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Original article

Antihypertensive activity of newer 1,4-dihydro-5-pyrimidine carboxamides: Synthesis and pharmacological evaluation

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ABSTRACT

A number of 5-(4-substituted phenyl)-2-(substituted benzylsulfanyl)-4-(substituted phenyl)-6-methyl-1,4-dihydro-5-pyrimidine carboxamides (**1**–**30**) were designed and synthesized keeping in view the structural requirements as suggested in the pharmacophore model for antihypertensive activity. All the synthesized compounds were tested for antihypertensive activity by non-invasive blood pressure (NIBP) measurements (tail-cuff method) in rats. Almost all the tested compounds displayed considerable decrease in the blood pressure as compared to control. Thirteen compounds showed significant antihypertensive activity comparable to the standard drug nifedipine.

1. Introduction

Hypertension remains a major health problem in most countries because of its impact on the mortality and morbidity of patients. Indeed, hypertension accounts for more than 5.8% of total deaths, 1.9% of years of life lost and 1.4% disability adjusted life years all over the world [1]. Therefore, hypertension prevention and control in the community is currently a pivotal challenge.

The present popularity of dihydropyrimidine (DHPM) is mainly due to their close structural relationship to the clinically important dihydropyridine (DHP) calcium channel blockers such as nifedipine, which are most studied class of medicinal compound since their introduction and have become immensely important for the treatment of hypertension [2]. DHPMs have been identified as a lead and found to be more potent as well as long lasting derivatives in spontaneously hypertensive rats. The traditional SAR is a useful tool in search for new drugs and therefore SAR analogy has played a vital role in designing compounds with higher potency [2–4]. One of such structural analogy has been noticed between DHP and DHPM.

In the past decades, a broad range of biological effects, including antiviral, anticancer, antibacterial and antihypertensive activity has been ascribed to the DHPM derivatives and few of them have even emerged as orally active antihypertensive agents [5,6].

In light of these facts, we designed our compounds keeping in view the suggested pharmacophore model for better antihypertensive agents as suggested by Rovnyak et al. [7]. The present work describes the synthesis of newer 1,4-dihydropyrimidine (DHPM) derivatives that are substituted by different benzyl groups on the 2-thioxo position and an aryl ring linked *via* an amide bond to the C-5 carboxy functionality.

2. Chemistry

The synthesis of titled compounds (**1**–**30**) was carried out according to Scheme 1. Ethylacetoacetate was refluxed with substituted anilines using toluene as solvent in basic conditions to yield oxobutyramides that were used as 1,3-diketone adducts for multicomponent Biginelli reaction. These were condensed with thiourea and substituted benzaldehydes in presence of concentrated hydrochloric acid to get pyrimidine carboxamides. The reaction time was found to vary from 7 to 9 h depending upon the substitution on aryl aldehydes. In the final step, pyrimidine carboxamides were treated with substituted benzyl chlorides in presence of potassium carbonate to afford the titled compounds (**1**–**30**). The physicochemical properties of compounds are presented in Table 1.

3. Pharmacology

All the synthesized compounds were tested for their antihypertensive activity by non-invasive tail-cuff method. The animals

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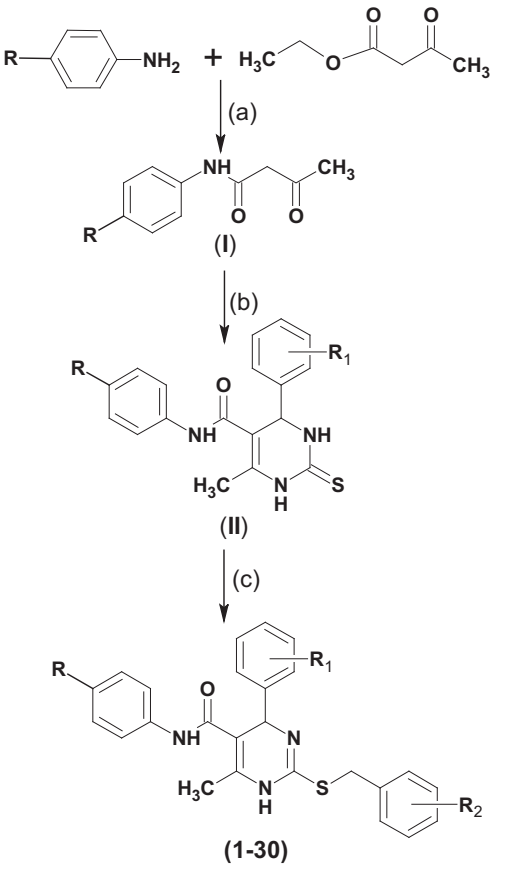

Scheme 1. Reagents and conditions: (a) NaOH, EtOH, reflux, 5 h; (b) Thiourea, substituted benzaldehydes, ethanol, conc. HCl, reflux, 7–9 h; (c) Substituted benzyl chloride, DMF, K_2CO_3, reflux, 8–10 h.

were previously treated with Deoxycorticosterone Acetate salt (DOCA-salt) that induces hypertension and the systolic blood pressure was measured. The change in blood pressure due to the synthesized compounds were noted and compared with that of standard drug nifedipine.

4. Results and discussion

4.1. Chemistry

All the synthesized compounds were obtained in good to high yields that were purified and characterized by different spectroscopic techniques. The IR spectra of compounds (**1**–**30**) showed characteristic absorption bands at 3331–3307 cm^{-1}, 1678–1637 cm^{-1}, and 652–614 cm^{-1} corresponding to the N–H_{str}, C=O_{str} and C–S_{str} functions in the structures. The formation of compounds was further supported by disappearance of the IR band at 1210 cm^{-1} due to the C=S group and appearance of a new band at 652–614 cm^{-1} due to C–S bond.

The ^1H NMR spectra of compounds (**1**–**30**) showed singlet at δ 2.21–2.32 ppm for CH_3 proton. Methoxy protons were observed as a singlet at δ 3.51–3.77 ppm. The singlet at δ 4.05–4.31 ppm was assigned to the benzyl SCH_2 proton.

Table 1
Physicochemical parameters of synthesized compounds (**1**–**30**).

