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SYNTHESIS, CHARACTERIZATION AND ANTIHYPERTENSIVE SCREENING OF DIHYDROPYRIDAZINONE ANALOGUES

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ABSTRACT

The main objective present research work to synthesis, characterization and biological evaluation of pyridazine analogues. To study the different synthesized derivative by using different analytical parameters. And also to find out the good pharmacologically active synthesized compounds. The studies on the hydralazine group drugs led to the synthesis of many pyridazinone derivatives with a wide activity spectrum on cardiovascular system. Pyridazinone derivatives, a class of compounds containing the N-N bond, exhibit a wide range of pharmacological activities such as antidepressant, antihypertensive, antithrombotic, anticonvulsant, cardiotonic, anti HIV and anticancer etc. All the synthesized compounds were obtained in good yield by optimizing various synthetic procedures. The structures of the compounds were established by elemental analysis, IR, ^{1}H-NMR and Mass spectral data analysis. The current work describes the synthesis of some new substituted pyridazine derivatives with encouraging antihypertensive activity by non-invasive method using Tail Cuff method. Some new dihydropyridazinone analogues were synthesized by a sequence of reactions starting from respective aryl hydrocarbons. Pyridazinone derivatives were synthesized under different reaction mechanism like Fredal craft acylation for substituted benzene, Claisen condensation and Manich reaction conditions. Total Ten compounds (4a-4i) were synthesized by mentioned scheme. The final compounds 4e and 4i were evaluated for antihypertensive activities by non-invasive method using Tail Cuff method. Compound 4e and 4i were found to show highly significant reduction in mean arterial blood pressure but at higher dose in comparison to standard drugs.

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INTRODUCTION

In the present scenario, a large number of medications acting through different mechanisms for the treatment of hypertension are available. Even the one has to admit that blood pressure of majority of hypertensive patients is inadequately controlled, partly because the treatment is not conducted intensively enough, but partly also because the medication(s) are not taken as prescribed. Lowering blood pressure in hypertensive patients requires therefore not only a broad choice of effective and well-tolerated medications, but also skills to motivate them to comply lifelong with the treatment. hypertension is the most common cardiovascular disease. The definition of hypertension, therefore using any specific cut off point is arbitrary. The studies on the hydralazine group drugs led to the synthesis of many pyridazinone derivatives with a wide activity spectrum on cardiovascular system[1-3]. Pyridazinone derivatives, a class of compounds containing the N-N bond, exhibit a wide range of pharmacological activities such as antidepressant[4], antihypertensive[5-8], antithrombotic[9], anticonvulsant[10], cardiotonic[11], antibacterial[12], diuretics[13], antiHIV[14] and anticancer[15]. Some pyridazinone derivatives like indolidan[16], bemoradan[17], primobendan[18], levosimendan[19] (antihypertensive), already approved in the clinical market. The current work describes the synthesis of some new substituted pyridazine derivatives with encouraging antihypertensive activity by non-invasive method using Tail Cuff method.

The main objective of present research work to synthesis, characterization and biological evaluation of pyridazine analogues. All the synthesized compounds were obtained in good yield by optimizing various synthetic procedures. The structures of the compounds were established by elemental analysis, IR, ^{1}H-NMR and Mass spectral data analysis. To study the different synthesized derivative by using different analytical parameters. And also to find out the good pharmacologically active synthesized compounds.

EXPERIMENTAL

Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked by thin layer chromatography (TLC) method. The FT-IR spectra were recorded on Bio-rad FTS-135 spectrophotometer using KBr pellets; υ_{max} values are given in cm^{-1}. ^{1}H-NMR spectra were recorded on Bruker Spectrospin DPX 300 MHz using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) scale and coupling constants (J values) are expressed in Hz. The FAB Mass spectra were obtained on JEOL-JMS-DX 303 system, equipped with direct inlet probe system. Elemental analysis was carried out on CHNS Elementar (Vario EL III) using sulphanilic acid as a standard and tugsten (VI) oxide as a combusting agent and analyses for C, H, N were within ±0.4% of the theoretical values.

General procedure for the synthesis of substituted *β*-aroyl propionic acids (1a-c)

The substituted β-aroyl propionic acids **(1a-c)** were synthesized from respective aromatic hydrocarbon and characterized on the basis of spectral data as per reported procedure[21,22].

General procedure for the synthesis of 6-Oxo-3-substituted-phenyl-5,6-dihydropyridazine-1(4*H*)-carbohydrazide (2a–c)

To a solution of substituted β-aroyl propionic acids (0.01 mol) in ethanol (30 mL) were added carbohydrazide (0.01 mol) and sodium acetate, and the mixture was refluxed for 6 hrs. After completion of the reaction, ethanol was distilled off and the residue was poured into cold water. The solid which separated was filtered and washed with water. The product was dried in air and crystallized from ethanol[23].

