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SYNTHESIS OF SOME NEW 2-(N-SUBSTITUTED)- 3H- PHTHALAZIN- 1, 4- DIONE DERIVATIVES FOR THEIR ANTIHYPERTENSIVE ACTIVITY

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Keywords:

Anti-hypertensive, Pthalazinedione, Hypotensive, Phthalazin-1, 4-Dione

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ABSTRACT: Present study is reporting the result of the synthesis and evaluation of antihypertensive activity for N-substituted pthalazine 1,4-dione derivatives. N-substituted pthalazine 1,4-dione derivatives were synthesized by taking the Heterocyclic system, ethylglycinate, hydrazine hydrate and pthalic anhydride and were subjected to preliminary screening for antihypertensive activity in albino rats. The synthesized compounds were characterized on the basis of their spectral (1H NMR, 13C NMR, Ms, IR) analysis. Antihypertensive activity of all the compounds was tested by non-invasive method using Tail Cuff method and all the compounds were found to be active. The significance of the work is to treat cardiovascular disorder implicated by Steroids and cholesterols.

INTRODUCTION: Cardiovascular diseases remain the most common cause of death in industrialized countries like India, it is not only the most common cardiovascular disease and the principal cause of stroke but also leads to disease of the coronary arteries with myocardial infarction and sudden cardiac death, it is a major contributor to cardiac failure, renal insufficiency and one of the most important treatable cause of morbidity and mortality leading to stroke and end stage renal disease in elderly [1]. The prevalence of hypertension in 2000 was 24% of the adult population globally and that in 2025 would increase by 26% in developed countries and 80% in developing countries [2, 3].

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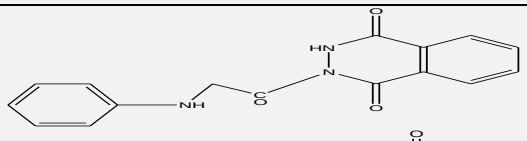
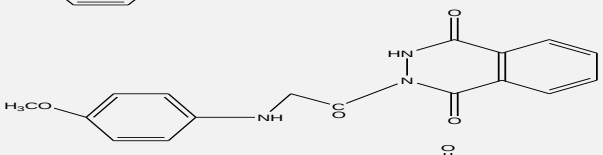
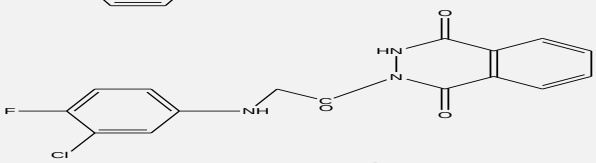
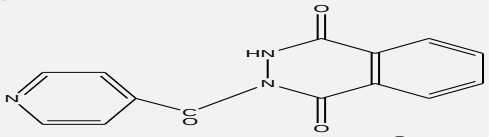
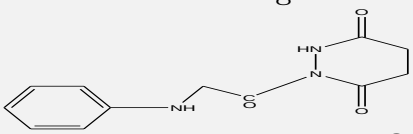
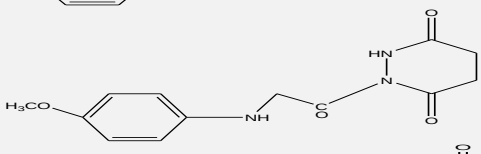
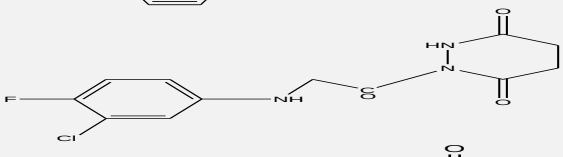
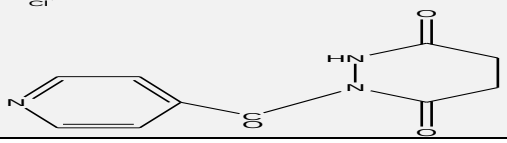
There are an estimated one billion hypertensives in the World; fifty million out of them are in India alone. As a consequence, great efforts have been made on obtaining novel antihypertensive agents acting on different mechanisms [4, 5]. Especially the studies on the hydralazine group drugs lead to the synthesis of many phthalazinone derivatives with a wide activity spectrum on cardiovascular system [6, 7].