Comp.	R	R_1	R_2	Mol. formula (M.W.)[a]	R_f[b] value	M.P. (°C)	% Yield
1	4-F	3,4-OCH_3	H	$C_{27}H_{26}FN_3O_3S$ (491.57)	0.61	212	61
2	4-F	3,4-OCH_3	2-Cl	$C_{27}H_{25}ClFN_3O_3S$ (526.02)	0.68	218	71
3	4-F	3,4-OCH_3	3-Cl	$C_{27}H_{25}ClFN_3O_3S$ (526.02)	0.52	176	59
4	4-F	3,4-OCH_3	4-Cl	$C_{27}H_{25}ClFN_3O_3S$ (526.02)	0.68	207	54
5	4-F	3,4-OCH_3	4-F	$C_{27}H_{25}F_2N_3O_3S$ (509.56)	0.60	204	66
6	4-F	4-NO_2	H	$C_{25}H_{21}FN_4O_3S$ (476.52)	0.74	215	69
7	4-F	4-NO_2	2-Cl	$C_{25}H_{20}ClFN_4O_3S$ (510.96)	0.78	167	52
8	4-F	4-NO_2	3-Cl	$C_{25}H_{20}ClFN_4O_3S$ (510.96)	0.75	225	62
9	4-F	4-NO_2	4-Cl	$C_{25}H_{20}ClFN_4O_3S$ (510.96)	0.62	222	48
10	4-F	4-NO_2	4-F	$C_{25}H_{20}F_2N_4O_3S$ (494.51)	0.71	234	71
11	4-Br	2,4-Cl	H	$C_{25}H_{20}BrCl_2N_3OS$ (561.32)	0.52	149	73
12	4-Br	2,4-Cl	2-Cl	$C_{25}H_{19}BrCl_3N_3OS$ (595.76)	0.67	188	63
13	4-Br	2,4-Cl	3-Cl	$C_{25}H_{19}BrCl_3N_3OS$ (595.76)	0.69	151	68
14	4-Br	2,4-Cl	4-Cl	$C_{25}H_{19}BrCl_3N_3OS$ (595.76)	0.77	162	57
15	4-Br	2,4-Cl	4-F	$C_{25}H_{19}BrCl_2FN_3OS$ (579.31)	0.65	187	51
16	4-Br	4-OCH_3	H	$C_{26}H_{24}BrN_3O_2S$ (522.45)	0.48	222	45
17	4-Br	4-OCH_3	2-Cl	$C_{26}H_{23}BrClN_3O_2S$ (556.90)	0.52	146	57
18	4-Br	4-OCH_3	3-Cl	$C_{26}H_{23}BrClN_3O_2S$ (556.90)	0.56	193	49
19	4-Br	4-OCH_3	4-Cl	$C_{26}H_{23}BrClN_3O_2S$ (556.90)	0.67	141	61
20	4-Br	4-OCH_3	4-F	$C_{26}H_{23}BrFN_3O_2S$ (540.44)	0.64	199	51
21	4-NO_2	4-Br	H	$C_{25}H_{21}BrN_4O_3S$ (537.42)	0.50	209	63
22	4-NO_2	4-Br	2-Cl	$C_{25}H_{20}BrClN_4O_3S$ (571.87)	0.64	211	61
23	4-NO_2	4-Br	3-Cl	$C_{25}H_{20}BrClN_4O_3S$ (571.87)	0.69	186	58
24	4-NO_2	4-Br	4-Cl	$C_{25}H_{20}BrClN_4O_3S$ (571.87)	0.78	201	54
25	4-NO_2	4-Br	4-F	$C_{25}H_{20}BrFN_4O_3S$ (555.41)	0.75	223	64
26	4-NO_2	3-NO_2	H	$C_{25}H_{21}N_5O_5S$ (503.52)	0.49	216	69
27	4-NO_2	3-NO_2	2-Cl	$C_{25}H_{20}ClN_5O_5S$ (537.97)	0.51	169	51
28	4-NO_2	3-NO_2	3-Cl	$C_{25}H_{20}ClN_5O_5S$ (537.97)	0.55	220	62
29	4-NO_2	3-NO_2	4-Cl	$C_{25}H_{20}ClN_5O_5S$ (537.97)	0.69	188	53
30	4-NO_2	3-NO_2	4-F	$C_{25}H_{20}FN_5O_5S$ (521.52)	0.62	192	62

[a] Solvent of crystallization – ethanol.
[b] Solvent system – toluene:ethyl acetate:formic acid (5:4:1).

The slightly upfield shift of methine (CH) protons present at C-4 position of 1,4-dihydropyrimidine ring was observed as a singlet at δ 5.07–5.18 ppm and is the most important diagnostic tool for titled compounds (**1**–**30**).

The two multiplet regions were obtained at δ 6.52–6.89 and δ 7.01–7.94 ppm for aromatic protons. Further, two broad singlets corresponding to NH (N-1 ring) and NH (carboxamides) were obtained at δ 8.61–9.16 ppm and δ 9.64–10.10 respectively that were D_2O exchangeable.

The structures of compounds (**1**–**30**) were further supported by their mass spectral data which showed presence of molecular ion peak M^+, M + 1 and M + 2 peaks at different *m*/*z* corresponding to

Table 2
Antihypertensive activity data shown by compounds (**1**–**30**) at 10 mg/kg dose.

