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Synthesis and Evaluation of Quinazolinone Derivatives for Cardiovascular Activity

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Abstract- Synthesis and evaluation of 3-(p methoxybenzylidene) hydrazinoacetylamino-2-methyl-6- bromoquinazolin-4-(3H)-one and 3-(p-N, N-dimethylbenzylidenylamino)hydrazine-acetylamino-2-methyi-quina-zolin-4 (3H)-one for cardiovascular activity.

Synthesis and evaluation of 3-(p methoxybenzylidene) hydrazinoacetylamino-2-methyl-6-bromoquinazolin-4-(3H)-one and 3-(p-N, N-dimethylbenzylidenylamino)hydrazine-acetylamino-2-methyi-quina-zolin-4 (3H)-one for cardiovascular activity methy-lmono substituted quinazolin-4(3H)-onyl)]-5'-(sub-stitu-tedphenyl)-tetrazolinum chloride (compounds 25-34).

Keywords: quinazolinone derivatives, formazan, hydrazi-noacetylamino, cardiovascular, antihypertensive activity.

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Synthesis and Evaluation of Quinazolinone Derivatives for Cardiovascular Activity

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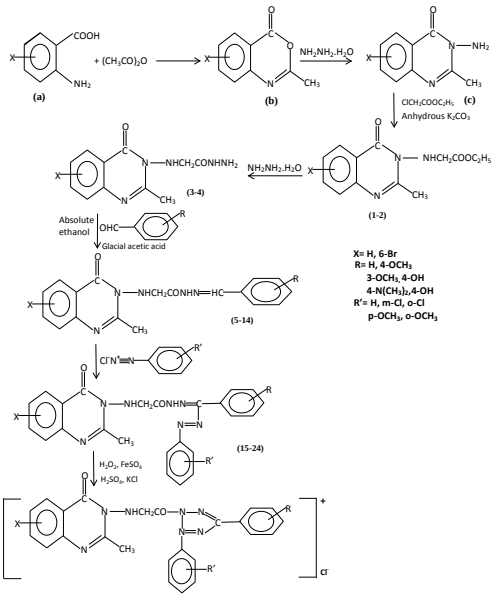
SCHEME I



Scheme I. Synthetic pathway for the preparation of quinazolinone derivatives

Abstract- 3-(ethylacetylamino)-2-methylmono substitutedquinazolin-4(3H)-ones (compounds 1-2) were prepared by the reaction of ethylchloroacetate with 3-amino-2-methylmono-substituted quinazolin-4(3H)-one in dry acetone in the presence of anhydrous K_2CO_3. Compounds 1-2, on reaction with hydrazine hydrate (99-100%) in methanol gave 3-(hydrazinoacetylamino) -2-methylmono substitutedquinazolin-4 (3H) -ones (comp-ounds 3-4), which on reaction with different aromatic aldehyde gave 3- (substitutedarylidene) hydrazine-oacetylamino-2-methylmono substitutedquinazolin-4 (3H) -ones (compounds 5-14). These compounds (5-14) on reaction with substituted benzene diazonium chloride yielded 3-[(acetylamino-2-methylmono substitutedquinazol in-4(3H)-onyl)]-1'-(substitutedphenyl)-3'- (substitutedaryl)- formazans (compounds 15-24). These compounds on oxidation with H_2O_2, ferrous sulphate and H_2SO_4 showed intramolecular cyclization to give- 2' (substitutedaryl) 4'-[3-(acetylamino)-2-methyl-mono substituted quinazolin4(3H)-onyl)]-5'-(sub-stitutedphenyl)-tetrazolinum chloride (compounds 25-34).

Keywords: quinazolinone derivatives, formazan, hydrazinoacetylamino, cardiovascular, antihypertensive activity.

I. Introduction

Quinazolin-4-(3H)-one, a potent pharmacodynamic heterocyclic nucleus has gained prominence in medicinal chemistry because it possess a wide spectrum of biological activities i.e. anticonvulsant [1], antibacterial [2], anti-inflammatory [3], antimicrobial [4] as well as antiproliferative [5]. Substitution at 2/3-position of quinazolinone ring imparts the cardiovascular activity [6-7], antitubercular activity [8], CNS depressant [9], antifungal [10], anticancer [11], analgesic [12] and antihypertensive [13]. Considering quinazolinone nucleus as potent pharmacophore for the cardiovascular activity, some newer derivatives of quinazolinone had been synthesized (Scheme I). The purity of the compounds was checked by TLC using silica gel G. The structure of all the compounds was confirmed by analytical and spectral data. All the newly synthesized compounds were screened for the elemental analysis (Table I) and their cardiovascular activity (Table II). The most active compounds of this series were 6 and 13. The ALD_{50} of these compounds were >2000 mg/kg p.o., indicating good safety margin.

