NEW HYPOGLYCEMIC AGENTS: SYNTHESIS AND HYPOGLYCEMIC ACTIVITY OF SOME NEW 1-[{*p*-(4-OXO-2-SUBSTITUTED-3(4H)-QUINAZOLINYL)-PHENYL}SULPHONYL]-3-ARYL/CYCLOHEXYL-2-THIOUREAS‡

G. RAMA MURTHY†, V. MALLA REDDY, A. BHASKAR RAO* and P. V. DIWAN*

Medicinal Chemistry Laboratory, University College of Pharmaceutical Sciences, Kakatiya University, Warangal 506 009, India.

**Regional Research Laboratory, Hyderabad 500 007, India.*

ABSTRACT

Fifteen new 1-[{*p*-(4-oxo-2-methyl/phenyl-3(4H)-quinazolinyl)-phenyl}sulphonyl]-3-aryl/cyclohexyl-2-thioureas have been synthesized by the condensation of four different aryl isothiocyanates or cyclohexyl-isothiocyanate with three N^4-(2-methyl/phenyl-4-quinazolinon-3-yl) sulphanilamides prepared for the purpose. Four of them have been found to exhibit a remarkable blood sugar lowering effect against the streptozotocin-diabetic rats.

INTRODUCTION

THE second generation of hypoglycemic sulphonyl ureas showed a notable change in the nature of substituents in the benzene ring as well as at the nitrogen. This resulted in introduction of the relatively bulkier and less polar or non-polar groups in place of simple alkyl groups[1]. In agreement with this, the synthesis and hypoglycemic activity of some quinazolinylsulphonyl ureas have been reported in recent years[2]. Interestingly, some sulphonylthioureas have also been shown to exhibit hypoglycemic activity[3]. In continuation of the work in the search of new hypoglycemic agents[4–6], it has been considered worthwhile to synthesize some of the new sulphonylthioureas containing quinazolinonyl and aryl groups as their N-substituents in order to evaluate them for their possible hypoglycemic activity.

Three different N^4-(2-methyl/phenyl-4-quinazolinon-3-yl)-sulphanilamides (I) have been obtained on the condensation of sulphanilamide with appropriate 2-methyl/phenyl-1, 3,4-benzoxazinones, in pyridine. Each of these N^4-quinazolinonylsulphanilamides (I) has been reacted with four different aryl isothiocyanates and cyclohexyl-isothiocyanate in the presence of anhydrous potassium carbonate, in dry dimethylformamide to get colourless crystalline solids which have been purified and characterized as the title compounds (II) by their physical, analytical and spectral data.

MATERIALS AND METHODS

The purity of the compounds was checked by TLC. Melting points were determined in open capillaries using a melting point apparatus (Toshniwal) and are uncorrected. IR spectra were recorded on a spectrophotometer Perkin-Elmer Infracord-283 in nujol and PMR spectra on a 60 MHz spectrophotometer (Varian EM-360) using TMS as the internal reference. Mass spectra of the compounds were recorded on a double focussing spectrometer (CEC, 2–110B), using direct inlet system.

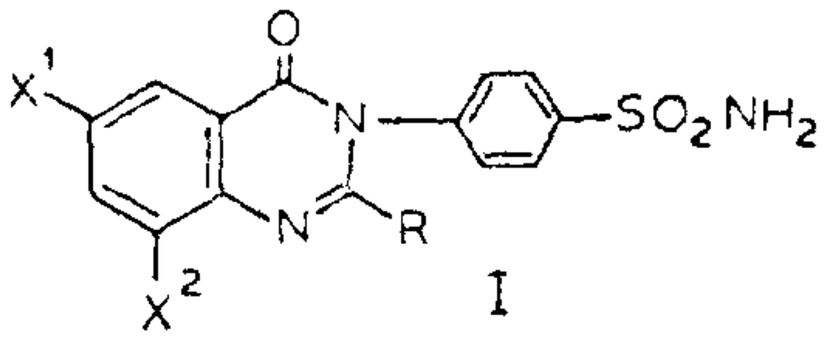
2-Methyl and 2-phenyl-1,3,4-benzoxazinones were prepared by the known procedure[7]. Similarly, 6,8-dibromo-2-methyl-1, 3-benzoxazin-4-one was also prepared by the known method[8].

