SYNTHESIS AND ANTIFERTILITY ACTIVITY OF 1,4-DISUBSTITUTED 3-[3′-(2′-PHENYL-4′-OXO-QUINAZOLINYL)]-2-AZETIDINONES

V. K. PANDEY and NAVEEN RAJ
Chemistry Department, University of Lucknow, Lucknow 226 007, India.

2-PHENYL-4-OXO-3,1-BENZOXAZINE (II) was condensed with glycine to give 2-phenyl-3-(acetic acid)-quinazolin(3H)4-one (III). The acid-chloride of (III) on condensation with benzalanilines (Schiff's bases) (I) afforded 1,4-diaryl-3-[3′-(2′-phenyl-4′-oxo-quinazolinyl)]-2-azetidinones (VI) in the yields ranging from 40–55%. These compounds exhibited pronounced antiimplantation activity.

The extent of the pharmacological effect of quinazolone derivative depends on the active group with which it is attached. The structural modifications at the 2 and 3 positions have shown excellent results in pharmacology. Recently, quinazoline derivatives with substitutions of 2 and 4 positions have been demonstrated to possess varying orders of antiestrogenic properties[1]. These compounds caused 83.3% inhibition of foetal implantation at a dose level of 10 mg/kg, intraperitoneally in rats. The antifertility activity of azetidinones has not been very well established although such class of compounds have been demonstrated to exhibit varying degrees of pharmacological properties[2]. This gave us an impetus to unite the two biologically active nuclei in one molecular union for the better therapeutic results.

The melting points are uncorrected. The IR spectra of the compounds were recorded in the 4000–400 cm^{-1} using KBr discs on Perkin Elmer spectrophotometer model 337. The NMR studies were done on Varian A60D spectrometer using $CDCl_3$ as solvent; the chemical shifts are in δ-scale.

2-Phenyl-4-oxo-3,1-benzoxazine (II)

2-Phenyl-4-oxo-3,1-benzoxazine was synthesized following the method of Bain and Smalley[3].

Schiff's bases (I)

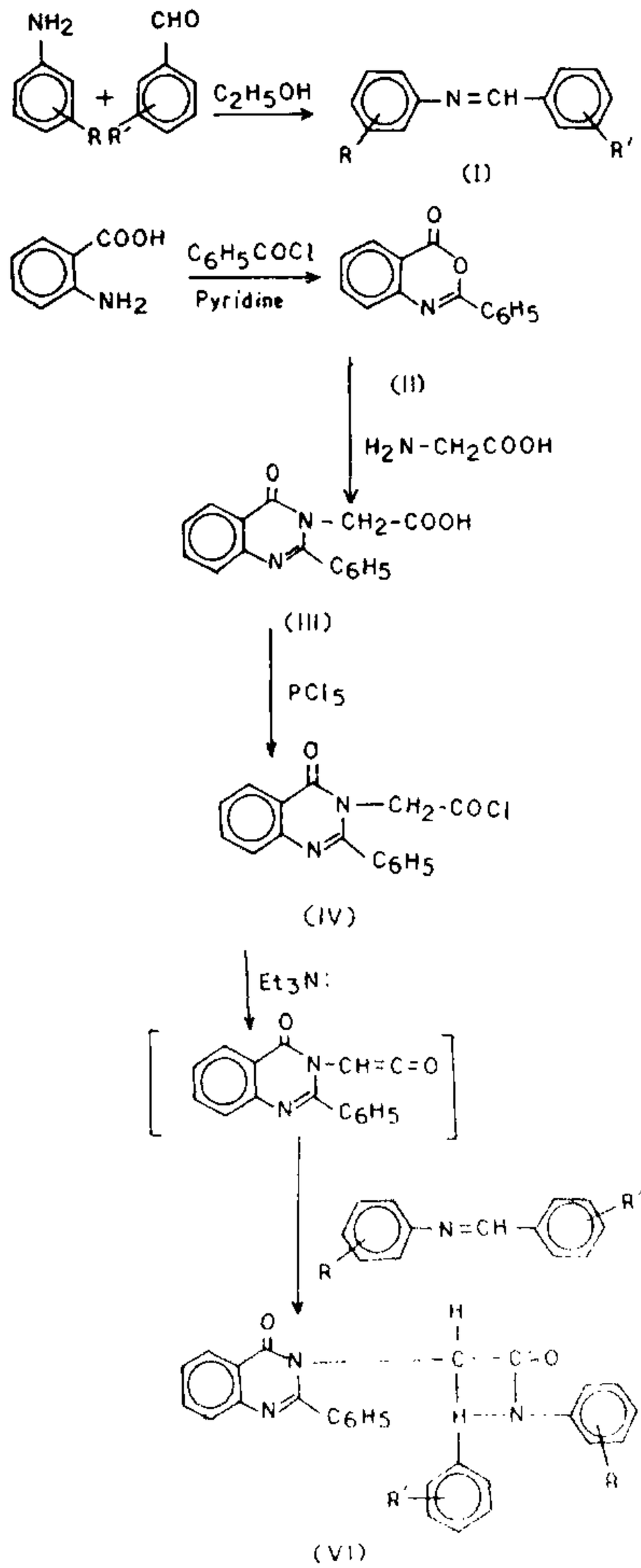
Benzalanilines (Schiff's bases) were prepared as reported in the literature[4].