II. Pharmacological Result and Discussion

Compounds 5, 7, 8 and 9 elicited potent immediate fall of varying degree (20-40 mmHg) and delayed fall of varying degree (10-40 mmHg) and duration (45-60 minutes) (Table II). Compounds 5 and 7 were associated with inhibition of CO and NA responses. Such a cardiovascular profile is suggestive of peripheral site of action. Compounds 8 and 9 were associated with inhibition of CO without affecting the NA response which might be suggestive of central site of action. In addition these compounds 8 and 9 showed increase in HR (tachycardia) of 1-2 beats per minutes and 3 bpm respectively. Compound 6 i.e. 3-(p-methoxybenzylidene) hydrazinoacetylamino-2-methyl-6-bromoquinazolin-4 (3H)-one showed an immediate fall in blood pressure (35 mmHg) followed by potent and gradual fall in blood pressure (70mmHg) as compared to the control value. The blood pressure lowering activity

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of this compound lasted for 95 minutes at a dose of 2.5 mg/kg i.v. In addition, this compound inhibited both pressor responses without affecting resting HR, which might be suggestive of peripheral site of action of this compound. As this compound had shown potent cardiovascular activity, it was studied at three graded doses (1.25, 2.5 and 5 mg/kg i.v.). The cardiovascular results are given in table II. Compounds 10, 11, 12 and 14 had also exhibited the promising hypotensive activity of varying degree (30-50 mmHg) and duration (60-75 minutes). In addition these compounds were associated with inhibition of CO without affecting the NA response, which might be suggestive of central site of action of these compounds. The most active compound of this series was 13 i.e. 3-(p-N,N-dimethylbenzylidenylamino)-hydrazinoacetylamino-2-methyl-quinazolin-4(3H)-one. Considering its potentiality it was further studied at 3 graded doses (1.25, 2.5 and 5 mg/kg i.v.). In lower doses 1.25 and 2.5 mg/kg i.v. it showed an immediate fall in blood pressure (35 mmHg and 52 mmHg) and delayed fall (70 mmHg and 100 mmHg) respectively. The hypotensive activity of this compound lasted for 100 and 130 minutes respectively. In higher doses i.e. 5 mg/kg i.v. it showed a very potent hypotensive activity i.e. an immediate fall (80 mmHg) and delayed fall (130 mmHg), which lasted for 195 minutes. Compound 13 was associated with inhibition or abolition of CO response without affecting the NA and heart rate. Such a pharmacological profile might be suggestive central site by action of this compound. The diazotized products i.e. compounds (15-24) showed moderate to potent hypotensive activity of varying degree (35-70 mmHg) and short duration (20-40 minutes). These compounds did not affect the heart rate and pressor responses (CO and NA). Moreover, the conversion of these compounds into their corresponding 5- member tetrazolinum salts resulted in compounds (25-34) having mild hypotensive activity (5-20 mmHg) of short duration (5-15 minutes). They appear to be acting directly on the smooth muscles of blood vessels (direct vasodilators) because these compounds did not affect the CO and NA responses and had short duration of action.

III. Conclusion

The intensive study of the cardiovascular profile of the synthesized compounds suggested that compounds 6 and 13 i.e. 3-(p-methoxybenzylidene) hydrazinoacetylamino-2-methyl-6-bromoquinazolin-4 (3H)-one and 3-(p-N, N-dimethylbenzylidenylamino)-hydrazinoacetylamino-2-methyl-quinazolin-4(3H)-one respectively had excellent cardiovascular activity. Therefore, these compounds should attract the interest of researchers and pharmaceutical companies for clinical studies and other applications in the therapy of cardiovascular diseases.

IV. Experimental Protocols

a) Chemistry

The melting point of the compounds was determined in open glass capillary with the help of themionic melting point apparatus and is uncorrected. Elemental analysis of all the newly synthesized compounds were determined by a Perkin-Elimer 2400 elemental analyzer, and results were found within the +/-0.4% of theoretical values. IR spectra were recorded in KBR on a Perkin-Elmer spectrum RX-I, spectrometer. 1H NMR spectra were recorded by Bruker AC-300 F instrument using $CDCl_3$/DMSO-Cl_6 as solvent and tetra methyl silane (TMS) as internal reference standard. All chemical shift values were recorded as δ (ppm). Mass spectra were determined on a VG-70-S instrument.

b) General procedure for the preparation of compounds

i. 6-bromoanthranilic acid (a)

This was prepared according to the method of Wheeler and Oats [14]. Bromine (0.8 mol) in acetic acid (20 ml) was added drop wise to the solution of anthranilic acid (0.4 mol) in absolute AcOH (50 ml). The solid was separated to give 6- bromoanthranilic acid. The solid product thus crystallized out, was washed with water and dried. It was recrystallized from ethanol/water M.P. 208°C, Yield 50%.

ii. Acetanthranils (b)