Compound	Average systolic blood pressure (mmHg) at time (min)											
	0	15	30	60	120	180	240	300	360	600	720	900
1	195 ± 2	192 ± 1	187 ± 2	183 ± 2	177 ± 3	169 ± 2	172 ± 3	181 ± 1	187 ± 3	189 ± 1	191 ± 2	193 ± 3
2	194 ± 1	190 ± 2	182 ± 1	172 ± 2	161 ± 1	145 ± 3	136 ± 2	125 ± 3	118 ± 2	136 ± 2	149 ± 3	154 ± 2
3	194 ± 2	191 ± 3	184 ± 2	179 ± 3	173 ± 2	168 ± 1	166 ± 2	163 ± 2	155 ± 1	161 ± 2	164 ± 3	169 ± 2
4	193 ± 2	189 ± 2	183 ± 1	175 ± 2	164 ± 3	155 ± 2	148 ± 2	134 ± 1	122 ± 2	143 ± 3	151 ± 2	156 ± 2
5	193 ± 1	188 ± 1	181 ± 2	172 ± 1	164 ± 2	151 ± 3	139 ± 2	121 ± 2	122 ± 3	154 ± 2	161 ± 3	165 ± 1
6	194 ± 3	189 ± 2	180 ± 2	171 ± 3	159 ± 4	148 ± 2	132 ± 1	120 ± 2	119 ± 4	132 ± 2	141 ± 1	154 ± 2
7	195 ± 1	192 ± 2	188 ± 2	183 ± 1	177 ± 3	170 ± 1	164 ± 3	159 ± 3	152 ± 4	161 ± 4	167 ± 3	173 ± 2
8	195 ± 3	191 ± 2	186 ± 1	181 ± 3	175 ± 2	171 ± 1	164 ± 3	159 ± 4	153 ± 2	163 ± 2	169 ± 1	174 ± 2
9	194 ± 2	188 ± 1	181 ± 3	172 ± 1	163 ± 1	149 ± 2	130 ± 1	121 ± 3	117 ± 2	140 ± 4	151 ± 2	162 ± 2
10	193 ± 3	189 ± 2	183 ± 1	174 ± 2	161 ± 2	155 ± 1	145 ± 2	136 ± 1	130 ± 2	145 ± 1	156 ± 3	168 ± 4
11	195 ± 2	192 ± 1	187 ± 1	182 ± 3	174 ± 2	168 ± 1	161 ± 3	152 ± 4	147 ± 1	161 ± 2	172 ± 3	179 ± 3
12	194 ± 1	189 ± 1	183 ± 2	172 ± 1	163 ± 3	151 ± 2	139 ± 1	124 ± 2	120 ± 3	147 ± 2	154 ± 4	163 ± 2
13	196 ± 2	192 ± 1	188 ± 1	183 ± 2	177 ± 2	171 ± 1	164 ± 3	159 ± 2	154 ± 1	165 ± 3	172 ± 3	181 ± 2
14	195 ± 2	187 ± 3	181 ± 1	172 ± 2	160 ± 2	149 ± 2	132 ± 4	120 ± 2	117 ± 3	136 ± 4	144 ± 2	152 ± 1
15	194 ± 1	188 ± 1	179 ± 2	162 ± 1	150 ± 4	139 ± 1	124 ± 2	120 ± 1	115 ± 2	130 ± 3	141 ± 2	150 ± 3
16	196 ± 3	193 ± 3	189 ± 2	184 ± 2	178 ± 1	174 ± 2	169 ± 4	163 ± 1	158 ± 3	173 ± 1	180 ± 1	184 ± 1
17	193 ± 1	189 ± 2	185 ± 1	182 ± 2	178 ± 3	172 ± 2	165 ± 1	160 ± 2	154 ± 1	169 ± 2	173 ± 3	181 ± 4
18	194 ± 2	189 ± 1	179 ± 2	165 ± 2	153 ± 3	141 ± 2	129 ± 3	119 ± 2	117 ± 1	131 ± 4	142 ± 2	151 ± 1
19	195 ± 2	189 ± 2	180 ± 1	171 ± 3	162 ± 2	150 ± 4	138 ± 1	121 ± 2	118 ± 2	136 ± 2	148 ± 1	156 ± 4
20	193 ± 3	188 ± 1	182 ± 2	178 ± 1	169 ± 2	161 ± 3	152 ± 3	144 ± 2	129 ± 3	148 ± 2	157 ± 1	165 ± 2
21	196 ± 1	191 ± 2	187 ± 3	179 ± 2	168 ± 1	156 ± 2	141 ± 2	137 ± 3	121 ± 2	142 ± 1	153 ± 2	157 ± 3
22	195 ± 3	192 ± 1	187 ± 2	182 ± 1	179 ± 2	172 ± 3	165 ± 2	162 ± 3	167 ± 1	176 ± 2	181 ± 3	187 ± 2
23	194 ± 2	191 ± 2	189 ± 1	187 ± 2	181 ± 2	176 ± 3	172 ± 1	177 ± 2	180 ± 1	185 ± 1	189 ± 1	190 ± 2
24	194 ± 1	189 ± 2	182 ± 1	174 ± 2	167 ± 1	157 ± 2	137 ± 3	121 ± 3	118 ± 2	128 ± 2	137 ± 2	158 ± 1
25	195 ± 3	190 ± 2	184 ± 3	176 ± 2	169 ± 2	160 ± 2	142 ± 3	128 ± 2	119 ± 1	132 ± 2	141 ± 3	151 ± 2
26	194 ± 2	190 ± 1	186 ± 2	180 ± 1	174 ± 2	162 ± 1	154 ± 2	145 ± 1	131 ± 2	142 ± 1	160 ± 2	166 ± 3
27	193 ± 3	191 ± 1	187 ± 3	182 ± 2	179 ± 1	176 ± 2	170 ± 2	164 ± 1	160 ± 1	169 ± 2	172 ± 2	181 ± 3
28	194 ± 2	190 ± 1	186 ± 2	179 ± 1	170 ± 2	165 ± 2	160 ± 1	154 ± 2	152 ± 1	158 ± 3	169 ± 2	174 ± 2
29	195 ± 1	191 ± 2	188 ± 3	182 ± 3	170 ± 1	165 ± 2	156 ± 2	148 ± 1	130 ± 3	144 ± 1	164 ± 2	171 ± 2
30	194 ± 1	190 ± 3	186 ± 2	181 ± 3	168 ± 1	160 ± 2	151 ± 2	142 ± 3	124 ± 1	136 ± 2	155 ± 1	165 ± 2
Control	195 ± 2	195 ± 3	194 ± 1	195 ± 2	194 ± 3	194 ± 2	195 ± 4	195 ± 1	194 ± 2	195 ± 3	194 ± 3	195 ± 2
Nifedipine	195 ± 3	192 ± 1	188 ± 2	180 ± 1	172 ± 1	160 ± 2	145 ± 1	132 ± 3	120 ± 2	148 ± 1	158 ± 2	162 ± 1

Table 3
Comparative study of inhibition (%) for antihypertensive activity shown by compounds (**1**–**30**) and standard as compared to control.

Compound	Inhibition (%)											
	0	15	30	60	120	180	240	300	360	600	720	900
1	0.0	1.5	3.6	6.2	8.8	12.9	11.8	7.2	3.6	3.1	1.5	1.0
2	0.5	2.6	6.2	11.8	17.0	25.3	30.3	35.9	39.2	30.3	23.2	21.0
3	0.5	2.1	5.2	8.2	10.8	13.4	14.9	16.4	20.1	17.4	15.5	13.3
4	1.0	3.1	5.7	10.3	15.5	20.1	24.1	31.3	37.1	26.7	22.2	20.0
5	1.0	3.6	6.7	11.8	15.5	22.2	28.7	37.9	37.1	21.0	17.0	15.4
6	0.5	3.1	7.2	12.3	18.0	23.7	32.3	38.5	38.7	32.3	27.3	21.0
7	0.0	1.5	3.1	6.2	8.8	12.4	15.9	18.5	21.6	17.4	13.9	11.3
8	0.0	2.1	4.1	7.2	9.8	11.9	15.9	18.5	21.1	16.4	12.9	10.8
9	0.5	3.6	6.7	11.8	16.0	23.2	33.3	37.9	39.7	28.2	22.2	16.9
10	1.0	3.1	5.7	10.8	17.0	20.1	25.6	30.3	33.0	25.6	19.6	13.8
11	0.0	1.5	3.6	6.7	10.3	13.4	17.4	22.1	24.2	17.4	11.3	8.2
12	0.5	3.1	5.7	11.8	16.0	22.2	28.7	36.4	38.1	24.6	20.6	16.4
13	−0.5	1.5	3.1	6.2	8.8	11.9	15.9	18.5	20.6	15.4	11.3	7.2
14	0.0	4.1	6.7	11.8	17.5	23.2	32.3	38.5	39.7	30.3	25.8	22.1
15	0.5	3.6	7.7	16.9	22.7	28.4	36.4	38.5	40.7	33.3	27.3	23.1
16	0.5	1.0	2.6	5.6	8.2	10.3	13.3	16.4	18.6	11.3	7.2	5.6
17	1.0	3.1	4.6	6.7	8.2	11.3	15.4	17.9	20.6	13.3	10.8	7.2
18	0.5	3.1	7.7	15.4	21.1	27.3	33.8	39.0	39.7	32.8	26.8	22.6
19	0.0	3.1	7.2	12.3	16.5	22.7	29.2	37.9	39.2	30.3	23.7	20.0
20	1.0	3.6	6.2	8.7	12.9	17.0	22.1	26.2	33.5	24.1	19.1	15.4
21	0.0	2.1	3.6	8.2	13.4	19.6	27.7	29.7	37.6	27.2	21.1	19.5
22	0.0	1.5	3.6	6.7	7.7	11.3	15.4	16.9	13.9	9.7	6.7	4.1
23	0.5	2.1	2.6	4.1	6.7	9.3	11.8	9.2	7.2	5.1	2.6	2.6
24	0.5	3.1	6.2	10.8	13.9	19.1	29.7	37.9	39.2	34.4	29.4	19.0
25	0.0	2.6	5.2	9.7	12.9	17.5	27.2	34.4	38.7	32.3	27.3	22.6
26	0.5	2.6	4.1	7.7	10.3	16.5	21.0	25.6	32.5	27.2	17.5	14.9
27	1.0	2.1	3.6	6.7	7.7	9.3	12.8	15.9	17.5	13.3	11.3	7.2
28	0.5	2.6	4.1	8.2	12.4	14.9	17.9	21.0	21.6	19.0	12.9	10.8
29	0.0	2.1	3.1	6.7	12.4	14.9	20.0	24.1	33.0	26.2	15.5	12.3
30	0.5	2.6	4.1	7.2	13.4	17.5	22.6	27.2	36.1	30.3	20.1	15.4
Control	–	–	–	–	–	–	–	–	–	–	–	–
Nifedipine	0.0	1.5	3.1	7.7	11.3	17.5	25.6	32.3	38.1	24.1	18.6	16.9

