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Original article

Novel pyridazine derivatives: Synthesis and antimicrobial activity evaluation

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ABSTRACT

A general method for the preparation of new hydrazones is reported. The 1-[4-(2-methoxybenzyl)-6-aryl pyridazin-3(2*H*)-ylidene] hydrazines or their tautomeric structures (**1**$_{a-d}$) were condensed with different aldehydes, dialdehydes, ketones, α-dicarbonyl compounds and simple carbohydrates to afford the hydrazones and dihydrazones (**2**$_{a-d}$), (**3**$_{a-d}$), (**4**$_{a-d}$), (**5**$_{a-d}$), (**6**$_{d}$), (**7**$_{c}$), (**8**$_{a-d}$), (**9**$_{a-d}$), (**10**$_{a-d}$), (**11**$_{a-d}$), (**12**$_{a,c,d}$), (**13**$_{a-d}$), (**14**$_{a-d}$), (**15**$_{a-d}$), (**16**$_{a-d}$) and (**17**$_{a-d}$). The structures of all synthesized compounds were confirmed from microanalytical and spectral data. Some of the products were screened for their antimicrobial activity against *Staphylococcus aureus* and *Streptococcus faecalis*, *Escherichia coli* and *Pseudomonas aeruginosa*. The hydrazone derivative **15**$_{d}$ (1-[4-(2-methoxybenzyl)-6-methylphenyl pyridazin-3(2*H*)-ylidene]-2-(2-carboxydiphenyl methyl) hydrazine) showed the highest biological activity.

1. Introduction

Pyridazines are an important class of heterocycles, which have been the subject of extensive research, particularly in the pharmaceutical and agrochemical areas due to their broad-activities, such as antihypertensive activity and anti-inflammatory [1–3]. Their synthesis and application have been comprehensively reviewed [4,5].

Information from several previous SAR (Structure–Activity Relationships) studies [6–18] allowed us to focus this investigation on a well-defined set of compounds, a series of diverse variations of the substitution at the pyridazine derivatives. In view of wide spread resistant strains of microorganism there is an urgent need for the development of new antimicrobial agents.

2. Chemistry

The required 1-[4-(2-methoxybenzyl)-6-aryl-pyridazin-3(2*H*)-ylidene] hydrazines or its tautomeric structures (**1**$_{a-d}$) were prepared following the literature method [14–17]. It was reported that hydrazones have been demonstrated to possess, amongst other activities, antimicrobial, anticonvulsant, analgesic, antiplatelet, antitubercular and antitumoral activity [19].

As a route for the synthesis of hydrazones, the reaction of compounds **1**$_{a-d}$ with aldehydes, dialdehydes, ketones, α-dicarbonyl compounds and simple carbohydrates seemed to be a logical method for preparation of these hydrazones (Scheme 1). Thus, condensation reaction of compounds **1**$_{a-d}$ with 3-methoxy-4-hydroxy benzaldehyde in ethanol gave **2**$_{a-d}$. The IR spectra of **2**$_{a-d}$ displayed bands at 3346–3325 (OH, NH) and 1598–1592 cm^{-1} (C=N). The presence of the OH group in compounds **2**$_{a-d}$ was confirmed chemically by an acetylation reaction to yield **3**$_{a-d}$. While the IR absorption spectra of **3**$_{a-d}$ showed bands at 3445–3418 (NH), 1767–1762 (C=O) and 1604–1598 cm^{-1} (C=N). While condensation reactions of compounds **1**$_{a-d}$ with dialdehydes such as 4,4′-diformyl, 2,2′-dimethoxy or 2,2′,6,6′-tertramethoxy-1,2-diphenoxyethane [20,21] in ethanol yielded monohydrazone derivatives (**4**$_{a-d}$), (**5**$_{a-d}$) and (**6**$_{d}$), the dihydrazone (**7**$_{c}$) was obtained by the solid phase reaction of the monohydrazone (**5**$_{c}$) with compound **1**$_{c}$. The spectral data of all structures of the new compounds are given in Section 4.

It was reported that several base-modified nucleosides act as antiviral and anticancer agents most likely due to their capability to mimic natural counterparts and function [22]. The synthesis and biological activities of sugar-modified nucleoside analogs have been active research areas for many years [23], so we report here the reaction of **1**$_{a-d}$ with simple carbohydrates such as D-arabinose and D-glucose in ethanol to yield the corresponding hydrazono derivatives **8**$_{a-d}$ and **9**$_{a-d}$, respectively. Acetylation of these compounds using Ac_2O in the presence of pyridine as a catalyst gave the acetyl derivatives **10**$_{a-d}$ and **11**$_{a-d}$.

This study was extended to report the reaction of **1**$_{a-d}$ with some ketones, α-keto benzoic acid and α-dicarbonyl compounds. Thus, condensation reactions of compounds **1**$_{a,c,d}$ with acetone in ethanol furnished compounds **12**$_{a,c,d}$. The IR spectra of **12**$_{a,c,d}$ displayed bands at 3422–3282 cm^{-1} (NH), 2927–2905 cm^{-1} (CH

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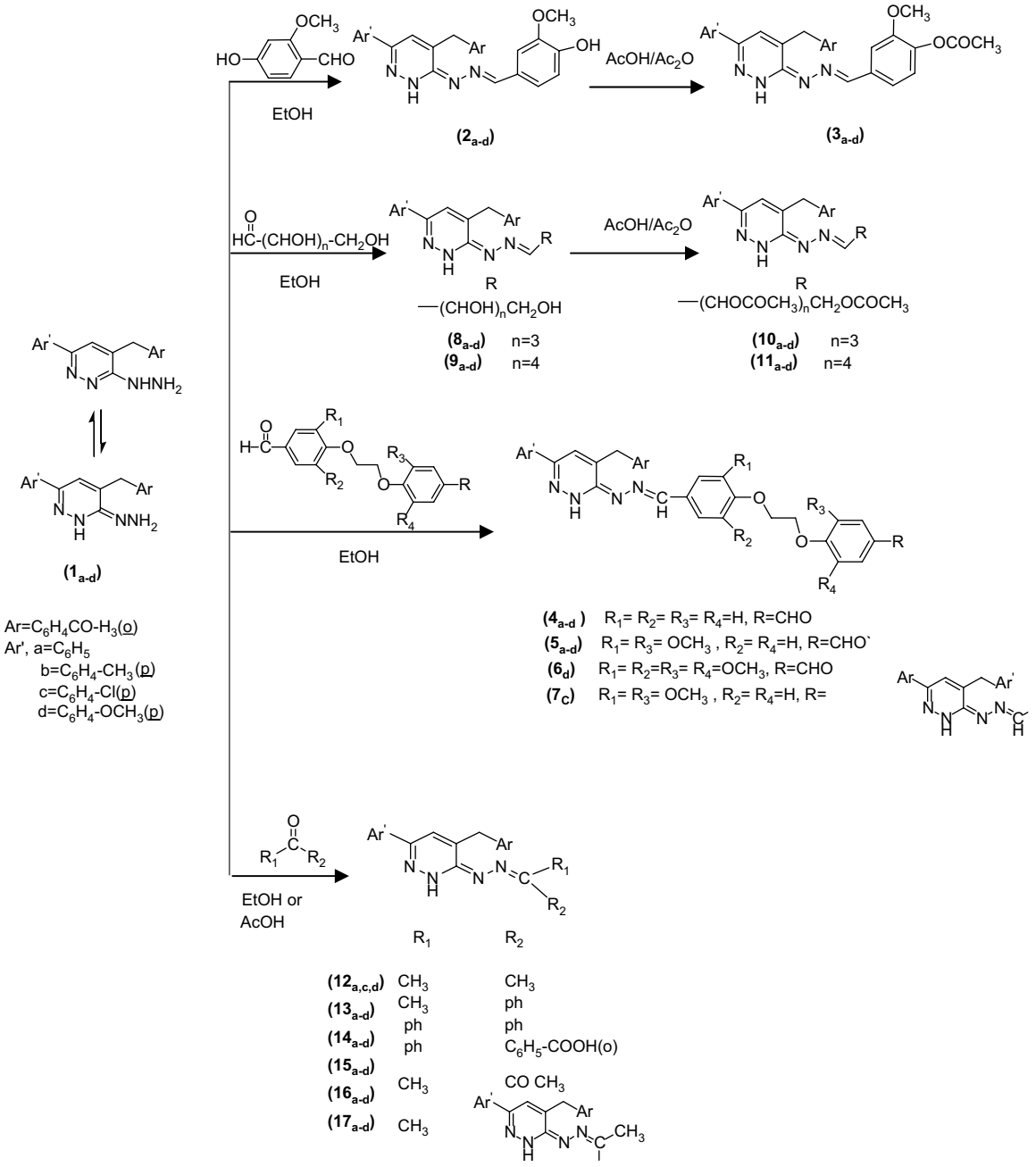