These were prepared according to the method of Bogert and Soil [15]. A mixture of appropriate anthranilic acid (0.01mol) and acetic anhydride (0.02 mol) were refluxed for 2-3 hours with occasional stirring. The excess of acetic anhydride was distilled off. On cooling, a solid separated out, which was filtered, washed with petroleum ether (40-60 °C) and dried in vacuo. The acetanthranils thus synthesized are given below:

a) Acetanthranils M.P. 78°C
b) 6-Bromoacetanthranils M.P. 172°C

iii. 3-amino-2-methyl monosubstitutedquinazolin-4(3H)-ones: (c)

These were prepared according to the method of Kumar et al [16]. A mixture of appropriate acetanthranils (0.01 mol) and hydrazine hydrate (99%, 0.02 mol) in methanol (dry, 50ml) were refluxed for 8 hours. The excess of solvent was distilled off in vacuo. The residue on cooling gave a crystalline solid, which was recrystallized from methanol-water (1:2).

iv. 3-(ethylacetylamino)-2-methylmono substituted quinazolin- 4 (3H)- one: (1-2)

A mixture of 3-amino-2-methyl mono substitutedquinazolin-4(3H)-one (0.01 mol), ethylchloroacetate (0.01 mol) and anhydrous K_2CO_3 (5.0g) in acetone (dry 80ml) were refluxed for 20 hours on water bath. The

acetone was distilled off and the resulting solid mass poured into water, filtered and the separated solid recrystallized from methanol/water to give compounds (1-2).

v. 3-(hydrazinoacetylamino) - 2 - methylmono substituted-quinazolin – 4 (3H) - one : (3-4)

A mixture of compounds (1-2) (0.01 mol) and hydrazine hydrate (0.02 mol) in methanol (dry, 50ml) were refluxed for 6-8 hours. The excess of solvent was distilled off. On cooling a crystalline solid is obtained which was recrystallized from methanol/water.

vi. 3-(substitutedarylidene)-hydrazinoacetyl-amino-2-methylmono substitutedquinazolin-4(3H)-ones: (5-14)

To a solution of compounds (3-4) (0.01 mol) in absolute ethanol (50 ml), substitutedbenzaldehyde (0.01 mol) and a few drops of glacial acetic acid were refluxed for 8 hours. The solvent was distilled off and the viscous mass thus obtained was
recrystallized from ethanol/water to give compounds (5-14).

vii. 3-[(acetylamino-2-methylmonosubstitutedquinazolin-4(3H)-onyl)]-1'-(substitutedphenyl)-3'-
(substitutedaryl)-formazans: (15-24)

Substituted phenyl (0.01 mol) was dissolved in 4ml glacial acetic acid and 3ml of concentrated HCl was added to 0-5°C. A solution of $NaNO_2$ (1 gm in 5 ml of water) was added drop wise. The diazonium salt solution thus prepared was added with stirring to compounds (5-14) (0.01mol) in 50 ml toluene. During the addition the temperature was maintained below 10°C. The reaction mixture thus obtained was left at room temperature for several hrs and then poured into 250 ml of cold water, The dark red solid which separated out was washed with water, filtered and recrystallized from methanol/water to give compounds (15-24).

viii. 2'-(substitutedaryl)-4'-[3-(acetyl amino-2-methy-lmono substituted quinazolin-4(3H)-onyl)] -5'-(substitutedphenyl)-tetrazolinum chlorides: (25-34)

Compounds (15-24) (0.1 mol) was suspended in ethanol (50 ml) and H_2SO_4 (2N, 5ml) containing a trace of ferrous sulphate and hydrogen peroxide (20%, 10ml). The reaction mixture was refluxed at 100°C for 3 hrs. The tetrazolinum chloride was precipitated by the addition of KCl which was washed with petroleum ether (40-60 °C) and recrystallized from methanol/water to give compounds (25-34).

c) Spectral data of the representative compounds

i. 3-(ethylacetylamino)-2-methyl-6- bromoquinazolin-4(3H)-one: 1

IR (KBr; cm^{-1}): 3250 (NH), 2840 (CH_2), 1730 (C=O), 1550 (C....C of aromatic ring); ^{1}H-NMR ($CDCl_3$): δ9.60 (ss, 1H, N<u>H</u>CH_2), 7.90-7.25 (m, 3H, Ar-H), 4.38(d, 2H, NHC<u>H</u>$_2$), 4.10(q, 2H, J=7Hz, COOC<u>H</u>$_2$CH$_3$), 2.30(s, 3H, CH3), 1.20 (t, 3H, J=7Hz, COOCH$_2$C<u>H</u>$_3$) ppm. MS: $[M]^+$ m/z 340.