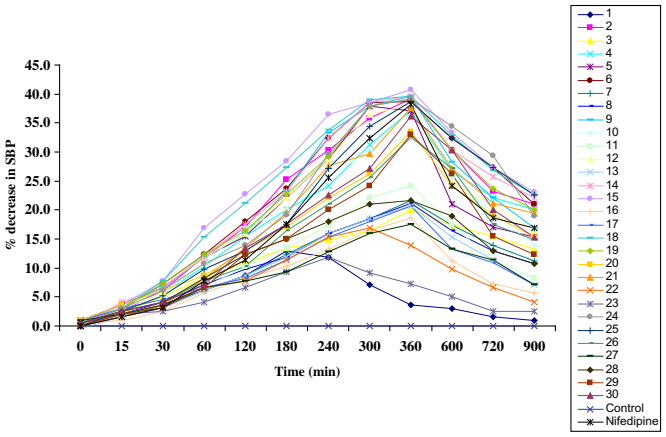

Fig. 1. Graph showing % decrease in the systolic blood pressure (SBP) exhibited by compounds (**1**–**30**) and standard as compared to control.

their molecular weights. In most compounds, prominent peaks resulted from the elimination of CO group.

4.2. Antihypertensive activity

All the synthesized compounds have been screened for their antihypertensive activity by using tail-cuff method that measures the systolic blood pressure. Change from control was observed and the activity was compared to the standard drug nifedipine. Data are summarized in Table 2. The percent decrease in the systolic blood pressure both by the synthesized compounds and by the standard drug has been calculated and the results are shown in Table 3. Almost all the tested compounds were found to be active against the hypertension induced by DOCA-salt. Thirteen compounds have shown significant antihypertensive activity as they markedly decrease the systolic blood pressure comparable to the standard drug nifedipine. They were found to decrease the blood pressure to normal after 6 h and a moderate rise afterwards, which may be due to the excretion of compound from body after 6 h as shown in graph in Fig. 1. Nifedipine was also found to express the similar profile when tested at the same dose at similar time intervals. Other compounds that have shown considerable antihypertensive activity were found to be **10**, **12**, **20**, **26** and **29**. These compounds decreased the blood pressure considerably but were not able to bring the blood pressure up to normal at any time interval. Rest all the compounds have shown moderate decrease in hypertension.

Structure activity relationship studies revealed that the substitutions at the phenyl ring attached to the pyrimidine moiety played a significant role in governing the antihypertensive activity. Substitutions by the electron releasing groups such as 4-OCH_3 and 3,4-OCH_3 tend to increase the activity. Substitutions at other phenyl rings were also seemingly important as the *para* substituted benzyl derivatives were more active in the series. The chloro substituted derivatives were found to be more active than the other halogen. The phenyl ring attached to the amide linkage does not seem to have any marked effect on antihypertensive activity.

5. Conclusions

A newer series of ring substituted pyrimidine carboxamides has been identified as antihypertensive agents. The promising activity of these agents further gave emphasis to the pharmacophore model suggested and need to be explored further to get better agents. These derivatives pose strong future commitments.

6. Experimental

6.1. Chemistry

The melting points were determined in open capillary tubes in a Hicon melting point apparatus and are uncorrected. The homogen elemental analyses (C, H, N) of all compounds were performed on the CHNS Elimentar (Analysen systime, GmbH) Germany Vario EL III. All the Fourier transform infra red (FTIR) spectra were recorded in KBr pellets on a Jasco FT/IR 410 spectrometer. The ^{1}H NMR spectra were taken on a Bruker 400 Ultra shield™ (400 MHz) NMR spectrometer. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane (TMS) as an internal standard. The homogeneity of the compounds was checked by thin layer chromatography (TLC) on silica gel G (Merck) coated plates by using toluene:ethyl acetate:formic acid (5:4:1) as solvent system. Iodine chamber and UV lamp were used for the visualization of TLC spots.

6.1.1. General procedure for the synthesis of titled compounds (*1*–*30*)

*N-(substituted phenyl)-3-oxo-butyramide (**I**).* A mixture of ethyl acetatoacetate (0.01 mol) and substituted aniline (0.01 mol) in 20 mL of ethanol containing 0.3 g sodium hydroxide was refluxed for 5 h. Reaction mixture was concentrated and the solid product was filtered off and recrystallized with ethyl acetate. Yield: 76%; M.p. 136 °C, IR (KBr, cm^{-1}): 3315 (NH), 3070 (Ar-CH_{str}), 1672 (C═O), 1629 (C═O); ^{1}H NMR (DMSO-d_6): δ 2.15 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 7.12–7.83 (m, 4H, ArH), 8.52 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 34.67 (*C*H_3), 55.43 (*C*H_2), 121.32 (Ar-*C*H), 128.46 (Ar-*C*H), 134. 45 (Ar-*C*H), 148.12 (Ar-*C*-), 174.24 (*C*═O), 215.34 (CH_3-*C*═O).

