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Synthesis, characterisation and antihypertensive activity of some 2,7,8-substituted-11*H*-pyrido [2,1-b] quinazolones

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ABSTRACT

Substituted pyrido quinazolones have been synthesized employing a convenient and easily accessible procedure. In this article pyrido quinazolones were synthesized for their characterisation and antihypertensive activity. Synthesized compounds were obtained in excess yields.

Keywords: Pyridoquinazolones, arylamido/imidoalknaols, anticancer, antibacterial, antifungal.

INTRODUCTION

Quinazolones and condensed quinazolones have diverse pharmacological properties which mainly include anticancer [1-3], antibacterial [4, 5], antifungal [6, 7], antiarrhythmic [8], antidiabetic [9-14] and anti-inflamatory[15-18] activities. Some pyridoquinazole derivatives are calcium antagonists and share some common property of interfering with the influx of extracellular calcium via the calcium L channel [19]. In addition, quinazolines/quinazolones as anti-convulsant, antibacterial and as anti-diabetic agents have also been reported by many schools of research [20-22]. Interest in quinazoline chemistry has increased manifolds because of their association with anticancer property [23, 24]. The strategy adopted was the synthesis of quinazolone derivatives that have some resemblance to folic acid [25, 26]. These compounds were mainly evaluated for inhibition of enzyme dihydrofolate reductase and were found inhibitors of dihydrofolate reductase in human lukemia cells [27, 28] and EGFR-tyrosine kinase (anti-tumor)[29].

In continuation of our research work on the synthesis of biologically active compounds the present communication, deals with the synthesis of 2, 7, 8-substituted-11*H*-pyrido [2, 1-*b*] quinazolin-11-ones.

MATERIALS AND METHODS

All the reagents and solvents used in this synthetic work were laboratory grade and procured from Sigma Aldrich India and SD fine chemicals. Some new 2, 7, 8-substituted-11*H*-pyrido [2, 1-*b*] quinazolone-11-ones were synthesized from 2-chloro benzoic acid on reacting with various chemicals. The synthesized compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis. Antihypertensive activity

was carried out by the experiment on male albino rats (wistar strain) under observed conditions at two different dose levels 1.0 mg/Kg and 5.0 mg/Kg respectively.

The melting points of compounds were determined in open glass capillaries in Toshniwal melting point apparatus and recorded values are uncorrected. IR spectra (v_{max} in cm^{-1}) were recorded in KBr on Perkin-Elmer 157 spectrophotometer in region v_{max} 4000-400 cm^{-1}, ^1H NMR in $CDCl_3$ on a DRX (300 MHz) NMR spectrometer using TMS as internal standard and ^{13}C NMR spectra in $CDCl_3$ on a DRX (40 MHz) NMR spectrometer using TMS as internal standard (Chemical shift in δ, ppm). The mass spectra were recorded on Jeol SX-102 (FAB) mass spectrometer in which m-nitrobenzylalcohol was used as matrix.

2-(Hydroxymethyl) - isoindolin- 1, 3- dione [(N- hydroxymethyl) - phthalimide]
Phthalimide (0.1 mole) and 7.5 ml of formaldehyde mixed with 100 ml of water were heated till a clear solution was obtained. Clear solution was refrigerated for overnight and separated product was removed by filtration. The product was washed with ice cold water and air dried. The crude N-(hydroxyl-methyl)-phthalimide thus obtained melted at 140^0C [137-141^0C] [30]. According to procedure of Skellarios[31]. 2.15 g of N-(hydroxyl-methyl)-phthalimide was dissolved in 5 ml of pyridine, filtered and left to crystallize. Pyridine complex crystallized in long lustrous needles and collected after cooling. On drying in vacuo over concentrated sulphuric acid, the crystals lost their lustre and came to constant weight after twenty four hours. Dried product melted at 148.5^0C and on recrystallization from acetone pure sample was obtained which melted at 149.5^0C; Yield 75%.

2- [2- (Hydroxyl ethyl) - isoindolin- 1, 3- dione [N-(hydroxyethyl) - phthalimide]
A mixture consisting of finely powdered phthalic anhydride (0.1 mole) and β-ethanolamine (0.1 mole) was heaeted for half an hour at 210^0C. During this period water, which formed, eliminated and the resultant clear solution solidified on cooling in white crystalline form. It was obtained in quantitative yield and was sufficiently pure for further reaction. It melted at 127 - 128^0C [127 - 128^0C] [32].

