

# SPASMOLYTIC ACTIVITY OF SOME NEWER QUINAZOLONES

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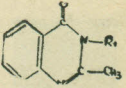
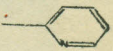

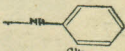
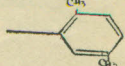
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The quinazolones were first reported as central nervous system depressants by Gujral *et al.* (3). The spasmolytic property of methaqualone (2-methyl-3-0-tolyl quinazolone) has been reported by Malhotra *et al* (5) on the isolated ileum of rabbit and guinea pig, isolated non-gravid uteri of guinea pig and rat and isolated tracheal chain preparation of dog. Marked bronchodilator activity of 6-7 benzoquinazolone has been reported out of a series of 22 compounds tested on bronchial musculature of the guinea pig. The 6-7 benzoquinazolone was isolated from the leaves of *Adhatoda vasica Nees* which chemically has been shown to be identical with hydroxy trimethylene-4-quinazolone (6). Kar *et al* (4) have also reported the spasmolytic activity of series of 3 substituted quinazolones, quinazolothiones and their quaternary salts on guinea pig ileum.

In this paper seven quinazolone compounds have been studied for their effect on isolated ileum preparation. Other pharmacological properties of these compounds have been reported elsewhere (1). Table I shows the chemical structure and melting points of the compounds tested.

TABLE I

| Sl. No. | Code No. | Chemical Structure                                 | M.P.  | Parent structure   |
|---------|----------|--|-------|--|
|         |          |  |       | <br>$R_1$ |
| 1       | PQZ-1    | 2-Methyl-3-(isopropyl) quinazolone Hcl.            | 263°C | -CH(CH <sub>3</sub> ) <sub>2</sub> HCL   |
| 2       | PQZ-2    | 2 Methyl-3-(n-butyl) quinazolone Hcl.              | 208°C | C <sub>4</sub> H <sub>9</sub> Hcl.   |
| 3       | PQZ-3    | 2 Methyl-3-(hydroxy ethyl) quainazolone Hcl.       | 195°C | CH <sub>2</sub> . CH <sub>2</sub> . OH. Hcl.   |
| 4       | PQZ-4    | 2 Methyl-3-(2-pyridyl) quinazolone                 | 164°C |         |
| 5       | PQZ-5    | 2 Methyl-3-(4-pyridyl) quinazolone                 | 144°C |         |
| 6       | PQZ-6    | 2 Methyl-3-(anilino) quinazolone                   | 203°C |         |
| 7       | PQZ-7    | 2 Methyl-3-(2, 5 dimethyl phenyl) quinazolone Hcl. | 216°C |         |

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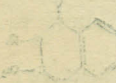

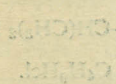
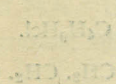


## MATERIALS AND METHODS

In our study Dale's isolated organ bath having capacity of 70 ml filled with tyrode solution was used. The temperature of the inner bath was kept constant at 37°C. The solution was continuously aerated. A piece of ileum 6 cm long removed from a freshly killed rabbit was suspended in the bath. The lever was carefully weighed with plasticine so that only small increases in tension in the gut were required to move it. Sufficient time was allowed for the preparation to stabilize after which a control record of normal movement was taken on the smoked drum. In no case more than 1 ml of the solution of the compound or spasmogenic agent was added. Effect of the compounds was tested on the normal motility and tone of the ileum and also on the spasm induced by acetylcholine ( $1 \times 10^{-7} \text{ gm/ml}$ ), histamine ( $2 \times 10^{-7} \text{ gm/ml}$ ), serotonin ( $2 \times 10^{-7} \text{ gm/ml}$ ), and barium chloride ( $7.1 \times 10^{-7} \text{ gm/ml}$ ) respectively. The compounds having spasmolytic effect on the ileum were studied to see if the responses produced by the spasmogenic agents could be blocked by tetraethyl ammonium ( $1 \times 10^{-5} \text{ gm/ml}$ ), mepyramine ( $1 \times 10^{-8} \text{ gm/ml}$ ) and atropine ( $1 \times 10^{-8} \text{ gm/ml}$ ).

## RESULTS

All the compounds except PQZ-5 decrease the normal tone and spontaneous motility of the rabbit's ileum. These compounds antagonise the spasmogenic activity of acetylcholine ( $1 \times 10^{-7} \text{ gm/ml}$ ), histamine ( $2 \times 10^{-7} \text{ gm/ml}$ ), serotonin ( $2 \times 10^{-7} \text{ gm/ml}$ ) and barium chloride ( $7.1 \times 10^{-7} \text{ gm/ml}$ ). The results are summarized in Table II.

