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Original article

Synthesis, characterization and antihypertensive activity of pyridazinone derivatives

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ABSTRACT

Some 6-(substituted-phenyl)-2-(substitutedmethyl)-4,5-dihydropyridazin-3(2*H*)-one derivatives were synthesized by reacting 6-substituted-phenyl-4,5-dihydropyridazin-3(2*H*)-one with cyclic secondary amine under Mannich reaction conditions. The final compounds (**15**–**70**) were evaluated for antihypertensive activities by non-invasive method using Tail Cuff method. The compounds **16**, **19**, **24**, **30**, **39**, **42** and **45** showed good antihypertensive activity.

1. Introduction

Pyridazinone derivatives were reported to exhibit diverse pharmacological activities such as antidepressant [1], antihypertensive [2,3], antithrombotic [4], anticonvulsant [5], cardiotonic [6], antibacterial [7], diuretics [8], antiHIV [9] and anticancer [10]. Some pyridazinone derivatives like indolidan [11], bemoradan [12], primobendan [13], levosimendan [14] (antihypertensive), minaprine [15] (antidepressant), emorfazone [16] (antiinflammatory), and azanrinone [17] (cardiotonic), already appeared in the clinical market. During our literature survey, it is observed that various pyridazinone derivatives possess antihypertensive activity due to vasorelaxant activity. Considering the 6-phenyl-3(2*H*)-pyridazinone residue as the pharmacophoric group for the activity, we have synthesized some new pyridazinone derivatives and evaluated them for antihypertensive activity by non-invasive method.

2. Chemistry

Some 6-(substituted-phenyl)-2-(substitutedmethyl)-4,5-dihydropyridazin-3(2*H*)-one derivatives are synthesized according to Scheme 1. The Friedel–Craft acylation of aromatic hydrocarbon with succinic anhydride afforded the β-substituted benzoyl propionic acid in presence of Lewis acid, aluminium chloride. The resulting β-benzoyl propionic acids (**1**–**7**) on hydrazinolysis gave the pyridazinones (**8**–**14**). The pyridazinones were subjected to Mannich reaction with cyclic secondary amine and formaldehyde to get the final compounds (**15**–**70**) (Table 1).

3. Result and discussion

The final compounds (**15**–**70**) were structurally elucidated on the basis of spectral data, explained with the example of compound **23**. The IR spectra revealed presence of band at 1685 cm^{-1} (C═O) and 1600 cm^{-1} (C═N). The ^1H NMR showed singlet at δ 2.29 for methyl group attached to phenyl ring. The two triplets at δ 2.62, $J = 8.7$ and 2.76, $J = 8.7$ confirmed the presence of methylene group at 4 and 5 position of pyridazinone ring respectively. The multiplets at δ 2.80–3.10 and δ 3.59–3.79 are indicative of 4 protons of methylene ring each for $-CH_2-N-CH_2-$ and $-CH_2-O-CH_2-$ moiety respectively. The singlet at δ 4.78 is due to methylene group flanked by two nitrogen atoms. In the aromatic region two double doublets (dd) appeared at δ 7.43, $J = 8.2$ and 7.73, $J = 8.2$ are due to equivalent protons at H-3′ & H-5′ and H-2′ & H-6′ of *p*-disubstituted phenyl ring attached at 6th position respectively. The mass spectrum shows the presence of peak at *m*/*z* 287 accordance to the molecular formula, $C_{16}H_{21}N_3O_2$. The structure is also supported by elemental analysis data and ^{13}C NMR data. The ^{13}C NMR showed the peaks at δ 176 and δ 155 for carbonyl carbon (C-3) and tertiary carbon (C-6). The other compounds are also identified in a similar manner,

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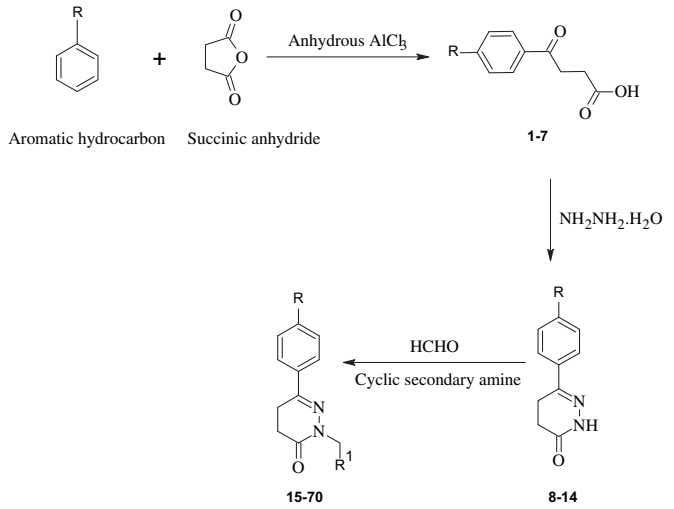


Compd no.	R	Compd no.	R
1,8	H	**5,12**	$CH_2CH(CH_3)_2$
2,9	CH_3	**6,13**	C_6H_5
3,10	OCH_3	**7,14**	Cl
4,11	C_2H_5		

Scheme 1. Synthesis of 6-(substituted-phenyl)-2-(substitutedmethyl)-4,5-dihydropyridazin-3(2*H*)-one derivatives.

except compounds substituted with aromatic amines like indole, phenothiazine, 1,2,4-triazole which showed the multiplet in aromatic region.

The final compounds (**15**–**70**) 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 [18]. Compound number **16**, **19**, **24**, **30**, **39**, **42** and **45** were found to show highly significant reduction in mean arterial blood pressure but at higher dose in comparison to hydralazine.

On the basis of activity reported, it can be concluded that groups like *p*-CH_3, *p*-C_2H_5 in phenyl ring at 6-position increases the activity as shown by the compound **16**, **19**, **24**, **30**, **39**, **42** and **45**. The various cyclic secondary amine at 2-position in a methylene group does not affect the antihypertensive activity. For example, the compound **16**, **19**, **30**, **39**, **42** and **45** possessing *N*-piperazine, *N*-phenothiazine, *N*-(1,2,4-triazole), *N*-morpholine, *N*-(4-*N*-methylpiperazine) and *N*-pyrrolidine at 2-position respectively showed good antihypertensive activity.

4. Experimental protocols

4.1. Chemistry

Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked by thin layer chromatography (TLC) plates (silica gel G) which were visualized by exposing to iodine vapors and UV light. The FT-IR spectra were recorded on Bio-rad FTS-135 spectrophotometer using KBr pellets; υ_{max} values are given in cm^{-1}. ^1H NMR and ^{13}C 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.

4.1.1. General procedure for the synthesis of substituted β-aroyl propionic acids (*1*–*7*)

The substituted β-aroyl propionic acids (**1**–**7**) were synthesized from respective aromatic hydrocarbon and characterized on the basis of spectral data as per reported procedure [19,20].

4.1.2. General procedure for the synthesis of 6-substituted-phenyl-4,5-dihydropyridazin-3(2H)-one (*8*–*14*)

The appropriate substituted β-aroyl propionic acids were reacted with hydrazine hydrate to get corresponding pyridazinone and characterized on the basis of spectral data as per earlier reported procedure [19,20].

4.1.3. General procedure for the preparation of 6-(substituted-phenyl)-2-(substitutedmethyl)-4,5-dihydropyridazin-3(2H)-one (*15*–*70*)

To a solution of 6-substituedphenyl-4,5-dihydropyridazine-3(2*H*)-one (0.001 mol) in absolute ethanol (30 mL), formaldehyde (37–41%) (1.5 mL) and cyclic secondary amine (0.001 mol) were added and the contents refluxed for 24 h. After completion of the reaction, ethanol was distilled off and the residue poured into crushed ice and kept in refrigerator for overnight to separate out the compound. The solid which separated out, was filtered and recrystallized from ethanol.

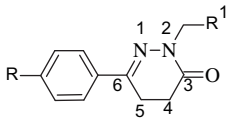
*4.1.3.1. 6-Phenyl-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**15**).* Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 72%; m.p. 103–104 °C; IR (KBr) υ_{max} (cm^{-1}): 2964 (CH), 1665 (C═O), 1446 (C═C); ^1H NMR ($CDCl_3$) δ (ppm): 2.60 (t, J = 7.8, 2H, C–CH_2), 2.73 (t, J = 7.8, 2H, CH_2–CO), 2.85–3.05 (m, 4H, 2 × CH_2), 3.59–3.79 (m, 4H, CH_2–O–CH_2), 4.78 (s, 2H, –N–CH_2–N–), 7.33–7.53 (m, 3H, Ar–H), 7.63–7.83 (m, 2H, Ar–H); Ms (*m*/*z*): 273/274 (M^+/M^+ + 1), 187 (100%), 100 (60%), 96 (30%). Anal. Calc. for $C_{15}H_{19}N_3O_2$: C: 65.91, H: 7.01, N: 15.37. Found: C: 65.88, H: 7.10, N: 15.32.