N- (Hydroxymethyl) - nicotinamide
A finely powdered mixture of nicotinamide (0.1 mole), formalin (0.25 mole), and anhydrous potassium carbonate (K_2CO_3) (1.0 g) in water (100 ml) was heated at 100^0C for two hours. During the period of heating the contents were stirred occasionally. On cooling at room temperature, solidification occurred which was completed in about half an hour. The solid thus separated out, was filtered off and washed with cold water. It was air dried and recrystallization from ethanol gave an analytically pure sample of N- (hydroxymethyl) nicotinamide which was in the form of colourless needles. It melted at 155^0C [156^0C] [33].

5- Arylamido/ imidoalkyl- 2- chlorobenzoic acids
Arylamido/imido alcanol (0.05 mole) was dissolved in 20 ml conc. sulphuric acid by stirring and cooling. Subsequently 2-chlorobenzoic acid was dissolved in minimum amount of conc. sulphuric acid with utmost care. Solution of arylamido/imido alcanol was added to the solution of 2-chlorobenzoic acid slowly with constant stirring. During this processs the mixture was kept at the temprature of zero degree centigrade. Stirring was continued for a period of an hour the mixture was left for 24 hours. The reaction mixture was poured in to crushed ice slowly with continuous stirring. The mixture was left for four hours to sattle down. The solid phase was filtered off and washed repeatedely with water, dried in vacuo and recrystallized from diluted ethanol.

5- (Phthalimidomethyl) - benzoic acid: White crystalline mass; m.p. 174^0C [175^0C] [34]; yield 60%.
5- (Phtalimidoethyl) - benzoic acid: White crystalline solid; m.p. 160^0C [160^0C] [35]; yield 55%.
5- (Nicotinamidomethyl) - benzoic acid: Colourless needles; m.p. 144^0C [145^0C] [36]; yield 56%.

5- Arylamido/imidoalkyl- 2- (pyrido- 2- yl- amino) benzoic acids
5-Arylamido/imidoalkyl-2-chlorobenzoic acid (0.02mole) and 0.02 mole of substituted 2-amino pyridine were mixed in dry pyridine and allowed to reflux for six hours in a moisture free medium. Subsequently, the reaction mixture was cooled up to the room temperature and poured in to crushed ice containing 5 ml concentrated hydrochloric acid. After completion of addition, solid mass was allowed to settle down. Solid phase was separated by filtration and washed repeatedly with cold water. The solid thus obtained, was treated with 10% $NaHCO_3$ solution till there was no effervescence. The remaining solid was rejected and filtrate was treated with diluted hydrochloric acid to neutralise the filterate. On completion of nutrilization precipitation occured which was filtered off and washed repeatedly with cold water and recrystallized from diluted ethanol.

2- [(11- Oxo- 11H- pyirdo [2, 1- b] quinazolin- 2- yl) alkyl] arylamido/ imides

5-Arylamido/imidoalkyl-2-(pyrido-2-yl-amino) benzoic acid (0.01mole) was dissolved in concentrated sulphuric acid by stirring continuously till a clear solution was obtained. Mixture was heated at 100^0C for three hours. Subsequently, the solution was allowed to cool at the room-temperature and further cooled to 0-5^0C and then it was added to previously cooled ammonia solution till the point of neutralization and was left undisturbed for half an hour. The solid phase was filtered and washed with a solution of $NaHCO_3$ solution in order to dissolve any unreacted acid residue. Finally the solid was washed with cold water repeatedly and the solid compound remaining was dried and recrystallized from diluted ethanol.