Synthesis of 6- (substituted-phenyl) -2- (4-substituted-phenyl-5-thioxo-4, 5-dihydro-*1H*-1, 2, 4-triazol-3-yl) -4, 5-dihydropyridazin-3 (*2H*) -one derivatives (4a-i)

A ethanolic solution of 6-Oxo-3-substituted-phenyl-5,6-dihydropyridazine-1(4*H*)-carbohydrazide (0.01 mole) and aromatic isothiocyanate (0.01 mole) was refluxed for 4 hrs. The contents were concentrated and poured into crushed ice, filtered and dried to crude thiosemicabazide intermediates as 6-substituted-phenyl-2-(N-phenylthiosemicarbazido)-4,5-dihydropyridazin-3(2*H*)-one derivatives **(3a-i)**. Crude thiosemicarbazide intermediates (0.005 mole) was refluxed in 2M sodium hydroxide solution (20 ml) for 5 hrs, cooled, poured into excess of water with continuous stirring and filtered to get the final compound. The filtrate on acidification with glacial acetic acid yielded a solid and recrystallized from ethanol.

6-Phenyl-2-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2*H*)-one, 4a

Yield: 40%; m.p. 180-182 °C; R_f 0.42; IR (KBr) υ_{max} (cm^{-1}): 3323 (NH), 2930 (CH), 2368 (C=S), 1685 (C=O), 1607 (C=N), 1030; ^{1}H-NMR (δ) $CDCl_3$: 2.54 (t, 2H, CH_2), 2.99 (t, 2H, CH_2), 7.13-7.93 (m, 10H, Ar-H), 10.78 (s, 1H, CSNH); Mass (m/z): 349/350 (M^+/M^++1); Anal Calc. for $C_{18}H_{15}N_5OS$: C: 61.87; H: 4.33; N: 20.04. Found: C: 61.82; H: 4.22; N: 19.96.

6-Phenyl-2-[4-(4-chlorophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4b

Yield: 46%; m.p. 148-150 ºC; R_f 0.46; IR (KBr) υ_{max} (cm^{-1}): 3330 (NH), 2922 (CH), 2365 (C=S), 1665 (C=O), 1612 (C=N), 1025, 817; ^{1}H-NMR (δ) $CDCl_3$: 2.48 (t, 2H, CH_2), 2.99 (t, 2H, CH_2), 7.13-7.93 (m, 9H, Ar-H), 10.82 (s, 1H, CSNH); Mass (m/z): 383 (M^+); Anal Calc. for $C_{18}H_{14}ClN_5OS$: C: 56.32; H: 3.68; N: 18.24. Found: C: 56.28; H: 3.56; N: 18.22.

6-Phenyl-2-[4-(4-methylphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5 dihydropyridazin-3(2*H*)-one, 4c

Yield: 60%; m.p. 188-190 °C; R_f 0.46; IR (KBr) υ_{max} (cm^{-1}): 3452 (NH), 2926 (CH), 2360 (C=S), 1648 (C=O), 1600 (C=N); ^{1}H-NMR (δ) $CDCl_3$: 2.40 (s, 3H, CH_3), 2.62 (t, 2H, CH_2), 3.2 (t, 2H, CH_2), 7.2-7.80 (m, 9H, Ar-H), 10.76 (s, 1H, CSNH); Mass (m/z): 363/364 (M^+/M^++1). Anal Calc. for $C_{19}H_{17}N_5OS$: C: 62.79; H: 4.71; N: 19.27. Found: C: 62.78; H: 4.66; N: 19.02.

6-(4-Methylphenyl)-2-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2*H*)-one, 4d

Yield: 40%; m.p. 192-194 °C; R_f 0.54; IR (KBr) υ_{max} (cm^{-1}): 3426 (NH), 3094 (CH), 2365 (C=S), 1658 (C=O), 1612 (C=N), 809, 699; ^{1}H-NMR (δ) $CDCl_3$: 2.30 (s, 3H, CH_3), 2.44 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 7.21-7.23 (dd, 2H, J=7.8,H-3',H-5'), 7.34-7.40 (m, 5H, Ar-H), 7.61-7.64 (dd, 2H, J=7.8, H-2', H-6'),10.82 (s, 1H, CSNH); Mass (m/z): 363/364 (M^+/M^++1); Anal Calc. for $C_{19}H_{17}N_5OS$: C: 62.79; H: 4.71; N: 19.27. Found: C: 62.74; H: 4.62; N: 19.16.