*4.1.3.2. 6-Phenyl-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**16**).* Piperazine was used as cyclic secondary amine for Mannich reaction. Yield: 52%; m.p. 117–118 °C; IR (KBr) υ_{max} (cm^{-1}): 3325 (NH), 2964 (CH), 1661 (C═O), 1424 (C═C); ^1H NMR ($CDCl_3$) δ (ppm): 2.60 (t, J = 7.7, 2H, C–CH_2), 2.69–2.89 (m, 8H, 4 × CH_2), 2.97 (t, J = 7.7, 2H, CH_2–CO), 5.2 (s, 2H, –N–CH_2–N–), 7.26–7.36 (m, 3H, Ar–H), 7.64–7.84 (m, 2H, Ar–H), 9.7 (s, 1H, NH); Ms (*m*/*z*): 272/273 (M^+/M^+ + 1), 187 (100%), 99 (40%). Anal. Calc. for $C_{16}H_{21}N_3O$: C: 66.15, H: 7.40, N: 20.57. Fond: C: 66.08, H: 7.36, N: 20.49.

*4.1.3.3. 6-Phenyl-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**17**).* Piperidine was used as cyclic secondary amine for Mannich reaction. Yield: 48%; m.p. 104–106 °C; IR (KBr) υ_{max} (cm^{-1}): 2933 (CH), 1677 (C═O), 1425 (C═C); ^1H NMR ($CDCl_3$) δ (ppm): 2.61 (t, J = 7.8, 2H, C–CH_2), 2.55–2.75 (m, 6H, 3 × CH_2), 2.89 (t, J = 7.8, 2H, CH_2–CO), 2.92–3.04 (m, 4H, 2 × CH_2), 5.2 (s, 2H, –N–CH_2–N–), 7.30–7.50 (m, 3H, Ar–H), 7.64–7.84 (m, 2H, Ar–H); Ms (*m*/*z*): 271/272 (M^+/M^+ + 1), 187 (100%), 98 (40%), 96 (40%). Anal. Calc. for $C_{16}H_{21}N_3O$: C: 70.82, H: 7.80, N: 15.49. Found: C: 70.80, H: 7.75, N: 15.46.

*4.1.3.4. 6-Phenyl-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one (**18**).* 1-Methylpiperazine was used as cyclic secondary amine for Mannich reaction. Yield: 56%; m.p. 109–110 °C; IR (KBr) υ_{max} (cm^{-1}): 3002 (CH), 1675 (C═O), 1500 (C═N);

Table 1
Mean arterial pressure (mm Hg) and substituents of compounds (**15**–**70**)



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Compound (20 mg/kg)	MAP (Mean ± SEM)	% Reduction in MAP	*R*	R^1
Control	101.33 ± 4.64			
Toxic control	162.33 ± 4.02**			
Hydralazine[a]	96.16 ± 4.70**	40.76		
15	111.66 ± 10.28**	31.21	H	*N*-Morpholine
16	94.16 ± 6.36**	41.99	H	*N*-Piperazine
17	108 ± 12.76**	33.46	H	*N*-Piperidine
18	97.5 ± 6.18**	39.93	H	*N*-(4-*N*-Methylpiperazine)
19	93.5 ± 3.09**	42.40	H	*N*-Phenothiazine
20	136.66 ± 1.76*	15.81	H	*N*-Indole
21	131.3 ± 2.06**	19.11	H	*N*-Pyrrolidine
22	99.5 ± 5.54**	38.70	H	*N*-(1,2,4-triazole)
23	139.4 ± 6.83[ns]	14.12	CH_3	*N*-Morpholine
24	95.8 ± 2.15**	40.98	CH_3	*N*-Piperazine
25	104.6 ± 2.78**	35.56	CH_3	*N*-Piperidine
26	98.8 ± 2.41**	39.13	CH_3	*N*-(4-N-Methylpiperazine)
27	105.6 ± 3.86**	34.94	CH_3	*N*-Phenothiazine
28	123.6 ± 3.18**	23.85	CH_3	*N*-Indole
29	110.8 ± 2.65**	31.74	CH_3	*N*-Pyrrolidine
30	95.5 ± 1.93**	41.16	CH_3	*N*-(1,2,4-triazole)
31	114 ± 6.60**	29.77	OCH_3	*N*-Morpholine
32	104.8 ± 3.92**	35.44	OCH_3	*N*-Piperazine
33	118 ± 7.56**	27.16	OCH_3	*N*-Piperidine
34	103.8 ± 4.59**	36.05	OCH_3	*N*-(4-*N*-Methylpiperazine)
35	107.4 ± 5.54**	33.83	OCH_3	*N*-Phenothiazine
36	109.2 ± 7.32**	32.72	OCH_3	*N*-Indole
37	111 ± 6.67**	31.62	OCH_3	*N*-Pyrrolidine
38	114.8 ± 6.28**	29.27	OCH_3	*N*-(1,2,4-triazole)
39	114.4 ± 5.49**	47.31	C_2H_5	*N*-Morpholine
40	113.4 ± 4.79**	36.05	C_2H_5	*N*-Piperazine
41	114.4 ± 3.65**	30.51	C_2H_5	*N*-Piperidine
42	120.8 ± 3.66**	47.14	C_2H_5	*N*-(4-*N*-Methylpiperazine)
43	121 ± 3.93**	36.17	C_2H_5	*N*-Phenothiazine
44	108 ± 7.92**	32.97	C_2H_5	*N*-Indole
45	113.4 ± 6.83**	44.31	C_2H_5	*N*-Pyrrolidine
46	98.2 ± 7.25**	29.52	C_2H_5	*N*-(1,2,4-triazole)
47	85.4 ± 1.77**	24.22	$-CH_2CH(CH_3)_2$	*N*-Morpholine
48	103.8 ± 4.43**	32.48	$-CH_2CH(CH_3)_2$	*N*-Piperazine
49	112.8 ± 3.92**	16.09	$-CH_2CH(CH_3)_2$	*N*-Piperidine
50	85.8 ± 1.11**	28.29	$-CH_2CH(CH_3)_2$	*N*-(4-*N*-Methylpiperazine)
51	103.6 ± 5.67**	25.58	$-CH_2CH(CH_3)_2$	*N*-Phenothiazine
52	108.8 ± 3.77**	28.91	$-CH_2CH(CH_3)_2$	*N*-Indole
53	90.4 ± 2.029**	32.97	$-CH_2CH(CH_3)_2$	*N*-Pyrrolidine
54	114.4 ± 5.54**	34.94	$-CH_2CH(CH_3)_2$	*N*-(1,2,4-triazole)
55	120.4 ± 7.38**	29.52	C_6H_5	*N*-Morpholine
56	115.6 ± 4.79**	30.14	C_6H_5	*N*-Piperazine
57	122 ± 4.85**	29.52	C_6H_5	*N*-Piperidine
58	98.2 ± 1.56**	25.58	C_6H_5	*N*-(4-*N*-Methylpiperazine)
59	99.2 ± 2.57**	25.91	C_6H_5	*N*-Phenothiazine
56	103.4 ± 1.88**	33.46	C_6H_5	*N*-Indole
61	113.6 ± 7.78**	30.14	C_6H_5	*N*-Pyrrolidine
62	114 ± 5.96**	39.50	C_6H_5	*N*-(1,2,4-triazole)
63	123 ± 4.02**	25.83	Cl	*N*-Morpholine
64	109.6 ± 6.17**	28.78	Cl	*N*-Piperazine
65	136.2 ± 2.90**	24.84	Cl	*N*-Piperidine
66	116.4 ± 6.615**	39.50	Cl	*N*-(4-*N*-Methylpiperazine)
67	120.8 ± 4.07**	38.88	Cl	*N*-Phenothiazine
68	115.4 ± 5.25**	36.30	Cl	*N*-Indole
69	108.8 ± 5.00**	30.01	Cl	*N*-Pyrrolidine
70	105.6 ± 7.52**	29.77	Cl	*N*-(1,2,4-triazole)

All values were expressed as Mean ± SEM (*$p \leq 0.05$), each group comprised of 5 animals (i.e. $n = 5$).
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.
**$p < 0.01$, *$p < 0.05$ and [ns]non significant.
[a] Dose of hydralazine was taken as 2.6 mg/kg [18].

