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ATTEMPTED LINEAR SYNTHESIS IN THE DEVELOPMENT OF COMPOUNDS DESIGNATED AS N-[(ARYLAMIDO/IMIDO-2-YL)ALKYL]-4-OXO-2-PHENYLQUINAZOLIN-3(4H)-CARBOXIMIDAMIDES FOR EXAMINING THEIR EFFECT ON SUGAR METABOLISM.

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***Abstract*—2-aminobenzoic acid (anthranilic acid) reacted with benzoyl chloride in pyridine to furnish 2-phenyl-4H-benzo[d][1,3]oxazin-4-one(I), which was heated with guanidine for 1 hour to give 4-oxo-2-phenylquinazoline-3(4H)-carboximidamide (II). (II) On reaction with N-(hydroxyalkyl) aryl-amides/ imides afforded the final compounds N-[(arylamido/ imido-2yl)alkyl]-4-oxo-2-phenyl-quinazolin-3(4H)-carboximidamides (III) in yields of 45 to 60%. The target compounds were examined for their effect on sugar metabolism.**

***Index Terms*— Antihyperglycemic, quinazole, guanidine, diabetes mellitus.**

I. INTRODUCTION

Quinazoline is a six-membered heterocyclic ring system reported for their biological activities. These compounds with multiple pharmacophores are of considerable interest because of the diverse range of biological properties1 associated with them. In addition, guanidine compounds2 such as metformin, phenformin ertc. have shown excellent results in controlling diabetes mellitus3 and a few such compounds are currently in clinical application4. It is therefore expected that union of two biologically active nuclei viz. quinazole and guanidine in one nuclear architecture might result in improved therapeutic results.

II. EXPERIMENTAL

2-Phenyl-4H-benzo[d][1,3]-oxazin-4-one(I)

Anthranilic acid (2-aminobenzoic acid) (0.1 mole) was dissolved in minimum volume of dry pyridine (30 ml) by shaking. To this solution an ice cold solution of benzoyl chloride (0.2 mole) taken in dry pyridine (30 ml), was added slowly with constant stirring. When the addition was completed (the operation of addition required half an hour), the resultant solution was subjected to vigorous stirring for one hour mechanically. Subsequently, it was left as such for one hour at room temperature and treated with a solution of sodium bicarbonate (10%). Addition of sodium bicaronate solution was continued till the effervescence due to the evolution of carbon dioxide ceased. The separated solid was washed with cold water repeatedly till there was no smell of pyridine and unreacted benzoyl chloride. The crude benzoxazine was dried in vacuo overnight and recrystallization from diluted ethanol afforded analytically pure sample of 2-phenyl benzo[d] [1,3]oxazin-4-one as white crystalline mass. It melted at 122-1230C [1240 C]5-7 yield 80%.

4-Oxo-2-phenylquinazolin-3(4H)-carboximidamide (II)

A mixture of finely powdered 2-phenyl-4H-benzo [d][1,3]oxazin-4-one (0.01 mole) and guanidine (0.01 mole) was heated in such a manner that the temperature of the reaction mixture did not exceed 1400C. At this temperature thick liquid was obtained and the heating was continued for two hours. The molted mass was allowed to attain the room temperature. On attaining the room temperature a solid was obtained which was washed with diluted hydrochloric acid (3x10). The properly washed material was dried at 1000C and recrystallization from diluted ethanol afforded analytically pure sample of 4-oxo-2-phenylquinazolin-3(4H)-carboximidamide (II) as white crystalline mass. It melted at 175-1760C, yield 85%.

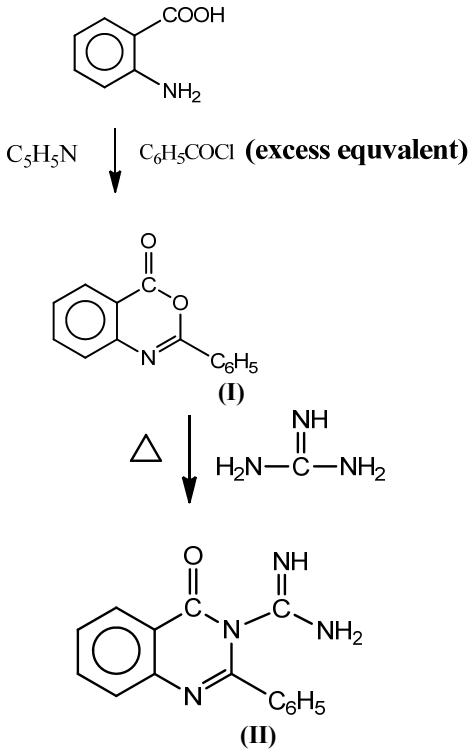
Anal. Calcd. for C15H12N4O, N, Calcd. 21.21 % Found 21.15%.

