

Synthesis and Hypoglycemic Activity of Substituted-3-(substituted-arylcarbiminoacetyl)aminomethyl-4(3H)-quinazoline

VEENA R. AGARWAL, SUDHA R. NAUTIYAL and D. D. MUKERJI*

Department of Chemistry, Lucknow University, Lucknow-226 007

Manuscript received 31 October 1985, accepted 25 June 1986

Thirtytwo new substituted-3-(substituted-arylcarbiminoacetyl)aminomethyl-4(3H)-quinazoline (2) were synthesised by condensation of substituted-3-(4-aryl substituted-carbamidoacetyl)aminomethyl-4(3H)-quinazolones (1) and *p*-substituted-aniline in anhydrous pyridine. The compounds were screened for hypoglycemic activity. Only eleven out of thirtytwo compounds were found to be hypoglycemic. The compounds were characterised by tlc, elemental analyses and ir spectra.

VARIOUS quinazolinones and related compounds are reported to possess bactericidal¹, virucidal², NS-depressant³ and hypoglycemic⁴⁻⁸ activities. Recently, thiadiazole derivative of quinazolin-4-ones were also found to possess hypoglycemic activity^{9,10}. Thus, substituted-3-(substituted-arylcarbiminoacetyl)aminomethyl-4(3H)-quinazolones were synthesised with a view of obtaining hypoglycemic compounds of high potency. Such compounds were synthesised by the reaction of substituted-3-(4'-aryl-substituted-carbamidoacetyl)aminomethyl-4(3H)-quinazolones and *p*-substituted-aniline in anhydrous pyridine. The compounds exhibited characteristic absorption bands at 3 250-1 320 (NH), 1 700-1 730 (C=O), 1 660-1 700 (CH₂-CONH), 1 620-1 625 (C=N) cm⁻¹ in their ir spectra.

Experimental

Melting points were taken in open capillaries and are uncorrected. Ir spectra were recorded on a Perkin-Elmer spectrophotometer in KBr pellets.

6- or 6,8-Di-substituted-3-aminomethyl-4(3H)-quinazolones: These were prepared according to the method of Mukerji and Nautiyal¹¹.

α -Chloroacetyl-N-arylureas: These were synthesised following the method of Jacobs *et al.*¹².

Substituted-3-(4'-substituted-arylcarbimidoacetyl)aminomethyl-4(3H)-quinazolones (1): These compounds were prepared according to the method of Mukerji *et al.*¹³.

Substituted-3-(substituted-arylcarbiminoacetyl)aminomethyl-4(3H)-quinazolones (2): Substituted-3-(4'-aryl-substituted-carbamidoacetyl)aminomethyl-4(3H)-quinazolones (0.005 mol) and *p*-methylaniline (0.005 mol) were refluxed in anhydrous pyridine (5 ml) for 4 h. The mixture was cooled and then poured on ice-cold water containing

TABLE 1—PHYSICAL DATA OF SUBSTITUTED-3-(SUBSTITUTED-ARYLCARBIMINOACETYL)AMINOMETHYL-4(3H)-QUINAZOLONE (SCHEME 3)

Compd. no.	R	R ₁	R ₂	M _p °C
	<u>R¹ = CH₃</u>			
1	C ₆ H ₅	H	H	270
2	C ₆ H ₅	Br	H	258
3	C ₆ H ₅	Br	Br	254
4	C ₆ H ₅	NO ₂	H	218
5	4-ClC ₆ H ₄	H	H	232
6	4-ClC ₆ H ₄	NO ₂	H	258
7	3-NO ₂ C ₆ H ₄	H	H	210
8	4-NO ₂ C ₆ H ₄	H	H	250
9	2-CH ₃ C ₆ H ₄	H	H	235
10	2-CH ₃ C ₆ H ₄	NO ₂	H	240
11	4-CH ₃ C ₆ H ₄	H	H	256
12	4-CH ₃ C ₆ H ₄	Br	H	186
13	2-CH ₃ OC ₆ H ₄	H	H	220
14	2-CH ₃ OC ₆ H ₄	Br	H	252
15	3-CH ₃ OC ₆ H ₄	H	H	235
16	3-CH ₃ OC ₆ H ₄	Br	H	242
	<u>R₁ = OCH₃</u>			
17	C ₆ H ₅	H	H	252
18	C ₆ H ₅	Br	H	245
19	C ₆ H ₅	Br	Br	232
20	C ₆ H ₅	NO ₂	H	235
21	4-ClC ₆ H ₄	H	H	251
22	4-ClC ₆ H ₄	NO ₂	H	230
23	3-NO ₂ C ₆ H ₄	H	H	247
24	4-NO ₂ C ₆ H ₄	H	H	206
25	2-CH ₃ C ₆ H ₄	H	H	231
26	2-CH ₃ C ₆ H ₄	NO ₂	H	200
27	4-CH ₃ C ₆ H ₄	H	H	210
28	4-CH ₃ C ₆ H ₄	Br	H	220
29	2-CH ₃ OC ₆ H ₄	H	H	204
30	2-CH ₃ OC ₆ H ₄	Br	H	195
31	3-CH ₃ OC ₆ H ₄	H	H	180
32	3-CH ₃ OC ₆ H ₄	Br	H	202

Yield of the compounds were in range of 65-75%. C, H and N values were found within $\pm 0.045\%$ of the calculated values.

concentrated hydrochloric acid. The solid mass separated was filtered, washed with ice-cold water, dried and recrystallised from ethanol (Table 1).