MATERIAL AND METHOD:

Dataset and Descriptor and Model Development: A series of (n=8) 2-(N-substituted)-3H-phthalazin-1, 4-diones and 1-(N- substituted) 2, 4, 5-trihydropyridazin-3, 6-diones derivatives with Nitric oxide donor property was taken as model dataset reported by Deshpande *et al*., [8]. Response was converted to negative logarithm ($-\log I_{50}$) and was subjected to QSAR analysis as the response variable using two dimensional (2D) descriptors (topological, physicochemical and structure indices) which were calculated from PaDEL. Genetic Function Approximation was used for QSAR model(s) development.

TABLE 1: STRUCTURE OF 2-(N-SUBSTITUTED)-3H-PHTHALAZIN-1, 4-DIONES AND 1-(N- SUBSTITUTED) 2, 4, 5-TRIHYDROPYRIDAZIN-3, 6-DIONES DERIVATIVES

S. no.	Structure	% NO_2^-
1		55±5.65
2		38 ± 2.01
3		49 ± 4.67
4		83 ± 1.86
5		32 ± 1.75
6		23 ± 3.53
7		16 ± 1.34
8		52 ± 2.33

RESULT AND DISCUSSION: The best combination of model using 1000 iterations, 0.5 mutation probability and 2 for the length of equations was selected and discussed.

BA = 2.3505(+/-0.1558)-0.0002(+/-0.0002) ATSC7 v-0.0225(+/-0.0046) AMR

R2: 0.9301, R2 Adjusted: 0.9021, SEE: 0.0714, Q2: 0.8297, SDEP: 0.0882

The above equation mainly governs by hydrophobicity indicated by two parameter AMR (molar refractivity) and ATSC7v (auto correlation descriptors).

Negative coefficient of AMR indicates that lesser value of the parameter favoured vasodilatory effect. Compounds like 8, 4 with hetero substitution like pyridine in place of $RNHCH_2CO$ directly to pthalazine nitrogen showed good activity than compounds with aromatic or substituted aromatic substitution at R.

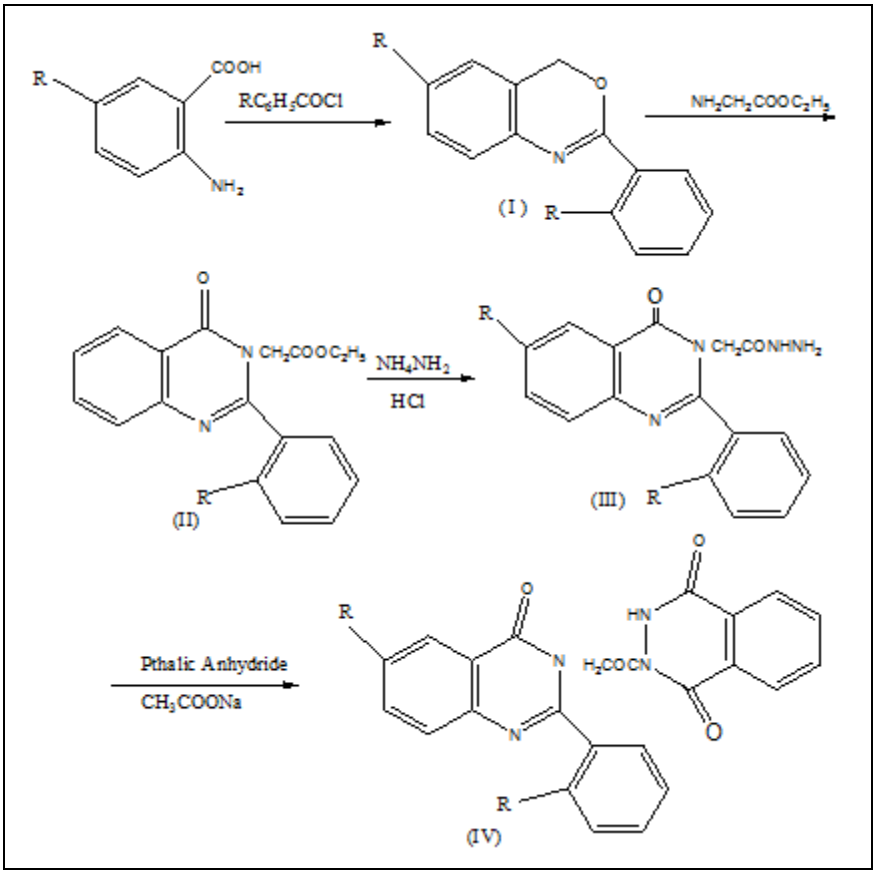
Similarly the parameter ATSC7v (Cantered Broto-Moreau autocorrelation - lag 7 / weighted by vander Waals volumes) is related to shapes of the molecules with the activity. Compounds with aromatic substitution at R show positive value for the descriptor ATSC7v and show less vaso dilatory effect than heteroaromatic substitution directly attached to pthalazine nitrogen (compound 4 and 8). Therefore design of analogues by direct heterocyclic group inclusion at N position of the pthalazine ring will show good vasodilatory activity.

