Research on Chemical Intermediates
https://doi.org/10.1007/s11164-020-04175-y

Synthesis and antibacterial evaluation of diaminomaleonitrile-based azo-Schiff bases and 8,9-dihydro-7*H*-purine-6-carboxamides

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Received: 18 December 2019 / Accepted: 6 May 2020

Abstract

Some new DAMN-based Schiff base **6a**–**6g** were synthesized via a condensation reaction of the corresponding azo dyes with 1-(2-amino-1,2-dicyanovinyl)-3-phenylurea. In continuation, facile synthesis of new 8,9-dihydro-7*H*-purine-6-carboxamide **7a**–**7g** was reported via an efficient reaction of azo dyes and 1-(2-amino-1,2-dicyanovinyl)-3-phenylurea in the presence of triethylamine as catalyst. All the synthesized compounds were evaluated for their antibacterial activities against both Gram-positive (*Micrococcus luteus* and *Staphylococcus aureus*) and Gram-negative (*Pseudomonas aeruginosa* and *Escherichia coli*) bacteria.

Keywords Diaminomaleonitrile · Azo dye · Schiff base · Purine-6-carboxamides

Introduction

Diaminomaleonitrile (DAMN), a tetramer of hydrogen cyanide, was considered as one of the versatile precursors to nucleotides and has been extensively utilized in the synthesizing of a wide variety of heterocyclic compounds. Over the last decade, there has been a great deal of interest in DAMN and its derivatives as intermediates for heterocyclic synthesis, including pyrimidines [1], purines [2, 3], imidazoles [4],

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11164-020-04175-y) contains supplementary material, which is available to authorized users.

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Published online: 15 May 2020

pyrazines [5], porphyrazines [6] and diimines [7]. The reaction of DAMN with aromatic aldehydes is widely known to produce DAMN-based Schiff base [8–11].

Structurally, Schiff bases are nitrogen analogs of aldehyde- or ketone-like compounds in which the carbonyl group is replaced by an imine or azomethine group. Schiff bases are important as synthetic intermediates, and they are also used in the synthetic precursor of jet-printing inks, optically active materials, chemical sensors, aggregation-enhanced emission luminogen, fluorescent and in the thermostable optical material industry [12–15]. Schiff base ligands are easily synthesized and form complexes with almost all metal ions. Many Schiff base complexes show excellent catalytic activity, pharmaceutical and biologically activities such as anticancer, antimalarial, anti-influenza, antiviral, antioxidative and antimicrobial activities [16–21].

The DAMN derivatives in the past decades have been widely used in synthetic dye chemistry due to their impressive and useful physical and chemical properties [22, 23]. Since azomethine and azo groups are chemically stable, it has prompted immense study of DAMN-based azo materials as new chemical sensors, thermally stable and optically active materials [24, 25].