Scheme 1.

aliphatic) and 1637–1630 cm^{-1} (C═N), while reaction of compounds **1a–d** with acetophenone in ethanol gave the corresponding hydrazone derivatives **13a–d**. The IR absorption spectra of **13a–d** showed bands at 3370–3356 cm^{-1} (NH), 2932–2916 cm^{-1} (CH aliphatic) and 1628–1625 cm^{-1} (C═N). Reaction of **1a–d** with benzophenone in ethanol yielded the corresponding hydrazones **14a–d**. Structures of **14a–d** were established from their analytical and spectral data. The IR spectra displayed bands at 3376–3282 cm^{-1} (NH) and 1631–1623 cm^{-1} (C═N).

However, reaction of **1a–d** with α-benzoyl benzoic acid in a mixture of acetic anhydride:glacial acetic acid (1:1) gave compounds **15a–d**. The IR absorption spectra of **15a–c** showed broad bands at 3447–3401 cm^{-1} (OH), 3316–3212 cm^{-1} (NH), 1718–1651 cm^{-1} (C═O) and 1604–1595 cm^{-1} (C═N).

The reaction of **1a–d** with diacetyl in different solvents involved one or both of the carbonyl groups in the reaction. Thus, refluxing equimolar amounts of **1a–d** with diacetyl in ethanol gave monohydrazone derivatives **16a–d**. When the reaction was carried out in glacial acetic acid, it yielded the corresponding dihydrazone derivative **17d,b** is{1-[4-(2-methoxybenzyl)-6-arylpyridazin-3(2*H*)-ylidene]-2-(butan-2,3-ylidene)} hydrazines (**17a–c**) which could be obtained also from refluxing the monohydrazone compounds (**17a–c**) with another mole of the pyridazine derivatives (**1a–c**) in glacial acetic acid. The spectral data of all structures of the new compounds are given in Section 4.

3. Antimicrobial activity

The in vitro antimicrobial activities for the synthesized compounds against *Staphylococcus aureus* and *Streptococcus faecalis* as (Gram +ve) bacteria and *Escherichia coli* and *Pseudomonas aeruginosa* as (Gram −ve) bacteria were determined .The biological

assay was performed according to the agar diffusion method [24–27] at a concentration 20 mg/mL using DMSO as the solvent.

The results of the in vitro antimicrobial activity of 18 compounds and of tetracycline, recorded as average diameter of inhibition zone in mm, are given in Table 1. The hydrazone derivative **15$_d$** showed the highest biological activity and the hydrazone derivative **5$_d$** showed the lowest biological activity.

4. Experimental

Melting points are uncorrected. The IR spectra of the compounds were recorded on a Perkin–Elmer spectrophotometer model 1430 as potassium bromide pellets and frequencies are reported in cm^{-1}. The ^1H NMR spectra were observed on a Varian Genini-300 MHz spectrometer and chemical shifts (δ) are in ppm. The mass spectra were recorded on a mass spectrometer HP model MS–QPL000EX (Shimadzu) at 70 eV. Elemental analyses and Antimicrobial activity Evaluation were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

*4.1. General procedure for the preparation of hydrazones from 1-[4-(2-methoxybenzyl)-6-aryl pyridazin-3(2H)-ylidene] hydrazines (**1$_{a–d}$**) and different aldehydes, dialdehydes, simple carbohydrates and ketones*

A solution of compounds **1$_{a–d}$** (1 mmol) in ethanol (20 ml) was treated with the corresponding aldehydes, dialdehydes and simple carbohydrates (1 mmol). The reaction mixture was refluxed for 5 h. The separated solid product was filtered off and crystallized from the appropriate solvent.

*4.1.1. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(3-methoxy-4-hydroxybenzylidene) hydrazine (**2$_a$**)*

Prepared from 3-methoxy-4-hydroxy benzaldehyde, orange crystals in 89.3% yield, mp 176–178 °C (DMF); MS: *m*/*e* 440 (M^+, 22.89), IR: 3328 cm^{-1} (OH, NH) and 1592 cm^{-1} (C=N); ^1H NMR (DMSO, 300 MHz) δ 9.33 (s, 1H, OH), 8.56 (s, 1H, N=CH), 8.23 (s,1H, NH), 7.79–6.81 (m, 12H, 3Ar-H), 6.78 (s, 1H, CH hetero), 3.91 (s, 2H, CH_2) and 3.86–3.80 (s, 6H, 2° CH_3). Anal. Calcd for $C_{26}H_{24}N_4O_3$: C, 70.89; H, 5.49; N, 12.72. Found: C, 70.60; H, 5.66; N, 12.70.

*4.1.2. 1-[4-(2-Methoxybenzyl)-6-methyl-phenyl pyridazin-3(2H)-ylidene]-2-(3-methoxy-4-hydroxybenzylidene) hydrazine (**2$_b$**)*

Prepared from 3-methoxy-4-hydroxybenzaldehyde, orange crystals in 86.67% yield, mp 218–220 °C (DMF); MS: *m*/*e* 454 (M^+, 69.49), IR: 3329 cm^{-1} (OH, NH) and 1595 cm^{-1} (C=N). Anal. Calcd for $C_{27}H_{26}N_4O_3$: C, 71.35; H, 5.77; N, 12.33. Found: C, 71.33; H, 5.80; N, 12.35.

*4.1.3. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(3-methoxy-4-hydroxybenzylidene) hydrazine (**2$_c$**)*

Prepared from 3-methoxy-4-hydroxybenzaldehyde, orange crystals in 87% yield, mp 232 °C (DMF); MS: *m*/*e* 475 ($M^+ + 1$, 21), 474 (M^+, 44.44) IR: 3325 cm^{-1} (OH, NH) and 1597 cm^{-1} (C=N). Anal. Calcd for $C_{26}H_{23}N_4O_3$ Cl: C, 65.75; H, 4.88; N, 11.80; Cl, 7.46. Found: C, 65.40; H, 5.02; N, 11.82; Cl, 7.42.

*4.1.4. 1-[4-(2-Methoxybenzyl)-6-methoxyphenyl pyridazin-3(2H)-ylidene]-2-(3-methoxy-4-hydroxybenzylidene) hydrazine (**2$_d$**)*

Prepared from 3-methoxy-4-hydroxy benzaldehyde, orange crystals in 88.89% yield, mp 226–228 °C (DMF); MS: *m*/*e* 471 ($M^+ + 1$, 21.86), 470 (M^+, 81), IR: 3346 cm^{-1} (OH, NH) and 1598 cm^{-1} (C=N); ^1H NMR (DMSO, 300 MHz) δ 9.30 (s, 1H, OH), 8.23 (s, 1H, N=CH), 7.80 (s, 1H, NH), 7.61–6.79 (m, 11H, 3Ar-H), 6.77 (s, 1H, CH hetero), 4.15 (s, 2H, CH_2) and 3.80–3.17 (s, 6H, 2° CH_3) . Anal. Calcd for $C_{27}H_{26}N_4O_4$: C, 68.92; H, 5.57; N, 11.91. Found: C, 69.16; H, 5.66; N, 11.90.