EXPERIMENTAL: In these studies the 2-(N-substituted)-3H-phthalazin-1, 4- dione derivatives synthesized in the three steps reactions by method described in the literature [8, 9] 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)

The Quinazolinone, Benzimidazole, Benztriazole and Pyrazine-2, 5 dione were taken as aryl group at N position.

a) Synthesis of 2-(N- Quinazolinone)-3H-Phthalazine-1, 4-Dione derivatives PT-a (Scheme-I):



SCHEME 1: SYNTHESIS OF 2-(N- QUINAZOLINONE)-3H-PHTHALAZINE-1, 4-DIONE DERIVATIVES PT-A

Step I- Synthesis of 1,3-benzoxazine-4-one(ia): Anthranilic acid / Substituted anthranilic acid (0.28M) was dissolved in 100 ml of pyridine, benzoyl chloride /substituted benzoyl chloride (0.28M) was added in the solution with continuous stirring at room temperature for 30 min. The obtained product (ia) was filtered, washed with distilled water and was recrystallised from the ethyl alcohol, the yield of the product was 80%, and M.P. was 168 ºC, 170 ºC, 210 ºC, 216 ºC.

Step II- Synthesis of 2-substituted phenyl-N-ethyl acetate 1, 3 Quinazoline-4-one (iia): The compound ia (0.1M) dissolved in minimum amount of dilute HCl and ethyl glycinate (0.1M) were taken in round bottom flask and refluxed for 6 h. Cooled the contents and poured into the cold water to get solid mass of the product iia. Filtered and washed the compound iia with cold water and recrystallised from the ethyl alcohol. The yield of the product was 75%, Rf-0.65 and M.P. was 191ºC, 199 ºC, 220 ºC and 230 ºC.

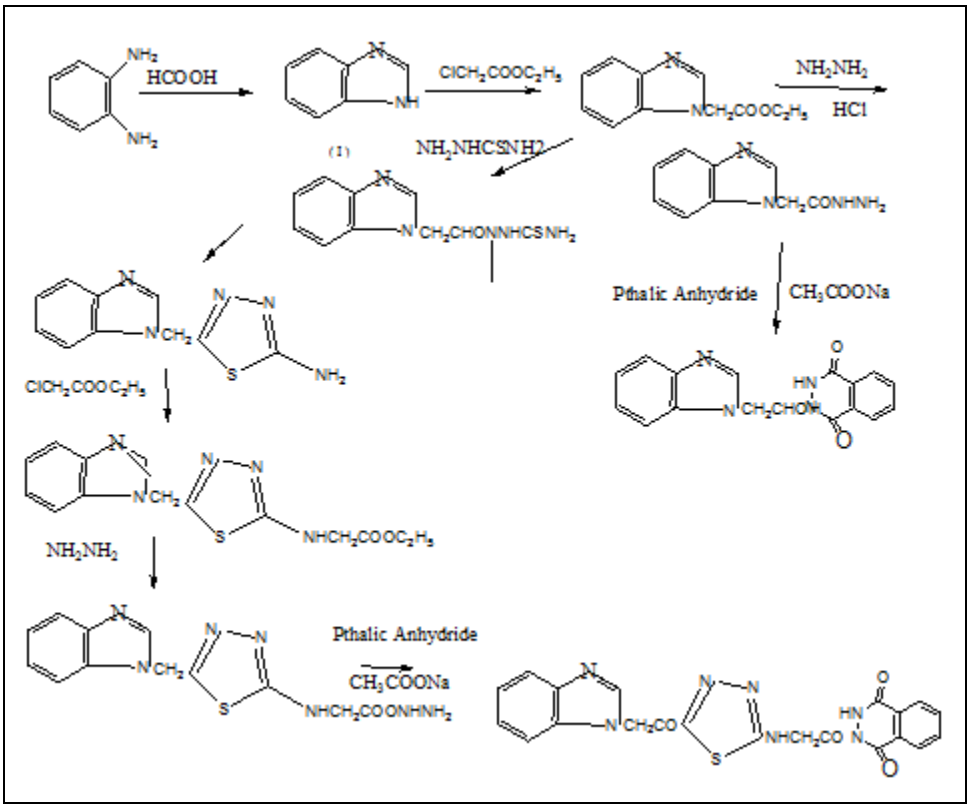
Step III - Synthesis of 2-substituted phenyl-1, 3 Quinazoline-4-one N-acetylhydrazide (iiia): The compound iia (0.1M) was taken in a round bottom flask, hydrazine hydrate (37 ml) (0.1M) was then added with constant stirring. Heat the mixture for 15 min. Then about 25 ml absolute ethanol was added to produce clear solution. Reaction mixture refluxed for 3 h. Ethanol was distilled off, cooled the content, filtered the product and recrystallised

from the ethyl alcohol. The yield of the products were 70-75%. MP were 110 ºC, 80 ºC, 166 ºC and 155 ºC.