TABLE II

| No. | Compound  | Dose<br>G/ml                             | Spontaneous<br>motility | Tone | Ach-<br>$1 \times 10^{-7}$<br>G/ml | Hist-<br>$2 \times 10^{-7}$<br>G/ml | Serotonin<br>$2 \times 10^{-7}$<br>G/ml | Barium<br>chloride<br>$7.1 \times 10^{-7}$<br>G/ml |
|-----|---|--|-------------------------|------|------------------------------------|-------------------------------------|---|--|
| 1   | PQZ-1   | $5 \times 10^{-5}$                       | +                       | +    | +++                                | +++                                 | +++                                     | +++  |
| 2   | PQZ-2   | $1 \times 10^{-5}$<br>$5 \times 10^{-5}$ | +                       | +    | +                                  | +                                   | +                                       | +  |
| 3   | PQZ-3  | $1 \times 10^{-5}$<br>$5 \times 10^{-5}$ | +                       | +    | +                                  | +                                   | +                                       | +  |
| 4   | PQZ-4  | $1 \times 10^{-5}$                       | +                       | +    | +                                  | +                                   | +                                       | +  |
| 5   | PQZ-6  | $1 \times 10^{-5}$<br>$5 \times 10^{-5}$ | +                       | +    | +                                  | +                                   | +                                       | +  |
| 6   | PQZ-7  | $1 \times 10^{-5}$<br>$5 \times 10^{-5}$ | +                       | +    | +                                  | +                                   | +                                       | +  |

Showing effect of compounds having spasmolytic activity on the isolated rabbits ileum  
+ = reduction ++ = marked reduction +++ = complete abolition.



Figure I demonstrates the effect of the compound PQZ-6 on the spasmogenic activity of acetylcholine, histamine, serotonin and barium chloride.

### EFFECT OF COMPOUND-6 ON ISOLATED RABBIT ILEUM

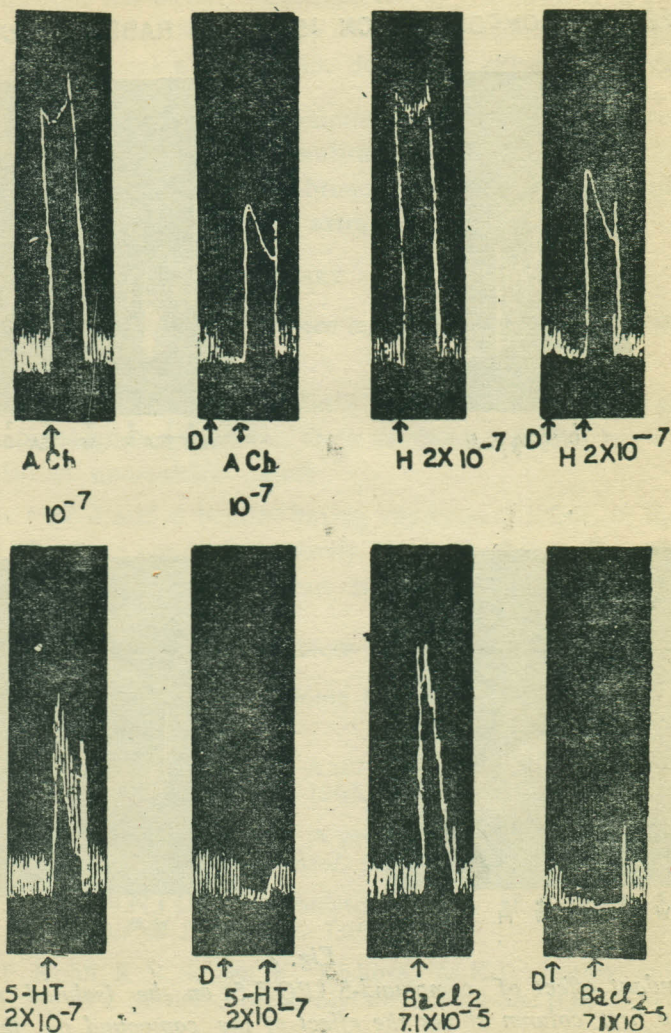
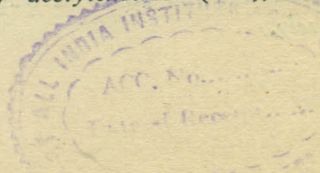


Fig. 1

Effect of compound 6 (PQZ-6) on the spasm induced by acetylcholine (Ach), Histamine (H), Serotonin (5-HT) and barium chloride (BaCl<sub>2</sub>).