*4.1.5. Compound **4$_a$***

Yellow crystals in 74.6% yield, mp 184–186 °C (DMF); MS: *m*/*e* 558 (M^+, 22.40), IR: 3381 cm^{-1} (NH), 2936 cm^{-1} (CH aliphatic), 1686 cm^{-1} (C=O) and 1629 (C=N). ^1H NMR (DMSO, 300 MHz) δ 9.88 (s, 1H, CHO), 8.63 (s, 1H, N=CH), 8.32 (s, 1H, NH), 8.15–6.93 (m, 17H, 4Ar-H), 6.93 (s, 1H, CH hetero), 4.48–4.18 (d, 4H, $2CH_2$), 3.83 (s, 2H, CH_2), 3.31 (s, 3H, OCH_3). Anal. Calcd for $C_{34}H_{30}N_4O_4$: C, 73.10; H, 5.41; N, 10.03. Found: C, 72.82; H, 5.25; N, 10.10.

*4.1.6. Compound **4$_b$***

Yellow crystals in 69% yield, mp 202–204 °C (DMF); MS: *m*/*e* 572 (M^+, 2.76), IR: 3333 cm^{-1} (NH), 2927 cm^{-1} (CH aliphatic), 1686 cm^{-1} (C=O) and 1628 cm^{-1} (C=N). Anal. Calcd for $C_{35}H_{32}N_4O_4$: C, 73.41; H, 5.63; N, 9.78. Found: C, 73.57; H, 5.64; N, 9.77.

*4.1.7. Compound **4$_c$***

Yellow crystals in 69% yield, mp 208–210 °C (DMF); MS: *m*/*e* 594 ($M^+ + 1$, 3.71), 593 (M^+, 5.20), IR: 3376 cm^{-1} (NH), 2927 cm^{-1} (CH aliphatic), 1685 cm^{-1} (C=O) and 1627 cm^{-1} (C=N). Anal. Calcd for $C_{34}H_{29}N_4O_4$ Cl: C, 68.86; H, 4.93; N, 9.45; Cl, 5.98; Found: C, 68.62; H, 4.26; N, 9.46; Cl, 5.80.

Table 1
Antimicrobial screening results of the tested compounds.

Compound	Inhibition zone diameter (mm/mg sample)			
	Staphylococcus aureus	*Streptococcus faecalis*	*Escherichia coli*	*Pseudomonas aeruginosa*
2$_d$	12	12	12	13
3$_d$	14	13	15	12
4$_a$	14	12	12	13
5$_c$	12	12	13	13
5$_d$	10	10	11	10
6$_a$	14	13	12	14
7$_c$	12	12	12	12
8$_c$	16	17	16	15
8$_d$	12	12	12	11
9$_d$	16	15	15	14
10$_b$	13	13	13	12
11$_d$	13	14	14	13
12$_a$	16	16	15	15
13$_a$	13	13	12	12
14$_a$	13	13	12	13
15$_d$	18	17	16	17
16$_d$	13	13	13	13
17$_b$	14	13	13	14
Tetracycline	20	26	22	24

4.1.8. Compound ***4d***

Yellow crystals in 66% yield, mp 214–216 °C (DMF); MS: *m/e* 589($M^+ + 1$, 1.63), 588 (M^+, 4.02), IR: 3381 cm^{-1} (NH), 2930 cm^{-1} (CH aliphatic), 1683 cm^{-1} (C=O) and 1630 cm^{-1} (C=N). ^1H NMR (DMSO, 300 MHz) δ 9.88 (s, 1H, CHO), 8.30 (s, 1H, N=CH), 7.95 (s, 1H, NH), 7.95–7.02 (m, 16H, 4Ar-H), 6.91 (s, 1H, CH hetero), 4.47–4.17 (d, 4H, $2CH_2$), 3.79 (s, 2H, CH_2), 3.36–3.23 (s, 6H, 2° CH_3). Anal. Calcd for $C_{35}H_{32}N_4O_5$: C, 71.41; H, 5.48; N, 9.52. Found: C, 71.14; H, 5.54; N, 9.59.

4.1.9. Compound ***5a***

Yellow crystals in 70% yield, mp 206–208 °C (DMF); MS: *m/e* 618 (M^+, 6.19), IR: 3198 cm^{-1} (NH), 2930 cm^{-1} (CH aliphatic), 1683 cm^{-1} (C=O) and 1597 cm^{-1}(C=N). ^1H NMR (DMSO, 300 MHz) δ 9.86 (s, 1H, CHO), 8.29 (s, 1H, N=CH), 7.68 (s,1H, NH), 7.58–6.92 (m, 15H, 4Ar-H), 6.90 (s, 1H, CH hetero), 4.48–4.37 (d, 4H, $2CH_2$), 3.82 (s, 2H, CH_2), 3.84–3.82 (s, 6H, 2° CH_3), 3.37–3.24 (s, 3H, OCH_3). Anal. Calcd for $C_{36}H_{34}N_4O_6$: C, 69.89; H, 5.54; N, 9.06. Found: C, 70.34; H, 5.46; N, 9.21.

4.1.10. Compound ***5b***

Yellow crystals in 90% yield, mp 190–192 °C (DMF); MS: *m/e* 633 ($M^+ + 1$, 0.59), 632 (M^+, 1.47), IR: 3395 cm^{-1} (NH), 2926 cm^{-1} (CH aliphatic), 1680 cm^{-1} (C=O) and 1628 cm^{-1} (C=N). Anal. Calcd for $C_{37}H_{36}N_4O_6$: C, 70.24; H, 5.74; N, 8.86. Found: C, 69.58; H, 5.94; N, 8.56.

4.1.11. Compound ***5c***

Yellow crystals in 80% yield, mp 196–198 °C (DMF); MS: *m/e* 652.5 (M^+, 1.42), IR: 3199 cm^{-1} (NH), 2933 cm^{-1} (CH aliphatic), 1683 cm^{-1} (C=O) and 1596 cm^{-1} (C=N). ^1H NMR (DMSO, 300 MHz) δ 9.86 (s, 1H, CHO), 8.65 (s, 1H, N=CH), 8.30 (s, 1H, NH), 7.85–6.96 (m, 14H, 4Ar-H), 6.94 (s, 1H, CH hetero), 4.47–4.37 (d, 4H, $2CH_2$), 3.88 (s, 2H, CH_2), 3.84–3.80 (s, 6H, 2° CH_3), 3.37–3.30 (s, 3H, OCH_3). Anal. Calcd for $C_{36}H_{33}N_4O_6Cl$: C, 66.20; H, 5.09; N, 8.58; Cl, 5.43. Found: C, 66.10; H, 4.90; N, 8.59; Cl, 5.53.

4.1.12. Compound ***5d***

Yellow crystals in 60% yield, mp 215–217 °C (DMF); MS: *m/e* 649 (M^+, 10.38), IR: 3388 cm^{-1} (NH), 2936 cm^{-1} (CH aliphatic), 1679 cm^{-1} (C=O) and 1629 cm^{-1} (C=N). ^1H NMR (DMSO, 300 MHz) δ 9.80 (s, 1H, CHO), 8.30 (s, 1H, N=CH), 7.87 (s, 1H, NH), 7.62–6.99 (m, 14H, 4Ar-H), 6.91 (s, 1H, CH hetero), 4.37 (d, 4H, $2CH_2$), 3.89 (s, 2H, CH_2), 3.84–3.82 (s, 6H, 2° CH_3), 3.31 (s, 6H, 2° CH_3). Anal. Calcd for $C_{37}H_{36}N_4O_7$: C, 68.51; H, 5.59; N, 8.64. Found: C, 68.30; H, 5.18; N, 8.86.

4.1.13. Compound ***6d***

Yellow crystals in 68% yield, mp 204–206 °C (DMF); MS: *m/e* 710 ($M^+ + 2$, 0.49), 708 (M^+, 0.59), IR: 3181 cm^{-1} (NH), 2934 cm^{-1} (CH aliphatic), 1688 cm^{-1} (C=O) and 1583 cm^{-1} (C=N). ^1H NMR (DMSO, 300 MHz) δ 9.80 (s, 1H, CHO), 8.29 (s, 1H, N=CH), 7.63 (s, 1H, NH), 7.60–6.95 (m, 12H, 4Ar-H), 6.92 (s, 1H, CH hetero), 4.18–4.15 (d, 4H, $2CH_2$), 3.84 (s, 2H, CH_2), 3.86–3.79 (s, 12H, 4° CH_3), 3.78–3.30 (s, 6H, 2° CH_3). Anal. Calcd for $C_{39}H_{40}N_4O_9$: C, 66.09; H, 5.69; N, 7.90. Found: C, 67.25; H, 5.50; N, 8.26.