6-(4-Methylphenyl)-2-[4-(4-chlorophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4e

Yield: 38%; m.p. 196-198 °C;, R_f 0.60; IR (KBr) υ_{max} (cm^{-1}): 3215 (NH), 2929 (CH), 2364 (C=S), 1682 (C=O), 1615 (C=N), 760; ^{1}H-NMR (δ) $CDCl_3$: 2.34 (s, 1H, CH_3), 2.48 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 3.20 (t, 2H, CH_2), 7.13-7.93 (m, 8H, Ar-H), 10.74 (s, 1H, CSNH); Mass (m/z): 397 (M^+); Anal Calc. for $C_{19}H_{16}ClN_5OS$: C: 57.35; H: 4.05; N: 17.60. Found: C: 57.25; H: 3.96; N: 17.52.

6-(4-Methylphenyl)-2-[4-(4-methylphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4f

Yield: 72%; m.p. 202-204 °C; R_f 0.48; IR (KBr) υ_{max} (cm^{-1}): 3450 (NH), 2924 (CH), 2352 (C=S), 1662 (C=O), 1602 (C=N); ^{1}H-NMR (δ) $CDCl_3$: 2.30 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.52 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 7.21-7.23 (dd, 2H, J=7.8, H-3', H-5'), 7.34-7.40 (m, 4H, Ar-H), 7.61-7.64 (dd, 2H, J=7.8, H-2', H-6'), 10.84 (s, 1H, CSNH); Mass (m/z): 377/378 (M^+/M^++1). Anal Calc. for $C_{20}H_{19}N_5OS$: C: 63.64; H: 5.07; N: 18.55. Found: C: 63.58; H: 4.88; N: 18.46.

6-(4-Methoxyphenyl)-2-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2*H*)-one, 4g

Yield: 42%; m.p. 170-172 °C, R_f 0.56; IR (KBr) υ_{max} (cm^{-1}): 3471 (NH), 2926 (CH), 2374 (C=S), 1647 (C=O), 1612 (C=N), 1092, 794; ^{1}H-NMR (δ) $CDCl_3$: 2.58 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 3.67 (s, 3H, CH_3O), 7.0-7.94 (m, 9H, Ar-H), 10.86 (s, 1H, CSNH); Mass (m/z): 379/390 (M^+/M^++1); Anal Calc. for $C_{19}H_{17}N_5O_2S$: C: 60.14; H: 4.52; N: 18.46. Found: C: 60.02; H: 4.48; N: 18.40.

6-(4-Methoxyphenyl)-2-[4-(4-chlorophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4h

Yield: 38%; m.p. 178-180 °C; R_f 0.58; IR (KBr) υ_{max} (cm^{-1}): 3499 (NH), 2920 (CH), 2360 (C=S), 1638 (C=O), 1562 (C=N), 801; ^{1}H-NMR (δ) $CDCl_3$: 2.62 (t, 2H, CH_2), 2.94 (t, 2H, CH_2), 3.82 (s, 3H, CH_3O), 7.12-7.96 (m, 8H, Ar-H), 10.72 (s, 1H, CSNH); Mass (m/z): 413 (M^+); Anal Calc. for $C_{19}H_{16}ClN_5O_2S$: C: 55.14; H: 3.90; N: 16.92. Found: C: 55.02; H: 3.84; N: 16.84.

6-(4-Methoxyphenyl)-2-[4-(4-methylphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4i

Yield: 52%; m.p. 182-184 °C; R_f 0.54; IR (KBr) υ_{max} (cm^{-1}): 3458 (NH), 2940 (CH), 2372 (C=S), 1672 (C=O), 1618 (C=N); ^{1}H-NMR (δ) $CDCl_3$: 2.40 (s, 3H, CH_3), 2.56 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 3.67 (s, 1H, CH_3O), 7.0-7.94 (m, 8H, Ar-H), 10.84 (s, 1H, CSNH); Mass (m/z): 393/394 (M^+/M^++1). Anal Calc. for $C_{20}H_{19}N_5O_2S$: C: 61.05; H: 4.87; N: 17.80. Found: C: 60.98; H: 3.94; N: 17.64.

Total Ten compounds (4a to 4i) were synthesized and subjected for IR, NMR and Mass analysis. The final compounds (4e and 4i) were evaluated for antihypertensive activities by non-invasive method using Tail Cuff method. The IR, NMR and Mass spectra of final compounds (4e and 4i) were mentioned below.

