SYNTHESIS OF 6,8-DISUBSTITUTED-2-METHYL/PHENYL-3-[4-(3-PHTHALIMIDO ACETAMIDO/PROPIONAMIDO)]PHENYL-QUINAZOLIN-4-ONES AS ANTHELMINTIC AGENTS

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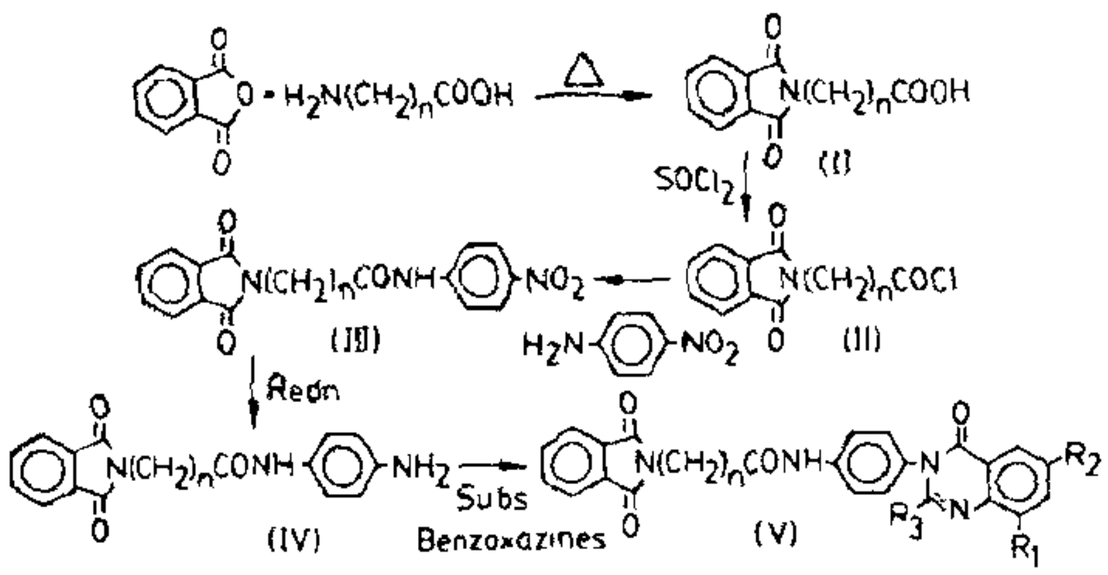
ABSTRACT

Quinazolone nucleus possesses a broad spectrum of anthelmintic activity. Certain phthalimide derivatives have also been reported to be active against helminth parasites. Attempts have been made to synthesise and evaluate the anthelmintic activity of compounds having both moieties. Various 6,8 disubstituted-2-methyl/phenyl-3-[4-(3-phthalimido acetamido/propionamido]phenyl quinazolin-4-ones(V) were synthesised, by the reaction of 2-(*p*-amino phenyl acetamido, propionamido)phthalimide (IV) with 6,8 disubstituted-2-phenyl benzoxazin-4-one, and screened for their anthelmintic activity.

INTRODUCTION

DIFFERENT types of quinazolones exhibit a wide range of biological activity and their therapeutic use is also well established[1-5]. Various quinazolones have been found to be useful pharmacophores in building anthelmintic agents[6]. Recently, phthalic acid derivatives were reported to possess marked anthelmintic activity[7]. These observations have prompted us towards designing the quinazolone derivatives containing the phthalimide nucleus with the expectation of getting interesting results.

The synthesis was accomplished along the following route.



EXPERIMENTAL PROCEDURE

Melting points were determined in open capillaries in conc. H_2SO_4 acid bath and are uncorrected. The IR spectra were recorded on a Perkin-Elmer spectrophotometer using KBr. PMR spectra were recorded on a Perkin-Elmer spectrometer using TMS internal reference (chemical shift in δ, ppm).

Purity of the compounds was checked on silica gel TLC plates and the spots were located by iodine vapours. All new compounds gave satisfactory N and C analysis.