ii. 3-(hydrazinoacetylamino)-2-methyl-6-bromo-quinazolin-4(3H)-one: 3

IR (KBr; cm^{-1}): 3340 (NH<u>H</u>NH_2), 3040 (aromatic C-H), 2850 (CH_2), 1720 (C=O), 1560 (C....C of aromatic ring), 600 (C-Br stretch); ^{1}H-NMR ($CDCl_3$): δ9.55 (ss, 1H, N<u>H</u>CH_2), 7.80-7.20 (m, 3H, Ar-<u>H</u>), 5.25 (brs, 1H, N<u>H</u>NH_2), 4.30 (d,2H, NHC<u>H</u>$_2$), 2.50 (ss, 2H, N<u>H</u>$_2$), 2.35 (s, 3H, C<u>H</u>$_3$) ppm. MS: $[M]^+$ m/z 326.

iii. 3-(p-hydroxybenzylidene)-hydrazinoacetylamino-2-methyl-6-bromo-quinazolin-4(3H)-one: 9

IR (KBr; cm^{-1}): 3240 (NH), 3030 (aromatic C-H), 1700 (C=O), 1630 (C=N), 1560 (C....C of aromatic ring); ^{1}H-NMR ($CDCl_3$): δ9.45 (ss, 1H, N<u>H</u>CH_2), 9.0 (s, 1H, O<u>H</u>), 8.85 (s, 1H, N=C<u>H</u>-Ar), 8.00-7.10 (m, 7H, Ar-<u>H</u>), 6.40 (ss, 1H, CON<u>H</u>), 4.40 (d, 2H, NHC<u>H</u>$_2$), 2.30 (s, 3H, C<u>H</u>$_3$) ppm. MS: $[M]^+$ m/z 430.

iv. 3-[(acetylamino-2-methyl-6-bromo-quinazolin-4(3H)-onyl)]-1'-(o-chloroaniline)-3'-(p-hydroxyphenyl)-formazan: 19

IR (KBr; cm^{-1}): 3248 (NH), 3040 (aromatic C-H), 1720 (C=O), 1640 (C=N), 1550 (C....C of aromatic ring), 1425 (N=N), 1260 (C-N); ^{1}H-NMR ($CDCl_3$): δ9.50 (ss, 1H, N<u>H</u>CH_2), 9.04 (s, 1H, OH), 8.20-7.00 (m, 11H, Ar-<u>H</u>), 6.45 (ss, 1H, CON<u>H</u>), 4.40 (d, 2H, NHC<u>H</u>$_2$), 2.25 (s, 3H, C<u>H</u>$_3$) ppm. MS: $[M]^+$ m/z 568.

v. 2'-(p-hydroxyphenyl)-4'-[3-acetylamino-2-methyl-6-bromo-quinazolin-4(3H)-onyl)]-5'-(o-chloroaniline)-tetrazolinum chloride: 29

IR (KBr; cm^{-1}): 3245 (NH), 3053 (aromatic C-H), 2853 (CH_2), 1740 (C=O), 1640 (C=N), 1580 (C....C of aromatic ring), 1520 (N-N), 1420 (N=N), 1250 (C-N); ^{1}H-NMR ($CDCl_3$): δ9.30 (ss, 1H, N<u>H</u>CH_2), 9.0 (s, 1H, OH), 8.30-7.50 (m, 11H, Ar-<u>H</u>), 4.35 (d, 2H, NHC<u>H</u>$_2$), 2.30 (s, 3H, C<u>H</u>$_3$) ppm. MS: $[M]^+$ m/z 603.

vi. Cardiovascular activity

Preliminary cardiovascular activity tests were carried out on albino rats 100-120g of either sex (the pregnancy was excluded) for all the synthesized indole derivatives. The newly synthesized compounds (test drugs) were administered intravenously (from right femoral vein) by dissolving them in propylene glycol and the effect on blood pressure (B.P), heart rate (HR) and pressor responses evoked either by carotid occlusion (CO) or intravenous noradrenalin (NA) 1-2 µg/Kg injection was observed. Injection of .20 mL of propylene glycol induced a mild and transient decrease of 1-2 mmHg in blood pressure without affecting the CO and NA response. The blood pressure was recorded from the left common carotid artery by means of a mercury manometer from femoral artery on one channel of "Encardiorite" (India) polygraph using stathus P25

transducer. Electrocardiogram (Lead II) was recorded on one channel of "Encardiorite" (India) polygraph in all the experiments.

vii. Acute toxicity study

The toxicity study was carried out on Charles foster mice of either sex (pregnancy was excluded). Approximate 50% lethal dose (ALD50) of the promising compounds was determined in albino mice. The mice of either sex weighing between 18-25 g were used for the study. The drugs were injected by intraperitonial (i.p.) route at different dose levels in separate groups of animals. After 24 hours of drugs administration, percent mortality in each group was observed. From the data obtained, ALD50 was calculated by using Smith method [17].