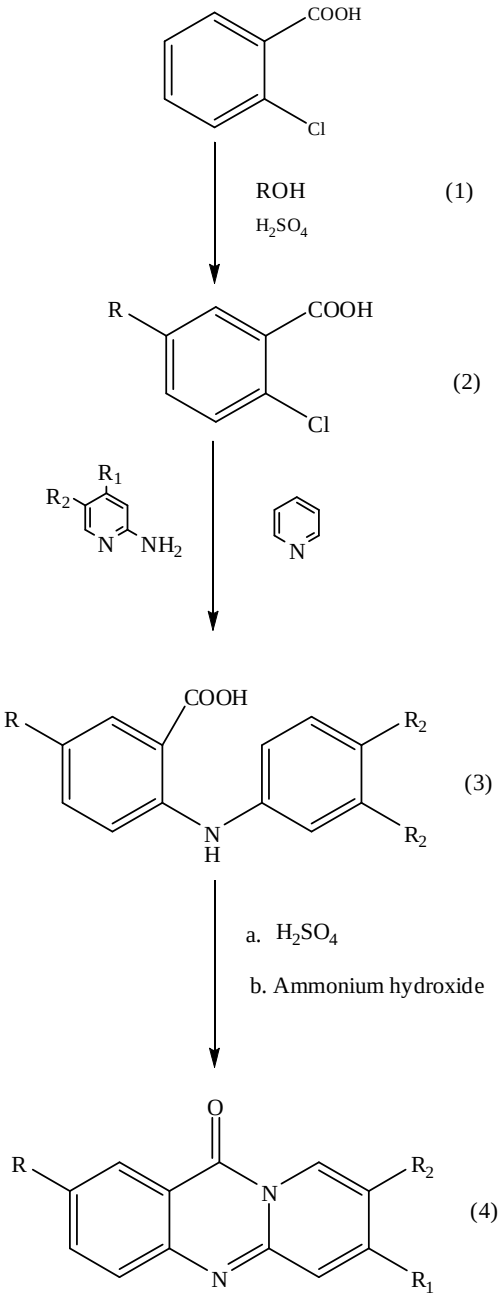
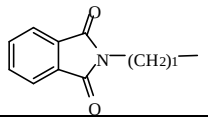
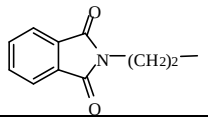
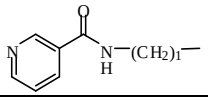
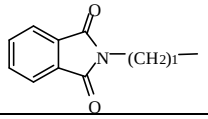
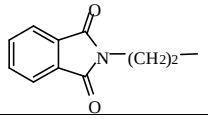
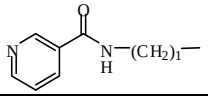
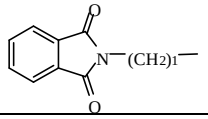
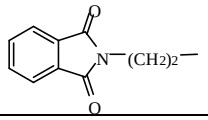
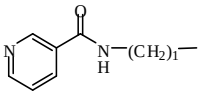


Table- 1.: Value for R, R_1, R_2, Physical data for synthesized compounds

Compound Code	R	R_1	R_2	Molecular Weight	Yield
4 A		-H	-H	355.35	55%
4 B		-H	-H	369.37	50%
4 C		-H	-H	330.34	52%
4 D		-OH	-H	371.35	46%
4 E		-OH	-H	385.37	49%
4 F		-OH	-H	346.34	42%
4 G		-H	$-CH_3$	369.37	62%
4 H		-H	$-CH_3$	383.40	65%
4 I		-H	$-CH_3$	344.37	58%

4 A. 2-((11-Oxo-11H-pyrido [2, 1-b] quinazolin-2-yl) methyl) isoindoline-1, 3-dione. Mp. 130^0C, white crystal, IR (KBr pellets, cm^{-1}) 1722 (imide C=O), 1680(ter. amide C=O), 1630 (C=N), 1357 (sec. amide); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 8.49 – 6.72 (m, 11H, Ar-H), 6. 4.99 (s, 2H, CH_2). ^{13}C NMR (40 MHz, $CDCl_3$, δ ppm) δ 170.9, 160.7, 150.3, 148.9, 140.3, 135.8, 134.3, 134.2, 133.7, 133.2, 131.5, 129.3, 125.5, 123.6, 118.1, 43.7; MS: m/z 355 (M^+). Anal. Calcd. For $C_{21}H_{13}N_3O_3$: C, 70.98; H, 3.69; N, 11.83; Found C, 70.65; H, 3.52; N, 11.54.