N^4-(2-methyl/phenyl-4-quinazolinon-3-yl)sulphanilamides (I)—General procedure:

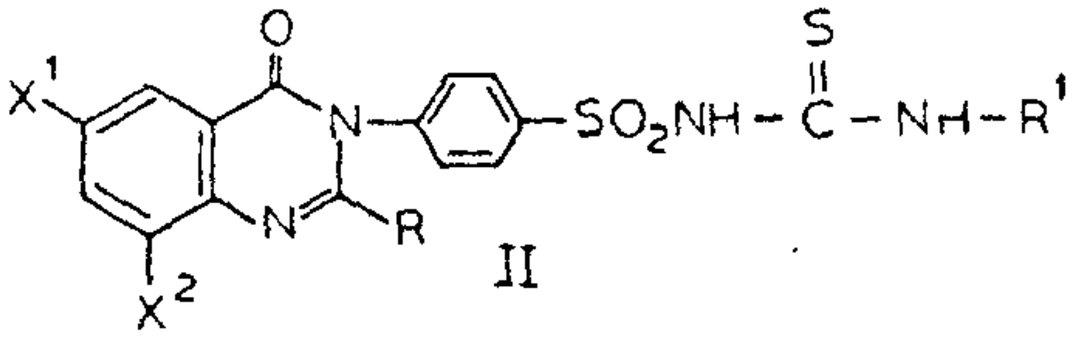
An equimolar mixture of the benzoxazinone and sulphanilamide (0.1 mol, each) was taken in a round-bottomed flask (100 ml) and extra pure pyridine (20 ml) was added to it, while shaking. The contents of the flask were refluxed on a low, nonluminous flame for 6–8 hr. Pyridine was distilled-off to a large extent and the residual liquid was then poured onto a little crushed ice with constant stirring. It was kept aside for cooling and the resultant product was filtered at the pump, washed with small portions of cold water and dried.

‡Presented in the Organic Chemistry Section of the Sixth Conference of Indian Council of Chemists held at Madurai during 27–29 December 1986, Abstr. No. 00/102.

† For correspondence.



I



II

i) *N^4-(2-methyl-4-quinazolinon-3-yl) sulphanilamide*

(*I*; $X^1 = X^2 = H$; $R = CH_3$): Recrystallized from alcohol and DMF, yield: 2.5 g (80%); m.p. 252° (Lit.[9] m.p. 254–55°).

ii) *N^4-(2-phenyl-4-quinazolinon-3-yl) sulphanilamide*

(*I*; $X^1 = X^2 = H$; $R = Ph$): Recrystallized from dimethylformamide, yield: 3.0 g (80%), m.p. 157° (Lit.[10] m.p. 157°).
IR (*in* cm^{-1}): 3200–3360 (NH_2); 1680 (C=O); 1610–1620 (C=N); 1220–1160 ($-SO_2NH$); *PMR (in DMSO-d_6; values in* δ, *ppm*): 6.8–8.2 (m, 13H, Ar-H), 10.4 (bs, 2H, NH_2):
Mass: M^+ at m/z 377.

iii) *N^4-(6,8-dibromo-2-methyl-4-quinazolinon-3-yl) sulphanilamide*

(*I*; $X^1 = X^2 = Br$; $R = CH_3$): Recrystallized from dimethylformamide, yield: 3.8 g (75%), m.p. 335°. [Found: C, 37.80; H,2.22; N,8.64; $C_{15}H_{11}N_3SO_3Br_2$ requires C,38.05; H,2.32; N,8.87%]. *IR* (*in* cm^{-1}): 16.80 (C=O of quinazolinone), 3200–3320 (NH_2), 1620 (C=N); 1170–1210 ($-SO_2NH$); *PMR (in DMSO-d_6: values in, ppm):* 2.2 (s, 3H, Ar-CH_3), 7.0–8.2 (m, 6H, Ar-H), 9.4(bs, 2H, NH_2).