Compound PQZ-5 in concentrations of  $5 \times 10^{-5} \text{ gm/ml}$  causes marked increase in the amplitude and slight increase in the tone. This stimulant effect is not prevented by pretreatment with tetraethyl ammonium ( $1 \times 10^{-5} \text{ gm/ml}$ ), mepyramine ( $1 \times 10^{-8} \text{ gm/ml}$ ) and atropine ( $1 \times 10^{-5} \text{ gm/ml}$ ). Fig. 2 demonstrates the stimulant effect of compound PQZ-5 on the isolated ileum preparation of rabbit and the effect of the drug after pretreatment with tetraethyl ammonium, mepyramine and atropine respectively.

### EFFECT OF COMPOUND-5 ON ISOLATED RABBIT ILEUM

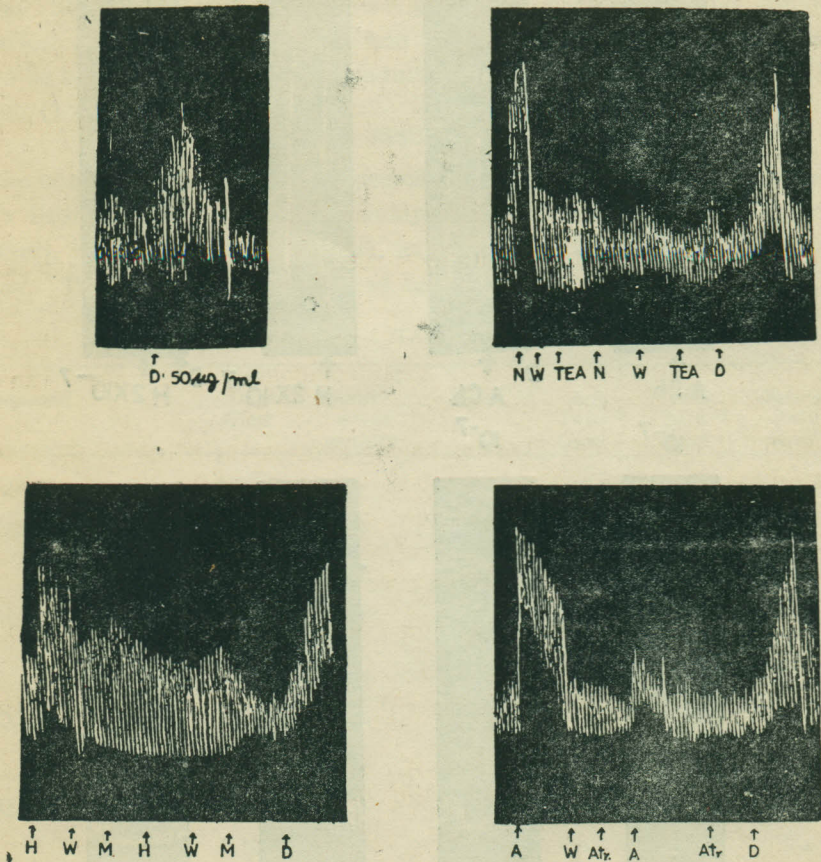


Fig. 2

Showing the stimulant effect of compound-5 (PQZ-5) on the isolated rabbit's ileum. The upper panel in the first column shows the effect of the compound on the normal tone and amplitude of contraction of the gut. The remaining panels show that the effect of the compound is not blocked by tetraethylammonium (TEA), Mepyramine (M) and atropine (At) respectively.



#### DISCUSSION

In this study all the compounds except PQZ-5 possess a marked suppressive effect on the amplitude of contraction and tone of the smooth muscle. Concentration of  $5 \times 10^{-5}$  gm/ml of the compounds were sufficient to reduce the amplitude of contraction and the tone of the smooth muscle. The spasmogenic effect of acetylcholine, histamine, serotonin and barium chloride was either reduced or abolished with a concentration of  $5 \times 10^{-5}$  gm/ml of the compounds. The depressant effect of these compounds appears to be of non-specific nature. The spasmolytic activity of methaqualone has already been reported by Malhotra *et al* (5). Our findings are also in conformity with those of Kar *et al* (4) who have studied some 3 substituted quinazolones and found them to possess a non-specific depressant effect on the smooth muscle.

We have not studied the effect of these compounds on the bronchial musculature. Since compounds PQZ-4 & 6 have at the same time antitussive activity in cat (2), it is worth while to study these compounds for their effect on the bronchial musculature. A bronchodilator activity in these compounds, if present, will be an extra advantage.

#### SUMMARY

- (i) Seven quinazolone compounds have been tested for their effects on the isolated ileum preparation of rabbit.
- (ii) Six of the seven compounds tested have a non-specific suppressant effect on the isolated ileum preparation of rabbit. Only compound PQZ-5 has a stimulant effect which is also of non-specific nature.
- (iii) Compounds PQZ-4 and 6 besides having suppressant effect on the isolated ileum preparation also have antitussive activity. A study of the effect of these two compounds on the bronchial musculature is indicated.

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