4 B. 2-(2-(11-Oxo-11H-pyrido [2, 1-b] quinazolin-2-yl) ethyl) isoindoline-1, 3-dione. Mp. $145\text{-}146^0$C, white powder, IR (KBr pellets, cm^{-1}) 1720.5 (imide C=O), 1670 (ter. amide C=O), 1632.5 (C=N), 1355 (sec. amide); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 8.54 – 6.68 (m, 11H, Ar-H), 4.46 – 2.93 (t, 4H, CH_2).). ^{13}C NMR (40 MHz, $CDCl_3$, δ ppm) δ 171.5, 161.0, 149.2, 148.23, 146.8, 140.25, 135.9, 134.2, 133.5, 132.6, 128.8, 127.7, 12.42, 122.1, 121.1, 118.14, 39.74, 32.01; MS: m/z 369 (M^+). Anal. Calcd. For $C_{22}H_{15}N_3O_3$: C, 71.54; H, 4.09; N, 11.38; Found C, 71.20; H, 3.98; N, 11.12.

4 C. N-((11-Oxo-11H-pyrido [2, 1-b] quinazolin-2-yl) methyl) nicotinamide. Mp. 136^0C, white crystal, IR (KBr pellets, cm^{-1}) 1675 (ter. amide C=O), 1635 (C=N), 1347 (sec. amide); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 9.16 (d, *J* = 25.0, 1H, NH), 9.03 – 8.69 (m, 2H, Ar-H), 8.49 – 7.38 (m, 8H, Ar-H), 6.91 – 6.71 (m, 1H, Ar-H).4.96 – 4.76 (d, 2H, CH_2).). ^{13}C NMR (40 MHz, $CDCl_3$, δ ppm) δ 169.5, 161.2, 152.8, 149.7, 148.9, 146.9, 139.6, 137.6, 134.9,

131.5, 129.4, 125.2, 123.0, 121.9, 121.1, 118.1, 41.2; MS: m/z 330 (M^+). Anal. Calcd. For $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96; Found C, 68.74; H, 4.1; N, 16.34

4 D. 2-((7-Hydroxy-11-oxo-11H-pyrido [2, 1-b] quinazolin-2-yl) methyl) isoindoline-1, 3-dione. Mp. 149^{0}C, light yellow, IR (KBr pellets, cm^{-1}) 1719 (imide C=O), 1665 (ter. amide C=O), 1630 (C=N),1352 (sec. amide); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 10.12 (s, 1H, OH), 8.52 – 7.63 (m, 8H, Ar-H), 6.71 (s, 1H, Ar-H), 6.24 – 6.03 (d, 1H Ar-H), 4.99 (s, 2H, CH_2).). ^{13}C NMR (40 MHz, $CDCl_3$, δ ppm) δ 170.9, 167.5, 160.3, 156.9, 150.4, 135.9, 134.3, 133.8, 132.1, 129.3, 125.5, 123.6, 121.9, 114.0, 99.9, 43.7; MS: m/z 371 (M^+). Anal. Calcd. For $C_{21}H_{13}N_2O_4$: C, 67.92; H, 3.53; N, 11.32; Found C, 67.52; H, 3.32; N, 10.94.

4 E. 2-(2-(7-Hydroxy-11-oxo-11H-pyrido [2, 1-b] quinazolin-2-yl) ethyl) isoindoline-1, 3-dione. Mp. 148-149^{0}C, white crystal, IR (KBr pellets, cm^{-1}) 1721 (imide C=O), 1668 (ter. amide C=O), 1631 (C=N),1357 (sec. amide); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 10.00 (s, 1H, OH), 8.52 – 7.41 (m, 8H, Ar-H), 6.71 (s, 1H, Ar-H), 6.24 – 6.01 (d, 1H), 4.39 – 4.07 (t, 2H, CH_2), 3.30 – 2.97 (t, 2H, CH_2).). ^{13}C NMR (40 MHz, $CDCl_3$, δ ppm) δ 171.5, 167.5, 160.7, 154.7, 149.2, 148.2, 135.9, 133.5, 132.6, 128.8, 127.9, 127.2, 122.1, 121.1, 114.1, 99.84, 39.73, 32.0; MS: m/z 385 (M^+). Anal. Calcd. For $C_{22}H_{15}N_3O_4$: C, 68.57; H, 3.92; N, 10.90; Found C, 67.99; H, 3.47; N, 10.24.