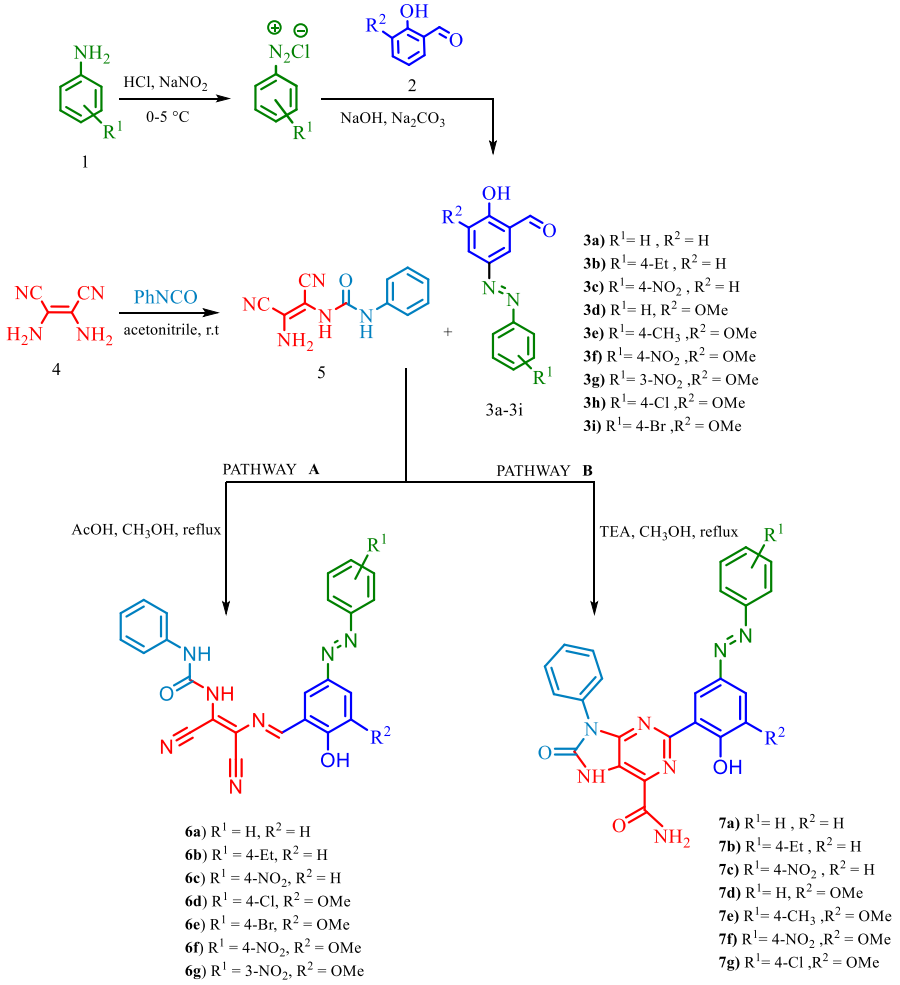
As mentioned before, DAMN is widely used as a precursor to the synthesis of heterocyclic compounds like pyrimido–pyrimidines and purines which are the most widely distributed nitrogen heterocycles in nature. Purine bases have a key role in the structure of the most important biomolecules: DNA, RNA, adenosine triphosphate (ATP), nicotinamide adenine dinucleotide (NAD), alkaloids, coenzyme, etc. Purine bases show a wide range of pharmaceutical and biological activity such as antiviral, antimycobacterial, anti-flavivirus, antioxidant and anticancer activity [26–32]. For this reasons, purines have been raised as promising structural units in the field of medicinal chemistry.

Previously, we reported versatile functionalized Schiff bases as the benzylidene hydrazides and sulfide connections to bind various transition metals and nanoparticles surfaces [12, 33]. In continuation of our previous works, in this work, first we synthesized a modified DAMN-based Schiff bases **6a**–**6g** (Scheme 1); then, in continuation of this research, we investigated the reaction between phenylurea **5** and azo dyes **(3a–3i)** in the presence of NEt_3 as a catalyst. A comprehensive investigation of the spectroscopic data including FT-IR, ^{1}H NMR, ^{13}CNMR and mass spectrometry indicated that the obtained products are 8,9-dihydro-7*H*-purine-6-carboxamide **7a**–**7g** (Scheme 1). In the end, all the synthesized compounds were evaluated for their antibacterial activities against both Gram-positive (*Micrococcus luteus* and *Staphylococcus aureus*) and Gram-negative (*Pseudomonas aeruginosa* and *Escherichia coli*) bacteria.

Results and discussion

Synthesis and spectral studies

Our approach involves an efficient method and convenient multi-component synthesis of DAMN-based Schiff bases (pathway A) and purine-6-carboxamides (pathway B) by the reaction of different azo dyes **3a**–**3i** and phenylurea **5** that catalyzed by



Scheme 1 Synthesis of diaminomaleonitrile-based Azo-Schiff bases **6a–6g** and azo-purine-6-carboxamides **7a–7g**

glacial-AcOH or NEt_3, respectively, in MeOH under reflux conditions. The reactions of DAMN with phenyl isocyanate proceeded as expected to give the phenylurea **5** in excellent yields. The azo-aldehyde dye precursors (**3a–3i**) separately were synthesized by the reaction of *o*-vanillin or salicylaldehyde with benzene diazonium chloride salts that in sequence made by diazotization of corresponding aniline derivatives (Scheme 1).

Initially, in order to optimize the reaction conditions, the reaction of azo dyes **3h** and 1-(2-amino-1,2-dicyanovinyl)-3-phenylurea **5** was selected as a typical reaction under the aspects of catalyst, temperature, solvent and reaction time. The conditions were optimized, and the results are shown in Table 1. Several solvents such as MeOH, EtOH, DMF, CH_2Cl_2, H_2O and CH_3CN at r.t. and reflux condition were

