A SUMMARY OF FINAL REPORT OF MAJOR RESEARCH PROJECT

ON

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL 2-(N-SUBSTITUTED)-3H-PHTHALAZINE-1,4-DIONE ANALOGUES FOR THEIR POTENTIAL ANTIHYPERTENSIVE ACTIVITY

SUBMITTED TO

UNIVERSITY GRANTS COMMISSION

NEW DELHI

By

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Annexure –I

SUMMARY OF PROJECT
UGC-Major Research Project

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(UGC approval Letter No .and Date- **F No. -43-488/2014(SR), dated 30th Oct 2015)**

The main objective of the present project was to carry out a comprehensive and systematic study of synthesized compounds that may lead to the discovery of the bioactive compound/ product 2-(N-Substituted)-3H-Phthalazine-1, 4-Diones to be used for the treatment of the hypertension

Following objective of project, Two series of some 2-(N-Substituted)-3H-phthalazin-1, 4- dione derivatives were synthesized.

Series1: 2-(N-Acetyl Substituted)-3H-phthalazin-1, 4- dione derivatives synthesized in the three steps reactions by method described as per Deshpande *et al* and stated below:

•Synthesis of Aryl-N- Ethylacetate (I)

• Synthesis of Aryl-Hydrazide (II)

• Synthesis of final product (2-(N-substituted)-3H-phthalazin-1, 4- dione (III)

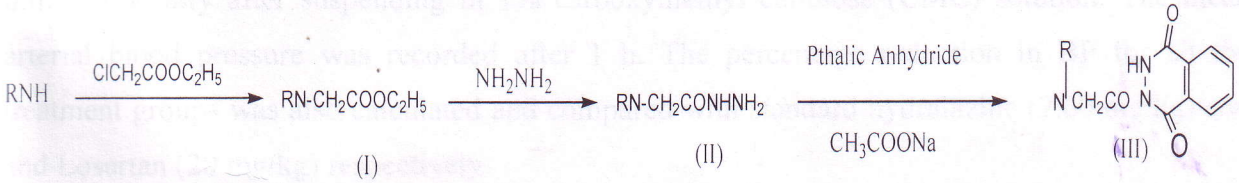
Series 2: 2-(N-Methyl Substituted)-3H-phthalazin-1, 4- dione derivatives synthesized in the two steps reactions by method described as per Rakhotiya *et al* and Siddiqui *et al* stated below:

•Synthesis of Phthalazin-1, 4- dione (I)

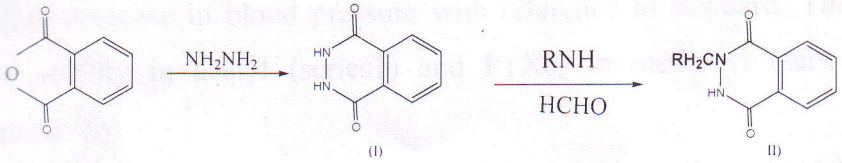
• Synthesis of final product 2-(N-Methyl Substituted)-3H-phthalazin-1, 4- dione (II)

The reactions followed the given path:

For series1:



For series2:



The purity of compounds were determined by TLC method using silica gel G and structures of the synthesized compounds were confirmed on the basis of IR, NMR and Mass spectra, Carbon, Hydrogen and Nitrogen analysis.

All the synthesized compounds were tested for antihypertensive activity using CODA non invasive blood pressure recorder by tail–cuff method (Kent Scientific Corporation, USA).The animals were kept in a restrainer for 10 min every day for one week. This exercise was done to avoid the fluctuation in blood pressure due to aggressive behavior of animal while keeping into the restrainer. The animals were divided into groups of 6 animals each. One group was taken as control. Hypertension was induced in the remaining groups by subcutaneous injection of methyl prednisolone acetate (20 mg/kg/wk)/ angiotensin II (1mg/kg) for 2 weeks as per method reported by Krakoff et al.

Mean arterial blood pressure was measured in conscious rats using CODA non invasive blood pressure recorder by tail–cuff method (Kent Scientific Corporation, USA). The restrainer carrying the rat was placed in the BP instrument with tail protruding out. The tail was gently placed in contact with a transducer membrane, which was connected to the digital BP display panel. The instrument was then turned on and allowed to stabilize until steady pulse rate was observed. Once the ''pulse level ready'' signal appeared, the BP recording button was pressed and the mean arterial BP was recorded. Albino rats (body weight 200–250 g) were used in present study. Each synthesized compound (20 mg/kg body weight) was injected intraperitoneally after suspending in 1% carboxymethyl cellulose (CMC) solution. The mean arterial blood pressure was recorded after 1 h. The percentage reduction in BP for all the treatment groups was also calculated and compared with standard hydralazine (2.60 mg/kg) and and Losartan (20 mg/kg) respectively.

In the synthesized compounds, all the compounds were found active as antihypertensive and showed significant decrease in blood pressure with reference to standard. The compound PT_f showed highest activity in acetyl (series1) and $PTXa_2$ in methenyl (series 2) substituted compounds respectively.

Findings from this project clearly indicate that 3H-phthalazin-1, 4- dione derivatives were potent antihypertensive is also incorporated together with different heterocyclics at 2N may produce strong hypotensive drug with no/minimal toxicity.

Understanding of the mechanisms of hypertension, safety profiles and synthetic procedure of 2-(N-Substituted)-3H-Phthalazine-1, 4-Diones with different heterocyclics is critical for designing As such, there remains a great deal of work to be accomplished not only on preclinically safe and potent derivatives but also on those currently being developed and for those yet to be developed to combat emerging cardiac diseases particularly hypertension.

These future efforts combined with work presented in this work will play a critical role in advancing the science of new-generation antihypertensive.

Project fellows were appointed in project, Mr. Harsh Yadav and Mrs. Shilpa Jaiswal.

One paper published in peer review Journal "International J of pharmaceutical sciences and research" and one more manuscript is under preparation based on findings from project work.

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