V. Acknowledgement

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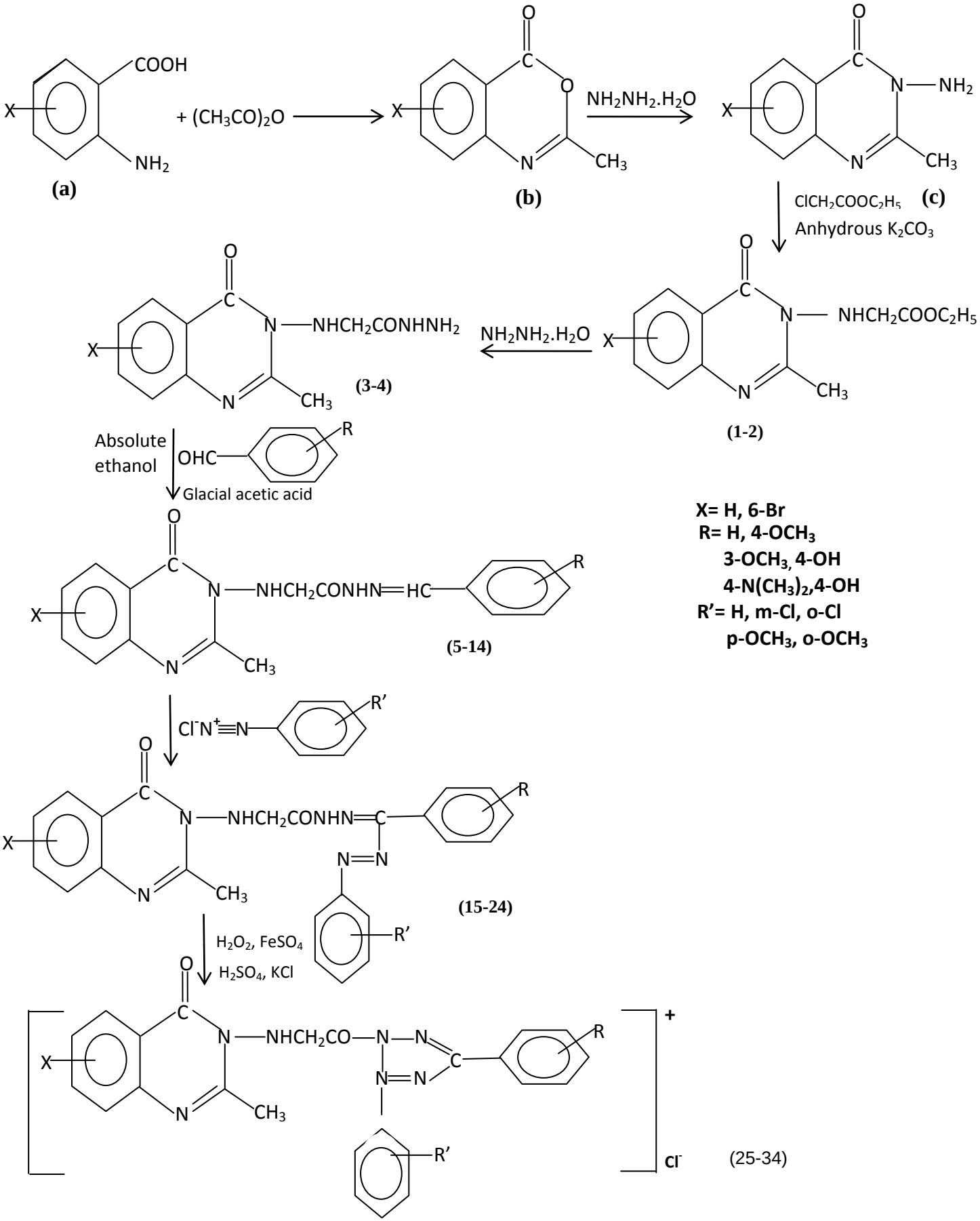
References Références Referencias

1. Helby, M.H. Abdel, Acta Pharma. 53 (2003) 127-138.
2. G. Grover, S.G. Kini, Eur. J. Med. Chem. 41 (2006) 256-262.
3. R.S. Giri, H.M. Thaker, T. Giordano, J. Williams, Eur. J. Med. Chem. 44 (2009) 2184-2189.
4. N.B. Patel, V.N. Patel, Iran. J. Pharm. Research 6 (2007) 251-258.
5. D. Raffa, G. Daidone, B. Maggio, D. Schillaci, F. Plescia, Pharmazie, 332 (1999) 317-320.
6. R.N. Brogdon, R.C. Hell, T.M. Speight, G.S. Avery, Drugs. 14 (1977), 163.
7. A. Kumar, S. Gurtu, J.N. Sinha, K.P. Bhargava, K. Shanker, Eur. J. Med. Chem. 20(1) (1985) 95-96.
8. S.R. Pattan, V.V.K. Reddy, F.V. Manvi, B.G. Desai, A.R. Bhat, Ind. J. Chem. 45B (2006) 1771-1781.
9. Jatav, P. Mishra, S. Kashaw, Eur. J. Med. Chem. 43 (2008) 1945-1951.
10. G. Grover, S.G. Kini, Eur. J. Med. Chem. 41 (2006) 256-262.
11. B.R. Shah, J.J. Bhatt, H.H. Patel, N.K. Undavia, P.B. Trivedi, N.C. Desai, Ind. J. Chem. 34 (1995) 201-208.
12. M.S. Mohamed, M.M. Kamel, E.M.M. Kassem, A. Nageh, S.M. Nofal, F.A. Marwa, Acta Poloniae Pharm. Drug Res. 66 (2009) 487-500.
13. R. Arora, A. Kapoor, N.S. Gill, A.C. Rana, IRJP 2(12) (2011) 22-28.
14. A.A. Wheeler, W.M. Oats, J. Amer. Chem. Soc. 32 (1910) 770.
15. M.T. Bogert, H.A. Soil H A, J. Amer. Chem. Soc. 29 (1907) 517.
16. A. Kumar, S. Sinha, A.K. Saxena, K. Shanker, Ind. J. Chem. 27 (1988) 443.
17. Q.E. Smith, Pharmacological Screening tests progress in Medicinal Chemistry,1,Butteworths, London, 1960.0