Step IV-Synthesis of 2-(N-2-substituted phenyl-1,3 Quinazolin-4-one)-3H-Phthalazine-1,4-Dione (iva): The mixture of compound iii (0.1M), Glacial acetic acid (0.05M) and Phthalic anhydride (0.1M) in absolute alcohol (50 ml), was taken and refluxed for 3 h. The content was poured into the ice cold water, filtered the product and recrystallised from the ethyl alcohol. The yield of the final products PTa_{1-4} were 70-85%.

MP of the compounds are respectively as follows- 252 ºC, 240 ºC, 218 ºC, & 238 ºC.

b) Synthesis of 2(N-Benzimidazol-3yl)-3H-Phthalazine-1,4-Dione derivatives PTb/PTc (Scheme II):



SCHEME II: SYNTHESIS OF 2(N-BENZIMIDAZOL-3YL)-3H-PHTHALAZINE-1,4-DIONE DERIVATIVES PTb/PTc

Step I: The Synthesis of Benzimidazole (ib): 2.7 gm of o-Phenylenediamine (0.025M) was taken in round bottom flask and then added 1.75 gm of Formic acid (1.6 ml 0.035M), stirred continuously for 15 min. Heated the mixture on water bath for two h at 100 ºC. Cooled the content and added 10% sodium hydroxide solution with constant stirring till alkaline to litmus. Filtered the product and recrystallized with hot water. The yield obtained was 85% and M.P. was 172 ºC.

Step II: The synthesis of N-Benzimidazolethylacetate (iib): A mixture of product (ib) (0.1M), ethyl acetate (0.1M) and 0.3g of K_2CO_3 in 60 ml of acetone was stirred for 10 h. The solvent was removed under reduced pressure. A solid mass was produced and then needle shaped brown crystals were obtained after recrystallization from the mixture of chloroform and ether (8:2% v/v). The yield obtained was 75% and M.P. was 169 ºC.

Step III: The synthesis of N-Benzimidazola-cetylthiosemicarbazide / N- Benzimidazolacetyl hydrazide (iiib): The crystals obtained from step II (0.08M) and thiosemicarbazide / Hyrazine hydrate (0.08M) were taken in 50 ml of ethanol, stirred for 6 h and then refluxed for 3 h. The yellow colored compound was obtained after recrystallization from the mixture of chloroform and hexane (9:1V/V). The yield was 88%, 82% and MP were 115 ºC, 139ºC of compounds IIIb & IIIc respectively.