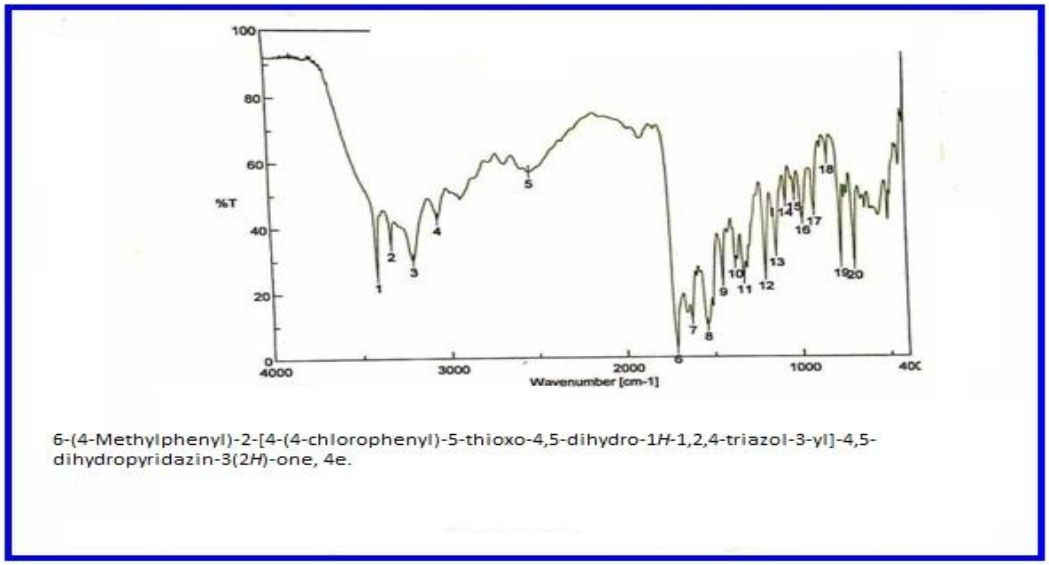

Fig 1: IR spectra of 6-(4-Methylphenyl)-2-[4-(4-chlorophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4e.

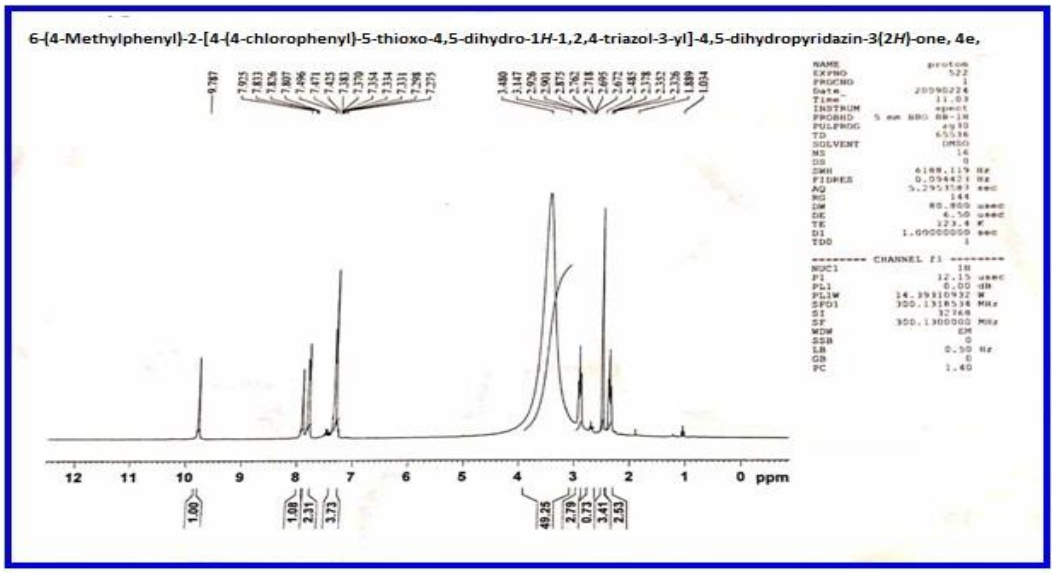

Fig 2: NMR spectra of 6-(4-Methylphenyl)-2-[4-(4-chlorophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4e.