*6-Methyl-4-(substituted phenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid (4-substituted phenyl)-amides (**II**).* A mixture of *N*-(4-substituted phenyl)-3-oxo-butyramide (**I**, 0.01 mol), substituted aryl aldehydes (0.011 mol) and thiourea (0.015 mol) in 20 mL of ethanol was refluxed for 7–9 h in presence of catalytic amount of concentrated hydrochloric acid. The reaction mixture was kept overnight and the precipitate obtained was filtered and recrystallized with ethanol. Yield: 63%; M.p. 179 °C, IR (KBr, cm^{-1}): 3416 (NH), 3358 (NH), 3340 (NH), 3019 (Ar-CH_{str}), 1658 (C═O), 1304 (C═S); ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, CH_3), 5.11 (s, 1H, CH), 7.09–7.73 (m, 8H, ArH), 9.20 (bs, 1H, NH, D_2O exchangeable), 9.65 (bs, 1H, NH, D_2O exchangeable), 9.86 (bs, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 17.41 (Ar-*C*H_3), 64.39 (Ar-*C*H), 118.45 (Ar-*C*-), 120.14 (Ar-*C*H), 123. 23 (Ar-*C*H), 125.14 (Ar-*C*H-), 127.23 (Ar-*C*H-), 129.31 (Ar-*C*H-), 132.45 (Ar-*C*H-), 144.32 (Ar-*C*-), 147.37 (Ar-*C*-), 170.13 (*C*═O), 181.54 (*C*═S).

5-(4-Substituted phenyl)-2-(substituted benzylsulfanyl)-4-(substituted phenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**1**–**30**). A mixture of substituted pyrimidine-5-carboxylic acid amides (**II**, 0.01 mol) and substituted benzyl chloride (0.01 mol) in 20 mL of anhydrous DMF was refluxed for 8–10 h in presence of 0.3 g anhydrous K_2CO_3. Reaction mixture was concentrated and poured into ice cold water and the solid product was filtered off and recrystallized from mixture of hexane and ethyl acetate to give desired compound.

5-(4-Fluorophenyl)-2-benzylsulfanyl-4-(3,4-dimethoxyphenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**1**). IR (KBr, cm^{-1}): 3354 (N–H_{str}), 3313 (N–H_{str}), 2975 (Ar-CH_{str}), 1653 (C═O), 635 (C–S); ^{1}H NMR (DMSO-d_6): δ ppm 2.31 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 4.07 (s, 2H, S–CH_2), 5.11 (s, 1H, CH-pyr.), 6.59–6.78 (m, 3H, ArH), 7.01–7.76 (m, 9H, ArH), 8.83 (bs, 1H, NH, D_2O exchangeable), 9.78 (bs, 1H, NH-Amide, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 19.23 (Ar-*C*H_3), 38.21 (*C*H_2), 55.18 (Ar-*C*H), 59.45 (OCH_3), 61.23 (OCH_3), 115.24 (Ar-*C*H), 116.24 (Ar-*C*H), 117.13 (Ar-*C*H),

118.33 (Ar-*C*-), 119.45 (Ar-*C*H), 120.56 (Ar-*C*H), 122.71 (Ar-*C*H), 123.34 (Ar-*C*H), 125.14 (Ar-*C*H-), 126.22 (Ar-*C*H-), 128.67 (Ar-*C*H-), 131.34 (Ar-*C*H-), 150.17 (Ar-*C*-), 158.23 (Ar-*C*-), 171.87 (*C*=O); %Anal. Cal. (found) = C 65.97 (65.94), H 5.33 (5.38), N 8.55 (8.51); Mass (EI): *m*/*z* 490.28 (M^+).

5-(4-Fluorophenyl)-2-(2-chlorobenzylsulfanyl)-4-(3,4-dimethoxyphenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**2**). IR (KBr, cm^{-1}): 3368 (N—H_{str}), 3331(N—H_{str}), 1665 (C=O), 642 (C—S); ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 4.11 (s, 2H, S—CH_2), 5.07 (s, 1H, CH-pyr.), 6.52–6.81 (m, 3H, ArH), 7.15–7.63 (m, 8H, ArH), 8.78 (bs, 1H, NH, D_2O exchangeable), 9.80 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal. (found) = C 61.65 (61.68), H 4.79 (4.74), N 7.99 (7.93); Mass (EI): *m*/*z* 527.36 (M + 1).

5-(4-Fluorophenyl)-2-(3-chlorobenzylsulfanyl)-4-(3,4-dimethoxyphenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**3**) IR (KBr, cm^{-1}): 3412 (N—H_{str}), 3318 (N—H_{str}),1638 (C=O), 619 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.25 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.14 (s, 2H, S—CH_2), 5.11 (s, 1H, CH-pyr.), 6.61–6.89 (m, 3H, ArH), 7.21–7.70 (m, 8H, ArH), 8.86 (bs, 1H, NH, D_2O exchangeable), 9.83 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal. (found) = C 61.65 (61.61), H 4.79 (4.76), N 7.99 (8.05); Mass (EI): *m*/*z* 526.98 (M + 1).

5-(4-Fluorophenyl)-2-(4-chlorobenzylsulfanyl)-4-(3,4-dimethoxyphenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**4**) IR (KBr, cm^{-1}): 3456 (N—H_{str}), 3312 (N—H_{str}), 1645 (C=O), 636 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.30 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 4.21 (s, 2H, S—CH_2), 5.11 (s, 1H, CH-pyr.), 6.58–6.72 (m, 3H, ArH), 7.18–7.82 (m, 8H, ArH), 8.69 (bs, 1H, NH, D_2O exchangeable), 9.90 (bs, 1H, NH-Amide, D_2O exchangeable); % Anal. Cal. (found) = C 61.65 (61.62), H 4.79 (4.84), N 7.99 (7.94); Mass (EI): *m*/*z* 527.10 (M + 1).

5-(4-Fluorophenyl)-2-(4-fluorobenzylsulfanyl)-4-(3,4-dimethoxyphenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**5**) IR (KBr, cm^{-1}): 3378 (N—H_{str}), 3324 (N—H_{str}), 1651 (C=O), 621 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.26 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 4.19 (s, 2H, S—CH_2), 5.08 (s, 1H, CH-pyr.), 6.62–6.88 (m, 3H, ArH), 7.32–7.85 (m, 8H, ArH), 8.88 (bs, 1H, NH, D_2O exchangeable), 10.01 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal. (found) = C 63.64 (63.62), H 4.95 (4.98), N 8.25 (8.19); Mass (EI): *m*/*z* 508.18 (M^+).

5-(4-Fluorophenyl)-2-benzylsulfanyl-4-(4-nitrophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**6**) IR (KBr, cm^{-1}): 3412 (N—H_{str}), 3314 (N—H_{str}), 1661 (C=O), 652 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.29 (s, 3H, CH_3), 4.09 (s, 2H, S—CH_2), 5.08 (s, 1H, CH-pyr.), 6.99–7.68 (m, 13H, ArH), 9.10 (bs, 1H, NH, D_2O exchangeable), 9.82 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 63.01 (63.05%), H 4.81 (4.84), N 11.76 (11.71); Mass (EI): *m*/*z* 475.23 (M^+).

5-(4-Fluorophenyl)-2-(2-chlorobenzylsulfanyl)-4-(4-nitrophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**7**) IR (KBr, cm^{-1}): 3379 (N—H_{str}), 3311 (N—H_{str}), 1644 (C=O), 633 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.30 (s, 3H, CH_3), 4.11 (s, 2H, S—CH_2), 5.16 (s, 1H, CH-pyr.), 7.23–7.76 (m, 12H, ArH), 8.99 (bs, 1H, NH, D_2O exchangeable), 9.92 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 58.76 (58.73), H 3.95 (4.02), N 10.96 (10.92); Mass (EI): *m*/*z* 511.17 (M + 1).