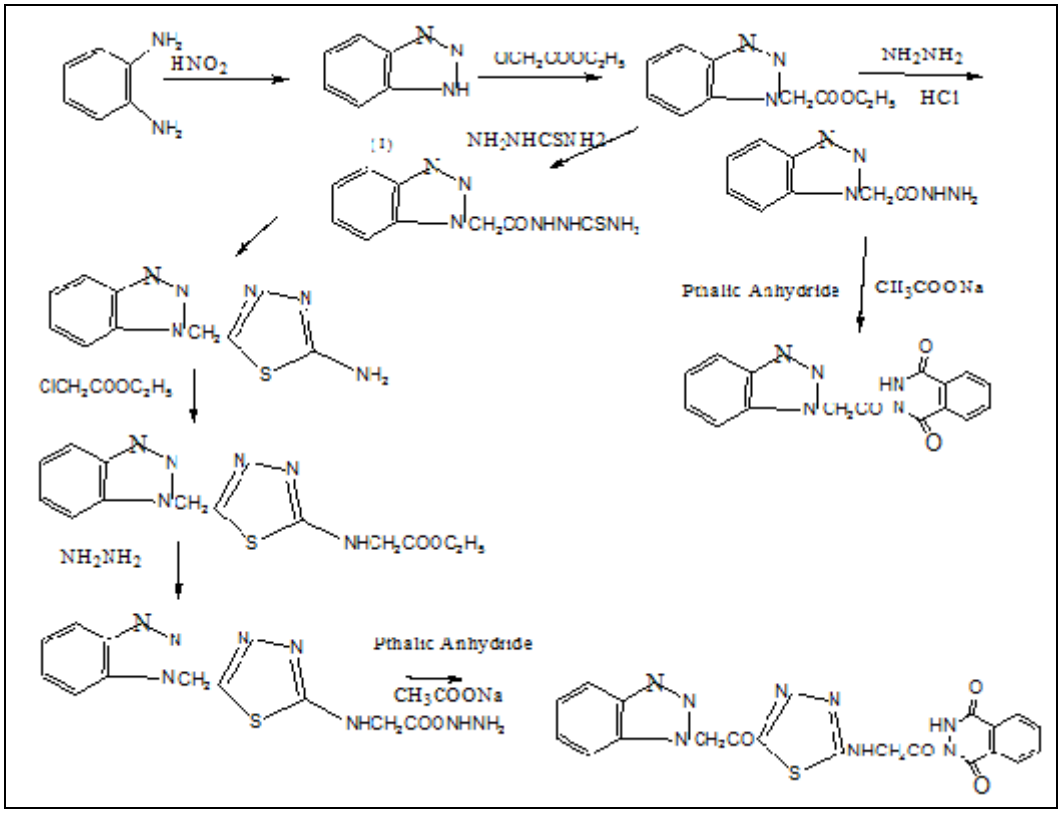
Step IV: The synthesis of 2-amino 5-(N-Benzimidazolomethyl)-1, 3, 4-Thiadiazole (ivc): Compound iiib (0.08M) was added in Conc.H_2SO_4 and kept overnight at room temperature, then neutralized with ammonia and extracted with ether. The ether was distilled off and the product recrystallised from methanol, the yield was 79% and M.P. 148 ºC.

Step V: Synthesis of 2-aminoethylacetate -5-(N-Benzimidazolomethyl)-1, 3, 4-Thiadiazole (vc): A mixture of compound IVc (0.1M), Chloroethyl acetate (0.12M) and Anhydrous sodium acetate (0.15M) in 50 ml absolute ethanol was refluxed for 6 h. Cooled the contents and poured into the cold water to get solid mass of the product (vb). Filtered and washed the compound (vb) with cold water and recrystallised from the ethyl alcohol. The yield of the product was 76% and M.P. was 113 ºC.

Step VI: Synthesis of 2-amino, 5-(N-Benzimidazolomethyl)-1,3,4-Thiadiazole N-acetylhydrazide (VIc): The compound vc (0.1M) was taken in a round bottom flask, hydrazine hydrate (37 ml) (0.1M) was then added with constant stirring. Heat the mixture for 15 min. Then about 25 ml absolute ethanol was added to produce clear solution. Reaction mixture refluxed for 3 h. Ethanol was distilled off, cooled the content, filtered the product and recrystallised from the ethyl alcohol. The yield of the products were 57% M.P. was 178 ºC.

Step VII: Synthesis of 2-amino,5-(N-Benzimidazolomethyl)-1, 3, 4-Thiadiazole N-acetyl/2-(N-Benzimidazolo)-N-acetyl -3H- Phthalazine-1, 4-Dione (PTb/PTc): The mixture of compound vic/compound IIIb (0.1M), Glacial acetic acid (0.05M) and Phthalic anhydride (0.1M) in absolute alcohol (50 ml), was taken and refluxed for 3 h. The content was poured into the ice cold water, filtered the product and recrystallised from the ethyl alcohol. The yield of the final products were 70-75% and MP were 254 ºC, 260 ºC of compounds PTb and PTc respectively.

C) Synthesis of 2(N-Benztrizol-3yl) / 2- [(N-Benzotriazolomethyl)-1, 3, 4- Thiadiazol-5- yl]- 3H-Phthalazine-1,4-Dione derivatives PTd/PTe (Scheme-IIIc):



SCHEME III: SYNTHESIS OF 2(N-BENZTRIZOL-3YL)/2-[(N-BENZOTRIAZOLOMETHYL)-1, 3, 4-THIADIAZOL-5-YL]-3H-PHTHALAZINE-1, 4-DIONE DERIVATIVES PTd/PTe

2-[(N-Benzotriazolomethyl)-1, 3, 4- Thiadiazol- 5-yl]- 3H-Phthalazine-1, 4-Dione derivatives were prepared as per the method described in the literature and the synthetic procedure involved the six steps as stated below.