Compound nos. 17–32 were prepared by using *p*-methoxyaniline (0.005 mol) in place of *p*-methylaniline in the above reaction (Table 1).

Hypoglycemic activity: All the compounds were screened on rats for their hypoglycemic activity following the method of Nelson¹⁴. Albino rats each weighing approximately 200 g, were kept fasting for 18 h. Blood samples were drawn from the tail vein of the rats and their glucose contents estimated. The compound to be tested, after being emulsified with 5% gum tragacanth, was administered orally at a single dose of 250 mg/kg body weight. The blood samples were again drawn from the tail vein at intervals of 1, 2 and 4 h and their glucose content estimated. The percentage inhibition in the blood glucose level was calculated. Every experiment was repeated twice. Tolbutamide was taken as a standard.

Results and Discussion

Hypoglycemic activity of the title compounds have been recorded in Table 2. Amongst the 32 compounds tested (Table 2) only 11 compounds were found to be active. These compound nos. 1, 13-17, 26, 29-33, exhibited 13-22% activity. The results show that the compounds having OCH_3 and CH_3 groups at phenyl rings exhibit maximum efficacy to reduce hyperglycemia in albino rats, *i.e.* compound nos. 13, 14, 16 and 26 have 18-20% activity. These compounds have OCH_3 group at one phenyl ring while CH_3 group on the other phenyl ring. The quinazolones were simple, mono-bromo and nitro substituted.

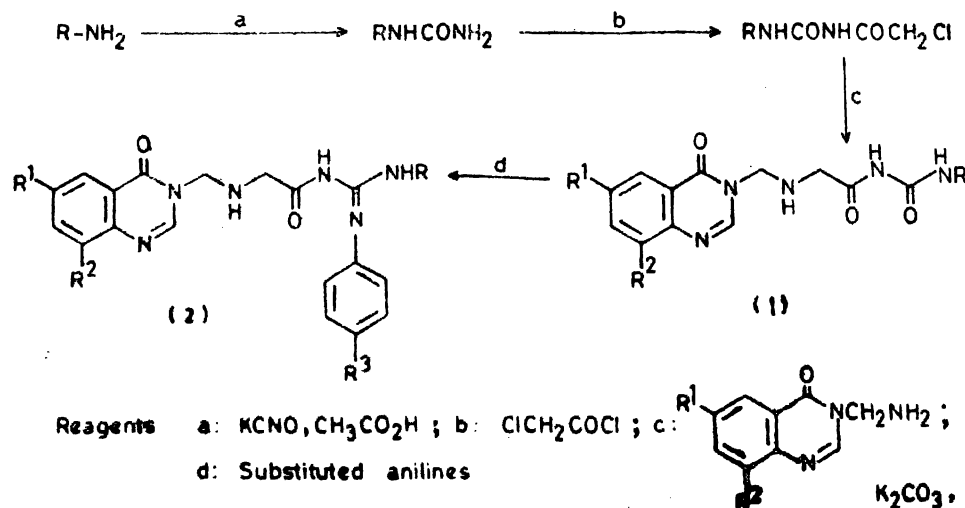
Title compounds **2** having CH₃ at R₃ position, exhibited 15% activity to lower the raised plasma glucose level due to diabetes, but when CH₃ is

TABLE 2—HYPOGLYCEMIC ACTIVITY OF SUBSTITUTED-3-(SUBSTITUTED-ARYLCARBIMINOACETYL)AMINOMETHYL-4(3*H*)-QUINAZOLONE (SCHEME 3)