^{1}H NMR ($CDCl_3$) δ (ppm): 2.2 (s, 1H, N–CH_3), 2.55 (t, J = 7.9, 2H, C–CH_2), 2.91 (t, J = 7.9, 2H, CH_2–CO), 2.92–3.10 (m, 4H, 2 × CH_2), 3.25–3.35 (m, 4H, 2 × CH_2), 5.20 (s, 2H, –N–CH_2–N–), 7.29–7.49 (m, 3H, Ar–H), 7.60–7.80 (m, 2H, Ar–H); Ms (*m*/*z*): 286/287 (M^+/M^+ + 1), 187 (100%), 99 (20%). Anal. Calc. for $C_{16}H_{22}N_4O$: C: 67.11, H: 7.74, N: 19.56. Found: C: 67.10, H: 7.63, N: 19.46.

*4.1.3.5. 6-Phenyl-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**19**).* Phenothiazine was used as cyclic secondary amine for Mannich reaction. Yield: 64%; m.p. 88–90 °C; IR (KBr) υ_{max} (cm^{-1}): 2965 (CH), 1661 (C═O), 1631 (C═N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.62 (t, J = 7.8, 2H, C–CH_2), 2.99 (t, J = 7.8, 2H, CH_2–CO), 5.39 (s, 2H, –N–CH_2–N–), 6.99–7.80 (m, 13H, Ar–H); Ms (*m*/*z*): 385/386 (M^+/M^+ + 1). Anal. Calc. for $C_{23}H_{19}N_3OS$: C: 71.66, H: 4.97, N: 10.90. Found: C: 71.56, H: 4.88, N: 10.78.

*4.1.3.6. 6-Phenyl-2-(1H-indol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**20**).* Indole was used as cyclic secondary amine for Mannich reaction. Yield: 40%; m.p. 98–100 °C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1680 (C═O), 1590 (C═N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.63 (t, J = 7.6, 2H, C–CH_2), 2.97 (t, J = 7.6, 2H, CH_2–CO), 5.30 (s, 2H, –N–CH_2–N–), 7.42–7.78 (m, 11H, Ar–H); Ms (*m*/*z*): 303/304 (M^+/M^+ + 1). Anal. Calc. for $C_{19}H_{17}N_3O$: C: 75.23, H: 5.65, N: 13.85. Found: C: 75.18, H: 5.54, N: 13.72.

*4.1.3.7. 6-Phenyl-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**21**).* Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 43%; m.p. 118–120 °C; IR (KBr) υ_{max} (cm^{-1}): 3006 (CH), 1682 (C═O), 1580 (C═N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.61 (t, J = 7.7, 2H, C–CH_2), 2.95 (t, J = 7.7, 2H, CH_2–CO), 2.90–3.12 (m, 8H, 4 × CH_2), 5.36 (s, 2H, –N–CH_2–N–), 7.30–7.48 (m, 3H, Ar–H), 7.68–7.80 (m, 2H, Ar–H); Ms (*m*/*z*): 257/258 (M^+/M^+ + 1). Anal. Calc. for $C_{15}H_{19}N_3O$: C: 70.01, H: 7.44, N: 16.33. Found: C: 69.88, H: 7.34, N: 16.22.

*4.1.3.8. 6-Phenyl-2-(1,2,4-triazolin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**22**).* 1,2,4-Triazole was used as cyclic secondary amine for Mannich reaction. Yield: 50%; m.p. 120–122 °C; IR (KBr) υ_{max} (cm^{-1}): 3010 (CH), 1680 (C═O), 1590 (C═N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.66 (t, J = 7.8, 2H, C–CH_2), 3.0 (t, J = 7.8, 2H, CH_2–CO), 5.30 (s, 2H, –N–CH_2–N–), 7.38–7.83 (m, 7H, Ar–H); Ms (*m*/*z*): 255/256 (M^+/M^+ + 1). Anal. Calc. for $C_{13}H_{13}N_5O$: C: 61.17, H: 5.13, N: 27.43. Found: C: 61.12, H: 4.98, N: 27.22.

*4.1.3.9. 6-(4-Methylphenyl)-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**23**).* Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 68%; m.p. 113–114 °C; IR (KBr) υ_{max} (cm^{-1}): 3010 (CH), 1685 (C═O), 1600 (C═N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.29 (s, 3H, CH_3), 2.62 (t, J = 7.8, 2H, C–CH_2), 2.76 (t, J = 7.8, 2H, CH_2–CO), 2.85–3.05 (m, 4H, 2 × CH_2), 3.59–3.79 (m, 4H, CH_2–O–CH_2), 4.78 (s, 2H, –N–CH_2–N–), 7.43 (dd, J = 8.2, 2H, H-3′, H-5′), 7.73 (dd, J = 8.2, 2H, H-2′, H-6′); ^{13}C NMR ($CDCl_3$) δ (ppm): 176 (C-3), 155 (C-6), 140 (C-4), 129 (C-2′, C-6′), 128 (C-3′, C-5′), 127 (C-1′), 71.5 (C-2″, C-6″), 53.9 (C-3″, C-5″), 33.5 (C-4), 27.4 (C-5), 20.9 (CH_3); Ms (*m*/*z*): 287/288 (M^+/M^+ + 1). Anal. Calc. for $C_{16}H_{21}N_3O_2$: C: 66.88, H: 7.37, N: 14.62. Found: C: 66.72, H: 7.32, N: 14.56.

*4.1.3.10. 6-(4-Methylphenyl)-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**24**).* Piperazine was used as cyclic secondary amine for Mannich reaction. Yield: 52%; m.p. 122–124 °C; IR (KBr) υ_{max} (cm^{-1}): 2970 (CH), 1664 (C═O), 1528 (C═C); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.30 (s, 3H, CH_3), 2.60 (t, J = 7.9, 2H, CH_2), 2.90 (t, J = 7.9, 2H, CH_2), 2.85–2.95 (m, 8H, 4 × CH_2), 4.78 (s, 2H, –N–CH_2–N–), 7.22 (dd, J = 8.4, 2H, H-3′, H-5′), 7.74 (dd, J = 8.4, 2H, H-2′, H-6′), 9.3 (br s, 1H, NH); Ms (*m*/*z*): 286/287 (M^+/M^+ + 1). Anal. Calc. for $C_{16}H_{22}N_4O$: C: 67.11, H: 7.74, N: 19.56. Fond: C: 66.96, H: 7.64, N: 19.50.

*4.1.3.11. 6-(4-Methylphenyl)-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**25**).* Piperidine was used as cyclic secondary amine for Mannich reaction. Yield: 41%; m.p. 123–125 °C; IR (KBr) υ_{max} (cm^{-1}): 2936 (CH), 1660 (C═O), 1420 (C═C); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.26 (s, 3H, CH_3), 2.63 (t, J = 7.8, 2H, C–CH_2), 2.58–2.78 (m, 6H, 3 × CH_2), 2.90 (t, J = 7.8, 2H, CH_2–CO), 2.90–3.12 (m, 4H, 2 × CH_2), 5.18 (s, 2H, –N–CH_2–N–), 7.38 (dd, J = 8.4, 2H, H-3′, H-5′), 7.72 (dd, J = 8.4, 2H, H-2′, H-6′); Ms (*m*/*z*): 285/286 (M^+/M^+ + 1). Anal. Calc. for $C_{17}H_{23}N_3O$: C: 71.56, H: 8.12, N: 14.72. Found: C: 71.38, H: 7.96, N: 14.52.

*4.1.3.12. 6-(4-Methylphenyl)-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one (**26**).* 1-Methylpiperazine was used as cyclic secondary amine for Mannich reaction. Yield: 52%; m.p. 119–120 °C; IR (KBr) υ_{max} (cm^{-1}): 3002 (CH), 1675 (C═O), 1500 (C═N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.25 (s, 1H, N–CH_3), 2.34 (s, 3H, CH_3), 2.52 (t, J = 7.7, 2H, C–CH_2), 2.90 (t, J = 7.7, 2H, CH_2–CO), 3.04–3.20 (m, 4H, 2 × CH_2), 3.22–3.42 (m, 4H, 2 × CH_2), 5.18 (s, 2H, –N–CH_2–N–), 7.42 (dd, J = 8.4, 2H, H-3′, H-5′), 7.76 (dd, J = 8.4, 2H, H-2′, H-6′); Ms (*m*/*z*): 300/301 (M^+/M^+ + 1). Anal. Calc. for $C_{17}H_{24}N_4O$: C: 67.97, H: 8.05, N: 18.65. Found: C: 67.84, H: 7.88, N: 18.54.

