# CYCLISED PRODUCTS OF N-(6′,8′-DISUBSTITUTED-2′-ETHYLQUINAZOLIN-4′-OXY-ACETYL) HYDRAZINES AND THEIR CONDENSATION WITH AROMATIC ALDEHYDES

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## ABSTRACT

Two new (1)-(6′,8′-disubstituted-2′-ethylquinazolin-4′-oxyacetyl)-3-methylpyrazolin-5-ones (II) and twelve of their condensation products with aromatic aldehydes have been evaluated for their antiviral action against plant virus sunnhemp rosette virus (SRV) using host *Cyamopsis tetragonoloba* at a concentration 1 mg/ml both *in vivo* as well as *in vitro*. The compounds decreased the viral infectivity in the range of 10–65% *in vivo* and 36–88% *in vitro*.

## INTRODUCTION

THE synthesis of N-(6′,8′-disubstituted-2′-ethylquinazolin-4′-oxyacetyl) substituted hydrazines and their respective hydrazones with different aromatic aldehyde was carried out and evaluated as antifungals and antibacterials[1]. N-substituted hydrazines (I) were cyclised with acetoacetic ester in methanol to give (II) which when condensed with different aromatic aldehydes in the presence of dry sodium acetate, aceticanhydride and glacial acetic acid, gave a benzylidine linkage at position 4- in 1-3-substituted pyrazolin-5-ones (II) yielding compound (III). Structural assignments were based on elemental analyses and spectral data. The sequence of reactions involved in the synthesis of III is shown in scheme 1.

IR spectra of the compound IIb reveal that this compound exists as keto-enol tautomer and at the same time, the presence of sharp peak at 3200 $cm^{-1}$ of OH group also shows that hydrogen bonding takes place in the enolic form of the compound (II). Further, tautomerism is also confirmed from PMR peaks in characteristic regions, doublet at 8.1 $\delta$, 1H of enol, reformed doublet at 7.6 $\delta$, 1H of $-\overset{H}{\underset{|}{C}}=\overset{OH}{\underset{|}{C}}$, singlet at 4.2 $\delta$, 2H of $-\overset{O}{\overset{\|}{C}}-CH_2$ of keto form.

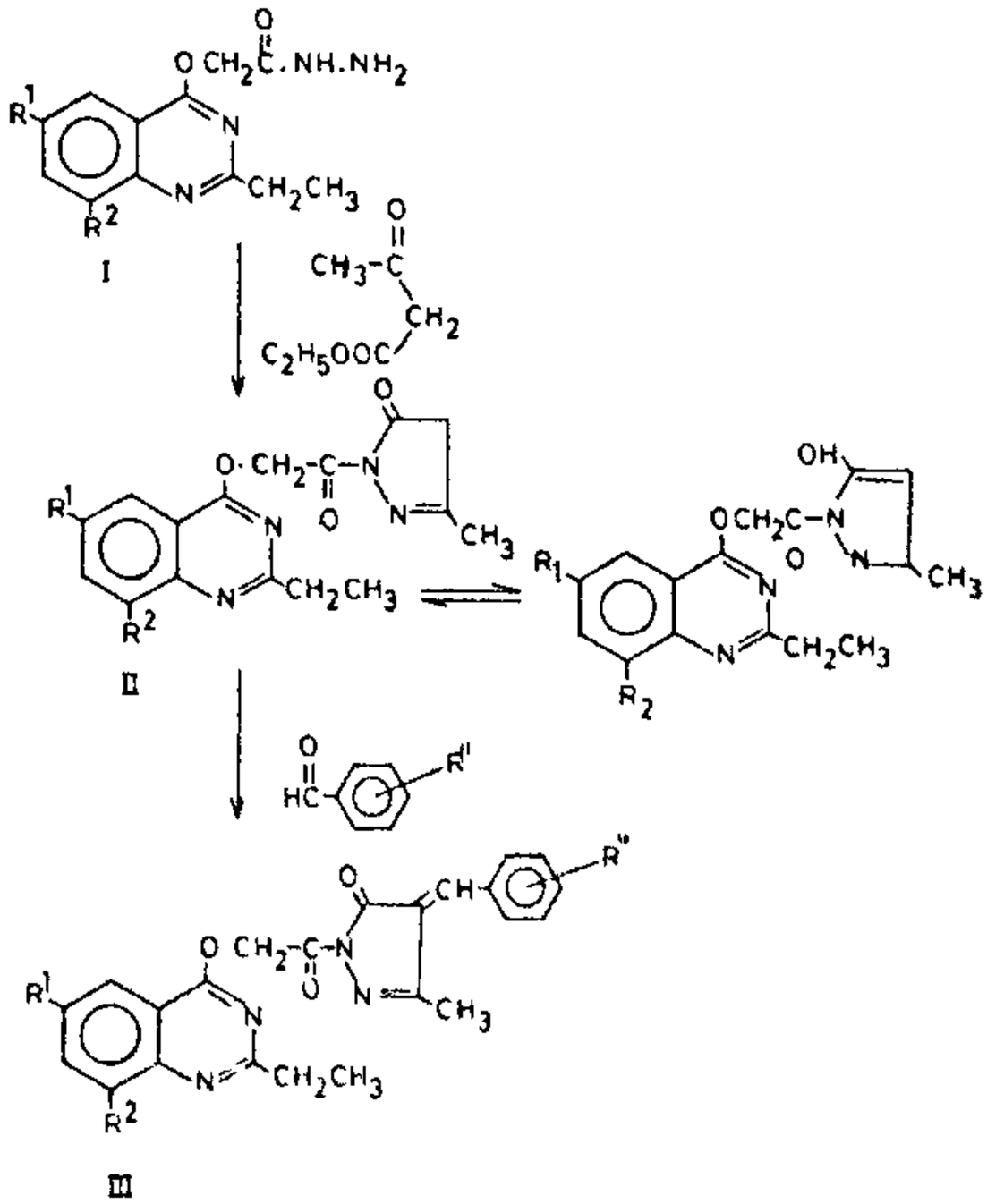
Most of the synthesised compounds were screened against plant virus SRV both *in vivo* as well as *in vitro* to find one if they are good antiviral agents. IIIg and IIIl showed a significant activity against the virus.