*4.1.14. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2*H*)-ylidene]-2-(penta-1-ylidene-2,3,4,5-tetraol) hydrazine (****8a****)*

Prepared from D-arabinose, yellow crystals in 80% yield, mp 187 °C (ethanol); MS: *m/e* 438 (M^+, 8.20), IR: broad band at 3382 cm^{-1} (OH, NH), 2930 cm^{-1} (CH aliphatic) and 1587 cm^{-1} (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.09 (s, 1H, N=CH), 7.84 (s,1H, NH), 7.48–6.94 (m, 9H, 2Ar-H), 6.91 (s, 1H, CH hetero), 4.52–4.15 (m, 3H, 3CH), 4.05–3.91 (d, 4H, $2CH_2$), 3.83 (s, 3H, OCH_3) and 3.82–3.73 (s, 4H, OH) . Anal. Calcd for $C_{23}H_{26}N_4O_5$: C, 63.00; H, 5.98; N, 12.78. Found: C, 63.02; H, 6.17; N, 12.48.

*4.1.15. 1-[4-(2-Methoxybenzyl)-6-methylphenyl pyridazin-3(2*H*)-ylidene]-2-(penta-1-ylidene-2,3,4,5-tetraol) hydrazine (****8b****)*

Prepared from D-arabinose, yellow crystals in 80% yield, mp 196–198 °C (ethanol); MS: *m/e* 423 ($M^+ - 29$, 1.29), 419 (77.23), 359 (48.64), 299 (100), 239 (18.45), 199 (14.05), 182 (29.21), 116 (18.23), 91 (19.03), IR: broad band at 3341 cm^{-1} (OH, NH), 2923 cm^{-1} (CH aliphatic) and 1603 cm^{-1} (C=N). Anal. Calcd for $C_{24}H_{28}N_4O_5$: C, 63.70; H, 6.24; N, 12.38. Found: C, 63.40; H, 6.30; N, 12.19.

*4.1.16. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2*H*)-ylidene]-2-(penta-1-ylidene-2,3,4,5-tetraol) hydrazine (****8c****)*

Prepared from D-arabinose, yellow crystals in 76% yield, mp 98–100 °C (ethanol); MS: *m/e* 442 ($M^+ - 30$, 4.65), 439 (48.28), 379 (10.29), 319 (100), 294 (21.41), 219 (23.04), 182 (55.16), 128 (19.94), 91 (42.30), IR: broad band at 3377 cm^{-1} (OH, NH), 2926 cm^{-1} (CH aliphatic) and 1580 cm^{-1} (C=N). Anal. Calcd for $C_{23}H_{25}N_4O_5Cl$: C, 58.41; H, 5.33; N, 11.85; Cl, 7.50. Found: C, 58.21; H, 5.44; N, 11.80; Cl, 7.57.

*4.1.17. 1-[4-(2-Methoxybenzyl)-6-methoxyphenyl pyridazin-3(2*H*)-ylidene]-2-(penta-1-ylidene-2,3,4,5-tetraol) hydrazine (****8d****)*

Prepared from D-arabinose, yellow crystals in 92% yield, mp 178–180 °C (ethanol); MS: *m/e* 467 ($M^+ - 1$, 1.18), IR: broad band at 3318 cm^{-1} (OH, NH), 2936 (CH aliphatic) and 1602 (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.09 (s, 1H, N=CH), 7.80 (s, 1H, NH), 7.76–6.93 (m, 8H, 2Ar-H), 6.91 (s, 1H, CH hetero), 4.50–4.46 (m, 3H, 3CH), 3.99–3.91 (d, 4H, $2CH_2$), 3.89–3.86 (s, 6H, 2° CH_3) and 3.83–3.80 (s, 4H, OH). Anal. Calcd for $C_{24}H_{28}N_4O_6$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.20; H, 5.62; N, 11.66.

*4.1.18. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2*H*)-ylidene]-2-(hexan-1-ylidene-2,3,4,5,6-pentaol) hydrazine (****9a****)*

Prepared from D-glucose, yellow crystals in 60% yield, mp 152–154 °C (ethanol); MS: *m/e* 462 ($M^+ - 6$, 1.11), 405 (78.65), 345 (31.26), 285 (100), 210 (10.36), 182 (20.29), 115 (5.12), 77 (20.59), IR: broad band at 3465 cm^{-1} (OH), 3284 cm^{-1} (NH), 2910 cm^{-1} (CH aliphatic) and 1600 cm^{-1} (C=N). Anal. Calcd for $C_{24}H_{28}N_4O_6$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.31; H, 6.04; N, 11.67.

*4.1.19. 1-[4-(2-Methoxybenzyl)-6-methyl phenyl pyridazin-3(2*H*)-ylidene]-2-(hexan-1-ylidene-2,3,4,5,6-pentaol) hydrazine (****9b****)*

Prepared from D-glucose, yellow crystals in 90% yield, mp 130–132 °C (ethanol); MS: *m/e* 480 ($M^+ - 2$, 1.06), IR: broad band at 3276 cm^{-1} (OH, NH), 2915 cm^{-1} (CH aliphatic) and 1602 cm^{-1} (C=N). Anal. Calcd for $C_{25}H_{30}N_4O_6$: C, 62.23; H, 6.27; N, 11.61. Found: C, 61.96; H, 5.80; N, 11.92.

*4.1.20. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2*H*)-ylidene]-2-(hexan-1-ylidene-2,3,4,5,6-pentaol) hydrazine (****9c****)*

Prepared from D-glucose, yellow crystals in 80% yield, mp 108–110 °C (ethanol); MS: *m/e* 494 ($M^+ - 8$, 2.94), 451 (8.15), 417 (7,25), 333 (12.80), 319 (100), 244 (5.80), 182 (24.35), 115 (15.97), 75 (18.91), IR: broad band at 3391 cm^{-1} (OH), 3323 cm^{-1} (NH), 2924 cm^{-1} (CH aliphatic) and 1626 cm^{-1} (C=N). Anal. Calcd for $C_{24}H_{27}N_4O_6Cl$: C, 57.31; H, 5.41; N, 11.14; Cl, 7.05. Found: C, 57.17; H, 5.30; N, 11.15; Cl, 7.13.

*4.1.21. 1-[4-(2-Methoxybenzyl)-6-methoxyphenyl pyridazin-3(2*H*)-ylidene]-2-(hexan-1-ylidene-2,3,4,5,6-pentaol) hydrazine (****9d****)*

Prepared from D-glucose, yellow crystals in 94% yield, mp 138–140 °C (ethanol); MS: *m/e* 490 ($M^+ - 8$, 2.24), 447 (29.38), 387 (7.38), 345 (11.26), 315 (100), 240 (11.71), 182 (42.38), 135 (6.83), 97 (9.75), IR: broad band at 3386 cm^{-1} (OH), 3298 cm^{-1} (NH), 2930 cm^{-1} (CH aliphatic) and 1607 cm^{-1} (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.09 (s, 1H, N=CH), 7.89 (s, 1H, NH), 7.58–6.73 (m, 8H, 2Ar-H), 6.64 (s, 1H, CH hetero), 4.50–4.08 (m, 4H, 4CH), 4.00–3.88

(d, 4H, $2CH_2$), 3.87–3.80 (s, 6H, 2° CH_3) and 3.76–3.60 (s, 4H, OH). Anal. Calcd for $C_{25}H_{30}N_4O_7$: C, 60.23; H, 6.07; N, 11.24. Found: C, 60.06; H, 6.03; N, 11.14.

*4.1.22. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(1-phenylethylidene) hydrazine (**13a**)*

Prepared from acetophenone, yellow crystals in 96% yield, mp 174 °C (ethanol); MS: *m/e* 410 ($M^+ + 2$, 1.14), 409 ($M^+ + 1$, 6.05), 408 (M^+, 19.07), IR: 3356 cm^{-1} (NH), 2920 cm^{-1} (CH aliphatic) and 1628 cm^{-1} (C═N); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.89 (s, 1H, NH), 7.87–6.93 (m, 14H, 3Ar-H), 6.87 (s, 1H, CH hetero), 4.03 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3) and 2.56 (s, 3H, CH_3). Anal. Calcd for $C_{26}H_{24}N_4O$: C, 76.45; H, 5.92; N, 13.72. Found: C, 76.39; H, 5.81; N, 13.75.