SCHEME I



X= H, 6-Br
R= H, 4-OCH_3
3-OCH_3, 4-OH
4-$N(CH_3)_2$,4-OH
R'= H, m-Cl, o-Cl
p-OCH_3, o-OCH_3

Scheme I. Synthetic pathway for the preparation of quinazolinone derivatives

Table 1 : Yield and elemental analysis of compounds

Co-mpd.	X	R	R'	M.P. (ºC)	Yield (%)	Recrystal llisation Solvent	Molecular Formula	Element Analysis (%) Calcd.(Found) C	H	N
1	6-Br	-	-	160	65	Methanol/Water	$C_{13}H_{14}N_3O_3Br$	45.88(45.90)	4.11(4.14)	12.35(12.37)
2	H	-	-	120	60	Methanol/Water	$C_{13}H_{15}N_3O_3$	59.77(59.72)	5.74(5.70)	16.09(16.06)
	6-Br	-	-	220	60	Methanol/Water	$C_{11}H_{12}N_5O_2Br$	40.49(40.45)	3.68(3.65)	21.47(21.45)
3	H	-	-	180	55	Methanol/Water	$C_{11}H_{13}N_5O_2$	53.44(53.40)	5.26(5.30)	28.34(28.30)
	6-Br	H	-	170	42	Methanol/Water	$C_{18}H_{16}N_5O_2Br$	52.17(52.14)	3.86(3.83)	16.90(16.92)
5	6-Br	$4\text{-}OCH_3$	-	182	45	Acetic acid/Water	$C_{19}H_{18}N_5O_3Br$	49.56(49.52)	3.91(3.88)	15.21(15.23)
7	6-Br	$3\text{-}OCH_3$, 4-OH	-	240	40	Benzene/Hexane	$C_{19}H_{18}N_5O_4Br$	49.56(49.52)	3.91(3.88)	15.21(15.23)
8	6-Br	$4\text{-}N(CH_3)_2$	-	186	42	THF	$C_{20}H_{21}N_6O_3Br$	52.51(52.54)	4.59(4.63)	18.38(18.35)
9	6-Br	4-OH	-	198	45	Ethanol/Water	$C_{18}H_{16}N_5O_3Br$	50.23(50.20)	3.72(3.70)	16.27(16.30)
10	H	H	-	170	48	Petroleum/Ether	$C_{18}H_{17}N_5O_2$	64.47(64.45)	5.07(5.04)	20.89(20.92)
11	H	$4\text{-}OCH_3$	-	194	46	Ethanol	$C_{19}H_{19}N_5O_3$	62.46(62.44)	5.20(5.24)	19.17(19.20)
12	H	$3\text{-}OCH_3$, 4-OH	-	200	42	Benzene	$C_{19}H_{19}N_5O_4$	59.84(59.80)	4.98(4.94)	18.37(18.40)
13	H	$4\text{-}N(CH_3)_2$	-	160	45	Benzene	$C_{20}H_{22}N_6O_2$	63.49(63.52)	5.82(5.80)	22.22(22.25)
14	H	4-OH	-	170	45	Acetone	$C_{18}H_{17}N_5O_3$	61.53(61.57)	4.84(4.82)	19.94(19.90)
15	6-Br	H	m-Cl	142	40	Methanol/Water	$C_{24}H_{19}N_7O_2ClBr$	52.12(52.10)	3.43(3.46)	17.73(17.70)
16	6-Br	$4\text{-}OCH_3$	H	195	42	Methanol/Water	$C_{25}H_{22}N_7O_4Br$	54.74(54.78)	4.01(4.05)	17.88(17.04)