1-[{p-(4-Oxo-2-substituted-3(4H)-quinazolinyl)-phenyl}sulphonyl]-3-aryl/cyclohexyl-2-thioureas (II)—General procedure:

In a round-bottomed flask, dry powder of N^4(2-substituted 4-quinazolinon-3-yl)sulphanilamide (I; 0.01 mol) was taken and dissolved in dry, hot dimethylformamide (20 ml). The freshly dried and powdered anhydrous potassium carbonate (2 g) was added to the solution followed by the appropriate isothiocyanate (0.01 mol). This mixture was refluxed gently over a low, nonluminous flame for 10 hr. The reaction mixture was filtered, the clear solution was poured onto a little crushed ice (while stirring) and carefully acidified with dil.hydrochloric acid, maintaining the temperature below 5°C. The resultant product was filtered at the pump, washed thoroughly with small portions of cold water and dried.

The compounds were purified by recrystallization from suitable solvents and their physical and analytical data are presented in table 1. Yields of the compounds generally ranged between 60 and 75%. Spectral data of a representative compound *IIf*: *IR:* 3240–3350 (−NH); 1680 (C=O; quinazolinone); 1170–1230 ($-SO_2-$) and 1120–1140 (C=S) cm^{-1}. *PMR (in DMSO-d_6*; δ, *ppm):* 2.49 (s, 3H, Ar-CH_3); 4.68 (s, 2H, N-CH_2-Ph), 6.90–7.79 (m, 13H, Ar-H), 8.14 (bs, 1H, SO_2NH, D_2O exchangeable); 8.40 (bs, 1H, CS-NH; D_2O exchangeable). *Mass:* M^+ at m/z 464.

Biologic activity

Toxicity studies

Healthy, random-breed mice weighing 25–30 g were starved overnight and the CMC-Na suspensions of test compounds, administered in graded doses. Each dose group consisted of 5 male and 5 female mice and observed over a period of four days, after administration of the test compounds. The LD_{50} values were determined by probit analysis method and are presented in table 1.

Hypoglycemic activity

The test compounds were evaluated for their oral hypoglycemic activity against the normal (non-diabetic) and streptozotocin-induced diabetic rats employing tolbutamide and phenformin.HCl as the standards. Male wister rats weighing 180–200 g were administered streptozotocin, 100 mg/kg (b.w.) intraperitoneally. After 8 days, the positive diabetic rats having blood-glucose levels 280–350 mg/ml were made use for the determination of hypoglycemic activity of the present compounds adopting standard procedure[11]. The results are presented in table 1.

RESULTS AND DISCUSSION

Table 1 indicates that the test compounds (except IIa and IIo) are quite safe with their LD_{50} values being 1500–1600 mg/kg (b.w.) orally and 500–600 mg/kg (b.w.) intraperitoneally.

It was observed that the test compounds failed to exhibit any hypoglycemic activity in normal (non-diabetic) rats when compared to the reference drug

Table 1 *Physical, analytical and pharmacological data of 1-[{p(4-oxo-2-substituted-3(4H)-quinazolinyl)-phenyl} sulphonyl]-3- aryl/cyclohexyl-2-thioureas (II)*