Step I: The Synthesis of Benztriazole (id): In a mixture of 11.5 ml glacial acetic acid and 30 ml water, 0.1M o-phenylenediamine was dissolved and then added a solution of 0.1M $NaNO_2$ in 15 ml of water, stirred continuously for 15 minutes. The temperature was maintained at 12 ºC, chilled in ice bath and product (ic) was collected by filtration. The yield obtained was 65% and M.P. was 99 ºC.

Step II: The synthesis of N-Benztriazol ethylacetate (iid): A mixture of product (ic) (0.1M), ethyl acetate (0.1M) and 0.3g of K_2CO_3 in 60 ml of acetone was stirred for 10 h. The solvent was removed under reduced pressure. A solid mass was produced and then needle shaped brown crystals were obtained after recrystallization from the mixture of chloroform and ether (8:2% v/v). The yield obtained was 60% and M.P. was 40 ºC.

Step III: The synthesis of N-Benztriazol-acetylthiosemicarbazide / N- Benztriazolacetyl-hydrazide (iiid / iiie): The crystals obtained from step II (0.08M) and thiosemicarbazide/ Hyrazine hydrate (0.08M) were taken in 50 ml of ethanol, stirred for 6 hrs and then refluxed for 3 h. The yellow colored compound was obtained after recrystallization from the mixture of chloroform and hexane (9:1V/V). The yield was 57%, 67% and MP were 102-103 ºC, 138 ºC of compounds IIId and IIIe respectively.

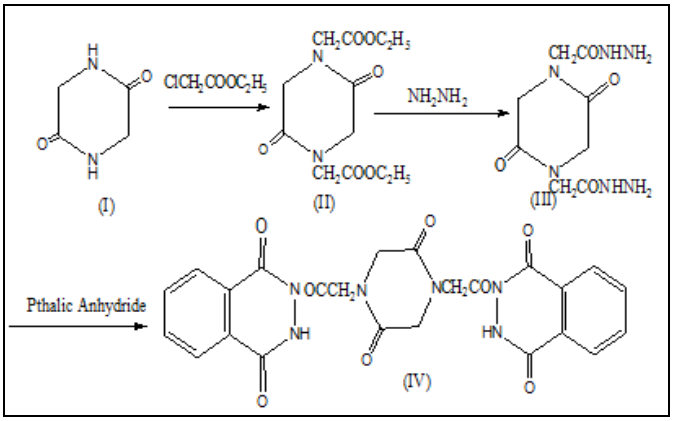
Step IV: The synthesis of 2-amino 5-(N-Benztriazolomethyl)-1, 3, 4-Thiadiazole (ive): Compound iiic (0.08M) was added in Conc.H_2SO_4 and kept overnight at room temperature, then neutralized with ammonia and extracted with ether. The ether was distilled off and the product recrystallised from methanol, the yield was 52% and M.P. 121 ºC.

STEP V- Synthesis of 2-aminoethylacetate 5-(N-Benztriazolomethyl)-1,3,4-Thiadiazole (ve): A mixture of compound Ve (0.1M), Chloroethyl acetate (0.12M) and Anhydrous sodium acetate (0.15M) in 50 ml absolute ethanol was refluxed for 6 h. Cooled the contents and poured into the cold water to get solid mass of the product vc. Filtered and washed the compound vc with cold water and recrystallised from the ethyl alcohol. The yield of the product was 50% and M.P. was 129 ºC.

Step VI: Synthesis of 2-amino, 5-(N-Benztriazolomethyl)-1, 3, 4-Thiadiazole N-acetylhydrazide (VIe): The compound ve (0.1M) was taken in a round bottom flask, hydrazine hydrate (37 ml) (0.1M) was then added with constant stirring. Heat the mixture for 15 min. Then about 25 ml absolute ethanol was added to produce clear solution. Reaction mixture refluxed for 3 hrs. Ethanol was distilled off, cooled the content, filtered the product and recrystallised from the ethyl alcohol. The yield of the products were 60 - 75% MP was 155 ºC.

Step VII: Synthesis of 2-amino, 5-(N-Benztriazolomethyl)-1, 3, 4-Thiadiazole N-acetyl/2-(N-Benztriazolo)-N-acetyl -3H- Phthalazine-1, 4-Dione (PTd/PTe): The mixture of compound vie / compound IIId (0.1M),Glacial acetic acid (0.05M) and Phthalic anhydride (0.1M) in absolute alcohol (50 ml), was taken and refluxed for 3 h. The content was poured into the ice cold water, filtered the product and recrystallised from the ethyl alcohol. The yield of the final products PTd and PTe were 60-75% and MP were 166 ºC, 184 ºC respectively.

