SYNTHESIS, CHARACTERIZATION AND ANTIHYPERTENSIVE ACTIVITY OF SOME NEW SUBSTITUTED PYRIDAZINE DERIVATIVES

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(Received: September 28, 2010 - Accepted: October 17, 2011)

ABSTRACT

Some new 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 were synthesized by a sequence of reactions starting from respective aryl hydrocarbons. The final compounds **(4a-i)** were screened for antihypertensive activities by non-invasive method using Tail Cuff method. The compounds **4e** and **4i** showed appreciable antihypertensive activity.

Key words: Pyridazine, Antihypertensive activity, Non invasive tail-cuff method.

INTRODUCTION

Hypertension is the most common cardiovascular disease and is the major risk factor for coronary artery disease leading to myocardial infarction and sudden cardiac death, heart failure, stroke and renal failure[1]. Great efforts have been made on obtaining novel antihypertensive agents acting on different mechanisms to control blood pressure[2]. The studies on the hydralazine group drugs led to the synthesis of many pyridazine derivatives with a wide activity spectrum on cardiovascular system[3]. Pyridazine 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.

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, and N were within ±0.4% of the theoretical values.

General procedure for the synthesis of *β*-aroylpropionic acids 1(a-c)

To liquid aromatic hydrocarbon (30 mL), anhydrous aluminum chloride (16.6 g, 0.125 mol) was added. The mixture was stirred using a magnetic stirrer at room temperature for 30 min. To this, succinic anhydride (5 g, 0.05 mol) was added in five portions with continuous stirring. Vigorous reaction started with the evolution of HCl gas. Stirring was continued for another 6 h at room temperature. The mixture was left at room temperature for 48 h and then decomposed by adding ice-cold hydrochloric acid (50%, 100 mL). The excess solvent was removed by steam distillation. The precipitated solid was treated with saturated sodium bicarbonate solution, filtered, washed with cold water, dried, and crystallized from the appropriate solvent to give **1a-c**[21,22].

General procedure for the synthesis of 6-Oxo-3-substituted-phenyl-5,6-dihydropyridazine-1(4*H*)-carbohydrazide 2(a-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 h. 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 4(a-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 hours. 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 **3(a-i)**. Crude thiosemicarbazide intermediates (0.005 mole) was refluxed in 2M sodium hydroxide solution (20 ml) for 5 hours, 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-(4-methoxyphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4a, Yield: 80%; m.p. 182-184 °C; R_f 0.45; IR (KBr) υ_{max} (cm^{-1}): 3323 (NH), 2930 (CH), 2368 (C=S), 1685 (C=O), 1607 (C=N), 1030; ^{1}H-NMR (δ) $CDCl_3$: 2.38 (s, 3H, OCH_3), 2.54 (t, 2H, CH_2), 2.99 (t, 2H, CH_2), 7.13-7.93 (m, 9H, Ar-H), 10.78 (s, 1H, CSNH); ^{13}C-NMR: 24.1, 32.6, 55.8, 114.6, 125.1, 128.2, 128.8, 131, 133.7, 143, 147.9 (C=N), 166.7 (C=S), 172.8 (C=O); Mass (m/z): 379/380 (M^+/M^++1); Anal Calc. for $C_{19}H_{17}N_5O_2S$: C: 60.14; H: 4.52; N: 18.46. Found: C: 60.32; H: 4.22; N: 18.26.

6-Phenyl-2-[4-(4-bromophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4b, Yield: 86%; m.p. 150-152 ºC; R_f 0.48; 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); ^{13}C-NMR: 24.2, 32.5, 122.7, 128.2, 128.8, 129, 131, 131.8, 135.6, 136.4, 143, 147.8 (C=N), 166.7 (C=S), 172.5 (C=O); Mass (m/z): 428 (M^+); Anal Calc. for $C_{18}H_{14}BrN_5OS$: C: 50.48; H: 3.29; N: 16.35. Found: C: 50.76; H: 3.56; N: 16.22.

6-Phenyl-2-[4-(3-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); ^{13}C-NMR: 21.3, 24.1, 32.6, 125, 128.2, 128.8, 128.9, 130, 133.8, 136.4, 138.7, 143, 147.9 (C=N), 166.7 (C=S), 172.5 (C=O); 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.