5-(4-Fluorophenyl)-2-(3-chlorobenzylsulfanyl)-4-(4-nitrophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**8**) IR (KBr, cm^{-1}): 3367 (N—H_{str}), 3328 (N—H_{str}), 1672 (C=O), 615 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.25 (s, 3H, CH_3), 4.18 (s, 2H, S—CH_2), 5.14 (s, 1H, CH-pyr.), 7.18–7.80 (m, 12H, ArH), 9.05 (bs, 1H, NH, D_2O exchangeable), 9.91 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 58.76 (58.78), H 3.95 (4.04), N 10.96 (10.98); Mass (EI): *m*/*z* 511.68 (M + 1).

5-(4-Fluorophenyl)-2-(4-chlorobenzylsulfanyl)-4-(4-nitrophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**9**) IR (KBr, cm^{-1}): 3416 (N—H_{str}), 3325 (N—H_{str}), 1649 (C=O), 645 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.23 (s, 3H, CH_3), 4.21 (s, 2H, S—CH_2), 5.18 (s, 1H, CH-pyr.), 7.15–7.72 (m, 12H, ArH), 9.12 (bs, 1H, NH, D_2O exchangeable), 10.05 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 58.76 (58.71), H 3.95 (3.92), N 10.96 (10.91); Mass (EI): *m*/*z* 511.89 (M + 1).

5-(4-Fluorophenyl)-2-(4-fluorobenzylsulfanyl)-4-(4-nitrophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**10**) IR (KBr, cm^{-1}): 3391 (N—H_{str}), 3308 (N—H_{str}), 1678 (C=O), 625 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.26 (s, 3H, CH_3), 4.25 (s, 2H, S—CH_2), 5.11 (s, 1H, CH-pyr.), 7.25–7.89 (m, 12H, ArH), 9.08 (bs, 1H, NH, D_2O exchangeable), 10.10 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal (found) = C 60.72 (60.75), H 4.08 (4.06), N 11.33 (11.36); Mass (EI): *m*/*z* 493.28 (M^+).

5-(4-Bromophenyl)-2-benzylsulfanyl-4-(2,4-dichlorophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**11**) IR (KBr, cm^{-1}): 3368 (N—H_{str}), 3321 (N—H_{str}), 1668 (C=O), 650 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.31 (s, 3H, CH_3), 4.05 (s, 2H, S—CH_2), 5.15 (s, 1H, CH-pyr.), 7.02–7.69 (m, 12H, ArH), 8.98 (bs, 1H, NH, D_2O exchangeable), 9.77 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal (found) = C 53.49 (53.45), H 3.59 (3.58), N 7.49 (7.46); Mass (EI): *m*/*z* 563.29 (M + 2).

5-(4-Bromophenyl)-2-(2-chlorobenzylsulfanyl)-4-(2,4-dichlorophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**12**) IR (KBr, cm^{-1}): 3426 (N—H_{str}), 3314 (N—H_{str}), 1661 (C=O), 652 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.28 (s, 3H, CH_3), 4.15 (s, 2H, S—CH_2), 5.18 (s, 1H, CH-pyr.), 7.19–7.71 (m, 11H, ArH), 9.10 (bs, 1H, NH, D_2O exchangeable), 9.82 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal (found) = C 50.40 (50.36), H 3.21 (3.24), N 7.05 (7.03); Mass (EI): *m*/*z* 597.68 (M + 2).

5-(4-Bromophenyl)-2-(3-chlorobenzylsulfanyl)-4-(2,4-dichlorophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**13**) IR (KBr, cm^{-1}): 3387 (N—H_{str}), 3311 (N—H_{str}), 1644 (C=O), 633 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.26 (s, 3H, CH_3), 4.12 (s, 2H, S—CH_2), 5.13 (s, 1H, CH-pyr.), 7.17–7.78 (m, 11H, ArH), 8.78 (bs, 1H, NH, D_2O exchangeable), 9.80 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal (found) = C 50.40 (50.42), H 3.21 (3.27), N 7.05 (7.09); Mass (EI): *m*/*z* 597.47 (M + 2).

5-(4-Bromophenyl)-2-(4-chlorobenzylsulfanyl)-4-(2,4-dichlorophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**14**) IR (KBr, cm^{-1}): 3416 (N—H_{str}), 3328 (N—H_{str}), 1672 (C=O), 615 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.22 (s, 3H, CH_3), 4.25 (s, 2H, S—CH_2), 5.14 (s, 1H, CH-pyr.), 7.31–7.82 (m, 11H, ArH), 9.02 (bs, 1H, NH, D_2O exchangeable), 9.81 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal (found) = C 50.40 (50.36), H 3.21 (3.18), N 7.05 (7.07); Mass (EI): *m*/*z* 597.29 (M + 2).

5-(4-Bromophenyl)-2-(4-fluorobenzylsulfanyl)-4-(2,4-dichlorophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**15**) IR (KBr, cm^{-1}): 3379 (N—H_{str}), 3325 (N—H_{str}), 1649 (C=O), 645 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.32 (s, 3H, CH_3), 4.30 (s, 2H, S—CH_2), 5.10 (s, 1H, CH-pyr.), 7.36–7.89 (m, 11H, ArH), 9.11 (bs, 1H, NH, D_2O exchangeable), 9.84 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal (found) = C 51.83 (51.86), H 3.31 (3.35), N 7.25 (7.22); Mass (EI): *m*/*z* 581.06 (M + 2).

5-(4-Bromophenyl)-2-benzylsulfanyl-4-(4-methoxyphenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**16**) IR (KBr, cm^{-1}): 3381 (N—H_{str}), 3308 (N—H_{str}), 1678 (C=O), 625 (C—S); ^{1}H NMR (DMSO-d_6): δ ppm 2.27 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 4.10 (s, 2H, S—CH_2), 5.09 (s, 1H, CH-pyr.), 6.55–6.72 (m, 4H, ArH), 7.15–7.55 (m, 9H, ArH), 8.73 (bs, 1H, NH, D_2O exchangeable), 9.69 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal. (found) = C 59.77 (59.73), H 4.63 (4.68), N 8.04 (8.08); Mass (EI): *m*/*z* 524.87 (M + 2).

5-(4-Bromophenyl)-2-(2-chlorobenzylsulfanyl)-4-(4-methoxyphenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**17**) IR (KBr, cm^{-1}): 3402 (N–H_{str}), 3311 (N–H_{str}),1643 (C=O), 621 (C–S); ^1H NMR (DMSO-d_6): δ ppm 2.30 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.19 (s, 2H, S–CH_2), 5.17 (s, 1H, CH-pyr.), 6.60–6.79 (m, 4H, ArH), 7.25–7.65 (m, 8H, ArH), 8.61 (bs, 1H, NH, D_2O exchangeable), 9.75 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal. (found) = C 56.07 (56.12), H 4.16 (4.18), N 7.55 (7.50); Mass (EI): *m*/*z* 558.98 (M + 2).