*4.1.3.13. 6-(4-Methylphenyl)-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**27**).* Phenothiazine was used as cyclic secondary amine for Mannich reaction. Yield: 62%; m.p. 100–102 °C; IR (KBr) υ_{max} (cm^{-1}): 3000 (CH), 1672 (C═O), 1510 (C═N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.35 (s, 3H, CH_3), 2.60 (t, J = 7.8, 2H, C–CH_2), 2.98 (t, J = 7.8, 2H, CH_2–CO), 5.40 (s, 2H, –N–CH_2–N–), 6.92–7.78 (m, 12H, Ar–H); Ms (*m*/*z*): 399/400 (M^+/M^+ + 1). Anal. Calc. for $C_{24}H_{21}N_3OS$: C: 72.15, H: 5.30, N: 10.52. Found: C: 71.98, H: 5.28, N: 10.36.

*4.1.3.14. 6-(4-Methylphenyl)-2-(1H-indol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**28**).* Indole was used as cyclic secondary amine for Mannich reaction. Yield: 44%; m.p. 105–107 °C; IR (KBr) υ_{max} (cm^{-1}): 2995 (CH), 1680 (C═O), 1570 (C═N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.36 (s, 3H, CH_3), 2.64 (t, J = 7.6, 2H, C–CH_2), 2.98 (t, J = 7.6, 2H, CH_2–CO), 5.36 (s, 2H, –N–CH_2–N–), 7.46–7.78 (m, 10H, Ar–H); Ms (*m*/*z*): 317/318 (M^+/M^+ + 1). Anal. Calc. for $C_{20}H_{19}N_3O$: C: 75.69, H: 6.03, N: 13.24. Found: C: 75.46, H: 5.88, N: 13.12.

*4.1.3.15. 6-(4-Methylphenyl)-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**29**).* Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 39%; m.p. 118–120 °C; IR (KBr) υ_{max} (cm^{-1}): 3006 (CH), 1682 (C═O), 1580 (C═N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.30 (s, 3H, CH_3), 2.62 (t, J = 7.9, 2H, C–CH_2), 2.96 (t, J = 7.9, 2H, CH_2–CO), 3.08–3.28 (m, 8H, 4 × CH_2), 5.24 (s, 2H, –N–CH_2–N–), 7.42 (dd, J = 8.0, 2H, H-3′, H-5′), 7.78 (dd, J = 8.0, H-2′, H-6′); Ms (*m*/*z*): 271/272 (M^+/M^+ + 1). Anal. Calc. for $C_{16}H_{21}N_3O$: C: 70.82, H: 7.80, N: 15.49. Found: C: 70.68, H: 7.74, N: 15.36.

*4.1.3.16. 6-(4-Methylphenyl)-2-(2,3-dihydro-1H-1,2,4-triazol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**30**).* 1,2,4-Triazole was used as cyclic secondary amine for Mannich reaction. Yield: 56%; m.p. 126–127 °C; IR (KBr) υ_{max} (cm^{-1}): 3020 (CH), 1675 (C═O), 1600 (C═N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.36 (s, 3H, CH_3), 2.68 (t, J = 7.7, 2H, C–CH_2), 3.02 (t, J = 7.7, 2H, CH_2–CO), 5.32 (s, 2H, –N–CH_2–N–), 7.40–7.84 (m, 6H, Ar–H); Ms (*m*/*z*): 269/270 (M^+/M^+ + 1). Anal. Calc. for $C_{14}H_{15}N_5O$: C: 62.44, H: 5.61, N: 26.01. Found: C: 62.22, H: 5.48, N: 25.92.

*4.1.3.17. 6-(4-Methoxylphenyl)-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**31**).* Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 53%; m.p.135–136 °C; IR (KBr) υ_{max} (cm^{-1}): 2970 (CH), 1672 (C=O), 1452 (C=C); ^1H NMR ($CDCl_3$) δ (ppm): 2.48 (t, J = 7.8, 2H, C–CH_2), 2.73 (t, J = 7.8, 2H, CH_2–CO), 2.80–3.0 (m, 4H, 2 × CH_2), 3.50–3.70 (m, 4H, 2 × CH_2), 3.85 (s, 3H, CH_3O), 4.76 (s, 2H, –N–CH_2–N–), 6.91 (dd, 2H, J = 8.7, H-3′, H-5′), 7.68 (dd, 2H, J = 8.7, H-2′, H-6′); Ms (*m*/*z*): 303/304 (M^+/M^+ + 1). Anal. Calc. for $C_{16}H_{21}N_3O_3$: C: 63.35, H: 6.98, N: 13.85. Found: C: 63.10, H: 6.88, N: 13.66.

*4.1.3.18. 6-(4-Methoxylphenyl)-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**32**).* Piperazine was used as cyclic secondary amine for Mannich reaction. Yield: 46%; m.p. 127–128 °C; IR (KBr) υ_{max} (cm^{-1}): 2972 (CH), 1678 (C=O), 1530 (C=C); ^1H NMR ($CDCl_3$) δ (ppm): 2.60 (t, J = 7.6, 2H, C–CH_2), 2.90 (t, J = 7.6, 2H, CH_2–CO), 2.90–3.10 (m, 8H, 4 × CH_2), 3.8 (s, 3H, CH_3O), 4.74 (s, 2H, –N–CH_2–N–), 7.32 (dd, J = 8.4, 2H, H-3′, H-5′), 7.74 (dd, J = 8.4, 2H, H-2′, H-6′), 9.30 (br s, 1H, NH); Ms (*m*/*z*): 302/303 (M^+/M^+ + 1). Anal. Calc. for $C_{16}H_{22}N_4O_2$: C: 63.55, H: 7.33, N: 18.53. Fond: C: 63.38, H: 7.12, N: 18.44.

*4.1.3.19. 6-(4-Methoxylphenyl)-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**33**).* Piperidine was used as cyclic secondary amine for Mannich reaction. Yield: 50%; m.p. 132–134 °C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1688 (C=O), 1455 (C=C); ^1H NMR ($CDCl_3$) δ (ppm): 2.61 (t, J = 7.8, 2H, C–CH_2), 2.55–2.75 (m, 6H, 3 × CH_2), 2.82 (t, J = 7.8, 2H, CH_2–CO), 2.86–3.10 (m, 4H, 2 × CH_2), 3.86 (s, 3H, CH_3O), 5.2 (s, 2H, –N–CH_2–N–), 7.42 (dd, J = 8.2, 2H, H-3′, H-5′), 7.78 (dd, J = 8.2, 2H, H-2′, H-6′); Ms (*m*/*z*): 301/302 (M^+/M^+ + 1). Anal. Calc. for $C_{17}H_{23}N_3O_2$: C: 67.75, H: 7.69, N: 13.94. Found: C: 67.55, H: 7.48, N: 13.76.

*4.1.3.20. 6-(4-Methoxylphenyl)-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one (**34**).* 1-Methylpiperazine was used as cyclic secondary amine for Mannich reaction. Yield: 56%; m.p. 135–137 °C; IR (KBr) υ_{max} (cm^{-1}): 2980 (CH), 1685 (C=O), 1590 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 2.20 (s, 1H, N–CH_3), 2.55 (t, J = 7.9, 2H, C–CH_2), 2.91 (t, J = 7.9, 2H, CH_2–CO), 2.92–3.10 (m, 4H, 2 × CH_2), 3.20–3.40 (m, 4H, 2 × CH_2), 3.86 (s, 3H, CH_3O), 5.24 (s, 2H, –N–CH_2–N–), 7.35 (dd, J = 8.4, 2H, H-3′, H-5′), 7.76 (dd, J = 8.4, 2H, H-2′, H-6′); Ms (*m*/*z*): 316/317 (M^+/M^+ + 1). Anal. Calc. for $C_{17}H_{24}N_4O_2$: C: 64.53, H: 7.65, N: 17.71. Found: C: 64.42, H: 7.53, N: 17.54.

*4.1.3.21. 6-(4-Methoxylphenyl)-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**35**).* Phenothiazine was used as cyclic secondary amine for Mannich reaction.Yield: 60%; m.p. 108–110 °C; IR (KBr) υ_{max} (cm^{-1}): 2986 (CH), 1664 (C=O), 1600 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 2.62 (t, J = 7.6, 2H, C–CH_2), 2.99 (t, J = 7.6, 2H, CH_2–CO), 3.82 (s, 3H, CH_3O), 5.40 (s, 2H, –N–CH_2–N–), 6.90–7.78 (m, 12H, Ar–H); Ms (*m*/*z*): 415/416 (M^+/M^+ + 1). Anal. Calc. for $C_{24}H_{21}N_3O_2S$: C: 69.37, H: 5.09, N: 10.11. Found: C: 69.18, H: 4.88, N: 9.92.