2-Phenyl-3-(acetic acid)-quinazolin(3H)4-one (III)

2-Phenyl-4-oxo-3,1-benzoxazine (II) (0.01 mol) and glycine (0.01 mol) were mixed together and heated on an oil bath at 180° for 1 hr. The contents were cooled and treated with 5% sodium bicarbonate solution. When the effervescence ceased, the brown solid was filtered and the residue rejected. The filtrate was acidified with dilute hydrochloric acid. A light brown precipitate appeared. More dil. HCl was added to ensure complete precipitation and the solid filtered off. The crude acid, thus isolated, was dried and recrystallized from ethanol as colourless crystalline solid, m.p. 120°, Anal. for $C_{16}H_{12}N_2O_3$; N, Calcd. 10%, Found N, 9.98%, Yield 82%.

2-Phenyl-3-(Chloroacetyl)-quinazolin(3H)4-one (IV)

2-Phenyl-3-(acetic acid) quinazolin (3H)4-one (III)



(0.02 mol) and PCl_5 (0.02 mol) were heated gently on a water bath with occasional shaking for 30 min. Subsequently dry benzene (30 ml) was added and the resultant solution refluxed for 1 hr under anhydrous conditions. Benzene was distilled off under reduced pressure and the residual liquid solidified on cooling. The acid chloride thus synthesized was used for further reaction without any purification.

1,4-Disubstituted-3-[3'-(2'-phenyl-4'-oxo-quinazolinyl)]-2-azetidinones (VI)

A mixture of Schiff's base(I) (0.001 mol) and triethylamine (2 ml) was dissolved in anhydrous benzene (20 ml). A solution of acid chloride (IV) (0.001 mol) in 20 ml of anhydrous benzene was added slowly with constant stirring and cooling. A brown precipitate was formed, the mixture became yellow after about 15 min and a raise in the temperature was noted. After stirring for a further 1 hr the solid was filtered, washed with benzene and dried at 70°. The product was further stirred with water filtered, washed with water and again dried at 70°. The combined benzene filtrate and wash was concentrated under reduced pressure to a semisolid which was digested for 30 min with 200 ml of boiling ethanol and filtered. The solid residue was almost pure β-lactam which was recrystallized from dioxane water (1:1) to yield colourless and fine needles. The compounds, thus synthesized, are recorded in table 1.

The compounds were subjected for their anti-implantation activity in female albino rats. The compounds under investigation were prepared as suspension in gum acacia and an equal amount of distilled water to obtain a final concentration of 4 mg/ml. The rats in the control group received the vehicle only.

Animal model and schedule of treatment[5,6]

Adult virgin albino female rats (body weight 200 ± 10 g) of proven fertility and regular cyclicity were selected for the assay of antifertility activity. Following cohabitation with the fertile males on the day of proestrus the vaginal smears were properly checked the next morning and the animals showing sperm positive smears (day 1 of pregnancy) were then put on treatment. The female animals were used for the test only after they had one or two litters proving their fertility. They were maintained at room temperature and fed with a commercial diet and tap water *ad libitum*. For the anti-implantation activity 4 to 8 rats were selected for investigation for each compound and the suspension of each compound was fed orally. Subsequently, the animals were laparotomized on day 9–10 of pregnancy and the numbers of implantation sites and corpus lutea were carefully recorded. The mean number of implantation sites and corpus lutea in the treated rats was calculated separately and the standard error (± value) from the mean value were calculated according to the following equation:

$$\text{Standard error} = \sqrt{\frac{\sum d^2}{n(n-1)}}$$

where d is the difference from the mean and n is the number of observations i.e. number of rats treated per compound. The per cent effectiveness of the com-

Table 1 1,4-*Disubstituted*-3-[3'-(2'-*phenyl*-4'-*oxo-quinazolinyl*)]-2-*azetidinones* (*VI*)

Comp. No.	R	R'	M.P.°C	Yield	Molecular Formula
+1.	4-OCH_3.C_6H_4	3-CH_3	98	48	$C_{31}H_{25}N_3O_3$
2.	4-OCH_3.C_6H_4	4-Cl	89	50	$C_{30}H_{22}N_3O_3Cl$
3.	2-NO_2.C_6H_4	4-Cl	61	47	$C_{29}H_{19}N_4O_4Cl$
*4.	C_6H_5	2-CH_3	103	52	$C_{30}H_{23}N_3O_2$
5.	$C_6H_5CH = CH$	3-CH_3	118	55	$C_{32}H_{25}N_3O_2$
6.	2-OH.C_6H_4	H	134	45	$C_{29}H_{21}N_3O_3$
7.	2-F.C_6H_4	4-Cl	127	54	$C_{29}H_{19}N_3O_2ClF$
8.	2-OH.C_6H_4	4-Cl	84	50	$C_{29}H_{20}N_3O_3Cl$
9.	C_6H_5-CH = CH	4-Cl	78	46	$C_{31}H_{22}N_3O_2Cl$