5-(4-Bromophenyl)-2-(3-chlorobenzylsulfanyl)-4-(4-methoxyphenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**18**) IR (KBr, cm^{-1}): 3369 (N–H_{str}), 3307 (N–H_{str}),1641 (C=O), 650 (C–S); ^1H NMR (DMSO-d_6): δ ppm 2.25 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 4.25 (s, 2H, S–CH_2), 5.11 (s, 1H, CH-pyr.), 6.62–6.71 (m, 4H, ArH), 7.21–7.69 (m, 9H, ArH), 8.63 (bs, 1H, NH, D_2O exchangeable), 9.78 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal. (found) = C 56.07 (56.02), H 4.16 (4.14), N 7.55 (7.59); Mass (EI): *m*/*z* 558.94 (M + 2).

5-(4-Bromophenyl)-2-(4-chlorobenzylsulfanyl)-4-(4-methoxyphenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**19**) IR (KBr, cm^{-1}): 3387 (N–H_{str}), 3315 (N–H_{str}),1652 (C=O), 641 (C–S); ^1H NMR (DMSO-d_6): δ ppm 2.27(s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.28 (s, 2H, S–CH_2), 5.16 (s, 1H, CH-pyr.), 6.52–6.78 (m, 4H, ArH), 7.20–7.72 (m, 8H, ArH), 8.75 (bs, 1H, NH, D_2O exchangeable), 9.64 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal. (found) = C 56.07 (56.09), H 4.16 (4.11), N 7.55 (7.53); Mass (EI): *m*/*z* 559.08 (M + 2).

5-(4-Bromophenyl)-2-(2-fluorobenzylsulfanyl)-4-(4-methoxyphenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**20**) IR (KBr, cm^{-1}): 3391 (N–H_{str}), 3310 (N–H_{str}),1672 (C=O), 638 (C–S); ^1H NMR (DMSO-d_6): δ ppm 2.32 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.30 (s, 2H, S–CH_2), 5.12 (s, 1H, CH-pyr.), 6.75–6.84 (m, 4H, ArH), 7.29–7.88 (m, 8H, ArH), 9.11 (bs, 1H, NH, D_2O exchangeable), 9.80 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal. (found) = C 57.78 (57.79), H 4.29 (4.23), N 7.78 (7.83); Mass (EI): *m*/*z* 542.68 (M + 2).

5-(4-Nitrophenyl)-2-(benzylsulfanyl)-4-(4-bromophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**21**) IR (KBr, cm^{-1}): 3394 (N–H_{str}), 3313 (N–H_{str}),1652 (C=O), 634 (C–S); ^1H NMR (DMSO-d_6): δ ppm 2.25 (s, 3H, CH_3), 4.05 (s, 2H, S–CH_2), 5.10 (s, 1H, CH-pyr.), 6.95–7.78 (m, 13H, ArH), 9.12 (bs, 1H, NH, D_2O exchangeable), 9.84 (bs, 1H, NH-Amide, D_2O exchangeable); %Anal. Cal. (found) = C 55.87 (55.89), H 3.94 (3.93), N 10.42 (10.43); Mass (EI): *m*/*z* 539.71 (M + 2).

5-(4-Nitrophenyl)-2-(2-chlorobenzylsulfanyl)-4-(4-bromophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**22**) IR (KBr, cm^{-1}): 3358 (N–H_{str}), 3331(N–H_{str}),1664 (C=O), 641 (C–S); ^1H NMR (DMSO-d_6): δ ppm 2.28 (s, 3H, CH_3), 4.15(s, 2H, S–CH_2), 5.21 (s, 1H, CH-pyr.), 7.27–7.82 (m, 12H, ArH), 9.08 (bs, 1H, NH, D_2O exchangeable), 9.99 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 52.51 (52.56), H 3.53 (3.51), N 9.80 (9.83); Mass (EI): *m*/*z* 573.84 (M + 2).

5-(4-Nitrophenyl)-2-(3-chlorobenzylsulfanyl)-4-(4-bromophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**23**). IR (KBr, cm^{-1}): 3429 (N–H_{str}), 3317 (N–H_{str}),1637 (C=O), 618 (C–S), ^1H NMR (DMSO-d_6): δ ppm 2.21 (s, 3H, CH_3), 4.26 (s, 2H, S–CH_2), 5.11 (s, 1H, CH-pyr.), 7.22–7.86 (m, 12H, ArH), 9.10 (bs, 1H, NH, D_2O exchangeable), 9.89 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 52.51 (52.54), H 3.53 (3.55), N 9.80 (9.77); Mass (EI): *m*/*z* 573.84 (M + 2).

5-(4-Nitrophenyl)-2-(4-chlorobenzylsulfanyl)-4-(4-bromophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**24**). IR (KBr, cm^{-1}): 3458 (N–H_{str}), 3311 (N–H_{str}), 1644 (C=O), 635 (C–S), ^1H NMR (DMSO-d_6): δ ppm 2.30 (s, 3H, CH_3), 4.23 (s, 2H, S–CH_2), 5.17 (s, 1H, CH-pyr.), 7.26–7.82 (m, 12H, ArH), 9.16 (bs, 1H, NH, D_2O exchangeable), 10.08 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 52.51 (52.47), H 3.53 (3.56), N 9.80 (9.78); Mass (EI): *m*/*z* 574.01 (M + 2).

5-(4-Nitrophenyl)-2-(4-fluorobenzylsulfanyl)-4-(4-bromophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**25**). IR (KBr, cm^{-1}): 3424 (N–H_{str}), 3323 (N–H_{str}), 1650 (C=O), 620 (C–S), ^1H NMR (DMSO-d_6): δ ppm 2.21(s, 3H, CH_3), 4.31 (s, 2H, S–CH_2), 5.16 (s, 1H, CH-pyr.), 7.26–7.94 (m, 12H, ArH), 9.11 (bs, 1H, NH, D_2O exchangeable), 9.88 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 54.06 (54.11), H 3.63 (3.67), N 10.09 (10.03); Mass (EI): *m*/*z* 557.12 (M + 2).

5-(4-Nitrophenyl)-2-(benzylsulfanyl)-4-(3-nitrophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**26**). IR (KBr, cm^{-1}): 3381 (N–H_{str}), 3315 (N–H_{str}), 1660 (C=O), 651 (C–S); ^1H NMR (DMSO-d_6): δ ppm 2.28 (s, 3H, CH_3), 4.08 (s, 2H, S–CH_2), 5.07 (s, 1H, CH-pyr.), 6.98–7.67 (m, 13H, ArH), 9.09 (bs, 1H, NH, D_2O exchangeable), 9.81 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 59.63 (59.61), H 4.20 (4.25), N 13.91 (13.93); Mass (EI): *m*/*z* 502.74 (M^+).