*4.1.23. 1-[4-(2-Methoxybenzyl)-6-methylphenyl pyridazin-3(2H)-ylidene]-2-(1-phenylethylidene) hydrazine (**13b**)*

Prepared from acetophenone, yellow crystals in 98% yield, mp 156 °C (ethanol); MS: *m/e* 424 ($M^+ + 2$, 1.18), 423 ($M^+ + 1$, 6.18), 422 (M^+, 13.49), IR: 3363 cm^{-1} (NH), 2916 cm^{-1} (CH aliphatic) and 1625 (C═N); Anal. Calcd for $C_{27}H_{26}N_4O$: C, 76.75; H, 6.20; N, 13.26. Found: C, 76.80; H, 5.97; N, 13.21.

*4.1.24. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(1-phenylethylidene) hydrazine (**13c**)*

Prepared from acetophenone, yellow crystals in 92% yield, mp 158–159 °C (ethanol); MS: *m/e* 445 ($M^+ + 2$, 1.11), 444 ($M^+ + 1$, 3.16), 443 (M^+, 3.09), IR: 3370 cm^{-1} (NH), 2926 cm^{-1} (CH aliphatic) and 1628 cm^{-1} (C═N); Anal. Calcd for $C_{26}H_{23}N_4OCl$: C, 70.50; H, 5.23; N, 12.65; Cl, 8.00. Found: C, 70.35; H, 5.35; N, 12.65; Cl, 8.11.

*4.1.25. 1-[4-(2-Methoxybenzyl)-6-methoxyphenyl pyridazin-3(2H)-ylidene]-2-(1-phenylethylidene) hydrazine (**13d**)*

Prepared from acetophenone, yellow crystals in 86% yield, mp 109–110 °C (ethanol); MS: *m/e* 440 (M^+, 1.04), IR: 3358 cm^{-1} (NH), 2932 cm^{-1} (CH aliphatic) and 1628 cm^{-1} (C═N); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (s, 1H, NH), 7.85–6.93 (m, 13H, 3Ar-H), 6.93 (s, 1H, CH hetero), 4.05 (s, 2H, CH_2), 3.90–3.77 (s, 6H, 2° CH_3) and 2.55 (s, 3H, CH_3). Anal. Calcd for $C_{27}H_{26}N_4O_2$: C, 73.95; H, 5.98; N, 12.78. Found: C, 73.71; H, 5.83; N, 12.75.

*4.1.26. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(diphenylmethyl) hydrazine (**14a**)*

Prepared from benzophenone, yellow crystals in 90% yield, mp 137–138 °C (ethanol); MS: *m/e* 471 ($M^+ + 1$, 28.95), 470 (M^+, 81.58), IR: 3282 cm^{-1} (NH) and 1631 cm^{-1} (C═N); ^1H NMR ($CDCl_3$) 7.79–7.77 (s, 1H, NH), 7.53–6.86 (m, 19H, 4Ar-H), 6.83 (s, 1H, CH hetero), 4.06 (s, 2H, CH_2) and 3.72 (s, 3H, OCH_3). Anal. Calcd for $C_{31}H_{26}N_4O$: C, 79.12; H, 5.56; N, 11.91. Found: C, 79.05; H, 5.56; N, 11.92.

*4.1.27. 1-[4-(2-Methoxybenzyl)-6-methylphenyl pyridazin-3(2H)-ylidene]-2-(diphenylmethyl) hydrazine (**14b**)*

Prepared from benzophenone, yellow crystals in 94% yield, mp 133–134 °C (ethanol); MS: *m/e* 486 ($M^+ + 2$, 1.40), 485 ($M^+ + 1$, 7.23), 484 (M^+, 16.30), IR: 3369 cm^{-1} (NH) and 1626 cm^{-1} (C═N). Anal. Calcd for $C_{32}H_{28}N_4O$: C, 79.31; H, 5.82; N, 11.56. Found: C, 79.01; H, 5. 61; N, 11.35.

*4.1.28. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(diphenylmethyl) hydrazine (**14c**)*

Prepared from benzophenone, yellow crystals in 94% yield, mp 134–135 °C (ethanol); MS: *m/e* 507 ($M^+ + 2$, 1.87), 506 ($M^+ + 1$, 4.19), 505 (M^+, 4.47), IR: 3369 cm^{-1} (NH) and 1623 cm^{-1} (C═N). Anal. Calcd for $C_{31}H_{25}N_4OCl$: C, 73.73; H, 4.99; N, 11.09; Cl, 7.02. Found: C, 73.80; H, 5.93; N, 11.08; 7.25.

*4.1.29. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(diphenylmethyl) hydrazine (**14d**)*

Prepared from benzophenone, yellow crystals in 92% yield, mp 117–118 °C (ethanol); MS: *m/e* 502 ($M^+ + 2$, 1.43), 501 ($M^+ + 1$, 8.52), 500 (M^+, 22.56), IR: 3376 cm^{-1} (NH) and 1627 cm^{-1} (C═N); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.25 (s,1H, NH), 7.83–6.90 (m, 18H, 4Ar-H), 6.87 (s, 1H, CH hetero), 4.20 (s, 2H, CH_2) and 3.87–3.76 (s, 6H, 2° CH_3). Anal. Calcd for $C_{32}H_{28}N_4O_2$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.60; H, 5.89; N, 11.19.

*4.2. General procedure for the preparation of hydrazones from 1-[4-(2-methoxybenzyl)-6-aryl pyridazin-3(2H)-ylidene] hydrazines (**1a,c,d**) and acetone*

A solution of compounds **1a–d** (1 mmol) in acetone (5 ml) was refluxed for 5 h. The separated solid product was filtered off and crystallized from an appropriate solvent.

*4.2.1. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(propan-2-ylidene) hydrazine (**12a**)*

Prepared from acetone, yellow crystals in 40% yield, mp 96 °C (ethanol); MS: *m/e* 347 ($M^+ + 1$, 4.59), 346 (M^+, 18.34), IR: 3282 cm^{-1} (NH), 2907 cm^{-1} (CH aliphatic) and 1637 cm^{-1} (C═N); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H, NH), 7.65–6.94 (m, 8H, 2Ar-H), 6.92 (s, 1H, CH hetero), 3.95 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3) and 2.17–2.08 (s, 6H, $2CH_3$). Anal. Calcd for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 73.01; H, 6.25; N, 15.96.

*4.2.2. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(propan-2-ylidene) hydrazine (**12c**)*

Prepared from acetone, yellow crystals in 40% yield, mp 93–94 °C (ethanol); MS: *m/e* 383 ($M^+ + 3$, 1.23), 382 ($M^+ + 2$, 6.18), 381 (M^+, 5.08), IR: 3347 cm^{-1} (NH), 2905 cm^{-1} (CH aliphatic) and 1631 cm^{-1} (C═N). Anal. Calcd for $C_{21}H_{21}N_4OCl$: C, 66.22; H, 5.56; N, 14.71; 9.31. Found: C, 66.01; H, 5.79; N, 14.73; 9.34.

*4.2.3. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(propan-2-ylidene) hydrazine (**12d**)*

Prepared from acetone, yellow crystals in 30% yield, mp 81–82 °C (ethanol); MS: *m/e* 377 ($M^+ + 1$, 7.13), 376 (M^+, 18.30), IR: 3422 cm^{-1} (NH), 2927 cm^{-1} (CH aliphatic) and 1630 cm^{-1} (C═N); Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.43. Found: C, 70.14; H, 6.22.

*4.3. General procedure for the preparation of compounds **3a–d**, **10a–d** and **11a–d***

Refluxing of **2a–d** and/or **10a–d** and/or **11a–d** (1 mmol) in a mixture of (10 ml) acetic anhydride and (0.3 ml) pyridine for 10 h. The reaction solution was concentrated under reduced pressure and left to cool. The separated solid product was filtered off and crystallized from an appropriate solvent.