*4.1.3.22. 6-(4-Methoxylphenyl)-2-(1H-indol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**36**).* Indole was used as cyclic secondary amine for Mannich reaction. Yield: 46%; m.p. 116–118 °C; IR (KBr) υ_{max} (cm^{-1}): 3005 (CH), 1680 (C=O), 1600 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 2.63 (t, J = 7.7, 2H, C–CH_2), 2.97 (t, J = 7.7, 2H, CH_2–CO), 3.80 (s, 3H, CH_3O), 5.28 (s, 2H, –N–CH_2–N–), 7.32–7.67 (m, 10H, Ar–H); Ms (*m*/*z*): 333/334 (M^+/M^+ + 1). Anal. Calc. for $C_{20}H_{19}N_3O_2$: C: 72.05, H: 5.74, N: 12.60. Found: C: 71.92, H: 5.54, N: 12.46.

*4.1.3.23. 6-(4-Methoxylphenyl)-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**37**).* Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 41%; m.p. 128–130 °C; IR (KBr) υ_{max} (cm^{-1}): 3001 (CH), 1685 (C=O), 1600 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 2.61 (t, J = 7.8, 2H, C–CH_2), 2.92 (t, J = 7.8, 2H, CH_2–CO), 2.94–3.14 (m, 8H, 4 × CH_2), 3.90 (s, 3H, CH_3O), 5.26 (s, 2H, –N–CH_2–N–), 7.41 (dd, J = 8.4, H-3′, H-5′), 7.79 (dd, J = 8.4, H-2′, H-6′); Ms (*m*/*z*): 287/288 (M^+/M^+ + 1). Anal. Calc. for $C_{16}H_{21}N_3O_2$: C: 66.88, H: 7.37, N: 14.62. Found: C: 66.64, H: 7.14, N: 14.56.

*4.1.3.24. 6-(4-Methoxylphenyl)-2-(1,2,4-triazolin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**38**).* 1,2,4-Triazole was used as cyclic secondary amine for Mannich reaction. Yield: 58%; m.p. 130–132 °C; IR (KBr) υ_{max} (cm^{-1}): 3005 (CH), 1680 (C=O), 1580 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 2.62 (t, J = 7.9, 2H, C–CH_2), 3.02 (t, J = 7.9, 2H, CH_2–CO), 3.76 (s, 3H, CH_3O), 5.34 (s, 2H, –N–CH_2–N–), 7.36–7.86 (m, 6H, Ar–H); Ms (*m*/*z*): 285/286 (M^+/M^+ + 1). Anal. Calc. for $C_{14}H_{15}N_5O_2$: C: 58.94, H: 5.30, N: 24.55. Found: C: 58.72, H: 5.16, N: 24.36.

*4.1.3.25. 6-(4-Ethylphenyl)-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**39**).* Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 62%; m.p. 133–135 °C; IR (KBr) υ_{max} (cm^{-1}): 2954 (CH), 1658 (C=O), 1448 (C=C); ^1H NMR ($CDCl_3$) δ (ppm): 0.92 (t, 2H, CH_3), 2.54 (q, 2H, CH_2), 2.60 (t, J = 7.9, 2H, C–CH_2), 2.74 (t, J = 7.9, 2H, CH_2–CO), 2.86–3.06 (m, 4H, 2 × CH_2), 3.58–3.78 (m, 4H, CH_2–O–CH_2), 5.16 (s, 2H, –N–CH_2–N–), 7.42 (dd, J = 8.2, 2H, H-3′, H-5′), 7.78 (dd, J = 8.2, 2H, H-2′, H-6′); Ms (*m*/*z*): 301/302 (M^+/M^+ + 1). Anal. Calc. for $C_{17}H_{23}N_3O_2$: C: 67.75, H: 7.69, N: 13.94. Found: C: 67.54, H: 7.46, N: 13.82.

*4.1.3.26. 6-(4-Ethylphenyl)-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**40**).* Piperazine was used as cyclic secondary amine for Mannich reaction. Yield: 50%; m.p. 137–138 °C; IR (KBr) υ_{max} (cm^{-1}): 3338 (NH), 2968 (CH), 1668 (C=O); ^1H NMR ($CDCl_3$) δ (ppm): 0.92 (t, 2H, CH_3), 2.54 (q, 2H, CH_2), 2.60 (t, J = 7.8, 2H, C–CH_2), 2.80–2.86 (m, 8H, 4 × CH_2), 2.96 (t, J = 7.8, 2H, CH_2–CO), 5.24 (s, 2H, –N–CH_2–N–), 7.32 (dd, J = 8.5, 2H, H-3′, H-5′), 7.78 (dd, J = 8.5, 2H, H-2′, H-6′), 9.6 (s, 1H, NH); Ms (*m*/*z*): 300/301 (M^+/M^+ + 1). Anal. Calc. for $C_{17}H_{24}N_4O$: C: 67.97, H: 8.05, N: 18.65. Found: C: 67.84, H: 7.88, N: 18.43.

*4.1.3.27. 6-(4-Ethylphenyl)-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**41**).* Piperidine was used as cyclic secondary amine for Mannich reaction. Yield: 48%; m.p. 147–148 °C; IR (KBr) υ_{max} (cm^{-1}): 2968 (CH), 1678(C=O), 1465 (C=C); ^1H NMR ($CDCl_3$) δ (ppm): 0.90 (t, 3H, CH_3), 2.54 (q, 2H, CH_2), 2.60 (t, J = 7.8, 2H, C–CH_2), 2.58–2.74 (m, 6H, 3 × CH_2), 2.82 (t, J = 7.8, 2H, CH_2), 2.92–3.08 (m, 4H, 2 × CH_2), 5.32 (s, 2H, –N–CH_2–N–), 7.38 (dd, J = 8.7, 2H, H-3′, H-5′), 7.78 (dd, J = 8.7, 2H, H-2′, H-6′); Ms (*m*/*z*): 299/300 (M^+/M^+ + 1). Anal. Calc. for $C_{18}H_{25}N_3O$: C: 72.16, H: 8.42, N: 14.03. Found: C: 71.96, H: 8.24, N: 13.97.

*4.1.3.28. 6-(4-Ethylphenyl)-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one (**42**).* 1-Methylpiperazine was used as cyclic secondary amine for Mannich reaction. Yield: 52%; m.p. 139–140 °C; IR (KBr) υ_{max} (cm^{-1}): 2970 (CH), 1680 (C=O), 1595 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 0.96 (t, 2H, CH_3), 1.18 (q, 2H, CH_3), 2.2 (s, 1H, N–CH_3), 2.50 (q, 2H, CH_2), 2.62 (t, J = 7.8, 2H, C–CH_2), 2.91 (t, J = 7.8, 2H, CH_2–CO), 2.95–3.07 (m, 4H, 2 × CH_2), 3.20–3.36 (m, 4H, 2 × CH_2), 5.2 (s, 2H, –N–CH_2–N–), 7.39 (dd, J = 8.2, 2H, H-3′, H-5′), 7.7 (dd, 2H, H-2′, H-6′); Ms (*m*/*z*): 314/315 (M^+/M^+ + 1). Anal. Calc. for $C_{18}H_{26}N_4O$: C: 68.76, H: 8.33, N: 17.82. Found: C: 68.66, H: 8.14, N: 17.76.

*4.1.3.29. 6-(4-Ethylphenyl)-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**43**).* Phenothiazine was used as cyclic secondary amine for Mannich reaction. Yield: 60%;

m.p. 126–128 °C; IR (KBr) υ_{max} (cm^{-1}): 2968 (CH), 1664 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 1.02 (t, 2H, CH_2), 2.54 (q, 2H, CH_2), 2.60 (t, J = 7.7, 2H, C–CH_2), 2.96 (t, J = 7.7, 2H, CH_2–CO), 5.32 (s, 2H, –N–CH_2–N–), 6.96–7.82 (m, 12H, Ar–H); Ms (*m*/*z*): 413/414 (M^+/M^+ + 1). Anal. Calc. for $C_{25}H_{23}N_3OS$: C: 72.16, H: 5.61, N: 10.16. Found: C: 71.92, H: 5.48, N: 9.98.