5-(4-Nitrophenyl)-2-(2-chlorobenzylsulfanyl)-4-(3-nitrophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**27**). IR (KBr, cm^{-1}): 3397 (N–H_{str}), 3310 (N–H_{str}), 1643 (C=O), 632 (C–S), ^1H NMR (DMSO-d_6): δ ppm 2.31 (s, 3H, CH_3), 4.12 (s, 2H, S–CH_2), 5.17 (s, 1H, CH-pyr.), 7.24–7.77 (m, 12H, ArH), 9.00 (bs, 1H, NH, D_2O exchangeable), 9.93 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 55.81 (55.83), H 3.75 (3.71), N 13.02 (13.03); Mass (EI): *m*/*z* 538.79 (M + 1).

5-(4-Nitrophenyl)-2-(3-chlorobenzylsulfanyl)-4-(3-nitrophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**28**). IR (KBr, cm^{-1}): 3402 (N–H_{str}), 3327 (N–H_{str}), 1671 (C=O), 614 (C–S), ^1H NMR (DMSO-d_6): δ ppm 2.24 (s, 3H, CH_3), 4.18 (s, 2H, S–CH_2), 5.13 (s, 1H, CH-pyr.), 7.17–7.81 (m, 12H, ArH), 9.04 (bs, 1H, NH, D_2O exchangeable), 9.91 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 55.81 (55.78), H 3.75 (3.77), N 13.02 (12.98); Mass (EI): *m*/*z* 539.06 (M + 1).

5-(4-Nitrophenyl)-2-(4-chlorobenzylsulfanyl)-4-(3-nitrophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**29**). IR (KBr, cm^{-1}): 3416 (N–H_{str}), 3324 (N–H_{str}), 1648 (C=O), 644 (C–S), ^1H NMR (DMSO-d_6): δ ppm 2.22 (s, 3H, CH_3), 4.20 (s, 2H, S–CH_2), 5.17 (s, 1H, CH-pyr.), 7.19–7.74 (m, 12H, ArH), 9.11 (bs, 1H, NH, D_2O exchangeable), 10.04 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 55.81 (55.79), H 3.75 (3.72), N 13.02 (13.08); Mass (EI): *m*/*z* 538.84 (M + 1).

5-(4-Nitrophenyl)-2-(4-fluorobenzylsulfanyl)-4-(3-nitrophenyl)-6-methyl-1,4-dihydro-5-pyrimidinecarboxamide (**30**). IR (KBr, cm^{-1}): 3429 (N–H_{str}), 3309 (N–H_{str}), 1677 (C=O), 624 (C–S); ^1H NMR (DMSO-d_6): δ ppm 2.27 (s, 3H, CH_3), 4.26 (s, 2H, S–CH_2), 5.12 (s, 1H, CH-pyr.), 7.26–7.90 (m, 12H, ArH), 9.09 (bs, 1H, NH, D_2O exchangeable), 10.10 (bs, 1H, NH-Amide, D_2O exchangeable), %Anal. Cal. (found) = C 57.58 (57.59), H 3.87 (3.83), N 13.43 (13.48); Mass (EI): *m*/*z* 520.66 (M^+).

6.2. Pharmacology

The investigations were conducted on albino rats weighing 200–250 g of either sex. All rats were housed in a temperature and humidity controlled room at an ambient temperature of 25 ± 2 °C with 12 h light/dark cycle and allowed free access to food and water except at the time they were brought out of the cage. All the experimental protocols were carried out with the permission from Institutional Animal Ethics committee (IAEC), form no. 443 and the guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments in Animal (CPCSEA). Animals were obtained from Central Animal House Facility, Hamdard University, New Delhi-62. Registration no. and date of registration is 173/CPCSEA, 28 Jan., 2000.

6.2.1. Antihypertensive activity

Antihypertensive activity of synthesized compounds was assessed by Deoxycorticosterone Acetate salt (DOCA-salt) induced hypertension in rats [8–11] and the non-invasive tail-cuff method was

employed to determine systolic blood pressure (SBP) in rats. Nifedipine was used as standard drug.

6.2.1.1. DOCA-salt hypertension. Hypertension in rats was induced by injecting twice weekly with 20 mg/kg sac. deoxycortisone acetate (DOCA) in olive oil for 4 weeks. Drinking water was replaced by 1% w/v NaCl solution [12]. Injection of DOCA-salt was not administered to the control group of rats that received vehicle injections and tap water instead. Blood pressure started to rise after one week and the systolic value reached between 160 and 180 mm Hg after 4 weeks. Animals were divided into three groups. Group-I served as control, group-II received newly synthesized compounds (**1**–**30**) and group-III received standard drug nifedipine.

6.2.1.2. Non-invasive blood pressure (NIBP) measurements (tail-cuff method). The blood pressure (BP) was determined with a BIOPAC student, Inc, NIBP with computerized BP monitor. This system measures blood pressure (BP) by recording the cuff pressure at which the interrupted blood flow returns to the tail. Training the rats for tail-cuff blood pressure measurements was necessary to reduce the stress associated with the BP measurements and hence reduces the variability of BP with successive measurements [13]. Training consisted of six sessions over 3 days. On day one, rats were introduced into cylindrical restrainer for 5 min per session. The tail-cuff was inflated five times in quick succession. By day three, the training was extended to 10 min per session. The effect of training was to reduce the standard deviation around mean BP. At the end of session rats were ready for BP recording. They were restrained by being placed into cylindrical restrainer. For better detection of tail pulse, the tail artery was dilated by placement of restrained rats into thermostatically controlled Lucite box, heated at it was placed on a heated surgical surface maintained at 37 °C for 2–5 min before BP measurement was started. Tail pulse was detected by passage of tail through a narrow tail-cuff sensor attached to the amplifier. BP measurements were started by automatic inflation of tail-cuff to greater than 200 mmHg and release of pressure. The results were recorded in form of graph. The computer provides two tracings that start and stop at the same time. The lower trace channel plots cuff pressure, which is calibrated at 500 mmHg at full scale. The tracing sharply rises when applied to the tail-cuff and falls off gradually during the 15–20 s of the test. The upper trace channel monitors pulse, with fluctuations about the centre line suddenly appearing at the onset of pulsations. The first onset of pulse is taken as the systolic blood pressure. Initiation of pulse pressure was determined when the baseline amplitude increased in accordance to the set maximal inflated cuff pressures, maximal inflation was set at 200 mmHg. Blood pressure recording was considered to be successful if the rat did not move and a clear initial pulse could be seen. Ten tail-cuff measurements were made in a session. The BP for the session was accepted as the average of four BP readings that were within 5 mm Hg or the average of 10 readings that were within 8 mmHg. BP measurements were done thrice per week for two weeks. Twelve groups of six rats weighing between 200 and 250 g were made. Animals hypertension was induced as detailed above. Rats were trained for the experiment. On the first day of experiment the test compounds were administered by oral feeding using an oral feeding needle. The test compounds (**1**–**30**) were prepared in 0.5% carboxymethyl cellulose (CMC) and dose of 10 mg/kg orally. One group of animal was treated with standard drug Nifedipine. One of the six groups was treated with vehicle. Prior to dosing the animals, initial graph reading was taken to record the BP. After 1 h of dosing recordings were taken as mentioned above. Each compound was evaluated three times in one week, and average of the recordings was recorded accordingly. Average readings were calculated by employing ANOVA method.

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