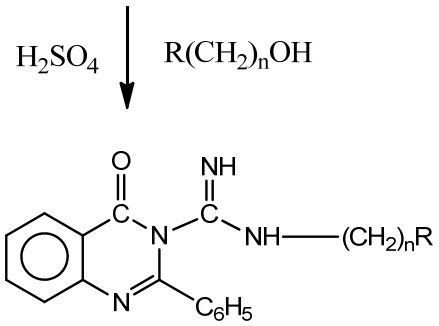
IR (KBr) (v cm-1) : 1709.1 (imide C=O), 3450, 3370 (primary amine free, two bands fairly sharp) 3500 (sec. amine, one band only), 1641.2 (C=N, cyclic), 1345 (C-N).

1H NMR (CDCl3) (δ ppm) : 7.25-7.78 (m, 9H,ArH), 4.50 (s,1H, C=NH), 5.75 (s, 2H, NH2).

N-[(Arylamido/imido-2-yl)alkyl]-4-oxo-2-phenyl quinazolin-3(4H)-carboximidamides (III)

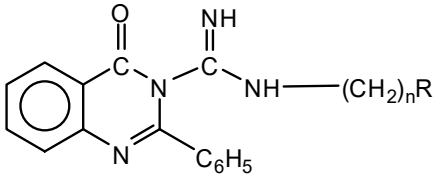
4-Oxo-2-phenylquinazolin-3(4H)-carboximid- amides (II) (0.05 mole) and an arylamido imido alcohol (0.05 mole) in their finely powdered form were dissolved in concentrated sulphuric acid (30 ml) by stirring vigorously with utmost care. After dissolution of the contents, the colour darkened which was further stirred mechanically for one hour. Subsequently, the resultant solution was cooled by leaving under refeigeration overnight. It was poured into ice-cold water in instalments with stirring after each addition. After the process of addition was completed the solution containing solidified mass was left undisturbed for one hour. During this period, precipitation was completed and the precipitated mass settled down. It was filtered off and the residual material was washed with cold water repeatedly. It was dried with ethanol vapours and recrystallization was done from ethanol containing decolourising carbon. The target compounds thus obtained are presented in table I along with their data of characterization.





SCHEME

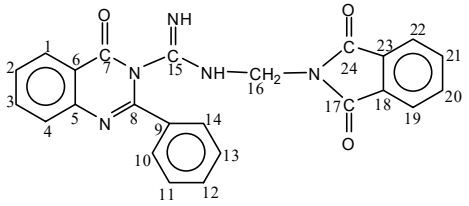
TABLE I



Characterization data of N-[(Arylamido/imido-2-yl) alkyl]-4-oxo-2-phenylquinazolin-3(4H)-carboximid- amides (III)

Compd. No.	R	n	M.P. (ºC)	Yield (%)	Colour	Molecular formula	Molecular weight	Analysis Nitrogen %	
								Calcd.	Found
III a.	Phthalimido	1	165-166	55	white	$C_{24}H_{17}N_5O_3$	423	16.54	16.17
III b.	Nicotinamido	1	155-156	50	white	$C_{22}H_{18}N_6O_2$	398	21.10	21.01
III c.	2-hydroxy benzamido	1	160-161	45	light brown	$C_{23}H_{19}N_5O_3$	413	16.94	16.55
III d.	Phthalimido	2	160-161	51	white	$C_{25}H_{19}N_5O_3$	437	16.01	15.85
III e.	3-[4-oxo-2-phenyl-quinazolin]-	2	158-159	60	white	$C_{31}H_{24}N_6O_2$	512	16.40	16.15

Spectral data of N-[(1,3-dioxoindolin-2-yl) methyl]-4-oxo-2-phenylquinazolin-3(4H)-carboximidamide (III a)



IR(KBr) IR(KBr) (vcm-1) : 1685.0 (imide C=O), 1643.9 (tert. amide C=O), 1611.2 (C=N) 3463.2 (sec. NH).

1H NMR (DMSO-d6) : 7.21-8.730 (m,13H, ArH), 3.34 (s, 2H, N-CH2),12.18 (s,1H, NH),13.63 (brs, 1H, C=NH).

^{13}C NMR (DMSO-d6) : 39.51(C-16), 116.54, 119.92, 123.00, 127.06, 129.04, 131.34, 132.24, 134.38, 134.56, 141.16 (C-1 to 6, C-9 to C-14, C-18 to C-23), 164.75 (C-8), 170.08 (C-7, C-19,C-24).

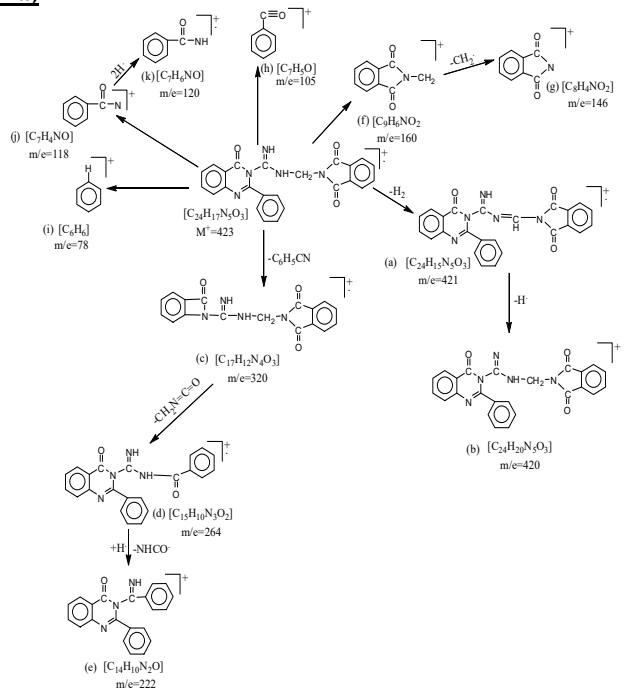
Important mass spectral peaks of N-[(1,3-dioxo isoindolin-2-yl)methyl]4-oxo-2-phenylquinazolin-3(4H)-carboximidamide (III a)