*4.1.3.30. 6-(4-Ethylphenyl)-2-(1H-indol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**44**).* Indole was used as cyclic secondary amine for Mannich reaction. Yield: 42%; m.p. 125–127 °C; IR (KBr) υ_{max} (cm^{-1}): 3001 (CH), 1680 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 0.88 (t, 2H, CH_3), 2.52 (q, 2H, CH_2), 2.60 (t, J = 7.8, 2H, C–CH_2), 2.96 (t, J = 7.8, 2H, CH_2–CO), 5.28 (s, 2H, –N–CH_2–N–), 7.38–7.78 (m, 10H, Ar–H); Ms (*m*/*z*): 331/332 (M^+/M^+ + 1). Anal. Calc. for $C_{21}H_{21}N_3O$: C: 67.11, H: 6.39, N: 12.68. Found: C: 66.92, H: 6.12, N: 12.51.

*4.1.3.31. 6-(4-Ethylphenyl)-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**45**).* Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 42%; m.p. 140–142 °C; IR (KBr) υ_{max} (cm^{-1}): 3000 (CH), 1680 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 1.01 (t, 2H, CH_3), 2.50 (t, 2H, CH_2), 2.60 (t, J = 7.7, 2H, C–CH_2), 2.94 (t, J = 7.7, 2H, CH_2–CO), 2.96–3.04 (m, 8H, 4 × CH_2), 5.16 (s, 2H, –N–CH_2–N–), 7.35–7.45 (m, 2H, Ar–H), 7.72–7.82 (m, 2H, Ar–H); Ms (*m*/*z*): 285/286 (M^+/M^+ + 1). Anal. Calc. for $C_{17}H_{23}N_3O$: C: 76.11, H: 6.39, N: 12.68. Found: C: 75.88, H: 6.28, N: 12.56.

*4.1.3.32. 6-(4-Ethylphenyl)-2-(1,2,4-triazolin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**46**).* 1,2,4-Triazole was used as cyclic secondary amine for Mannich reaction. Yield: 51%; m.p. 141–143 °C; IR (KBr) υ_{max} (cm^{-1}): 3002 (CH), 1680 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 1.18 (t, 2H, CH_3), 2.59 (t, 2H, CH_2), 2.66 (t, J = 7.9, 2H, C–CH_2), 3.01 (t, J = 7.9, 2H, CH_2–CO), 5.32 (s, 2H, –N–CH_2–N–), 7.36–7.86 (m, 6H, Ar–H); Ms (*m*/*z*): 283/284 (M^+/M^+ + 1). Anal. Calc. for $C_{15}H_{17}N_5O$: C: 63.59, H: 6.05, N: 24.72. Found: C: 63.52, H: 5.82, N: 24.58.

*4.1.3.33. 6-(4-Isobutylphenyl)-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**47**).* Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 38%; m.p. 152–154 °C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1675 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 0.9 (d, 6H, 2 × CH_3), 1.75–1.85 (m, H, –CH), 2.69 (t, J = 7.8, 2H, C–CH_2), 2.92 (t, J = 7.8, 2H, CH_2–CO), 2.96–3.04 (m, 4H, 2 × CH_2), 3.15–3.25 (m, 4H, 2 × CH_2), 4.78 (s, 2H, –N–CH_2–N–), 7.34 (dd, J = 8.2, 2H, H-3′, H-5′), 7.42 (dd, J = 8.2, 2H, H-2′, H-6′); Ms (*m*/*z*): 329/330 (M^+/M^+ + 1). Anal. Calc. for $C_{19}H_{27}N_3O_2$: C: 69.27, H: 8.26, N: 12.76. Found: C: 69.12, H: 8.12, N: 12.58.

*4.1.3.34. 6-(4-Isobutylphenyl)-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**48**).* Piperazine was used as cyclic secondary amine for Mannich reaction.Yield: 52%; m.p. 147–148 °C; IR (KBr) υ_{max} (cm^{-1}): 3000 (CH), 1680 (C═O), 1590 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 0.89 (d, 6H, 2 × CH_3), 1.74–1.86 (m, H, –CH), 2.62 (t, J = 7.8, 2H, C–CH_2), 2.70–2.86 (m, 8H, 4 × CH_2), 2.92 (t, J = 7.8, 2H, CH_2–CO), 4.79 (s, 2H, –N–CH_2–N–), 7.42 (dd, J = 8.3, 2H, H-3′, H-5′), 7.80 (dd, J = 8.2, 2H, H-2′, H-6′), 8.10 (s, 1H, NH); Ms (*m*/*z*): 328/329 (M^+/M^+ + 1). Anal. Calc. for $C_{19}H_{28}N_4O$: C: 69.48, H: 8.59, N: 17.06. Fond: C: 69.24, H: 8.36, N: 16.86.

*4.1.3.35. 6-(4-Isobutylphenyl)-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**49**).* Piperidine was used as cyclic secondary amine for Mannich reaction. Yield: 48%; m.p. 137–138 °C; IR (KBr) υ_{max} (cm^{-1}): 3010 (CH), 1685 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 0.80 (d, 6H, 2 × CH_3), 1.80–1.90 (m, H, –CH), 2.55–2.75 (m, 4H, 2 × CH_2), 2.90 (t, J = 7.8, 2H, CH_2–CO), 2.90–3.28 (m, 10H, 5 × CH_2), 5.02 (s, 2H, –N–CH_2–N–), 7.42 (dd, J = 8.4, 2H, H-3′, H-5′), 7.8 (dd, J = 8.4, 2H, H-2′, H-6′); Ms (*m*/*z*): 327/328 (M^+/M^+ + 1). Anal. Calc. for $C_{20}H_{29}N_3O$: C: 73.36, H: 8.93, N: 12.83. Found: C: 73.23, H: 8.86, N: 12.76.

*4.1.3.36. 6-(4-Isobutylphenyl)-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one (**50**).* 1-Methylpiperazine was used as cyclic secondary amine for Mannich reaction.Yield: 51%; m.p. 129–131 °C; IR (KBr) υ_{max} (cm^{-1}): 2995 (CH), 1680 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 0.78 (d, 6H, 2 × CH_3), 1.76–1.88 (m, H, –CH), 2.50 (s, 3H, N–CH_3), 2.60–2.70 (m, 4H, 2 × CH_2), 2.85 (t, J = 7.8, 2H, CH_2–CO), 3.0–3.30 (m, 8H, 4 × CH_2), 4.78 (s, 2H, –N–CH_2–N–), 7.35 (dd, J = 8.5, 2H, H-3′, H-5′), 7.80 (dd, J = 8.5, 2H, H-2′, H-6′); Ms (*m*/*z*): 342/343 (M^+/M^+ + 1). Anal. Calc. for $C_{20}H_{30}N_4O$: C: 70.14, H: 8.83, N: 16.36. Found: C: 69.88, H: 8.67, N: 16.18.

*4.1.3.37. 6-(4-Isobutylphenyl)-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**51**).* Phenothiazine was used as cyclic secondary amine for Mannich reaction. Yield: 44%; m.p. 150–152 °C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1680 (C═O), 1602 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 0.80 (d, 6H, 2 × CH_3), 1.76–1.94 (m, H, –CH), 2.52–2.72 (m, 4H, 2 × CH_2), 2.90 (t, J = 7.8, 2H, CH_2–CO), 4.78 (s, 2H, –N–CH_2–N–), 7.42–7.89 (m, 12H, Ar–H); Ms (*m*/*z*): 441/442 (M^+/M^+ + 1). Anal. Calc. for $C_{27}H_{27}N_3OS$: C: 73.44, H: 6.16, N: 9.52. Found: C: 73.28, H: 5.96, N: 9.24.

*4.1.3.38. 6-(4-Isobutylphenyl)-2-(1H-indol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**52**).* Indole was used as cyclic secondary amine for Mannich reaction. Yield: 43%; m.p. 134–136 °C; IR (KBr) υ_{max} (cm^{-1}): 2990 (CH), 1685 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 0.85 (d, 6H, 2 × CH_3), 1.70–1.86 (m, H, –CH), 2.28–2.52 (m, 2H, CH_2), 2.62 (t, J = 7.8, 2H, C–CH_2), 2.92 (t, J = 7.8, 2H, CH_2–CO), 5.02 (s, 2H, –N–CH_2–N–), 7.32–7.89 (m, 10H, Ar–H); Ms (*m*/*z*): 359/360 (M^+/M^+ + 1). Anal. Calc. for $C_{23}H_{25}N_3O$: C: 76.85, H: 7.01, N: 11.69. Found: C: 76.68, H: 6.86, N: 11.64.