Phthalimido acetic/propionic acid (I):

These were prepared according to the reported method[8].

6,8-disubstituted-2-Me/Ph-benzoxazine-4-ones:

6,8-disubstituted-2-Me/Ph-Benzoxazine-4-ones[9,10] were prepared from anthranilic acid and substituted anthranilic acids[11,12].

Phthalimidoacetyl/propionyl chloride (II)

Phthalimidoacetic acid (0.001 mol) or phthalimidopropionic acid (0.001 mol) and thionyl chloride (0.001 mol) were refluxed on water bath under anhydrous conditions. Excess of thionyl chloride was distilled under reduced pressure. The liquid thus obtained was used as such for further work.

2-(p-nitrophenylacetamido/propionamido)phthalimide (III)

Phthalimidoacetyl or phthalimidopropionyl chloride and *p*-nitroaniline (equimolar amounts) were dissolved in dry chloroform. The reaction mixture was refluxed on a water bath for 6 hr. Excess of chloroform was distilled and the crude products were recrystallised from benzene/pet ether.

IR ν_{max} ~3250 cm^{-1} (amide NH), 1780 cm^{-1} (C=N
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|| ||
–C), 1710 cm^{-1} (C–), 1600 cm^{-1} (phenyl), 1510 $^{-1}$ and 1310 cm^{-1} (Nitro gr.).

2-(p-aminophenyl acetamido/propionamido)phthalimide (IV)

2-(*p*-nitrophenylacetamido)phthalimide or 2-(*p*-nitro phenyl propionamido)phthalimide (0.001 mol)

was dissolved in absolute alcohol. The mixture was refluxed on a water bath under anhydrous conditions. Raney Ni (100 mg) was added to it and hydrazine hydrate solution (5 ml) was dropped carefully when the nascent hydrogen evolved reduced the nitro to the -amino group. IR(KBr): Bands at 3300 cm^{-1} and 3400 cm^{-1} for NH_2 support their structure.

6,8-disubstituted-2-methyl/phenyl-3-[4-(3-phthalimido acetamido/propionamido)]phenyl quinazoline-4-ones (V)

A mixture of 2-(*p*-aminophenyl acetamido/propionamido) phthalimide and 6,8-disubstituted-2-methyl/phenyl benzoxazine-4-ones (both 0.001 mol) was dissolved in pyridine. It was refluxed on a sand bath for 10 hr. The resulting mixture was poured in crushed ice containing HCl to remove the excess pyridine. The solid thus obtained was crystallised from methanol.

IR ν_{max}: 3300 cm^{-1} (C(=O)–NH), 2900 cm^{-1} (aliphatic H), 1780 cm^{-1} (CO of CO–N–CO), 1700 cm^{-1} (CO of NH), 1640 cm^{-1} (C=N), 1600 cm^{-1} (ArH).

BIOASSAY

All the compounds were tested *in vivo* for their anthelmintic activity against *H. nana* in mice, *N. brasiliensis* in rats and *A. ceylanicum* in Hamesters.