*4.3.1. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(3-methoxy-4-O-acetylbenzylidene) hydrazine (**3a**)*

Dark brown crystals in 85.33% yield, mp 190 °C (benzene); MS: *m/e* 481 (M^+, 0.87), IR: 3421 cm^{-1} (NH), 2935 cm^{-1} (CH aliphatic), 1767 cm^{-1} (C═O) and 1603 cm^{-1} (C═N); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H, N═CH), 8.27 (s, 1H, NH), 7.89–6.97 (m, 12H, 3Ar-H), 6.94 (s, 1H, CH hetero), 4.56 (s, 2H, CH_2), 3.98–3.82 (s, 6H, 2° CH_3) and 2.85 (s, 3H,$COCH_3$). Anal. Calcd for $C_{28}H_{26}N_4O_4$: C, 69.70; H, 5.43; N, 11.61. Found: C, 69.29; H, 5.12; N, 11.24.

*4.3.2. 1-[4-(2-Methoxybenzyl)-6-methyl phenyl pyridazin-3(2H)-ylidene]-2-(3-methoxy-4-O-acetylbenzylidene) hydrazine (**3b**)*

Dark brown crystals in 89.56% yield, mp 154–156 °C (benzene); MS: *m/e* 496 (M^+, 0.45), IR: 3421 cm^{-1} (NH), 2940 cm^{-1} (CH aliphatic), 1762 cm^{-1} (C=O) and 1603 cm^{-1} (C=N). Anal. Calcd for $C_{29}H_{28}N_4O_4$: C, 70.15; H, 5.68; N, 11.28. Found: C, 69.89; H, 5.83; N, 11.09.

*4.3.3. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(3-methoxy-4-O-acetylbenzylidene) hydrazine (**3c**)*

Dark brown crystals in 80% yield, mp 130–132 °C (benzene); MS: *m/e* 516.5 (M^+, 1.01), IR: 3445 cm^{-1} (NH), 2938 cm^{-1} (CH aliphatic), 1762 cm^{-1} (C=O) and 1598 cm^{-1} (C=N). Anal. Calcd for $C_{28}H_{25}N_4O_4Cl$: C, 65.05; H, 4.87; Cl, 6.86. Found: C, 64.61; H, 5.09; Cl, 6.94.

*4.3.4. 1-[4-(2-Methoxybenzyl)-6-methoxyphenyl pyridazin-3(2H)-ylidene]-2-(3-methoxy-4-O-acetylbenzylidene) hydrazine (**3d**)*

Dark brown crystals in 55% yield, mp 82–84 °C (benzene); MS: *m/e* 480 ($M^+ - 32$, 1.24), 479 (3.73), 437 (3.73), 329 (100), 313 (5.15), 254 (7.38), 196 (42.14), 153 (3.73), 77 (6.89), 63 (4.92), 52 (5.64), IR: 3418 cm^{-1} (NH), 2933 cm^{-1} (CH aliphatic), 1766 cm^{-1} (C=O) and 1604 cm^{-1} (C=N); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1H, N=CH), 8.26 (s,1H, NH), 7.85–6.96 (m, 11H, 3Ar-H), 6.94 (s, 1H, CH hetero), 4.54 (s, 2H, CH_2), 3.98–3.82 (s, 9H, 3° CH_3) and 2.85 (s, 3H, $COCH_3$). Anal. Calcd for $C_{29}H_{28}N_4O_5$: C, 67.96; H, 5.51; N, 10.93. Found: C, 67.67; H, 5.90; N, 10.49.

*4.3.5. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(penta-1-ylidene-2,3,4,5-tetra-O-acetyl) hydrazine (**10a**)*

Dark brown crystals in 35% yield, mp 90–92 °C (benzene); MS: *m/e* 576 ($M^+ - 30$, 6.56), 573 (100), 551 (12.28), 501 (17.34), 383 (9.46), 313 (54.36), 239 (32.37), 129 (51.29), 57 (76.51), IR: 3418 cm^{-1} (NH), 2928 cm^{-1} (CH aliphatic), 1750 cm^{-1} (C=O) and 1601 cm^{-1} (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.09 (s, 1H, N=CH), 7.86 (s, 1H, NH), 7.84–6.93 (m, 9H, 2Ar-H), 6.82 (s, 1H, CH hetero), 5.90–5.44 (m, 3H, 3CH), 4.48–4.24 (d, 4H, $2CH_2$), 3.82 (s, 3H, OCH_3) and 2.19–2.00 (s, 12H, $4COCH_3$). Anal. Calcd for $C_{31}H_{34}N_4O_9$: C, 61.38; H, 5.65; N, 9.24. Found: C, 61.96; H, 5.67; N, 8.96.

*4.3.6. 1-[4-(2-Methoxybenzyl)-6-methyl phenyl pyridazin-3(2H)-ylidene]-2-(penta-1-ylidene-2,3,4,5-tetra-O-acetyl) hydrazine (**10b**)*

Dark brown crystals in 32.67% yield, mp 86–88 °C (benzene); MS: *m/e* 619 ($M^+ - 1$, 0.25), IR: 3421 cm^{-1} (NH), 2927 cm^{-1} (CH aliphatic), 1751 cm^{-1} (C=O) and 1604 cm^{-1} (C=N). Anal. Calcd for $C_{32}H_{36}N_4O_9$: C, 61.93; H, 5.85; N, 9.03. Found: C, 62.24; H, 5.44; N, 8.66.

*4.3.7. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(penta-1-ylidene-2,3,4,5-tetra-O-acetyl) hydrazine (**10c**)*

Dark brown crystals in 30% yield, mp 56–58 °C (benzene); MS: *m/e* 609 ($M^+ - 32$, 9.88), 333 (72.70), 320 (15.17), 196 (25.02), 129 (51.15), 73 (100), IR: 3449 cm^{-1} (NH), 2930 cm^{-1} (CH aliphatic), 1752 cm^{-1} (C=O) and 1598 cm^{-1} (C=N). Anal. Calcd for $C_{31}H_{33}N_4O_9Cl$: C, 58.08; H, 5.19; N, 8.74; Cl, 5.53. Found: C, 58.30; H, 5.06; N, 8.71; Cl, 5.54.

*4.3.8. 1-[4-(2-Methoxybenzyl)-6-methoxyphenyl pyridazin-3(2H)-ylidene]-2-(penta-1-ylidene-2,3,4,5-tetra-O-acetyl) hydrazine (**10d**)*

Dark brown crystals in 53% yield, mp 64–66 °C (benzene); MS: *m/e* 605 ($M^+ - 31$, 5.49), 531 (6.50), 459 (4.70), 343 (16.37), 315 (100), 240 (15.36), 182 (45.48), 79 (31.52), IR: 3424 cm^{-1} (NH), 2933 cm^{-1} (CH aliphatic), 1751 cm^{-1} (C=O) and 1604 cm^{-1} (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.09 (s, 1H, N=CH), 7.84 (s,1H, NH), 7.81–6.93 (m, 8H, 2Ar-H), 6.82 (s, 1H, CH hetero), 5.94–5.44 (m, 3H, 3CH), 4.46–4.24 (d, 4H, $2CH_2$), 3.87–3.81 (s, 6H, 2° CH_3) and 2.18–2.00 (s, 12H, $4COCH_3$). Anal. Calcd for $C_{32}H_{36}N_4O_{10}$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.70; H, 5.88; N, 8.49.

*4.3.9. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(hexan-1-ylidene-2,3,4,5,6-penta-O-acetyl) hydrazine (**11a**)*

Dark brown crystals in 36.87% yield, mp 100–102 °C (benzene); MS: *m/e* 679 ($M^+ + 1$, 0.05), 678 (M^+, 0.10), IR: 3422 cm^{-1} (NH), 2928 cm^{-1} (CH aliphatic), 1751 cm^{-1} (C=O) and 1601 cm^{-1} (C=N). Anal. Calcd for $C_{34}H_{38}N_4O_{11}$: C, 60.17; H, 5.64; N, 8.26. Found: C, 60.50; H, 5.64; N, 7.89.