*4.1.3.39. 6-(4-Isobutylphenyl)-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**53**).* Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 40%; m.p. 136–138 °C; IR (KBr) υ_{max} (cm^{-1}): 3000 (CH), 1680 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 0.80 (d, 6H, 2 × CH_3), 1.78–1.92 (m, H, –CH), 2.60 (t, J = 7.7, 2H, C–CH_2), 2.85 (t, J = 7.7, 2H, CH_2–CO), 2.90–3.20 (m, 10H, 5 × CH_2), 5.1 (s, 2H, –N–CH_2–N–), 7.42 (dd, J = 8.6, 2H, H-3′, H-5′), 7.80 (dd, J = 8.6, 2H, H-2′, H-6′); Ms (*m*/*z*): 313/314 (M^+/M^+ + 1). Anal. Calc. for $C_{19}H_{27}N_3O$: C: 72.81, H: 8.68, N: 13.41. Found: C: 72.57, H: 8.48, N: 13.22.

*4.1.3.40. 6-(4-Isobutylphenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**54**).* 1,2,4-Triazole was used as cyclic secondary amine for Mannich reaction. Yield: 53%; m.p. 144–146 °C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1678 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$-d_6) δ (ppm): 0.82 (d, 6H, 2 × CH_3), 1.85–1.95 (m, H, –CH), 2.42–2.58 (m, 2H, CH_2), 2.65 (t, J = 7.9, 2H, C–CH_2), 2.86 (t, J = 7.9, 2H, CH_2–CO), 4.79 (s, 2H, –N–CH_2–N–), 7.40–7.86 (m, 6H, Ar–H); Ms (*m*/*z*): 311/312 (M^+/M^+ + 1). Anal. Calc. for $C_{17}H_{21}N_5O$: C: 65.57, H: 6.80, N: 22.49. Found: C: 65.44, H: 6.68, N: 22.13.

*4.1.3.41. 6-(4-Biphenyl)-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**55**).* Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 68%; m.p. 163–165 °C; IR (KBr) υ_{max} (cm^{-1}): 2970 (CH), 1674 (C═O), 1556 (C═C); ^1H NMR ($CDCl_3$) δ (ppm): 2.62 (t, J = 7.6, 2H, C–CH_2), 2.96 (t, J = 7.6, 2H, CH_2–CO), 2.97–2.99 (m, 4H, 2 × CH_2), 3.59–3.79 (m, 4H, CH_2–O–CH_2), 5.28 (s, 2H, –N–CH_2–N–), 7.06–7.80 (m, 9H, Ar–H); Ms (*m*/*z*): 349/350

($M^+/M^+ + 1$). Anal. Calc. for $C_{21}H_{23}N_3O_2$: C: 72.18, H: 6.63, N: 12.03. Found: C: 71.89, H: 6.44, N: 11.92.

*4.1.3.42. 6-(4-Biphenyl)-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**56**).* Piperazine was used as cyclic secondary amine for Mannich reaction. Yield: 47%; m.p. 162–164 °C; IR (KBr) υ_{max} (cm^{-1}): 3325 (NH), 2964 (CH), 1661 (C═O), 1524 (C═C); ^1H NMR ($CDCl_3$) δ (ppm): 2.61 (t, $J = 7.7$, 2H, C–CH_2), 2. 92 (t, $J = 7.7$, 2H, CH_2–CO), 2.95–3.07 (m, 8H, 4 × CH_2), 5.25 (s, 2H, –N–CH_2–N–), 7.04–7.78 (m, 9H, Ar–H), 9.8 (br s, 1H, NH); Ms (*m*/*z*): 348/349 (M^+/$M^+ + 1$). Anal. Calc. for $C_{21}H_{24}N_4O$: C: 72.39, H: 6.94, N: 16.08. Fond: C: 72.14, H: 6.78, N: 15.84.

*4.1.3.43. 6-(4-Biphenyl)-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**57**).* Piperidine was used as cyclic secondary amine for Mannich reaction. Yield: 56%; m.p. 170–172 °C; IR (KBr) υ_{max} (cm^{-1}): 2944 (CH), 1678(C═O), 1520 (C═C); ^1H NMR ($CDCl_3$) δ (ppm): 2.60 (t, $J = 7.8$, 2H, C–CH_2), 2.62–2.68 (m, 6H, 3 × CH_2), 2.90–3.06 (m, 4H, 2 × CH_2), 5.24 (s, 2H, –N–CH_2–N–), 7.14–7.82 (m, 9H, Ar–H); Ms (*m*/*z*): 347/348 ($M^+/M^+ + 1$). Anal. Calc. for $C_{16}H_{21}N_3O$: C: 70.05, H: 6.94, N: 12.09. Found: C: 69.86, H: 6.82, N: 11.92.

*4.1.3.44. 6-(4-Biphenyl)-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one (**58**).* 1-Methylpiperazine was used as cyclic secondary amine for Mannich reaction. Yield: 70%; m.p. 154–156 °C; IR (KBr) υ_{max} (cm^{-1}): 3010 (CH), 1684 (C═O), 1590 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.21 (s, 1H, N–CH_3), 2.54 (t, $J = 7.4$, 2H, C–CH_2), 2.96 (t, $J = 7.4$, 2H, CH_2–CO), 3.02–3.18 (m, 4H, 2 × CH_2), 3.22–3.38 (m, 4H, 2 × CH_2), 5.2 (s, 2H, –N–CH_2–N–), 7.10–7.80 (m, 9H, Ar–H); Ms (*m*/*z*): 362/363 ($M^+/M^+ + 1$). Anal. Calc. for $C_{16}H_{22}N_4O$: C: 72.90, H: 7.23, N: 15.46. Found: C: 72.76, H: 6.98, N: 15.40.

*4.1.3.45. 6-(4-Biphenyl)-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**59**).* Phenothiazine was used as cyclic secondary amine for Mannich reaction. Yield: 76%; m.p. 166–168 °C; IR (KBr) υ_{max} (cm^{-1}): 2968 (CH), 1670 (C═O), 1604 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.62 (t, $J = 7.6$, 2H, C–CH_2), 2.96 (t, $J = 7.6$, 2H, CH_2–CO), 5.26 (s, 2H, –N–CH_2–N–), 6.80–6.98 (m, 9H, phenyl protons), 7.14–7.78 (m, 9H, Ar–H); Ms (*m*/*z*): 461/462 (M^+/$M^+ + 1$). Anal. Calc. for $C_{23}H_{19}N_3OS$: C: 75.46, H: 5.02, N: 9.10. Found: C: 75.18, H: 4.88, N: 8.88.

*4.1.3.46. 6-(4-Biphenyl)-2-(1H-indol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**60**).* Indole was used as cyclic secondary amine for Mannich reaction.Yield: 60%; m.p. 150–152 °C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1680 (C═O), 1602 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.63 (t, $J = 7.5$, 2H, C–CH_2), 3.02 (t, $J = 7.5$, 2H, CH_2–CO), 5.02 (s, 2H, –N–CH_2–N–), 7.12–7.76 (m, 15H, Ar–H); Ms (*m*/*z*): 379/380 ($M^+/M^+ + 1$). Anal. Calc. for $C_{19}H_{17}N_3O$: C: 79.13, H: 5.58, N: 11.07. Found: C: 78.86, H: 5.32, N: 10.86.

*4.1.3.47. 6-(4-Biphenyl)-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**61**).* Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 67%; m.p. 174–176 °C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1685 (C═O), 1598 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.63 (t, $J = 7.8$, 2H, C–CH_2), 2.96 (t, $J = 7.8$, 2H, CH_2–CO), 3.02–3.18 (m, 8H, 4 × CH_2), 5.40 (s, 2H, –N–CH_2–N–), 7.16–7.82 (m, 9H, Ar–H); Ms (*m*/*z*): 333/334 ($M^+/M^+ + 1$). Anal. Calc. for $C_{15}H_{19}N_3O$: C: 75.65, H: 6.95, N: 12.60. Found: C: 75.48, H: 6.92, N: 12.48.

*4.1.3.48. 6-(4-Biphenyl-4-yl)-2-(1H-1,2,4-triazol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**62**).* 1,2,4-Triazole was used as cyclic secondary amine for Mannich reaction. Yield: 59%; m.p. 146–148 °C; IR (KBr) υ_{max} (cm^{-1}): 2995 (CH), 1685 (C═O), 1592 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.66 (t, $J = 7.5$, 2H, C–CH_2), 3.0 (t, $J = 7.5$, 2H, CH_2–CO), 5.3 (s, 2H, –N–CH_2–N–), 7.38–7.83 (m, 11H, Ar–H); Ms (*m*/*z*): 331/332 ($M^+/M^+ + 1$). Anal. Calc. for $C_{13}H_{13}N_5O$: C: 68.87, H: 5.17, N: 21.13. Found: C: 68.62, H: 4.96, N: 20.94.