17	6-Br	$3\text{-}OCH_3$, 4-OH	o-Cl	238	40	Methanol/Water	$C_{25}H_{21}N_7O_4BrCl$	50.12(50.16)	3.50(3.54)	16.37(16.35)
18	6-Br	$4\text{-}N(CH_3)_2$	$p\text{-}OCH_3$	210	40	Methanol/Water	$C_{27}H_{27}N_8O_3Br$	54.82(54.80)	4.56(4.52)	18.95(18.98)
	6-Br	4-OH	o-Cl	230	40	Methanol/Water	$C_{24}H_{19}N_7O_3ClBr$	50.65(50.62)	3.34(3.37)	17.23(17.23)
19	H	H	$o\text{-}OCH_3$	190	42	Methanol/Water	$C_{25}H_{23}N_7O_3$	63.96(63.98)	4.90(4.94)	20.89(20.86)
21	H	$4\text{-}OCH_3$	o-Cl	185	45	Methanol/Water	$C_{25}H_{22}N_7O_3Cl$	59.58(59.56)	4.36(4.34)	19.46(19.48)
22	H	$3\text{-}OCH_3$, 4-OH	H	235	40	Methanol/Water	$C_{25}H_{23}N_7O_4$	61.85(61.88)	4.74(4.72)	20.20(20.22)
23	H	$4\text{-}N(CH_3)_2$	m-Cl	142	40	Methanol/Water	$C_{26}H_{25}N_8O_2Cl$	60.40(60.42)	4.84(4.88)	21.68(21.70)
24	H	4-OH	$o\text{-}OCH_3$	195	45	Methanol/Water	$C_{25}H_{23}N_7O_4$	61.85(61.88)	4.74(4.78)	20.20(20.24)
25	6-Br	H	m-Cl	165	30	Methanol/Water	$C_{24}H_{18}N_7O_2Cl_2Br$	49.06(49.08)	3.06(3.02)	16.69(16.65)
26	6-Br	$4\text{-}OCH_3$	H	220	30	Methanol/Water	$C_{25}H_{21}N_7O_2ClBr$	51.50(51.54)	3.60(3.58)	16.82(16.84)
27	6-Br	$3\text{-}OCH_3$, 4-OH	o-Cl	250	35	Methanol/Water	$C_{25}H_{21}N_7O_3Cl_2Br$	47.31(47.35)	3.31(3.35)	15.45(15.42)
28	6-Br	$4\text{-}N(CH_3)_2$	$p\text{-}OCH_3$	270	38	Methanol/Water	$C_{27}H_{26}N_8O_3ClBr$	51.79(51.75)	4.15(4.12)	17.90(17.94)
	6-Br	4-OH	o-Cl	240	38	Methanol/Water	$C_{24}H_{18}N_7O_3Cl_2Br$	47.76(47.72)	2.98(2.95)	16.25(16.23)
29	H	H	$p\text{-}OCH_3$	200	38	Methanol/Water	$C_{25}H_{23}N_7O_3Cl$	59.98(59.55)	4.36(4.38)	19.46(19.42)
31	H	$4\text{-}OCH_3$	o-Cl	225	38	Methanol/Water	$C_{25}H_{21}N_7O_3Cl_2$	55.76(55.72)	3.90(3.94)	18.21(18.25)
32	H	$3\text{-}OCH_3$, 4-OH	H	244	35	Methanol/Water	$C_{25}H_{22}N_7O_4Cl$	57.74(57.78)	4.23(4.20)	18.86(18.82)
33	H	$4\text{-}N(CH_3)_2$	m-Cl	165	30	Methanol/Water	$C_{26}H_{24}N_8O_2Cl_2$	56.62(56.65)	4.35(4.32)	20.32(20.30)
34	H	4-OH	$o\text{-}OCH_3$	240	35	Methanol/Water	$C_{25}H_{22}N_7O_4Cl$	57.74(57.70)	4.23(4.27)	18.86(18.84)