d) Synthesis of Piperazine 2, 5-dione -1, 4-diyl-bis-2, 2', 3H- Phthalazine- 1, 4- Dione PTf (Scheme-IV):



SCHEME IV: SYNTHESIS OF PIPERAZINE 2, 5-DIONE -1, 4-DIYL-BIS-2, 2', 3H-PHTHALAZINE-1,4-DIONE PTF

Step I: Synthesis of Piperazine-2,5-Dione(If): 10 g (0.133M) Glycine and 50 ml of ethylene glycol

(0.28M) were taken in the round bottom flask and refluxed for an hour at 170 ºC. Cooled the contents and kept for a overnight in the refrigerator. The obtained pink color product (id) was filtered, washed with distilled water and was recrystallised from the hot water, the yield of the product was 50% and M.P. was 312 ºC.

Step II: Synthesis of N,N-diethyl-diacetyl, Piperaazine-2, 5-Dione (iif): A mixture of compound If (0.1M), ethyl Chloroacetate (0.12M) and Anhydrous sodium acetate (0.15M) in 50 ml absolute ethanol was refluxed for 6 h. Cooled the contents and poured into the cold water to get solid mass of the product IId. Filtered and washed the compound iid with cold water and recrystallised from the ethyl alcohol. The yield of the product was 88% (Rf 0.61) and M.P. was 165 ºC.

Step III: Synthesis of N,N-di-ethyl,di-acetyl, di-hydrazide, Piperaazine-2,5-Dione (iiif): The compound iid (0.1M) was taken in a round bottom flask, hydrazine hydrate (37 ml) (0.1M) was then added with constant stirring. Heat the mixture for 15 min. Then about 25 ml absolute ethanol was added to produce clear solution. Reaction mixture refluxed for 3 h. Ethanol was distilled off, cooled the content, filtered the product and recrystallised from the ethyl alcohol. The yield of the products were 56% (Rf 0.48) M.P. was 172 ºC.

Step IV: Synthesis of N,N-bis-(2N-acetyl-3H-Phthalazine-1, 4-Dione) Piperaazine-2, 5-Dione (PTf): The mixture of compound IIIf (0.1M), Glacial acetic acid (0.05M) and Phthalic anhydride (0.1M) in absolute alcohol (50 ml), was taken and refluxed for 3 h. The content was poured into the ice cold water, filtered the product and recrystallised from the ethyl alcohol. The yield of the final product PTf were 62% (Rf 0.6) and MP was 260 ºC. .

Physico-Chemical Studies: The synthesized N-Pthalazine-1, 4-dione derivatives were evaluated chemically by performing the qualitative chemical tests and thin layer chromatography. They gave positive qualitative tests for Ester and Amide functional groups with Nitrogen as element. The melting points were determined in open capillary tubes in liquid paraffin and were uncorrected, presented in **Table 2**.

The purity of compounds were established by TLC using 2% silica gel G, Benzene: Methanol as eluents (9:1), Iodine chamber and UV light used for detecting the compounds.

All the structure of synthesized compounds were confirmed by UV, IR and NMR Spectroscopy and on the basis of C, H and N analysis.

Evaluation:

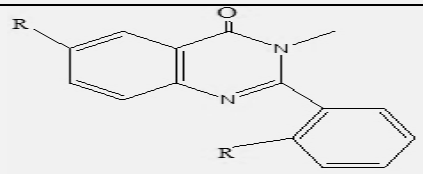
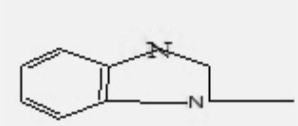
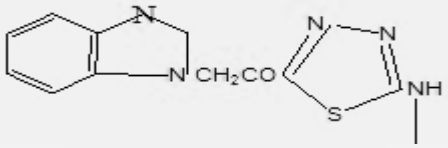
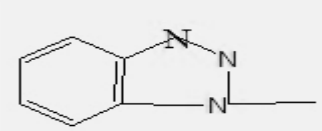
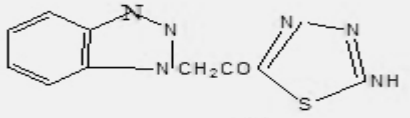
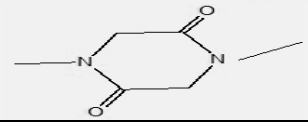
Experimental Animals: Healthy albino rats of either sex (Wistar strain) weighing 100 - 160g were used in present study. The animals had free access to food and water and were maintained under controlled temperature (27 ± 2 ºC) and 12h: 12h light and dark cycle. Initial body weight of each animal was recorded.