Compd. no.	R	R ₁	R ₂	R ₃	Average maximum reduction of blood glucose <i>in vivo</i> (%)
1	C ₆ H ₅	H	H	CH ₃	15.00
2	C ₆ H ₅	Br	H	CH ₃	4.8
3	C ₆ H ₅	Br	Br	CH ₃	2.5
4	C ₆ H ₅	NO ₂	H	CH ₃	3.0
5	4-ClC ₆ H ₄	H	H	CH ₃	1.0
6	4-ClC ₆ H ₄	NO ₂	H	CH ₃	4.9
7	3-NO ₂ C ₆ H ₄	H	H	CH ₃	5.2
8	4-NO ₂ C ₆ H ₄	H	H	CH ₃	5.5
9	2-CH ₃ C ₆ H ₄	H	H	CH ₃	3.2
10	2-CH ₃ C ₆ H ₄	NO ₂	H	CH ₃	4.0
11	4-CH ₃ C ₆ H ₄	H	H	CH ₃	3.9
12	4-CH ₃ C ₆ H ₄	Br	H	CH ₃	5.0
13	2-CH ₃ OC ₆ H ₄	H	H	CH ₃	20.0
14	2-CH ₃ OC ₆ H ₄	Br	H	CH ₃	18.0
15	3-CH ₃ OC ₆ H ₄	H	H	CH ₃	13.2
16	3-CH ₃ OC ₆ H ₄	Br	H	CH ₃	19.5
17	C ₆ H ₅	H	H	OCH ₃	22.0
18	C ₆ H ₅	Br	H	OCH ₃	6.5
19	C ₆ H ₅	Br	Br	OCH ₃	7.0
20	C ₆ H ₅	NO ₂	H	OCH ₃	3.2
21	4-ClC ₆ H ₄	H	H	OCH ₃	4.0
22	4-ClC ₆ H ₄	NO ₂	H	OCH ₃	2.0
23	3-NO ₂ C ₆ H ₄	H	H	OCH ₃	0.0
24	4-NO ₂ C ₆ H ₄	H	H	OCH ₃	2.8
25	2-CH ₃ C ₆ H ₄	H	H	OCH ₃	5.5
26	2-CH ₃ C ₆ H ₄	NO ₂	H	OCH ₃	18.5
27	4-CH ₃ C ₆ H ₄	H	H	OCH ₃	4.6
28	4-CH ₃ C ₆ H ₄	Br	H	OCH ₃	5.0
29	2-CH ₃ OC ₆ H ₄	H	H	OCH ₃	15.0
30	2-CH ₃ OC ₆ H ₄	Br	H	OCH ₃	13.4
31	3-CH ₃ OC ₆ H ₄	H	H	OCH ₃	16.0
32	3-CH ₃ OC ₆ H ₄	Br	H	OCH ₃	18.0

replaced by OCH_3 group at R_2 position the compound no. 17 showed maximum activity against hyperglycemia.

Thus it was concluded that the compounds having minimum substitution at quinazolone, OCH₃,



or CH₃ at R₂ and at the *para* position of phenyl ring (at R), exhibited good hypoglycemic activity.

Acknowledgement

The authors express their sincere thanks to the Head, Chemistry Department, Lucknow University, for providing facilities, and to Director, C.D.R.I., for micro and spectral analyses. One of the authors (S R N) thanks C S I.R., New Delhi, for P.D F.

References

1. R. S. VARMA, *J. Indian Chem. Soc.*, 1975, 52, 344.
2. M. YAMAMOTO, K. ISHIZUMI, S. MOROOKA, K. MORI and H. NOGUCHI, Ger. Pat. 2 242 375/1973 (*Chem. Abstr.*, 1973, 78, 159660).
3. D. D. Mukerji, S. R. NAUTIYAL and C. R. PRASAD, *Indian J Pharm. Sci.*, 1978, 40, 44.
4. W. MERKEL, H. G. ALPERMANN, K. GEISEN, N. KOTHE and W. REID, Ger. Pat. 2 623 846/1977 (*Chem. Abstr.*, 1978, 88, 121229).
5. M. YAMAMOTO, M. KOSHIBA and H. YAMAMOTO, Jap. Pat. 7 805 180/1978 (*Chem. Abstr.*, 1978, 89, 43474).
6. C. M. GUPTA, S. T. HUSAIN, A. P. BHADURI, N. M. KHANNA and S. K. MUKHERJEE, *Nature*, (London), 1969, 223, 524.
7. M. SETH and N. M. KHANNA, *Indian J. Chem., Sect. B*, 1976, 14, 536.
8. M. I. HUSAIN and G. C. SRIVASTAVA, *Indian J. Chem., Sect. B*, 1980, 19, 916.
9. M. I. HUSAIN and K. B. GUPTA, *Indian J. Pharm. Sci.*, 1982, 44, 37.
10. D. D., MUKERJI, V. R. AGARWAL and S. R. NAUTIYAL, *Indian J. Pharm. Sci.*, 1985, 47, 8.
11. D. D. MUKERJI and S. R. NAUTIYAL, *J. Indian Chem. Soc.*, 1979, 56, 1226.
12. W. A. JACOBS, M. HEIDELBERGER and I. P. ROLF, *J. Am. Chem. Soc.*, 1919, 41, 458.
13. D. D. MUKERJI, S. R. NAUTIYAL and C. R. PRASAD, *J. Trakt. Chem. Band*, 1980, 322, 5, 855.
14. N. NELSON, *J. Biol. Chem.*, 1944, 153, 375.