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6-(4-Methylphenyl)-2-(4-methoxyphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2*H*)-one, 4d, Yield: 90%; m.p. 194-196 ºC; R_f 0.52; 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), 2.40 (s, 3H, OCH_3), 2.44 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 7.21-7.64 (m, 8H, Ar-H), 10.82 (s, 1H, CSNH); ^{13}C-NMR: 21.2, 24.1, 32.6, 55.8, 114.6, 125.1, 127, 128.2, 128.8, 128.9, 129.3, 130, 133.4, 136.4, 138.7, 140.7, 142.9, 147.6 (C=N), 159.3, 166.6 (C=S), 172.4 (C=O); 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: 59.84; H: 4.62; N: 17.56.

6-(4-Methylphenyl)-2-[4-(4-bromophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4e, Yield: 88%; m.p. 210-212 ºC;, R_f 0.62; 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); ^{13}C-NMR: 21.3, 24.3, 32.6, 122.7, 128.3, 128.8, 129.2, 131, 131.7, 135.5, 136.6, 143.1, 147.7 (C=N), 166.8 (C=S), 172.8 (C=O); Mass (m/z): 442 (M^+); Anal Calc. for $C_{19}H_{16}BrN_5OS$: C: 51.59; H: 3.65; N: 15.83. Found: C: 51.25; H: 3.96; N: 15.52.

6-(4-Methylphenyl)-2-[4-(3-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 ºC; 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); ^{13}C-NMR: 21.3, 24.1, 32.6, 125, 127, 128.9, 129.2, 130, 134, 133.8, 138.7, 143, 166.7, 172.5; 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-methoxyphenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2*H*)-one, 4g, Yield: 92%; m.p. 172-174 ºC, R_f 0.54; 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) $CDCl_3$: 2.40 (s, 3H, OCH_3), 2.58 (t, 2H, CH_2), 2.96 (t, 2H, CH_2), 3.67 (s, 3H, CH_3O), 7.0-7.94 (m, 8H, Ar-H), 10.86 (s, 1H, CSNH); ^{13}C-NMR: 24.1, 32.6, 55.8, 114.4, 114.6, 125.1, 128.7, 133.7, 143, 147.9, 159.3, 162.9, 166.7; Mass (m/z): 409/410 (M^+/M^{+}+1); Anal Calc. for $C_{20}H_{19}N_5O_3S$: C: 58.67; H: 4.68; N: 17.10. Found: C: 58.42; H: 4.48; N: 17.40.

6-(4-Methoxyphenyl)-2-[4-(4-bromophenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4h, Yield: 85%; m.p. 188-190 ºC; R_f 0.56; 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); ^{13}C-NMR: 24.2, 32.5, 55.8, 122.7, 128.2, 128.8, 129, 131, 131.8, 135.6, 136.4, 143, 147.8 (C=N), 166.7 (C=S), 172.5 (C=O); Mass (m/z): 458 (M^+); Anal Calc. for $C_{19}H_{16}ClN_5O_2S$: C: 49.79; H: 3.52; N: 15.28. Found: C: 50.02; H: 3.84; N: 14.94.

6-(4-Methoxyphenyl)-2-[4-(3-methylphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2*H*)-one, 4i, Yield: 78%; m.p. 182-184 ºC; 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); ^{13}C-NMR: 21.3, 24.2, 32.5, 55.8, 122.7, 128.2, 128.8, 129, 131, 131.8, 135.6, 136.4, 143, 147.8 (C=N), 166.7 (C=S), 172.5 (C=O); 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.

Antihypertensive activity

Procurement, identification, and housing of animals

Albino rats (body weight 200–250 g) were supplied by Central Animal House facility (Registration Number: 173/CPCSEA and Date of Registration: 28, JAN-2000), Jamia Hamdard and kept under standard laboratory conditions in 12 h light/dark cycle at 25 ºC ± 2 ºC. 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 h.

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(2*H*)-pyridazinone has been carried out according to the steps shown in the **Figure 1**.