## EXPERIMENTAL

The melting points were determined in open capillaries and are uncorrected. Structures of the compounds were confirmed by elemental analyses, IR and PMR spectra. IR spectra were recorded on Perkin-Elmer 137G spectrophotometer ($\nu_{max}$ $cm^{-1}$) and PMR in $CDCl_3$ on a Varian of A-90D instrument using TMS as internal standard (chemical shift $\delta$ ppm). The purity of the compounds was checked on TLC:

*N-(6′,8-Disubstituted-2′-ethylquinazolin-4′-oxyacetyl)-substituted hydrazines* were prepared according to the previously reported method[1]. 1-(6′,8′-*Disubstituted-2′-ethylquinazolin-4′-oxyacetyl*)-3-*methyl pyrazolin-5-ones* (II)

A mixture of compound (I) (0.01 mol) and aceto-



acetic ester (0.015 mol) in methanol (50 ml) was refluxed on a water bath for 8 hr. The excess solvent was distilled and the solid, which separated out on cooling, was filtered and recrystallised from methanol. Yields of the compounds were 60–70%. Two compounds were thus synthesised.

IIa (R = R' = H) m.p. = 125°C N% Calc. 17.94, found 18.00, yield 60%. IIb (R = R' = Br) m.p. 144°C N% Calc. 11.91, found 11.65, yield 70%. IR of IIb showed characteristic bands around 3200 (hydrogen bonded OH enolic), 2950 (OH), 1680–1730 (broad peak with shoulder for two –C(=O)– groups), 1600 (C=N): PMR of IIa 1.1–1.4 (m, 6H, $CH_3$ of ethyl group and $CH_3$ of pyrazolinone moiety) 2.5–2.8 (q, 2H, $CH_2$ of ethyl group) 4.2 (s, 2H, methylene group of pyrazolinone moiety in keto form) 4.7 (s, 2H, $CH_2$ of acetyl group) 7.1–7.4 (h, 4H, Ar-H) 7.5 (d, 1H of –C(OH)=CH–) of enolic form of pyrazolin nucleus) 8.1 (d, 1H of –OH of enolic form).

m = multiplet, q = quartet, s = singlet, h = hump, d = doublet

*1-(6',8'-Disubstituted-2-ethylquinazolin-4'-oxyacetyl)-3-methyl-4-substituted benzylidene-pyrazolin-5-ones* (III).

A mixture of compound (II) (0.01 mol) and aromatic aldehyde (0.01 mol) was heated in the presence of dry sodium acetate (0.015 mol) and 4 drops of acetic anhydride in 25 ml of glacial acetic acid on a wire gauge for 12 hr. Thereafter the reaction mixture was cooled and poured over crushed ice. The solid, which separated out, was filtered, washed well with ice cooled water and recrystallised from methanol. The compounds obtained in 50–72% yield are listed in table 1.

IR of IIIg showed bands around 2950 (CH) 1680 (C=O) 1600 (C=N). Complete disappearance of the peak at 3200 $cm^{-1}$ showed formation of the final compound and also complete conversion of enolic form into keto form under the above reaction conditions.

*Antiviral activity against plant virus*

One compound (IIa) and twelve compounds (IIIa-l) were screened for their antiviral action against *sunnhemp rosette virus* (SRV) using host *C. tetragonoloba* at a concentration 1 mg/ml. The virus was maintained in the plant virus laboratory following the methods reported earlier[2,3]. The compound (5 mg) was dissolved in one ml of methanol and the solution was then made up to 5 ml by adding distilled water and the solution was used as test solution for screening both *in vivo* and *in vitro*. The results were calculated by the formula $\frac{C-T}{C} \times 100$, $C$ = Lesions on controlled leaf, $T$ = Lesions on the treated leaf and are listed in table 1.