4 F. N-((7-hydroxy-11-oxo-11H-pyrido[2,1-b]quinazolin-2-yl)methyl)nicotinamide. Mp. 156^{0}C, light green powder, IR (KBr pellets, cm^{-1}) 1672 (ter. amide C=O), 1633 (C=N),1350 (sec. amide); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 9.67 (m, 2H, NH, OH), 9.03 – 8.67 (m, 2H, Ar-NCH), 8.43 – 7.42 (m, 6H, Ar-H), 6.71 (s, 1H, Ar-H), 6.24 – 6.03 (d, 1H, Ar-H), 5.00 – 4.76 (d, 2H, NCH_2).). ^{13}C NMR (40 MHz, $CDCl_3$, δ ppm) δ 169.5, 162.0, 160.9, 156.9, 152.8, 149.7, 147.0, 137.7, 135.0, 132.14, 131.9, 129.4, 125.2, 123.0, 122.0, 114.1, 99.9, 41.3; MS: m/z 346 (M^+). Anal. Calcd. For $C_{19}H_{14}N_4O_3$: C, 65.89; H, 4.07; N, 16.18; Found C, 65.28; H, 3.79; N, 15.87.

4 G. 2-((8-Methyl-11-oxo-11H-pyrido [2, 1-b] quinazolin-2-yl) methyl) isoindoline-1, 3-dione. Mp. 169^{0}C, brown crystal, IR (KBr pellets, cm^{-1}) 1724 (imide C=O), 1672 (ter. amide C=O), 1634 (C=N), 1352 (sec. amide); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 8.53 – 7.34 (m, 10H, Ar-H), 4.99 (s, 2H, CH_2), 2.07 (s, 3H, CH_3).). ^{13}C NMR (40 MHz, $CDCl_3$, δ ppm) δ 170.9, 160.8, 150.4, 148.6, 138.9, 135.9, 134.3, 133.8, 132.3,131.5, 129.4, 125.5, 125.2, 123.7, 121.7, 43.7, 14.1; MS: m/z 369 (M^+). Anal. Calcd. For $C_{22}H_{15}N_3O_3$: C, 71.54; H, 4.09; N, 11.38; Found C, 71.15; H, 3.89; N, 10.95.

4 H. 2-(2-(8-Methyl-11-oxo-11H-pyrido [2, 1-b] quinazolin-2-yl) ethyl) isoindoline-1, 3-dione. Mp. 152^{0}C,light brown crystal, IR (KBr pellets, cm^{-1}) 1719 (imide C=O), 1668 (ter. amide C=O), 1634 (C=N), 1360 (sec. amide); ^{1}H NMR (300 MHz, , $CDCl_3$, δ ppm) δ 8.59 – 7.31 (m, 10H, Ar-H), 4.32 – 4.10 (m, 2H, NCH_2), 3.21 – 3.00 (m, 2H, CH_2), 2.07 (s, 3H, CH_3).). ^{13}C NMR (40 MHz, $CDCl_3$, δ ppm) δ 171.5, 161.2, 149.2, 148.3, 146.4, 138.9, 135.9, 133.5, 132.6, 131.5, 128.8, 127.8, 125.3, 122.1, 120.9, 39.8, 32.0, 14.0; MS: m/z 383 (M^+). Anal. Calcd. For $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96; Found C, 71.85; H, 3.98; N, 12.10.

4 I. N-((8-Methyl-11-oxo-11H-pyrido [2, 1-b] quinazolin-2-yl) methyl) nicotinamide. Mp.147^{0}C, black powder, IR (KBr pellets, cm^{-1}) 1676.5 (ter. amide C=O), 1631 (C=N), 1356 (sec. amide); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) δ 9.03 – 8.69 (m, 2H, Ar-NCH), 8.53 – 7.35 (m, 8H, Ar-H), 4.98 – 4.75 (m, 2H, CH_2), 2.07 (s, 3H, CH_3).). ^{13}C NMR (40 MHz, $CDCl_3$, δ ppm) δ 169.5, 161.3, 152.8, 149.7, 148.6, 146.9, 138.9, 137.7, 134.9, 131.8, 131.6, 129.4, 125.2, 123.01, 121.8, 41.3, 14.0; MS: m/z 344 (M^+). Anal. Calcd. For $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27; Found C, 68.98; H, 4.09; N, 15.89.