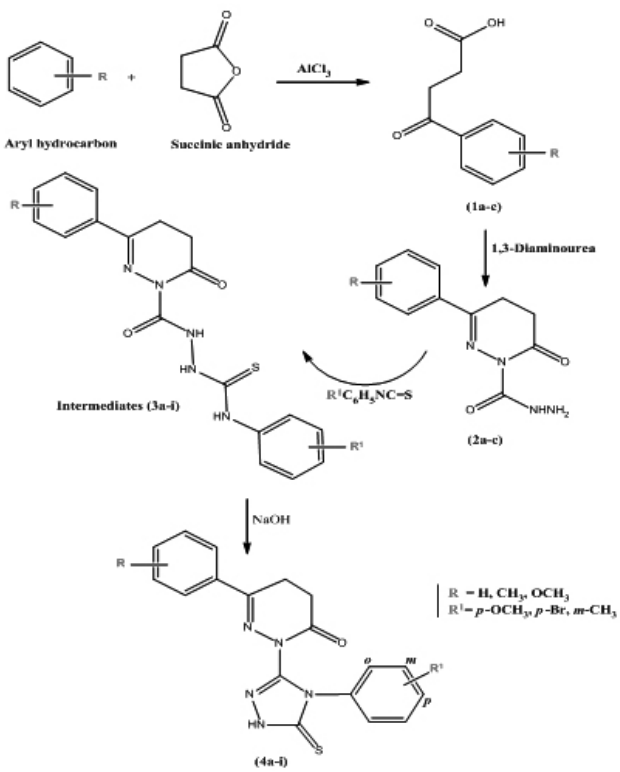


Figure 1. Synthesis of 6-(substituted phenyl)-2-(4-substituted phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2*H*)-one derivatives.

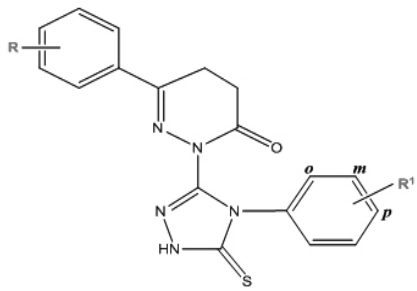
In the initial step, *b*-aroyl propionic acids **(1a-c)** were synthesized by Friedel-Crafts acylation of appropriate hydrocarbons with succinic anhydride in the presence of anhydrous aluminium chloride.The intermediates **(2a–c)** were synthesized by reacting *b*-aroyl propionic acids with carbohydrazide 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 structure is also supported by elemental analysis data and 13C NMR data. The other compounds are also identified in a similar manner. 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.

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 propranolol. 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. The mechanism of action of pyridazine (similar to vasodilators) derivatives has been shown in **Figure 2.**

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



General structure of **4(a-e)**

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	*p*-OCH_3
4b	122±4.85**	24.84	H	*p*-Br
4c	107.4±5.54**	38.83	H	*m*-CH_3
4d	118±7.56**	27.30	CH_3	*p* -OCH_3
4e	94.41±7.32**	41.84	CH_3	*p*-Br
4f	111.6±10.28**	31.25	CH_3	*m*-CH_3
4g	109.6±6.17**	32.48	OCH_3	*p*-OCH_3
4h	136.2±2.9**	16.09	OCH_3	*p*-Br
4i	95.8±3.93**	40.98	OCH_3	*m*-CH_3

[a]Dose of Propranolol 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. **$P < 0.01$, *$P < 0.05$.

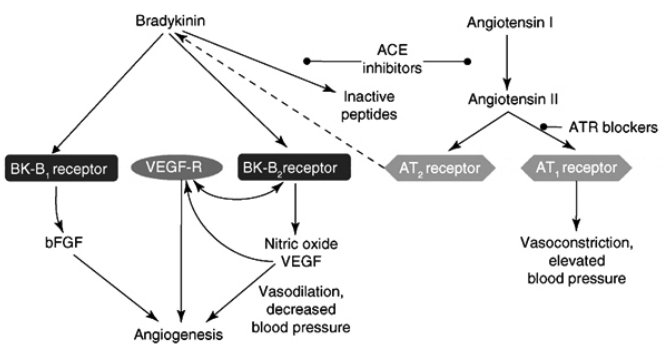


Figure 2. Angiotensin and bradykinin interact to induce angiogenesis. Bradykinin (BK), a potent vasodilator involved in regulation of blood pressure, induces angiogenesis. BK upregulates angiogenic molecules such as basic fibroblast growth factor (bFGF), via the BK B1 receptor[25], or VEGF and NO, via the BK B2 receptor[26]. The BK B2 receptor can also activate the VEGF receptor on endothelial cells. ACE inhibition results in BK accumulation and promotion of neovascularization. Moreover, angiotensin II activates the AT2 receptor during AT1 receptor blockade, thereby upregulating BK and contributing to an angiogenic response[27]. ATR, angiotensin receptor.

CONCLUSIONS

Various 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 can be further modified to exhibit better potency than the standard drugs. Further studies to acquire more information about Quantitative Structure Activity Relationships (QSAR) are in progress in our laboratory. The substituted pyridazine derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of hypertension.

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ACKNOWLEDGEMENTS

One of the authors (Ravinesh Mishra) expresses sincere thanks to the University Grant Commission (UGC), New Delhi, India, for the award of Research Fellowship in Science for Meritorious Students (RFSMS). The authors are also thankful to Jamia Hamdard, New Delhi, India for providing facility for the research work.