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

Index terms— quinazolinone derivatives, formazan, hydrazinoacetylamino, cardiovascular, antihypertensive activity.

1 Introduction

uinazolin-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 **??**) and their cardiovascular activity (Table **??**I). 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.

2 II.

3 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 **??**I). 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-(pmethoxybenzylidene) hydrazinoacetylamino-2-methyl-6bromoquinazolin-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 azolin-4(3H)-ones (compounds 1-2) were prepared by the reaction of ethylchloroacetate with 3-amino-2-methylmonosubstituted quinazolin-4(3H)-one in dry acetone in the presence of anhydrous K 2 CO 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.

4 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.

5 IV.

6 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 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 ? (ppm). Mass spectra were determined on a VG-70-S instrument.

7 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 o C, Yield 50%.

8 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 o C) and dried in vacuo. The acetanthranils thus synthesized are given below: a) Acetanthranils M.P. 78 o C b) 6-Bromoacetanthranils M.P. 172 o C

9 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).

10 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 2 CO 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).

11 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.

12 vi. 3-(substitutedarylidene)-hydrazinoacetyl-amino-2methylmono 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)(6)(7)(8)(9)(10)(11)(12)(13)(14).

13 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 o 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 o 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)(16)(17) ??18) ??19) ??20) ??21) ??22) ??23) ??24).

14 ii. 3-(hydrazinoacetylamino)-2-methyl-6-bromoquinazolin-4(3H)-one: 3

C of aromatic ring);

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

C of aromatic ring);

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

C of aromatic ring), 1425 (N=N), 1260 (C-N); 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 ?g/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 (25-34) X + (CH 3 CO) 2 O O C N X O CH 3 O C N X N NH 2 CH 3 NH 2 NH 2 .H 2 O O C N X N NHCH 2 COOC 2 H 5 CH 3 ClCH 2 COOC 2 H 5 Anhydrous K 2 CO 3 O C N X N NHCH 2 CONHNH 2 CH 3 NH 2 NH 2 .H 2 O Glacial acetic acid Absolute ethanol R OHC R' Cl -N + N O C N X N NHCH 2 CONHN CH 3 R HC R N N O C N X N NHCH 2 CONHN C CH 3 R' H 2 O 2 , [1]

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Figure 1:

Figure 2:

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Co-md.	X	R	R'	M.P. (o C)	Yield (%)	Recrystallisation Solvent	Molecular Formula	Element Analysis (%) Calcd.(Found) C	H	N
1	6-Br	-	-	160	65	Methanol/Water	C13H14N3O3Br	45.88(45.90)	4.11(4.14)	12.35(12.37)
2	H	-	-	120	60	Methanol/Water	C13H15N3O3	59.77(59.72)	5.74(5.70)	16.09(16.06)
	6-Br	-	-	220	60	Methanol/Water	C11H12N5O2Br	40.49(40.45)	3.68(3.65)	21.47(21.45)
3	H	-	-	180	55	Methanol/Water	C11H13N5O2	53.44(53.40)	5.26(5.30)	28.34(28.30)
	6-Br	H	-	170	42	Methanol/Water	C18H16N5O2Br	52.17(52.14)	3.86(3.83)	16.90(16.92)
5	6-Br	4-OCH3	-	182	45	Acetic acid/Water	C19H18N5O4Br	49.56(49.52)	3.91(3.88)	15.21(15.23)
7	6-Br	3-OCH3, 4-OH	-	240	40	Benzene/Hexane	C19H18N5O4Br	49.56(49.52)	3.91(3.88)	15.21(15.23)
8	6-Br	4-N(CH3)2	-	186	42	THF	C20H21N6O2Br	52.51(52.54)	4.59(4.63)	18.38(18.35)
9	6-Br	4-OH	-	198	45	Ethanol/Water	C18H16N5O3Br	50.23(50.20)	3.72(3.70)	16.27(16.30)
10	H	H	-	170	48	Petroleum/Ether	C18H17N5O2	64.47(64.45)	5.07(5.04)	20.89(20.92)
11	H	4-OCH3	-	194	46	Ethanol	C19H19N5O3	62.46(62.44)	5.20(5.24)	19.17(19.20)
12	H	3-OCH3, 4-OH	-	200	42	Benzene	C19H19N5O4	59.84(59.80)	4.98(4.94)	18.37(18.40)
13	H	4-N(CH3)2	-	160	45	Benzene	C20H22N6O2	63.49(63.52)	5.82(5.80)	22.22(22.25)
14	H	4-OH	-	170	45	Acetone	C18H17N5O3	61.53(61.57)	4.84(4.82)	19.94(19.90)
15	6-Br	H	m-Cl	142	40	Methanol/Water	C24H19N7O2ClBr	52.12(52.10)	3.43(3.46)	17.73(17.70)
16	6-Br	4-OCH3	H	195	42	Methanol/Water	C25H22N7O3Br	54.74(54.78)	4.01(4.05)	17.88(17.04)
17	6-Br	3-OCH3, 4-OH	o-Cl	238	40	Methanol/Water	C25H21N7O4BrCl	50.12(50.16)	3.50(3.54)	16.37(16.35)
18	6-Br	4-N(CH3)2	p-OCH3	210	40	Methanol/Water	C27H27N8O3Br	54.82(54.80)	4.56(4.52)	18.95(18.98)
	6-Br	4-OH	o-Cl	230	40	Methanol/Water	C24H19N7O3ClBr	50.65(50.62)	3.34(3.37)	17.23(17.23)
19	H	H	o-OCH3	190	42	Methanol/Water	C25H23N7O3	63.96(63.98)	4.90(4.94)	20.89(20.86)
21	H	4-OCH3	o-Cl	185	45	Methanol/Water	C25H22N7O3Cl	59.58(59.56)	4.36(4.34)	19.46(19.48)
22	H	3-OCH3, 4-OH	H	235	40	Methanol/Water	C25H23N7O4	61.85(61.88)	4.74(4.72)	20.20(20.22)
23	H	4-N(CH3)2	m-Cl	142	40	Methanol/Water	C26H25N8O2Cl	60.40(60.42)	4.84(4.88)	21.68(21.70)
24	H	4-OH	o-OCH3	195	45	Methanol/Water	C25H23N7O4	61.85(61.88)	4.74(4.78)	20.20(20.24)

