

A mixture of **1f** (0.015 mol) and 4-chlorobenzoyl chloride (0.02 mol) in glacial acetic acid (20 ml) was heated on a water bath for 2h. The reaction mixture was cooled and added to cold water. The resulting solid was filtered of, dried and crystallized from methanol to afford **6b** in 78% yield; m.p: 118-120°C. Analysis: $C_{15}H_{12}ClNO$ (257.2); Calcd.: %C, 69.9, %H, 4.7, %N, 5.4; Found: %C, 69.7 %H, 4.5, %N,5.5 . IR(cm^{-1}): 1625 (C=O), 1590 (C=C). ^{1}H NMR (δ ppm): 3.03 (t, 2H, CH_2), 4.0 (t, 2H, CH_2), 6.7-8.0 (m, 8H, Ar-H).

Method 2:

A mixture of **1f** (0.015 mol) and 4-chlorobenzoyl (0.02 mol) was refluxed in dry dioxane (20 ml) for 2h. The reaction mixture was cooled and added to cold water. the resulting solid was filtered of, dried and crystallized from methanol to afford the same compound **6b**.

c) Formation of 1-(4-methoxybenzoyl)indoline (6b):

A mixture of **1f** (0.15 mol) and 4-methoxybenzoyl chloride (0.02 mol) was refluxed in dry dioxan (20 ml) for 2h. Work up of the reaction mixture as stated in method 2 gave **6b** (crystallized from methanol) in 72% yield; m.p: 112-114°C. Analysis: $C_{16}H_{12}NO_2$ (250.4); Calcd.: %C, 76.8; %H, 4.8; %N, 5.6; Found: %C, 76.6; %H, 4.7; %N,5.7. IR(cm^{-1}): 1635 (C=O), 1595 (C=C). ^{1}H NMR (δ ppm): 3.05 (t, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.10 (t, 2H. CH_2), 6.70-7.70 (m, 8H, Ar-H).

d) Formation of 1-(4-cinnamoyl)indoline (6c):

A mixture of **1f** (0.15 mol) and cinnamoyl chloride (0.02 mol) in glacial acetic acid (20 ml) was heated under reflux for 1h. The reaction mixture was cooled and worked up as stated in method 1 to give **6c** (crystallized from methanol) in 55% yield; m.p: 120-122°C. Analysis: $C_{17}H_{15}NO$ (249.3); Calcd.: %C, 81.9, %H, 6.1, %N, 5.6; Found: %C, 81.8, %H, 6.0, %N,5.8. IR(cm^{-1}): 1645 (C=O), 1610, 1585 (C=C). ^{1}H NMR (δ ppm): 3.15 (t, 2H, CH_2), 4.20 (t, 2H, CH_2), 6.70-8.50 (m, 11H, -HC=CH- and Ar-H).

REFERENCES

1. W. E. Coyne and J.W. Cusic, **J. Med. Chem. 11**,1208 (1968)
2. H. Ott (Sandoz Ltd); **U.S Pat. 3, 819, 625** (1974). Appl. 849, 863 (1971). Chem. Abstr. **83**, 79273m (1975).

Zagazig J. Pharm. Sci., June 1997
Vol.6, No. 1, pp 21-25

3. K. Ishizumi, S. Inaba and H. Yamamoto; **J. Org. Chem.** 39 (17), 2581 (1974).
4. J.W Perrine, W.J. Houlihan and E.I. Takesue; **Arzneim Forsch (Drug Res.) 34** (11), 879 (1984).
5. S. P. Clissold and R. Beresford; **Drugs 33**, 478 (1987).
6. S. Gabriel and T. Posner; **Ber. Dtsch. Chem. Ges. 28**,1029 (1895)
7. S. Gabriel and K. Stelzner; **Ber. Dtsch. Chem. Ges. 29,** 1310 (1896)..
8. K.W. Breukink and P.E. Verkade; **Rec. Trav. Chim. Pays-Bas 79,** 443 (1960). Chem. Abstr. **54**, 24778b.
9. H. Ott. (Sandz Ltd.); **Ger. Pat.** 1,932,402 (1970). Chem. Abstr. **72**, 100737a (1970).
10. M.I. Jaeda, Z.K. Abd El-Samii, and ; A.Z. Britten; **J. Chem. Tech. Biotechnol. 58**, 391 (1993).
11. Z. Budesinsky and P. lederer; **Coll. Czech. Chem. Commun. 37**, 2779 (1972).
12. J. March; " Advanced Organic Chemistry: Reactions, Mechanisms and Structure" 2nd Edition, McGraw-Hill Inc., p. 805 (1977).
13. I. Rault, S. Rault and M. Robba; **Tetrahedron letters. 34**, 1929 (1993).
14. M.P. Foloppe, P. Sonnet, I. Burea, S. Rault and M. Robba; **J. Heterocyclic Chem. 33**, 75 (1996).
15. A. Vogel; "Text Book of Practical Organic Chemistry", 4th Edition, Longman Group Limited, p. 735 (1978).
16. F. Arndt; **Ber. Dtsch. Chem. Ges. 46**, 3322 (1913).

Received : April, 26 / 1997
Accepted : May, 29 / 1997

تشييد مشتقات ٢(١يد)-كينازولينون فى خطوة واحدة

زكريا كامل محمد عبد السميع
قسم الكيمياء العضوية الصيدلية - كلية الصيدلة - جامعة الزقازيق - مصر

انطلاقا من الأهميه الطبية لمشتقات ٢(١يد)-كينازولينون كمجموعة فعاله ضد الالتهابات والمتمثله فى عقارى بروكوازون وفلوبروكوازون فقد اهتم هذا البحث باستنباط طريقه مباشره لتحضير مثل هذه المركبات بعد أن لاحظنا قصورا واضحا فى طرق تشييدها . وتعتمد الطريقه على التكثيف المباشر لمركبات (٣-ميسوكسى فينيل) يوريا أو جوانيدين مع كلوريد الاسيل فى وجود حامض البولى فوسفوريك الذى يؤدى الى عملية الحولقه وتكوين العديد من مشتقات ٢(١يد)-كينازولينون الجديدة .

أيضا شملت الدراسه امكانية تكوين الحلقات الثلاثيه لمركبات ٢(٢يد)-كينازولينون عن طريق التكثيف المباشر لمركب ١-كربوكساميدواندولين مع كلوريد الأسيل وجود حامض البولى فوسفوريك ، وان لم يحالفها التوفيق . وقد تم التعرف على المركبات الناتجه بالتحليل الدقيق لعناصرها الأساسيه ودراسه اطيافها فى الاشعه تحت الحمراء والاشعه فوق البنفسجيه والرنين النووى المغناطيسى لذرة الهيدروجين .