Table 2 : Cardiovascular activity of the synthesized compounds

Co-mpd.	X	R	R'	Dose Mg/kg i.v.	Change in mean blood pressure mmHg Control Mean± SE	Immediate Mean± SE	Delayed Mean± SE	Duration in minutes Mean± SE	Change in resting HR bpm	Effect on pressure responses CO	NA	ALD_{50} mg/kg p.o.
5	6-Br	H	-	2.5	138±11.51	118.6±12.42*	127±12.02	49.6±1.67	-	Inhibited	Inhibited	>1000
6	6-Br	$4\text{-}OCH_3$	-	1.25	151±5.94	136±4.18***	106±4.04***	72.4±6.38	-	Inhibited	Inhibited	
				2.5	154.4±4.98	119±5.76***	83.8±4.52***	95±5.00	-	Inhibited	Inhibited	>2000
				5.0	158.4±5.87	108.4±6.68***	58.4±5.20***	134.8±7.59	-	Inhibited	Inhibited	
7	6-Br	$3\text{-}OCH_3$, 4-OH	-	2.5	138.4±8.96	114±7.48**	98.4±9.00***	45.2±2.16	-	Inhibited	Inhibited	>1000
8	6-Br	$4\text{-}N(CH_3)_2$	-	2.5	138.2±11.54	104.6±11.61**	106.2±12.77***	60.8±1.09	Potentiated 1-2 bpm	Inhibited	-	>1000
9	6-Br	4-OH	-	2.5	146±7.41	106.8±6.18**	126.2±5.93**	56.67±2.81	Potentiated 3 bpm	Inhibited	-	>1000
10	H	H	-	2.5	145.5±7.46	116.6±5.77***	96.6±5.60***	74.4±3.08	-	Inhibited	-	>1000
11	H	$4\text{-}OCH_3$	-	2.5	145.6±6.50	126.2±4.32	105±4.04***	59.8±2.86	-	Blocked	-	>1000
12	H	$3\text{-}OCH_3$, 4-OH	-	2.5	141±13.87	91.6±13.84***	118.4±16.19	59±2.64	-	Inhibited	-	>1000
13	H	$4\text{-}N(CH_3)_2$	-	1.25	159.6±7.30	124.6±8.73***	89.6±9.81***	99.6±2.96	-	Inhibited	-	
				2.5	156.4±6.98	104.2±7.38***	55.8±6.79***	128.2±2.86	-	Inhibited	-	>2000
				5.0	169.2±7.80	90.8±9.09	38.8±7.67***	195±4.12	-	Inhibited	-	
14	H	4-OH	-	2.5	143.2±8.16	93.2±5.54***	133.2±6.45***	60.2±1.67	-	Blocked	-	>1000
15	6-Br	H	m-Cl	2.5	136±4.18	-	76±3.80***	30.6±1.94	-	–	–	>1000
16	6-Br	$4\text{-}OCH_3$	H	2.5	134±4.18	-	69±7.21***	29.2±2.28	-	–	–	>2000
17	6-Br	$3\text{-}OCH_3$, 4-OH	o-Cl	2.5	139±9.61	-	99.8±9.98***	42.33±2.51	-	-	-	>1000
18	6-Br	$4\text{-}N(CH_3)_2$	$p\text{-}OCH_3$	2.5	138.2±11.54	-	104.6±11.61**	29±2.64	-	-	-	>1000
19	6-Br	4-OH	m-Cl	2.5	137.4±6.06	-	120±7.21***	23.8±2.77	-	-	-	>1000
20	H	H	$p\text{-}OCH_3$	2.5	139±9.61	-	99.8±9.98***	22.6±3.97	-	-	-	>1000
21	H	$4\text{-}OCH_3$	o-Cl	2.5	134.2±13.04	-	105±11.57***	39.2±2.20	-	-	-	>1000
22	H	$3\text{-}OCH_3$, 4-OH	H	2.5	137.6±11.67	-	95±12.18***	21.6±2.70	-	-	-	>1000
23	H	$4\text{-}N(CH_3)_2$	m-Cl	2.5	138.4±8.97	-	104.6±9.01***	29.6±1.67	-	-	-	>1000
24	H	4-OH	$o\text{-}CH_3$	2.5	135±9.61	-	93.4±9.86***	30±1.41	-	-	-	>1000
25	6-Br	H	m-Cl	2.5	132±8.13	-	122±8.68	9.6±1.81	-	–	–	>1000
26	6-Br	$4\text{-}OCH_3$	H	2.5	133.8±8.37	-	116.4±6.50**	14±3.08	-	–	–	>2000
27	6-Br	$3\text{-}OCH_3$, 4-OH	o-Cl	2.5	132.2±10.77	-	120.2±13.40*	9.6±2.60	-	-	-	>1000
28	6-Br	$4\text{-}N(CH_3)_2$	$p\text{-}OCH_3$	2.5	132±9.61	-	115.2±10.18*	12±1.87	-	-	-	>1000
29	6-Br	4-OH	m-Cl	2.5	132.2±10.77	-	117±9.54*	14±3.08	-	-	-	>1000
30	H	H	$p\text{-}OCH_3$	2.5	130.6±7.53	-	120.4±6.73*	13.6±2.70	-	-	-	>1000
31	H	$4\text{-}OCH_3$	o-Cl	2.5	132.2±6.01	-	127.2±6.37*	5.2±1.48	-	-	-	>1000
32	H	$3\text{-}OCH_3$, 4-OH	H	2.5	132±9.46	-	123±8.68***	5.8±1.92	-	-	-	>1000
33	H	$4\text{-}N(CH_3)_2$	m-Cl	2.5	133.6±6.10	-	128.6±5.77*	8.8±3.11	-	-	-	>1000
34	H	4-OH	$o\text{-}CH_3$	2.5	133.8±9.90	-	121.4±9.60*	10±1.58	-	-	-	>1000

* $p > 0.05$; ** $p < 0.01$; *** $p < 0.001$