2

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 rest-ing HR bpm	Effect o respons CO
	6-Br	H	-	2.5	138±11.51	118.6±12.42*	127±12.02	49.6±1.67	-	Inhibite
	6-Br	4-OCH 3	-	1.25	151±5.94	136±4.18***	106±4.04***	72.4±6.38	-	Inhibite
				2.5	154.4±4.98	119±5.76***	83.8±4.52***	95±5.00	-	Inhibite
				5.0	158.4±5.87	108.4±6.68***	68.4±5.20***	134.8±7.59	-	Inhibite
	6-Br	3-OCH 3 , 4-OH	-	2.5	138.4±8.96	114±7.48**	98.4±9.00***	45.2±2.16	-	Inhibite
	6-Br	4-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	I
	6-Br	4-OH	-	2.5	146±7.41	106.8±6.18**	126.2±5.93**	56.67±2.81	Potentiated 3 bpm	Inh
	H	H	-	2.5	145.5±7.46	116.6±5.79***	96.6±5.60***	74.4±3.08	-	Inhibite
	H	4-OCH 3	-	2.5	145.6±6.50	126.2±4.32*	105±4.04***	59.8±2.86	-	Blocked
	H	3-OCH 3 , 4-OH	-	2.5	141±13.87	91.6±13.84**	118.4±16.19	59±2.64	-	Inhibite
	H	4-N(CH 3) 2	-	1.25	159.6±7.30	124.6±8.73***	99.6±9.81***	99.6±2.96	-	Inhibite
				2.5	156.4±6.98	104.2±7.35***	85.8±6.79***	128.2±2.86	-	Inhibite
				5.0	169.2±7.80	90.8±9.09***	88.8±7.67***	195±4.12	-	Inhibite
	H	4-OH	-	2.5	143.2±8.16	93.2±5.54***	133.2±6.45***	60.2±1.67	-	Blocked
	6-Br	H	m-Cl	2.5	136±4.18	-	76±3.80***	30.6±1.94	-	-
	6-Br	4-OCH 3	H	2.5	134±4.18	-	69±7.21***	29.2±2.28	-	-
	6-Br	3-OCH 3 , 4-OH	o-Cl	2.5	139±9.61	-	99.8±9.98***	42.33±2.51	-	-
	6-Br	4-N(CH 3) 2	p-OCH 3	2.5	138.2±11.54	-	104.6±11.61**	29±2.64	-	-
	6-Br	4-OH	m-Cl	2.5	137.4±6.06	-	120±7.21***	23.8±2.77	-	-
	H	H	p-OCH 3	2.5	139±9.61	-	99.8±9.98***	22.6±3.97	-	-
	H	4-OCH 3	o-Cl	2.5	134.2±13.04	-	105±11.57***	39.2±2.20	-	-
	H	3-OCH 3 , 4-OH	H	2.5	137.6±11.67	-	95±12.18***	21.6±2.70	-	-
	H	4-N(CH 3) 2	m-Cl	2.5	138.4±8.97	-	104.6±9.01***	29.6±1.67	-	-
	H	4-OH	o-CH 3	2.5	135±9.61	-	93.4±9.86***	30±1.41	-	-
	6-Br	H	m-	2.5	132±8.13		122±8.68	9.6±1.81		

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