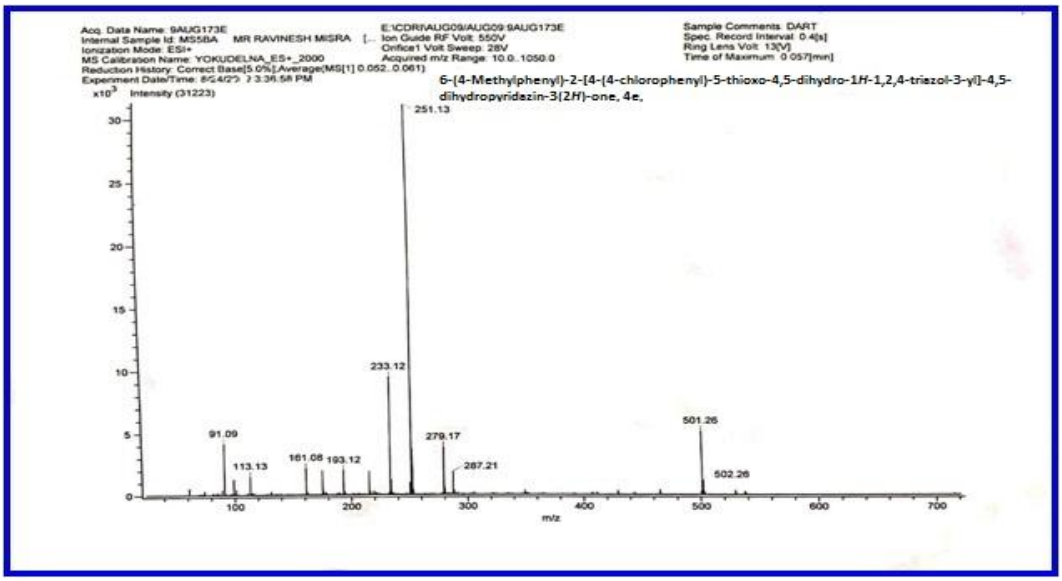

Fig 3: MASS spectra of 6-(4-Methylphenyl)-2-[4-(4-chlorophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4e.

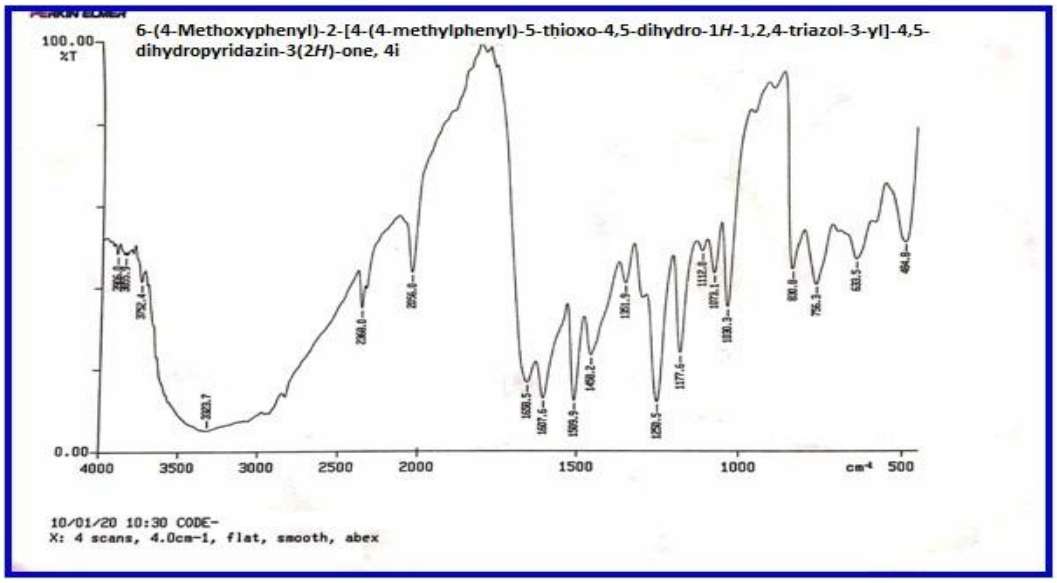

Fig 4: IR spectra of 6-(4-Methoxyphenyl)-2-[4-(4-methylphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4i.