Antihypertensive Activity

The experimental rats were anaesthetized with sodium pentobarbitone at a dose level of 40 mg/kg i.p. The blood pressure was recorded from the carotid artery through a pressure transducer (Stanthan P_{23}dc, Grass Instruments Co. Quincy, MA, and USA) or alternatively the right common carotid artery was cannulated and the blood pressure was recorded on a smoked paper or on a kymograph. The carotid artery and jugular vein of the rat were exposed and cannulated. The blood pressure of the rat was monitored for over fifteen minutes and once a stable blood pressure was obtained, the standard responses of adrenaline hydrochloride (1μg/kg), isoprenaline sulphate (1.2μg/kg), histamine acid phosphate (1μg/kg) and acetyl choline (1μg/kg) were obtained. All the test substances and the above reference standards were administered through an indwelling polythene cannula in the right jugular vein (1μg/kg, onward i.v.) followed by 1 ml of normal saline. The change in blood pressure to each of the compounds was noted. The effect of the test compound was monitored on blood pressure. After the recovery in blood pressure, the standard

parallel responses were repeated. The change in each of the responses was calculated with reference to the control. Respiration was recorded through a Marey's Tambour after cannulating the trachea. The contraction of the nictitating membrane of the rat was recorded by stimulating the preganglionic sympathetic nerve by a pair of bipolar electrode, using stimulator with square wave pulses (0.101 Hz) of 0.5 m/sec. duration with 2.5 volts for five seconds. The contractions were recorded by means of a frontal writing lever on kymograph. The antihypertensive activity data were collected at two dose levels i.e. at 1.0mg/kg i.v. and 5.0 mg/kg, i.v.

Table- 2.: Antihypertensive Activity

Compound Number	Antihypertensive activity in rats (dose in mg/Kg.)			
	1.0 mg/kg		5.0 mg/Kg	
	Fall in b.p. mm Hg.	Duration in min.	Fall in b.p. mm Hg.	Duration in min.
4A	NA	-	NA	-
4B	25	38	70	60
4C	60	60	120	80
4D	15	Tr	40	30
4E	55	20	135	65
4F	75	58	146	60
4G	NA	-	NA	-
4H	20	10	60	45
4I	62	65	134	54

Tr - Transitory, b.p. - blood pressure min. – minutes

RESULTS AND DISCUSSION

It is seen from the antihypertensive activity data presented in **Table-2** that out of nine quinazolone compounds, two such compounds completely failed to elicit any response. However, the seven other quinazolone compounds viz; compounds 4B ,4C, 4D, 4E, 4F, 4H and 4I showed definite antihypertensive activity at both the dose levels. Thus, compounds 4B, 4E and 4H bearing R = phthalimidoethyl substituent caused a reduction in blood pressure to the extent of 25 mmHg, 55 mmHg and 20 mmHg transiently lasting for 38, 20 and 10 minutes at 1.0mg/kg i.v. dose level while the same compounds caused a decrease in b.p. to the extent of 70 mmHg, 135 mmHg and 60 mmHg lasting for 60, 65 and 45 minutes at 5.0 mg/kg, i.v. dose level. Nicotinamido substituted quinazolone compounds 4C, 4F and 4I were found most active of the series since they caused a diminution of blood pressure to the extent of 60 mmHg, 75 mmHg and 62 mmHg respectively which lasting for 60, 58 and 65 minutes at 1.0 mg/kg i.v. dose level and 120 mmHg, 146 mmHg and 134 mmHg decrease lasting for 80, 60 and 54 minutes at 5.0mg/kg i.v. dose level. It is very interesting to observe here that even a minor alternation in the molecular framework may cause a profound effect on the antihypertensive activity. Thus, compounds 4A and 4G bearing phthalimidomethyl substituent were found completely inactive while phthalimido ethyl substituted quinazolone compounds caused a decrease in blood pressure at both the dose levels.

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