*4.1.3.49. 6-(4-Chlorophenyl)-2-(morpholin-4-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**63**).* Morpholine was used as cyclic secondary amine for Mannich reaction. Yield: 70%; m.p. 178–180 °C; IR (KBr) υ_{max} (cm^{-1}): 3010 (CH), 1685 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.60 (t, $J = 7.8$, 2H, C–CH_2), 2.73 (t, $J = 7.8$, 2H, CH_2–CO), 2.90–3.05 (m, 4H, 2 × CH_2), 3.59–3.79 (m, 4H, CH_2–O–CH_2), 4.28 (s, 2H, –N–CH_2–N–), 7.37 (dd, 4H, $J = 8.4$, H-3′-H-5′), 7.82 (dd, 2H, $J = 8.4$, H-2′, H-6′); Ms (*m*/*z*): 307/309 ($M^+/M^+ + 2$). Anal. Calc. for $C_{15}H_{18}ClN_3O_2$: C: 58.54, H: 5.89, N: 13.65. Found: C: 58.46, H: 5.84, N: 13.36.

*4.1.3.50. 6-(4-Chlorophenyl)-2-(piperazin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**64**).* Piperazine was used as cyclic secondary amine for Mannich reaction. Yield: 62%; m.p. 166–168 °C; IR (KBr) υ_{max} (cm^{-1}): 3005 (CH), 1685 (C═O), 1590 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.60 (t, $J = 7.7$, 2H, C–CH_2), 2.86 (t, $J = 7.7$, 2H, CH_2–CO), 2.90–3.40 (m, 8H, 4 × CH_2), 4.78 (s, 2H, –N–CH_2–N–), 7.36 (dd, $J = 8.2$, 2H, H-3′, H-5′), 7.65 (dd, $J = 8.2$, 2H, H-2′, H-6′), 8.50 (s, 1H, –NH); Ms (*m*/*z*): 306/308 ($M^+/M^+ + 2$). Anal. Calc. for $C_{15}H_{19}ClN_4O$: C: 58.72, H: 6.24, N: 18.26. Fond: C: 58.56, H: 6.02, N: 18.16.

*4.1.3.51. 6-(4-Chlorophenyl)-2-(piperidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**65**).* Piperidine was used as cyclic secondary amine for Mannich reaction. Yield: 58%; m.p. 152–154 °C; IR (KBr) υ_{max} (cm^{-1}): 3010 (CH), 1680 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.65 (t, $J = 7.6$, 2H, C–CH_2), 2.90 (t, $J = 7.6$, 2H, CH_2–CO), 3.0–3.40 (m, 10H, 5 × CH_2), 5.01 (s, 2H, –N–CH_2–N–), 7.40 (dd, $J = 8.4$, 2H, H-3′, H-5′), 7.70 (dd, $J = 8.4$, 2H, H-2′, H-6′); Ms (*m*/*z*): 305/307 ($M^+/M^+ + 2$). Anal. Calc. for $C_{16}H_{20}ClN_3O$: C: 62.84, H: 6.59, N: 13.74. Found: C: 62.75, H: 6.44, N: 13.68.

*4.1.3.52. 6-(4-Chlorophenyl)-2-[(4-methylpiperazin-1-yl)methyl]-4,5-dihydropyridazin-3(2H)-one (**66**).* 1-Methylpiperazine was used as cyclic secondary amine for Mannich reaction. Yield: 66%; m.p. 172–174 °C; IR (KBr) υ_{max} (cm^{-1}): 3005 (CH), 1685 (C═O), 1598 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.40 (s, 3H, N–CH_3), 2.80 (t, $J = 7.8$, 2H, C–CH_2), 2.88 (t, $J = 7.8$, 2H, CH_2–CO), 2.90–3.20 (m, 8H, 4 × CH_2), 4.79 (s, 2H, –N–CH_2–N–), 7.40 (dd, $J = 8.6$, 2H, H-3′, H-5′), 7.70 (dd, 2H, $J = 8.6$, H-2′, H-6′); Ms (*m*/*z*): 320/322 ($M^+/M^+ + 2$). Anal. Calc. for $C_{16}H_{21}ClN_4O$: C: 59.90, H: 6.60, N: 17.46. Found: C: 59.64, H: 6.48, N: 17.26.

*4.1.3.53. 6-(4-Chlorophenyl)-2-(1,2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**67**).* Phenothiazine was used as cyclic secondary amine for Mannich reaction. Yield: 64%; m.p. 190–192 °C; IR (KBr) υ_{max} (cm^{-1}): 3010 (CH), 1685 (C═O), 1602 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.48 (s, 3H, N–CH_3), 2.60 (t, $J = 7.7$, 2H, C–CH_2), 2.90 (t, $J = 7.7$, 2H, CH_2–CO), 4.78 (s, 2H, –N–CH_2–N–), 7.15–7.55 (m, 12H, Ar–H); Ms (*m*/*z*): 419/421 ($M^+/M^+ + 2$). Anal. Calc. for $C_{23}H_{18}ClN_3OS$: C: 65.78, H: 4.32, N: 10.01. Found: C: 65.52, H: 4.16, N: 9.84.

*4.1.3.54. 6-(4-Chlorophenyl)-2-(1H-indol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**68**).* Indole was used as cyclic secondary amine for Mannich reaction. Yield: 38%; m.p. 146–148 °C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1680 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.62 (t, $J = 7.8$, 2H, C–CH_2), 2.86 (t, $J = 7.8$, 2H, CH_2–CO), 4.79 (s, 2H, –N–CH_2–N–), 7.35–7.80 (m, 10H, Ar–H); Ms (*m*/*z*): 337/339

($M^+/M^+ + 2$). Anal. Calc. for $C_{19}H_{16}ClN_3O$: C: 67.56, H: 4.77, N: 12.44. Found: C: 67.32, H: 4.65, N: 12.26.

*4.1.3.55. 6-(4-Chlorophenyl)-2-(pyrrolidin-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**69**).* Pyrrolidine was used as cyclic secondary amine for Mannich reaction. Yield: 63%; m.p. 166–168 °C; IR (KBr) υ_{max} (cm^{-1}): 2998 (CH), 1680 (C═O), 1600 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.60 (t, $J = 7.6$, 2H, C–CH_2), 2.90 (t, $J = 7.6$, 2H, CH_2–CO), 2.95–3.20 (m, 8H, 4 × CH_2), 4.78 (s, 2H, –N–CH_2–N–), 7.36 (dd, $J = 8.2$, 2H, H-3′, H-5′), 7.60 (dd, $J = 8.2$, 2H, H-2′, H-6′); Ms (m/z): 291/293 ($M^+/M^+ + 2$). Anal. Calc. for $C_{15}H_{18}ClN_3O$: C: 61.75, H: 6.22, N: 14.40. Found: C: 61.61, H: 6.02, N: 14.26.

*4.1.3.56. 6-(4-Chlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-4,5-dihydropyridazin-3(2H)-one (**70**).* 1,2,4-Triazole was used as cyclic secondary amine for Mannich reaction. Yield: 48%; m.p. 136–138 °C; IR (KBr) υ_{max} (cm^{-1}): 2990 (CH), 1675 (C═O), 1598 (C═N); ^1H NMR ($CDCl_3$) δ (ppm): 2.65 (t, $J = 7.8$, 2H, C–CH_2), 2.95 (t, $J = 7.8$, 2H, CH_2–CO), 4.79 (s, 2H, –N–CH_2–N–), 7.42–7.80 (m, 6H, Ar–H); Ms (m/z): 289/291 ($M^+/M^+ + 2$). Anal. Calc. for $C_{13}H_{12}ClN_5O$: C: 53.89, H: 4.17, N: 24.17. Found: C: 53.66, H: 4.12, N: 23.96.

4.2. Pharmacology

4.2.1. Procurement, identification, and housing of animals

Albino rats (body weight 200–250 g) were supplied by Central Animal House facility of Hamdard University and kept under standard laboratory conditions in 12 h light/dark cycle at 25 °C ± 2 °C. Animals were provided with pellet diet (Lipton, Calcutta, India) and water ad libitum. They were marked for easy identification.

4.2.2. 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.

4.2.3. 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. [21].

4.2.4. 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 five 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.

4.2.5. 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 BP for all the treatment groups was also calculated and compared.

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