TABLE II

Fragment no.	Molecular formula	m/e
M^+	$C_{24}H_{17}N_5O_3$	423
(a)	$C_{24}H_{15}N_5O_3$	421
(b)	$C_{24}H_{14}N_5O_3$	420
(c)	$C_{17}H_{12}N_4O_3$	320
(d)	$C_{15}H_{10}N_3O_2$	264
(e)	$C_{14}H_{10}N_2O$	222
(f)	$C_9H_6NO_2$	160
(g)	$C_8H_4NO_2$	146
***(h)**	C_7H_5O	105
(i)	C_6H_6	78
(j)	C_7H_4NO	118
(k)	C_7H_6NO	120

*Base peak

Mass spectral pattern of N-[(1,3-dioxoisoindolin-2-yl) methyl]4-oxo-2-phenylquinazolin-3(4H)-carboximidamide (III a)



III. BIOLOGICAL ACTIVITY

A. Materials and method

In order to perform antihyperglycemic activity in sucrose-loaded rat model, male albino rats of either Charles Foster or Wistar strain of average body weight 160 + 20g each were selected. Fasting blood glucose level of each animal was checked by glucometer using glucostrips (Roche) after an overnight starvation. Animals showing blood glucose between 60 to 80 mg/dl (3.33 to 4.44 mM) were finally selected and were divided into groups of five animals in each.

Rats of experimental group were administered the suspension of the test compound orally (made in 1.0% gum acacia) at desired dose level (100mg/kg body weight). Animals of control groups were given an equal amount of 1.0% gum acacia. A sucrose load of 10g/kg body weight was always given to each animal orally exactly after 30 minutes post administration of the test sample/ vehicle. Blood glucose profile of each rat was again determined at 30, 60, 90 and 120 minutes post administration of sucrose by glucostrips. Food but not water was withheld from the cages during the course of experimentation. Comparing the Area Under Curve (AUC) of experimental and control groups determined the percentage improvement on oral glucose tolerance.

B. Statistical analysis

Quantitative glucose tolerance of each animal was calculated by Area Under Curve (AUC) method using Prism Software. Comparing the AUC of experimental and control groups determined the percentage antihyperglycemic activity. Statistical comparison was made by Dunett's test. Results are expressed as mean + SEM.

Antihyperglycemic activity data of N-[2-(aryl-amido/imido-2-yl)alkyl]-4-oxo-2-phenyl-quinazolin-3(4H)-carboximidamides (III)

Compound no.	R	n	Dose (mg/kg)	Precent antihyperglycemic activity (2h AUC)
III a.	Phthalimido	1	100	-7.07
III b.	Nicotinamido	1	100	+31.8
III d.	Phthalimido	2	100	+34.2

Three (III a, III b, III d) of the five target quinazole compounds were subjected for their bioevaluation against sucrose loaded rat models with a dose of 100mg/kg body weight of the experimental animal. Two quinazole compounds viz; III b and III d displayed 31.8 and 34.2 percent antihypertensive activity, respectively, while the compound no. III a showed a negative value of 7.07%. This implies that this compound (compound no.III a) increased the diabetic condition in the experimental animal i.e. increased the glucose level in the blood of the rat as compared to control. It is very interesting to notice here that even a slight change in the molecular structure has a profound effect on the activity and potency. Thus, the compound no. III a bearing a phthalimido methyl substituent was found to increase

the glucose level in the experimental animals while the compound no. III d having a phthalimido ethyl substituent showed antihyperglycemic activity to the extent of 34.2 percent. This suggests that the phthalimido ethyl substituted quinazole compound binds effectively with the receptor to form a complex for providing a response while phthalimido methyl substituted compound is behaving like an antagonist. Further, the compound no. III b having R=nicotinamido and n=1 i.e. a nicotinamido methyl substituent showed antihyperglycemic activity to the magnitude of 31.8 percent. Interest in quinazole chemistry has increased manifolds because of their association with various biological properties. Literature survey reveals that a few quinazole compounds cause the depletion of glucose either by inhibiting the gluconeogenesis or by stimulating the release of insulin from pancreas. Secondly because of an easy access to the synthesis of quinazole compounds, such compounds are preferable for the generation of antihyperglycemic agents in future.

IV. CONCLUSION

Qualitative structure activity relationship (QSAR) study provides a valuable information with regard to antihyperglycemic activity and the structural characteristic of the compound. It has also been observed that a phthalimidoethyl substituent provides a better biologic response than a phthalimidomethyl substituent.

V. ACKNOWLEDGEMENT

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