Acute Toxicity Studies: The synthesized N-substituted pthalazine 1, 4-dione derivatives at different doses (50-2000 mg/kg) were administered orally to normal rats. During the first four hours after the drug administration, the animals were observed for gross behavioral changes if any for 7 days. The parameters such as hyperactivity, grooming, convulsions, sedation, hypothermia, mortality was observed. No mortality observed with oral administration of all the compounds even at the highest dose (2000 mg/kg). Institutional Animal Ethics Committee (IAEC) had approved the experimental protocol (994/GO/ERC/ S/06/CPCSEA, 124/IAEC/Pharmacy/2016, dated 08/032016) and care of animals was taken as per the guidelines of CPCSEA, Department of animal welfare, Government of India.

Test for Antihypertensive Activity: 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) for two 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 [10].

TABLE 2: PHYSICAL PROPERTIES OF SYNTHESIZED COMPOUNDS

S. no.	Code	R	M.F/ M.W	Yield (%)	Color	m.p. (ºC)	R_f	% Reduction in MAP
1	PT-a_{1-4}	 A1=H, H/A2= H,Cl A3=Br,H/A4=Br,Cl	$C_{24}H_{17}O_3N4$ (409) $C_{24}H_{17}O_3N4$ (445) $C_{24}H_{17}O_3N4$ (488) $C_{24}H_{17}O_3N4$ (524)	70 82 81 85	Cream Yellow Turmeric Orange	252 ºC 240 ºC 218 ºC 238 ºC	0.49 0.5 0.42 0.44	35.4 33.4 34.9 31.74
2	PTb		$C_{17}H_{14}O_3N_4$ (322)	75	White	254 ºC	0.32	34.94
3	PT-c		$C_{20}H_{17}O_3N_7$ (371)	72	Orange	260 ºC	0.39	39.93
4	PT-d		$C_{16}H_{13}O_3N_5$ (291)	64	Light Yellow	166 ºC	0.42	33.45
5	PT-e		$C_{19}H_{16}O_3N_8$ (372)	75	Brown	184 ºC	0.50	31.21
6	PT-f		$C_{24}H_{18}O_8N_6$ (518)	62	Yellow	260 ºC	0.6	41.99

Standard Hydralazine = 40.76 (% red MAP)

RESULTS: All the synthesized compounds have shown a comparable antihypertensive activity and almost equal % mortality with that of Hyhralazine (20 mg/kg) and showed a significant ($p<0.01$) inhibition of hypertension induced by Methyl Prednisolone (20 mg/kg) in albino rats and the results are presented in **Table 2**. The synthesized compounds showed 33.4%, 34.9%, 31.74%, 34.9%, 39.93%, 33.45%, 31.21% and 41.99% reduction in BP at 20 mg/kg dose respectively.

In the synthesized compound PT-f was found to exhibit high and equal activity with standard followed by PT-c, PT-a, PT-b, PT-d and PT-e at 20 mg/kg dose respectively. Maximum activity was found in the synthesized compound code PT-f even more than standard in the same dose. Anti-hypertensive activity of PT-f is comparable to that of Hydralazine at dose 20 mg/kg respectively and duration of action found to be almost same as the standard drug.

These studies showed that this type of N-substituted pthalazine 1, 4-dione analogues producing significant antihypertensive activity by increasing vasodilation and inhibit the effect of Methyl Prednisolone. However, more elaborate work is required to establish the efficacy of the synthesized N-substituted pthalazine 1, 4-dione derivatives as potent antihypertensive drugs.

DISCUSSION: These compounds were synthesized with the objectives of developing better antihypertensive molecules like hydralazine with optimal antihypertensive activity. From the screening result, it can be concluded that all the synthesized compounds were effective against hypertension induced by Methyl Prednisolone (20 mg/kg). The presence of pthalazinone increases the antihypertensive activity in same dose of standard. It can also be concluded that piperazine-substituted compound was more active than compounds substituted with Benzimidazole, Quinazolinone and Benztriazole. Unsubstituted compounds were more active than halide group substituted compounds. Compound PT-f was most effective than compound PT-c, PT-a and PT-b because it is piperazine substituted, on the other hand compounds PT-c, PT-a and PT-b are Benzimidazole Quinazolinone and Benztriazole substituted respectively. It is assumed that activity was due to the the piperazine and pthalazine hetero nucleus present in the structure.

CONCLUSION: This study provided a convenient synthetic method for synthesis a new titled compound and results of antihypertensive screening are encouraging. Further investigations with appropriate structural modification of title compounds may result in therapeutically useful products.

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CONFLICT OF INTEREST: None

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