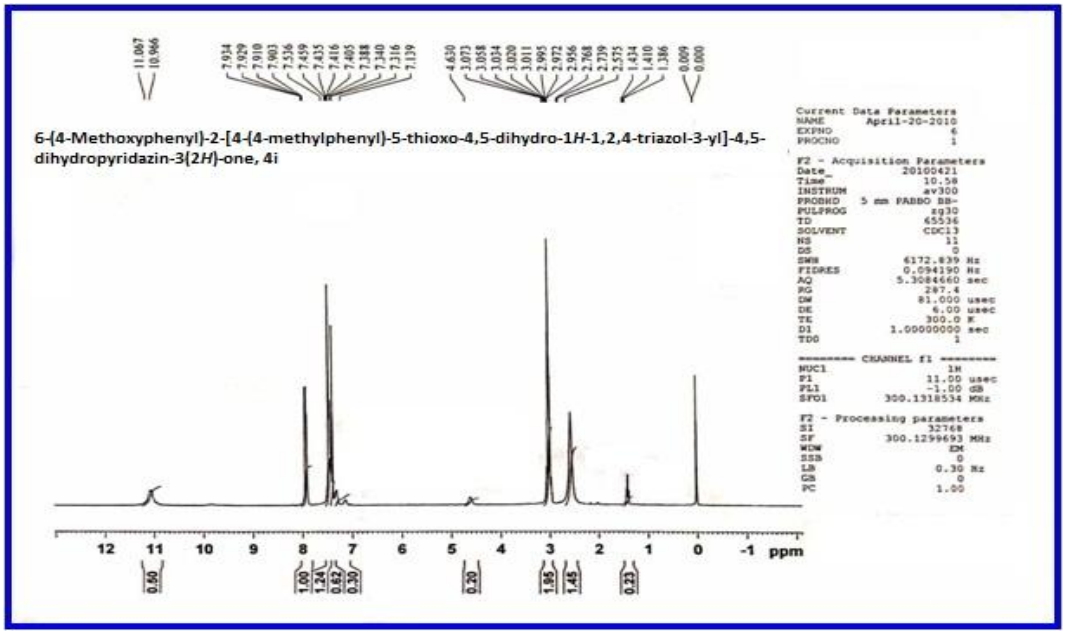

Fig 5: NMR spectra of 6-(4-Methoxyphenyl)-2-[4-(4-methylphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4i.

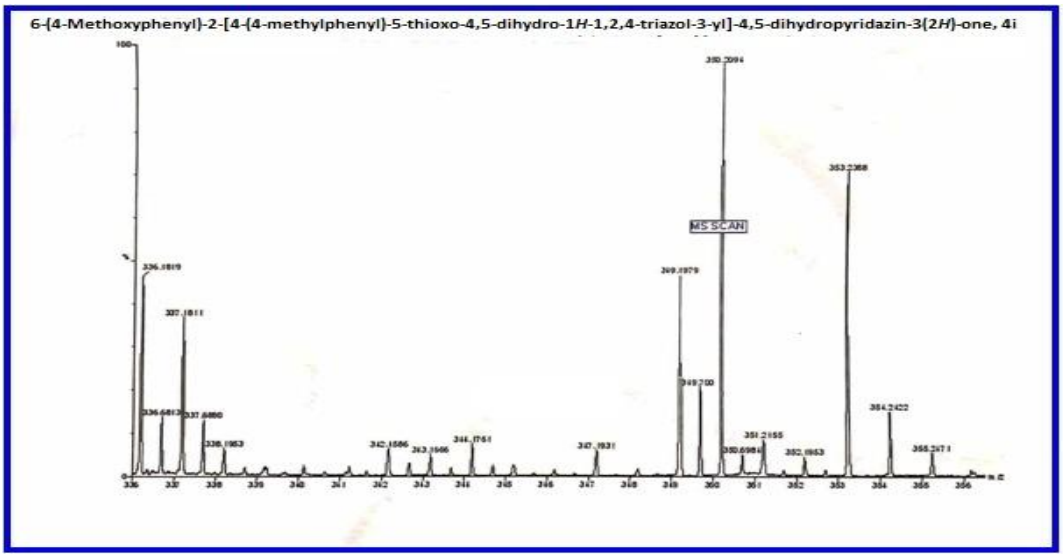

Fig 6: MASS spectra of 6-(4-Methoxyphenyl)-2-[4-(4-methylphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4i.

ANTIHYPERTENSIVE SCREENING:

Procurement, identification, and housing of animals:

Albino rats (body weight 200–250 g) were kept under standard laboratory conditions in 12 h light/dark cycle at 25ºC ± 2ºC. Animals were provided with pellet diet (Lipton, Calcutta, India) and water ad libitum. They were marked for easy identification.

Conditioning/training of animals:

For conducting the BP measurement studies, 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 for measuring the activity.

Induction of hypertension in normotensive rats:

After recording the initial BP of rats, the animals were divided into groups of 5 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 2 weeks as per method reported by Krakoff et al.[24].

Measurement of mean blood pressure of rats:

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. Rats were assigned to groups of four animals in each. Each 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 hrs.