*4.3.10. 1-[4-(2-Methoxybenzyl)-6-methylphenyl pyridazin-3(2H)-ylidene]-2-(hexan-1-ylidene-2,3,4,5,6-penta-O-acetyl) hydrazine (**11b**)*

Dark brown crystals in 44.73% yield, mp 76–78 °C (benzene); MS: *m/e* 692 (M^+, 0.24), IR: 3422 cm^{-1} (NH), 2927 cm^{-1} (CH aliphatic), 1753 cm^{-1} (C=O) and 1603 cm^{-1} (C=N). Anal. Calcd for $C_{35}H_{40}N_4O_{11}$: N, 8.09. Found: N, 7.85.

*4.3.11. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(hexan-1-ylidene-2,3,4,5,6-penta-O-acetyl) hydrazine (**11c**)*

Dark brown crystals in 37.50% yield, mp 86–88 °C (benzene); MS: *m/e* 715 ($M^+ + 2$, 0.16), 713(M^+, 0.16), IR: 3429 cm^{-1} (NH), 2929 cm^{-1} (CH aliphatic), 1753 cm^{-1} (C=O) and 1597 cm^{-1} (C=N). Anal. Calcd for $C_{34}H_{37}N_4O_{11}Cl$: C, 57.26; H, 5.23; N, 7.86; Cl, 4.97. Found: C, 56.89; H, 4.90; N, 7.87; Cl, 4.85.

*4.3.12. 1-[4-(2-Methoxybenzyl)-6-methoxy phenyl pyridazin-3(2H)-ylidene]-2-(hexan-1-ylidene-2,3,4,5,6-penta-O-acetyl) hydrazine (**11d**)*

Dark brown crystals in 38.60% yield, mp 90–92 °C (benzene); MS: *m/e* 675 ($M^+ - 28$, 3.00), 413 (5.16), 329 (100), 254 (6.78), 196 (37.38), 77 (8.47), IR: 3422 cm^{-1} (NH), 2932 cm^{-1} (CH aliphatic), 1752 cm^{-1} (C=O) and 1605 cm^{-1}(C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ 9.10 (s, 1H, N=CH), 7.82 (s, 1H, NH), 7.40–6.99 (m, 8H, 2Ar-H), 6.97 (s, 1H, CH hetero), 5.25–5.14 (m, 4H, 4CH), 4.48–4.13 (d, 4H, $2CH_2$), 3.86–3.81(s, 6H, 2° CH_3) and 2.28–1.87 (s, 15H, $5COCH_3$). Anal. Calcd for $C_{35}H_{40}N_4O_{12}$: N, 7.91. Found: N, 7.90.

*4.4. Reaction of hydrazone derivative **5c** with **1c***

The hydrazone derivatives (**5c**) (1 mmol) were heated above their melting points with **1c** (1 mmol) in a sand bath for 3 h. The product which solidified on cooling was triturated with pet. ether 40–60 °C, filtered off and crystallized from an appropriate solvent.

*4.4.1. Compound **7c***

Dark brown crystals in 45% yield, mp 214–216 °C (DMF); IR: 3395 cm^{-1} (NH), 2932 cm^{-1} (CH aliphatic) and 1594 cm^{-1} (C=N). Anal. Calcd for $C_{54}H_{48}N_8O_6Cl_2$: C, 66.46; H, 4.96; Cl, 7.27. Found: C, 66.70; H, 4.71; Cl, 7.03.

*4.5. General procedure for the preparation of hydrazones from 1-[4-(2-methoxybenzyl)-6-aryl pyridazin-3(2H)-ylidene] hydrazines (**1a–d**) and 2-benzoylbenzoic acid*

A solution of compounds **1a–d** (1 mmol) in glacial acetic acid (20 ml) was treated with 2-benzoylbenzoic acid (1 mmol) and freshly prepared anhydrous sod. acetate. The reaction mixture was refluxed for 8 h. The separated product was filtered off and crystallized from an appropriate solvent.

*4.5.1. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(2-carboxydiphenyl methyl) hydrazine (**15a**)*

Prepared from 2-benzoylbenzoic acid, pale brown crystals in 60% yield, mp 119–120 °C (benzene); MS: *m/e* 497 ($M^+ - 17$, 2.35), 405

(100), 361 (29.40), 299 (26.25), 258 (25.31), 202 (13.30), 130 (17.73), 77 (35.83), IR: 3401 cm^{-1} (OH), 3300 cm^{-1} (NH), 1662 cm^{-1} (C=O) and 1597 cm^{-1} (C=N); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 (s, 1H, OH), 8.11 (s,1H, NH), 7.85–6.95 (m, 18H, 4Ar-H), 6.93 (s, 1H, CH hetero), 4.46 (s, 2H, CH_2) and 3.81 (s, 3H, OCH_3). Anal. Calcd for $C_{32}H_{26}N_4O_3$: C, 74.69; H, 5.09; N, 10.89. Found: C, 74.11; H, 5.18; N, 10.92.

*4.5.2. 1-[4-(2-Methoxybenzyl)-6-methylphenyl pyridazin-3(2H)-ylidene]-2-(2-carboxydiphenyl methyl) hydrazine (**15b**)*

Prepared from 2-benzoylbenzoic acid, pale brown crystals in 80% yield, mp 122 °C (benzene); MS: *m/e* 511 ($M^+ - 17$, 1.39), 419 (27.50), 375 (100), 284 (6.06), 258 (11.19), 207 (9.88), 110 (10.94), 105 (15.84), IR: 3447 cm^{-1} (OH), 3203 cm^{-1}(NH), 1651 cm^{-1} (C=O) and 1604 cm^{-1} (C=N). Anal. Calcd for $C_{33}H_{28}N_4O_3$: C, 74. 98; H, 5.34; N, 10.60. Found: C, 74.67; H, 5.83; N, 10.41.

*4.5.3. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(2-carboxydiphenyl methyl) hydrazine (**15c**)*

Prepared from 2-benzoylbenzoic acid, pale brown crystals in 52% yield, mp 162–163 °C (benzene); MS: *m/e* 470 ($M^+ - 78.5$, 0.42), 439 (100), 395 (54.57), 264 (3.62), 284 (4.29), 258 (11.53), 189 (4.67), 111 (16.13), 91(18.31), IR: 3425 cm^{-1} (OH), 3316 cm^{-1} (NH), 1666 (C=O), 1595 (C=N). Anal. Calcd for $C_{32}H_{25}N_4O_3Cl$: C, 70.01; H, 4.59; N, 10.20; Cl, 6.46. Found: C, 69.90; H, 4.40; N, 10.22; 6.64.

*4.5.4. 1-[4-(2-Methoxybenzyl)-6-methoxyphenyl pyridazin-3(2H)-ylidene]-2-(2-carboxydiphenyl methyl) hydrazine (**15d**)*

Prepared from 2-benzoylbenzoic acid, pale brown crystals in 56% yield, mp 135–136 °C (benzene); MS: *m/e* 544 (M^+, 0.27), 443 (0.35), 402 (0.57), 329 (1.08), 263 (0.38), 182 (51.82), 149 (57.20), 105 (10), 77 (92.11), IR: 3401 cm^{-1} (OH), 3212 cm^{-1} (NH), 1718 cm^{-1} (C=O) and 1604 cm^{-1} (C=N); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.14 (s, 1H, OH), 8.11 (s, 1H, NH), 7.78–6.94 (m, 17H, 4Ar-H), 6.90 (s, 1H, CH hetero), 4.33 (s, 2H, CH_2) and 3.84–3.78 (s, 6H, 2° CH_3). Anal. Calcd for $C_{33}H_{28}N_4O_4$: C, 72.78; H, 5.18; N, 10.29. Found: C, 71.92; H, 4.94; N, 10.18.

*4.6. General procedure for the preparation of hydrazones from 1-[4-(2-methoxybenzyl)-6-aryl pyridazin-3(2H)-ylidene] hydrazines (**1a–d**) (1 mmol) and diacetyl*

Compounds **1_{a-d}** (1 mmol) in ethanol (20 ml) were treated with the corresponding ketones (1 mmol). The reaction mixtures were refluxed for 5 h. The product that separated during reflux was filtered off and crystallized from the appropriate solvent.