The activity results showed that the introduction of benzylidene nucleus at position 4- in the compound

**Table 1** *Characterization data and antiviral activity of* 1-(6',8'-*disubstituted-2'-ethylquinazolin-4'-oxyacetyl*)-3-*methyl*-4-*substituted benzylidene pyrazolin-5-ones* (*III*)

| Compound No. | R | R' | R'' | Yield (%) | m.p. °C | Molecular formulae | Molecular weight | Antiviral activity against SRV (%) *in vivo* | *in vitro* |
|---|---|---|---|---|---|---|---|---|---|
| IIIa | H | H | 2-Cl | 65 | 248 | $C_{23}H_{19}N_4O_3Cl$ | 434.5 | 40.5 | 78 |
| IIIb | H | H | 4-Cl | 60 | 145 | $C_{23}H_{19}N_4O_3Cl$ | 434.5 | 15 | 48 |
| IIIc | H | H | 4-$OCH_3$ | 70 | 170 | $C_{24}H_{22}N_4O_4$ | 430.0 | 23 | 54 |
| IIId | H | H | 4-$N(CH_3)_2$ | 55 | 155 | $C_{25}H_{25}N_5O_3$ | 443.0 | 31 | 42 |
| IIIe | H | H | 4-OH,3-$OCH_3$ | 50 | 240 | $C_{24}H_{22}N_4O_5$ | 446.0 | 10 | 53.2 |
| IIIf | H | H | 4-$NO_2$ | 65 | above 280 | $C_{23}H_{19}N_5O_5$ | 445.0 | 33 | 36 |
| IIIg | Br | Br | 2-Cl | 68 | 262 | $C_{23}H_{17}N_4O_3ClBr_2$ | 597.5 | 65 | 88 |
| IIIh | Br | Br | 4-Cl | 72 | 270 | $C_{23}H_{17}N_4O_3ClBr_2$ | 596.5 | 32 | 44.5 |
| IIIi | Br | Br | 4-$OCH_3$ | 62 | 180 | $C_{24}H_{20}N_4O_4Br_2$ | 588.0 | 50 | 53.2 |
| IIIj | Br | Br | 4-$N(CH_3)_2$ | 58 | 275 | $C_{24}H_{23}N_5O_3Br_2$ | 601.0 | 35.5 | 85 |
| IIIk | Br | Br | 4-OH,3-$OCH_3$ | 56 | 165 | $C_{24}H_{20}N_5O_5Br_2$ | 604.0 | 26 | 80.4 |
| IIIl | Br | Br | 4-$NO_2$ | 60 | 246 | $C_{23}H_{17}N_5O_5Br_2$ | 603.0 | 61 | 85 |

(i) Elemental analysis of all the compounds were found within satisfactory limits.

(II) enhanced the activity of the compounds *in vitro* as well as *in vivo* (except four IIb, IIc, IIe and IIk). Of these compounds, those with chlorine at position 2- of the benzylidene nucleus are significantly more active than compounds with chlorine atom at position 4-. Presence of nitro group at position 4- also appears to cause significant inhibition of the virus. Presence of bromine atoms at positions 6′,8′- of quinazolin moiety also caused an increase in the activity both *in vivo* as well as *in vitro*. Compounds IIIg and IIIl showed significant inhibitions of 65%, 61% *in vivo* and 88%, 85% *in vitro* respectively.

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# NEWS

## FOOD TOXINS

A common consumer may feel that all natural foods are safe and ideal for health. But the fact remains that some of them are not all that harmless as they are generally believed to be. They contain chemical substances called food toxins which create physiological disorder in the body, sometimes even leading to death. For example, fresh cabbage, known so much for its Vitamin C content, contains a goitrogenic substance. Lathyras (or *Khesari dal*), grown extensively in Madhya Pradesh, Bihar and UP and consumed mostly by the poorer sections of society, contains a powerful toxin which causes paralysis in the lower legs. Several varieties of fresh water fish contain thiamonose—a compound which destroys an essential water-soluble vitamin, thiamine, whose absence causes a dreadful disease called beri-beri.

Many food materials develop toxins as a result of microbiological infestation or chemical contamination. The ears of wheat, *bajra*, rye and millet plants sometimes contain a powdery substance in place of grains on account of a fungal disease called ergot. This powdery substance gets mixed up with healthy grains at the time of harvesting and produces a toxic effect on the human system, when consumed. Similarly, groundnuts, if stored in humid conditions, develop a mould which produces a powerful toxin known as aflatoxin—one of the most potent cancer-producing agents. Two common bacterial toxins normally developed on prepared foods or carried with food into the system are botulinum toxin which causes death due to food poisoning and staphycoccus toxin which produces severe stomach disorder. Then there are toxic chemicals which migrate from packing materials to the foods packed in them. Metal containers, when in direct contact with food leave toxic residues. Similarly, plastics packing materials leave plastic polymers in food when food reacts with them.

Aware of the hazards resulting from toxins to the human system, the Indian Standards Institution has drawn up a number of standards which lay down methods for the detection of toxins in food and provide guide-lines for proper storage and handling of commodities likely to develop toxins. Besides, a code for hygienic conditions in food processing units, prescribes the sanitary requirements necessary for preventing bacterial contamination during the preparation and processing of food articles. (*ISI Bulletin, Vol. 36, Jaunary 1984, p. 3*).