Statistical analysis of data:

The statistical analysis was performed using GRAPHPAD INSTAT 3 software (Graph Pad Software Inc, San Diego, CA). Data obtained from animal experiments were expressed as arithmetic mean ± SEM. The comparison between various groups was performed by one-way analysis of variance (ANOVA), and the effect in treatment groups were compared with toxic control group by Dunnet multiple comparison test. $p < 0.05$ was considered to be significant [*$p < 0.05$; **$p < 0.01$]. The percentage reduction in MABP for all the treatment groups was also calculated and compared.

RESULTS AND DISCUSSION

Chemistry:

The synthesis of some new 1,2,4-triazole derivatives of 4,5-dihydro-3(2H)-pyridazinone has been carried out according to the steps shown in the Figure 1. In the initial step, β-aroyl propionic acids (1a-c) were synthesized by Friedel-Crafts acylation of appropriate hydrocarbons with succinic anhydride in the presence of anhydrous aluminium chloride. The intermediates (2a–c) were synthesized by reacting β-aroyl propionic acids with carbohydrazide in absolute ethanol. The thiosemicarbazides (3a-3i) conveniently synthesized by refluxing carbohydrazide derivatives (2a-2c) with aryl isothiocyanate in ethanol. Intermediate thiosemicarbazide (0.05 M) was refluxed in 2M sodium hydroxide solution (reaction time varies from 4 to 5 h), cooled and poured into excess of water containing crushed ice which on acidification with glacial acetic acid yielded a solid, crystallized from ethanol to give final compounds (4a-4i). The purity of the compounds was checked by single-spot TLC, and the compounds were characterized on the basis of spectral data (IR, ^{1}H-NMR, Mass and elemental analysis). Spectral data of all the newly synthesized compounds were in full agreement with proposed structures. In general, Infra Red Spectra (IR) revealed NH, CH, C=S, C=O and C=N peak at 3323, 2926, 2368, 1685 and 1607 cm^{-1}, respectively. In the Nuclear Magnetic Resonance Spectra (^{1}H-NMR) the signals of the respective protons of the prepared titled compounds were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The two triplets at δ 2.54 and 2.99 confirmed the presence of methylene group at 4 and 5 position of pyridazinone ring respectively. The multiplets at δ 7.13–7.93 are indicative of aromatic protons. The singlet at δ 10.78 is due to CSNH group flanked by two nitrogen atoms. The mass spectrum shows the presence of peak at definite m/z value in accordance to the molecular formula. The elemental analysis results were within ±0.4% of the theoretical values.