+ IR(KBr): The characteristic infrared spectral band at 1695 cm^{-1} is attributable to the β-lactam structure;

*PMR($CDCl_3$): δ7.1 to 8.2 (m, aromatic), δ4.9 (s, CH–N) and δ5.5 (s, CH–O)

Table 2 *Antiimplantation activity of* 1,4-*disubstituted*-3-[3'-(2'-*phenyl*-4'-*oxo-quinazolinyl*)]-2-*azetidinones, days of pregnancy*: = 5: *dose*: 10 *mg*

Comp. No.	Rats rendered infertile/ Rats treated	Implantation sites (mean ± S.E.)	Corpus luteum (mean ± S.E)	% Effectiveness Incidence	Rate
Control	0/6	10.7 ± 0.6	13.2 ± 0.8	—	—
1.	0/6	10.2 ± 0.9	12.9 ± 1.1	—	5.2
2.	2/6	4.5 ± 1.1	13.7 ± 1.0	33.3	58.2
3.	2/6	3.8 ± 1.0	13.1 ± 1.0	50.0	64.7
4.	0/6	9.2 ± 0.7	13.4 ± 0.7	—	14.5
5.	0/6	9.9 ± 0.9	12.7 ± 0.8	—	7.7
6.	0/6	10.2 ± 0.8	12.9 ± 0.9	—	5.1
7.	1/6	7.5 ± 1.0	13.3 ± 0.8	33.3	30.3
8.	2/6	4.8 ± 1.1	14.3 ± 1.1	33.3	55.4
9.	3/6	4.2 ± 1.0	13.5 ± 0.9	50.0	61.0

pounds tested for their antiimplantation activity was calculated in two terms;

(i) Incidence: The per cent effectiveness in terms of incidence of pregnancy was calculated as;

$$\frac{\text{Animals rendered infertile}}{\text{Total number of animals treated}} \times 100$$

(ii) Rate: The per cent effectiveness in terms of rate of pregnancy was calculated by comparing the mean number of implantation sites found in the treated animals to that of control.

The anti-implantation data thus determined are recorded in table 2.

Four compounds viz 2,3,8 and 9 were found to possess high antiimplantation activity in terms of incidence and pregnancy. All the four compounds possess a 4-chloro substituent on the phenyl ring joined with the nitrogen atom. Further, a nitrosubstituent in the phenyl ring attached with the –CH causes enhanced anti-implantation activity. Thus the compound No. 3 with a nitro-substituent was found 50% effective in terms of incidence of pregnancy and 64.7% effective in terms of pregnancy rate while compound No. 2 with a 4-OCH_3 substituent was only 33.3% effective in terms of incidence of pregnancy and 58.2% effectiveness in terms in the rate of pregnancy. All the four compounds with a 4-Cl substituent in the phenyl attached with the nitrogen were found to exhibit anti-implantation activity by more than 50% in terms of pregnancy rate and 33.3 to 50% in terms of the incidence of pregnancy. The remaining compounds had diminished antiimplantation activity.

The authors thank Dr U. K. Srivastava and the Director of CDRI, Lucknow, for their assistance in this study.

29 November 1985; Revised 5 February 1986

1. Misra, V. S., Pandey, R. N., Dhar, S. and Dhawan, B. N., *Indian J. Med. Res.*, 1978, **67,** 310.
2. Manhas, M. S., Hoffmann, W. A. and Bose, A. K., *J. Het. Chem.*, 1979, **16,** 711.
3. Bain, D. I. and Smalley, R. K., *J. Chem. Soc.*, 1968, **2,** 1593.
4. Mann, F. G. and Sounders, B. C., In *Practical organic chemistry*, 4th ed., 1974, 230.
5. Srivastava, U.K. and Laumas, K. R., *Contraception*, 1975, **12,** 549.
6. Srivastava, U. K., *Indain J. Exp. Biol.*, 1981, **19,** 416.

INSECT FEEDING STUDIES ON *MICROSORIUM MEMBRANACEUM* (DON) CHING AND THEIR RELATIONSHIPS

D. R. MISRA, D. K. CHAUHAN
and S. P. TIWARI
Department of Botany, University of Allahabad, Allahabad 211 002, India.

REPORTS are scanty about the insect-fern relationships and their feeding studies. Field observations indicate that the ferns are rarely attacked by feeding insects[1] probably because ferns are biochemically much less versatile than angiosperms[2]. They lack definite flowers, colours and odours and are seldom attacked by the insects. Further, the ferns secrete secondary compounds like phenols and flavonoids which are injurious to these insects and thus these chemicals possibly