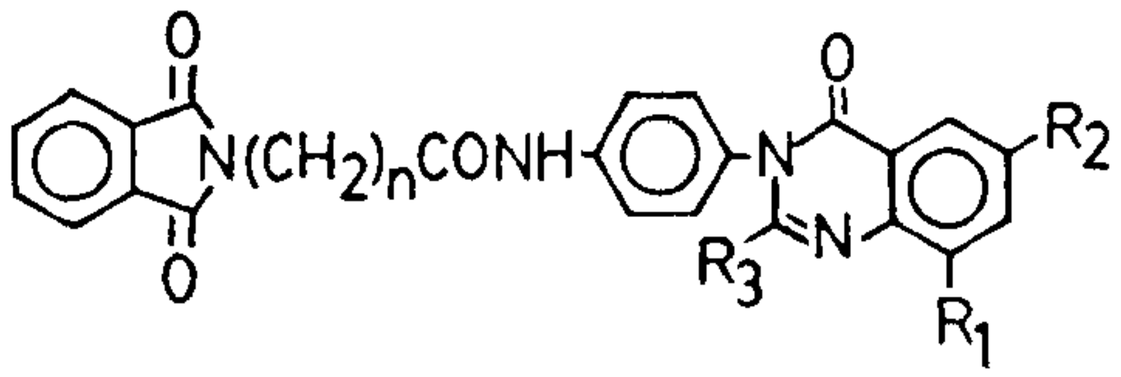
MATERIALS AND METHODS

The compounds were tested for their cestodicidal activity against *H. nana* in mice using the technique of Steward[13]. The animals were infected by feeding 200 mature viable ova of *H. nana*. On the 17th day after infection the faeces of animals were examined. The oral dose was 250 mg/kg daily given for 3 days. Niclosamide was used as the standard drug which cleared 100% the above infection. In the above test all the compounds were found to be inactive.

Against *N. brasiliensis* the infection was tested in rats at the dose of 250 mg/kg using 3 doses by standard method[14]. Thiabendazole was used as the standard drug which clears the infection at a dose of 50 mg/kg daily for 3 days.

Hamesters of either sex (40–60 g) were infected orally with 603rd stage larvae of *A. ceylanicum*. On day 17–20 post inoculation, the infection was checked by ovoscopic examination. Hamesters found positive were treated with test compound and antihookworm drug[15] in groups of 3–5 animals in each dose.

Table 1 6,8-*Disubstituted-2-methyl/phenyl-3-[4-(3-phthalimido acetamido/propionamido)]phenyl quinazoline-4-ones*



Sl. No.	R_1	R_2	R_3	Mol. formula	m.p. °C	Anthelmintic Activity *N. brasiliensis*	*A. ceylanicum*
		$n=1$					
1.	H	H	C_6H_5	$C_{30}H_{20}N_4O_4$	130	18.4	38
2.	Br	Br	C_6H_5	$C_{30}H_{18}N_4O_4Br_2$	195	26 3	35
3	H	I	C_6H_5	$C_{30}H_{19}N_4O_4I$	190	22 5	38
4.	H	I	CH_3	$C_{25}H_{17}N_4O_4I$	155	16 2	40
5.	Br	Br	CH_3	$C_{25}H_{16}N_4O_4Br_2$	165	26 5	36
*6.	H	H	CH_3	$C_{25}H_{18}N_4O_4$	130	30 6	36
		$n=2$					
7.	H	I	C_6H_5	$C_{31}H_{21}N_4O_4I$	165	21	35
8	Br	Br	C_6H_5	$C_{31}H_{20}N_4O_4Br_2$	180	43	16
9	H	H	C_6H_5	$C_{31}H_{22}N_4O_4$	160	26	21
10	H	H	CH_3	$C_{26}H_{19}N_4O_4I$	160	15 2	38
11	Br	Br	CH_3	$C_{26}H_{18}N_4O_4Br_2$	170	28 5	40
12.	H	H	CH_3	$C_{26}H_{20}N_4O_4$	130	30	70

The yield ranged from 50–60%.

* PMR 8 50 δ(m, 1H, NH), 7 9–7 2 δ(m, 12H, Ar H), 4 50 δ(s, 2H, $COCH_2N$), 1 5 δ(s, 3H, CH_3).

RESULTS AND DISCUSSION

All the compounds gave negative results against cestodicidal activity.

It is observed from the results recorded in table 1 that compound 8 was the most active (43%) of the series against *N. brasiliensis*.

For *A. ceylanicum* the best activity (70%) was exhibited by compound 12.

It is evident from the results that a propionamido group enhances the activity both in *N. brasiliensis* and *A. ceylanicum*. When R_1 and R_2 are replaced by Br then the activity increased in case of *N. brasiliensis* while when it is replaced by H then the activity enhances in *A. ceylanicum*.

In case of *A. ceylenicum* R_3 replaced by CH_3 gives desirable activity whereas in *N. brasiliensis* it gives no clear observation.

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