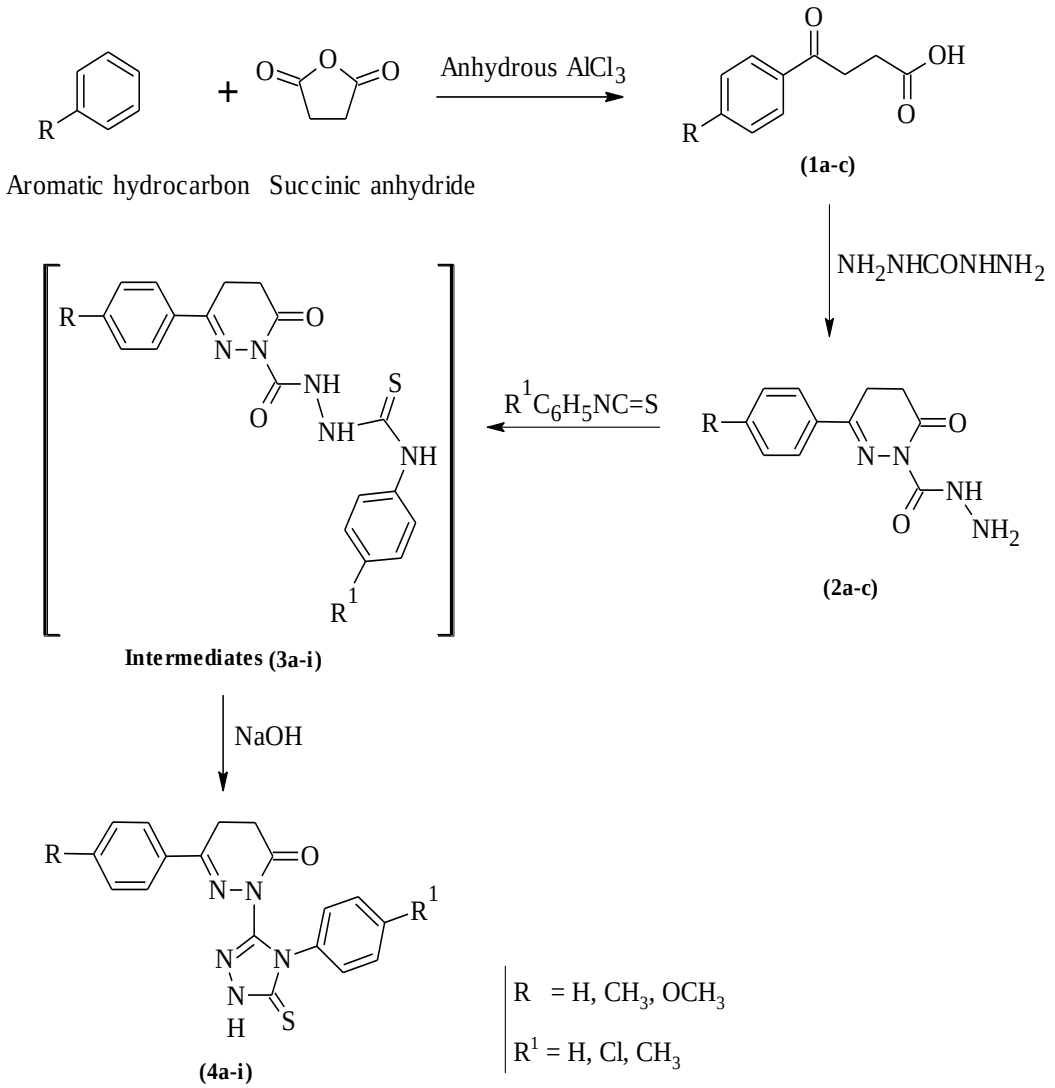

Fig 7: Synthesis of 6-(substituted phenyl)-2-(4-substituted phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2*H*)-one derivatives.

Antihypertensive activity:

The final compounds (4a-4i) were evaluated for antihypertensive activity by non-invasive method using Tail Cuff method. The results were shown in Table 1 and compared with standard drug, hydralazine[20] and propanolol. Compound 4e and 4i were found to show highly significant reduction in mean arterial blood pressure but at higher dose in comparison to standard drugs.

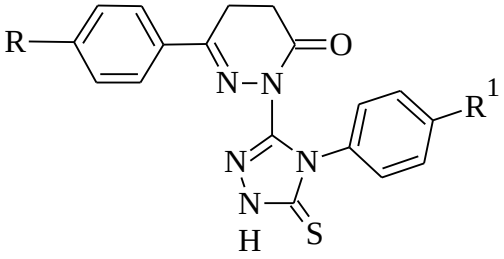

Table 1: Mean arterial blood pressure (mm Hg) and substituents of compounds (4a-i).

Compound (20mg/kg)	MABP (Mean ± SEM)	% Reduction in MABP	R	R^1
Control	101.33±4.64			
Toxic control	162.33±4.02**			
Propranolol[a]	95.12±4.68**	41.40		
Hydralazine[b]	96.16±4.70**	41.76		
4a	113.6±7.78**	30.01	H	H
4b	122±4.85**	24.84	H	Cl
4c	107.4±5.54**	38.83	H	CH_3
4d	118±7.56**	27.30	CH_3	H
4e	94.41±7.32**	41.84	CH_3	Cl
4f	111.6±10.28**	31.25	CH_3	CH_3
4g	109.6±6.17**	32.48	OCH_3	H
4h	136.2±2.9**	16.09	OCH_3	Cl
4i	95.8±3.93**	40.98	OCH_3	CH_3

[a] Dose of Propanolol was taken as 14 mg/kg.

[b] Dose of hydralazine was taken as 2.6 mg/kg.

All values were expressed as Mean ±SEM (*$p \leq 0.05$), each group comprised of four animals (i.e. n=4).

Toxic control group was compared with control group. All the treatment groups were compared with toxic control group and $p < 0.05$ was considered to be significant.

**$P < 0.01$, *$P < 0.05$.

CONCLUSIONS

From above research study concluded that different pyridazine analogues compounds were synthesized by using different analytical parameters. And also to find out the good pharmacologically active synthesized compounds. All the synthesized compounds were obtained in good yield by optimizing various synthetic procedures. The structures of the compounds were established by elemental analysis, IR, ^{1}H-NMR and Mass spectral data analysis. The final compounds (4a-4i) were evaluated for antihypertensive activity by non-invasive method using Tail Cuff method. Compound 4e and 4i were found to show highly significant reduction in mean arterial blood pressure but at higher dose in comparison to standard drugs. Dihydropyridazinone analogues can be further modified to exhibit better potency than the standard drugs. The substituted pyridazine derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of hypertension.

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