Compd. No.	Substituents R	Substituents R^1	Mol. formula	m.p. °C	Recrystallization solvent	% of nitrogen * obs. (calc.)	LD_{50} values (mg/kg) Oral	LD_{50} values (mg/kg) I.P.	Anti-hyperglycemic activity p.o.**
			$X^1 = X^2 = H$						
IIa	Ph	benzyl	$C_{28}H_{22}O_3N_3S_2$	110	$CHCl_3$	10.82 (10.64)	1200	400	17.33 ± 3.86
IIb	Ph	phenyl	$C_{27}H_{20}O_3S_2N_4$	185	EtOH	10.42 (10.93)	1600	600	35.83 ± 3.60
IIc	Ph	*o*-anisyl	$C_{28}H_{22}O_4S_2N_4$	150	Me_2CO	10.02 (10.33)	1600	600	23.75 ± 2.85
IId	Ph	*o*-tolyl	$C_{28}H_{22}O_3S_2N_4$	182	DMF	10.24 (10.64)	1500	500	26.46 ± 1.02
IIe	Ph	cyclohexyl	$C_{27}H_{26}O_3S_2N_4$	125	Me_2CO	10.92 (10.81)	1500	600	18.30 ± 3.35
IIf	CH_3	benzyl	$C_{23}H_{20}O_3S_2N_4$	210	EtOH	12.30 (12.06)	1500	600	8.03 ± 2.34
IIg	CH_3	*o*-anisyl	$C_{23}H_{20}O_4S_2N_4$	165	Me_2CO	11.82 (11.68)	1600	600	44.16 ± 5.80
IIh	CH_3	*o*-tolyl	$C_{23}H_{20}O_3S_2N_4$	172	EtOH:DMF(3:1)	12.05 (12.60)	1600	600	20.12 ± 3.38
IIi	CH_3	cyclohexyl	$C_{22}H_{24}O_3S_2N_4$	184	Me_2CO	12.08 (12.28)	1600	600	18.72 ± 3.20
IIj	CH_3	phenyl	$C_{22}H_{18}O_3S_2N_4$	200	EtOH	12.22 (12.44)	1500	600	41.25 ± 2.50
			$X^1 = X^2 = Br$						
IIk	CH_3	benzyl	$C_{23}H_{18}O_3S_2N_4Br_2$	115	$CHCl_3$	9.20 (9.00)	1600	600	11.32 ± 3.48
IIl	CH_3	phenyl	$C_{22}H_{16}O_3S_2N_4Br_2$	215	DMF	9.42 (9.21)	1600	600	10.00 ± 2.58
IIm	CH_3	*o*-anisyl	$C_{23}H_{18}O_4S_2N_4Br_2$	145	EtOH:DMF(3:1)	8.22 (8.77)	1600	600	38.33 ± 3.33
IIn	CH_3	*o*-tolyl	$C_{23}H_{18}O_3S_2N_4Br_2$	205	Me_2CO	9.32 (9.00)	1600	600	41.12 ± 5.53
IIo	CH_3	cyclohexyl	$C_{22}H_{23}O_3S_2N_4Br_2$	165	EtOH	9.40 (9.12)	1200	400	19.85 ± 4.34
	Phenformin.HCl (for streptozotocin-induced diabetic rats)								32.50 ± 5.00

*Satisfactory analyses were also obtained for carbon and hydrogen; **The antihyperglycemic activity of the test compounds and phenformin was determined using streptozotocin-induced diabetic rats at a dose of 100 mg/kg (b.w.) The value are mean of the percentage blood sugar change ± S.E. of 5 rats.

tolbutamide (38.0±2.5). On the other hand, it is interesting to note from the blood-sugar reduction values that the compounds IIg, IIj, IIn and IIm (44.16, 41.25, 41.12 and 38.33 respectively) exhibit a strong anti-hyperglycemic activity in that order and found to be superior over the standard drug phenformin.HCl against streptozotocin-induced diabetic rats. Therefore, in view of their lower toxicity and higher anti-hyperglycemic potency these four new compounds may be exploited, further.

ACKNOWLEDGEMENT

One of the authors (GRM) is grateful to CSIR, New Delhi for a fellowship.

20 April 1987; Revised 21 September 1987

1. Feldman J. M., *Pharmacotherapy*, 1985, **5**, 43.
2. Imtiaz Husain, M. and Srivastava, G. C., *Indian J. Chem.*, 1980, **B19**, 916.
3. Raafat S., Feid-Allah Hassan, M. and Mohamed Hosny, F., *J.Pharm. Sci.*, 1981, **70**, 952.
4. Rama Murthy, G., Bhaskar Rao, A., Malla Reddy, V. and Sisodia, P., *Indian Drugs*, 1986, **23**, 354.
5. Rama Murthy, G., Bhaskar Rao, A. and Malla Reddy, V., *Indian Drugs*, 1986, **24**, 92.
6. Rama Murthy, G. and Malla Reddy, V., *Indian J. Pharm. Sci.*, 1987, **49**, 175.
7. David, T. and Wagner, E. C., *J. Org. Chem.*, 1949, **14**, 967.
8. Wheeler, A. S. and Oats, W. M., *J. Am. Chem. Soc.*, 1910, **32**, 770.
9. Soliman Raafat and Soliman Farid, S. G., *Synthesis*, 1979, 803.
10. Bahadur, S., Srivastava, N. and Saxena, M., *J. Indian Chem. Soc.*, 1983, **60**, 684.
11. Fujii, T. *et al.*, *Arzneim-Forsch/Drug Res.*, 1983, **33**, 11.