*4.6.1. 1-[4-(2-Methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(2-oxo-butan-3-ylidene) hydrazine (**16a**)*

Prepared from diacetyl, red crystals in 40% yield, mp 145–146 °C (benzene); MS: *m/e* 375 ($M^+ + 1$, 3.31), 374 (M^+, 13.73), 331 (100), 259 (39.68), 230 (14.84), 202 (10.51), 140 (10.20), 91 (19.32), 55 (14.99), IR: 3238 cm^{-1} (NH), 2922 cm^{-1} (CH aliphatic), 1660 cm^{-1} (C=O) and 1628 cm^{-1} (C=N); ^1H NMR (DMSO, 300 MHz) δ 7.97–7.95 (s, 1H, NH), 7.72–6.90 (m, 9H, 2Ar-H), 6.88 (s, 1H, CH hetero), 3.90 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3) and 3.33 (s, 6H, $2CH_3$). Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 69.78; H, 5.67; N, 15.02.

*4.6.2. 1-[4-(2-Methoxybenzyl)-6-methylphenyl pyridazin-3(2H)-ylidene]-2-(2-oxo-butan-3-ylidene) hydrazine (**16b**)*

Prepared from diacetyl, red crystals in 32% yield, mp 242 °C (benzene); MS: *m/e* 376 ($M^+ - 12$, 3.36), 339 (23.25), 313 (40.17), 274 (20.67), 213 (13.28), 199 (18.88), 129 (50.59), 97 (79.89), 93 (20.11), 77 (33.33), IR: 3369 cm^{-1} (NH), 2920 cm^{-1} (CH aliphatic), 1653 cm^{-1} (C=O) and 1625 cm^{-1} (C=N). Anal. Calcd for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23; N, 14.42. Found: C, 71.20; H, 6.20; N, 14.13.

*4.6.3. 1-[4-(2-Methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(2-oxo-butan-3-ylidene) hydrazine (**16c**)*

Prepared from diacetyl, red crystals in 50% yield, mp 237–238 °C (benzene); MS: *m/e* 407 ($M^+ - 1$, 5.83), IR: 3365 cm^{-1} (NH), 2921 cm^{-1} (CH aliphatic), 1675 cm^{-1} (C=O) and 1623 cm^{-1} (C=N); ^1H NMR (DMSO, 300 MHz) δ 8.01–7.98 (s,1H, NH), 7.74–6.91 (m, 8H, 2Ar-H), 6.89 (s, 1H, CH hetero), 3.89 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3) and 3.30 (s, 6H, $2CH_3$). Anal. Calcd for $C_{22}H_{21}N_4O_2Cl$: C, 64.62; H, 5.18; N, 13.70; Cl, 8.67. Found: C, 64.50; H, 5.00; N, 13.72; Cl, 8.67.

*4.6.4. 1-[4-(2-Methoxybenzyl)-6-methoxyphenyl pyridazin-3(2H)-ylidene]-2-(2-oxo-butan-3-ylidene) hydrazine (**16d**)*

Prepared from diacetyl, red crystals in 34% yield, mp 255–256 °C (benzene); MS: *m/e* 410 ($M^+ + 6$, 6.51), 368 (18.91), 313 (925.27), 236 (17.83), 201 (23.10), 155 (100), 127 (78.45), 57 (37.83), IR: 3379 cm^{-1} (NH), 2928 cm^{-1} (CH aliphatic), 1734 cm^{-1} (C=O) and 1625 cm^{-1} (C=N); ^1H NMR (DMSO, 300 MHz) δ 7.82–7.66 (s, 1H, NH), 7.69–6.91 (m, 8H, 2Ar-H), 6.89 (s, 1H, CH hetero), 3.97 (s, 2H, CH_2), 3.89–3.68 (s, 6H, 2° CH_3) and 3.30 (s, 6H, $2CH_3$). Anal. Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.40; H, 5.74; N, 14.89.

*4.7. Preparation of bis [1-[4-(2-methoxybenzyl)-6-aryl pyridazin-3(2H)-ylidene]-2-(butan-2,3-ylidene) hydrazines from **1a–d** and diacetyl*

Method A. Refluxing a mixture of **1_{a-c}** (1 mmol) and **16_{a-c}** (1 mmol) in glacial acetic acid (20 ml) for 8 h. The solution obtained was concentrated under reduced pressure. The solid product obtained was crystallized from an appropriate solvent.

Method B. Refluxing a mixture of **1_d** (2 mmol) and diacetyl (1 mmol) in glacial acetic acid 20 ml for 8 h. The solution obtained was concentrated under reduced pressure. The solid product obtained was crystallized from an appropriate solvent.

*4.7.1. Bis{1-[4-(2-methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(butan-2,3-ylidene)} hydrazine (**17a**)*

Prepared from **7_a**, pale brown crystals in 48.5% yield, mp 190 °C (pet .ether 40–60 °C); MS: *m/e* 665 ($M^+ + 3$, 2.49), 664 ($M^+ + 2$, 3.12), 663 ($M^+ + 1$, 3.12), IR: 3445 cm^{-1} (NH), 2941 cm^{-1} (CH aliphatic) and 1600 cm^{-1} (C=N); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.87–7.83 (s, 2H, 2NH), 7.50–6.97 (m, 18H, 4Ar-H), 6.96–6.93 (s, 2H, 2CH hetero), 4.52–4.50 (s, 4H, $2CH_2$), 3.82–3.80 (s, 6H, 2° CH_3) and 2.87–2.85 (s, 6H, $2CH_3$). Anal. Calcd for $C_{40}H_{38}N_8O_2$: C, 72.49; H, 5.78; N, 16.91. Found: C, 72.71; H, 5.60; N, 16.79.

*4.7.2. Bis{1-[4-(2-methoxybenzyl)-6-phenyl pyridazin-3(2H)-ylidene]-2-(butan-2,3-ylidene)} hydrazine (**17b**)*

Prepared from **7_b**, pale brown crystals in 74.7% yield, mp 80 °C (pet. ether 40–60 °C); MS: *m/e* 692 ($M^+ + 2$, 2.55), IR: 3444 cm^{-1} (NH), 2923 cm^{-1} (CH aliphatic) and 1605 cm^{-1} (C=N). Anal. Calcd for $C_{42}H_{42}N_8O_2$: N, 16.22. Found: N, 16.64.

*4.7.3. Bis{1-[4-(2-methoxybenzyl)-6-chlorophenyl pyridazin-3(2H)-ylidene]-2-(butan-2,3-ylidene)} hydrazine (**17c**)*

Prepared from **7_c**, pale brown crystals in 40% yield, mp 77–78 °C (pet. ether 40–60 °C); MS: *m/e* 704 ($M^+ - 27$, 4.26), 696 (4.79), 551 (45.74), 523 (25.00), 423 (17.02), 313 (100), 264 (58.51), 207 (25.00), 95 (82.98), IR: 3389 cm^{-1} (NH), 2933 cm^{-1} (CH aliphatic) and 1596 cm^{-1} (C=N). Anal. Calcd for $C_{40}H_{36}N_8O_2Cl_2$: N, 15.31; Cl, 9.69. Found: N, 15.98; Cl, 10.18.

*4.7.4. Bis{1-[4-(2-methoxybenzyl)-6-methoxyphenyl pyridazin-3(2H)-ylidene]-(butan-2,3-ylidene)} hydrazine (**17d**)*

Prepared from **1_d**, pale brown crystals in 20% yield, mp 136–137 °C (pet. ether 40–60 °C); MS: *m/e* 724 ($M^+ + 2$, 0.08), IR: 3380 cm^{-1} (NH), 2932 cm^{-1} (CH aliphatic) and 1604 cm^{-1} (C=N);

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82–7.79 (s, 2H, 2NH), 7.41–6.97 (m, 16H, 4Ar-H), 6.95–6.93 (s, 2H, 2CH hetero), 4.48–4.40 (s, 4H, $2CH_2$), 3.86–3.82 (s, 12H, 4° CH_3) and 2.85–2.80 (s, 6H, $2CH_3$). Anal. Calcd for $C_{42}H_{42}N_8O_4$: C, 69.79; H, 5. 86; N, 15.50. Found: C, 69.78; H, 5.77; N, 14.94.

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