Table 1 Variation of reaction conditions for the synthesis of **6d**

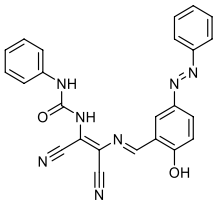
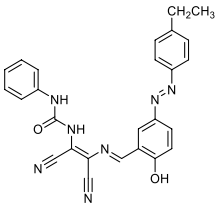
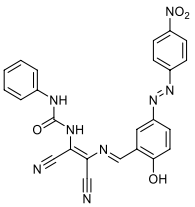
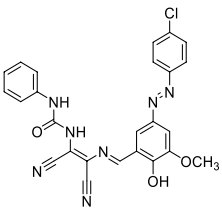
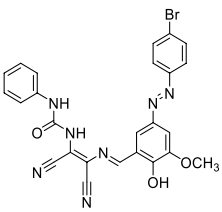
Entry	Catalyst	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	–	EtOH	r.t	180	20
2	Glacial-AcOH	EtOH	r.t	60	55
3	Glacial-AcOH	CH_3CN	r.t	60	25
4	Glacial-AcOH	CH_2Cl_2	r.t	60	10
5	Glacial-AcOH	H_2O	r.t	60	–
6	Glacial-AcOH	DMF	r.t	60	45
7	Glacial-AcOH	MeOH	r.t	60	64
8	Glacial-AcOH	EtOH	Reflux	60	79
9	Glacial-AcOH	CH_3CN	Reflux	60	78
10	Glacial-AcOH	CH_2Cl_2	Reflux	60	42
11	Glacial-AcOH	H_2O	Reflux	60	20
12	Glacial-AcOH	DMF	Reflux	60	77
13	Glacial-AcOH	MeOH	Reflux	60	80
14	Glacial-AcOH	EtOH	Reflux	20	79
15	Glacial-AcOH	CH_3CN	Reflux	20	78
16	Glacial-AcOH	DMF	Reflux	20	76
17	Glacial-AcOH	MeOH	Reflux	20	80

examined. As shown in Table 1, entry 1, in the absence of catalyst, this reaction was very slow, and only 20% of the desired product was isolated after 2 h. When this reaction was carried out over acid catalysts glacial-AcOH, the yield and rate of the reaction were increased (entry 2). The reaction efficiency in CH_3CN was 25% (entry 3). When the solvent was replaced by DMF or CH_3OH, the reaction yields decreased to 45% and 64%, respectively (Table 1, entries 6 and 7). In continuance, in order to further improve the efficiency of the reaction, the reaction was carried out at reflux condition. The results showed that the reaction efficiency in the MeOH as solvent is higher at both reflux and r.t. than the other solvents (Table 1, entries 7, 13 and 17). As a result, the presence of glacial-AcOH as the catalyst in MeOH at reflux condition for 20 min was found to be the best reaction conditions to give **6d** in an 80% yield (Table 1, entry 17). The precursors dissolve in H_2O in very small amounts, which is why low efficiency is seen in H_2O. The CH2Cl2 has the lowest polarity solvent, and the lowest yield was observed. Among the other solvents, MeOH and EtOH, which are protic solvents, show slightly higher yields.

After reaction optimization, all the DAMN-based Schiff bases **6a**–**6g** were synthesized using glacial-AcOH in MeOH at reflux temperature with high yields and simple product isolation. In most cases, upon addition of precursor **5** to a solution of azo dyes **(3a, b, c, f, g, h, i)** in optimized condition, after 5 min desired product was precipitated and purified by crystallization. The products were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The structure and physical properties are summarized in Table 2.

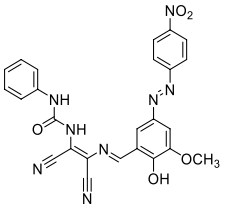
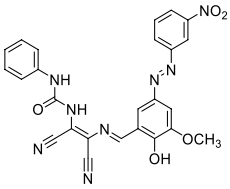
The characteristic FT-IR absorption bands of compounds were determined in KBr disk. The total absence of aldehyde C=O absorption band in the FT-IR

Table 2 Physical properties of DAMN-based Schiff bases **6a–6g**

Entry	Compounds	M.p. (°C)	λ_{max} (in DMSO)	Yield%	Color
6a		199–200	373	86	
6b		221–222	374	88	
6c		233–234	378	78	
6d		243–245	383	80	
6e		250	382	81	

spectra of **6a–6g** together with the appearance of new imine absorption bands, in the range of 1598–1605 cm^{-1}, clearly indicated that new Schiff base compound had formed in **6a–6g**. The NH stretching band of **6a–6g** was observed in the region of 3236–3344 cm^{-1} and a CN absorption bands of medium intensity at 2224–2226 cm^{-1}. The ^{1}H NMR spectra of **6a–6g** revealed an imine proton (CH=N) as singlet signal between 8.94 and 8.98 ppm. The OH and NH protons appeared

Table 2 (continued)

Entry	Compounds	M.p. (°C)	λ_{max} (in DMSO)	Yield%	Color
6f		225	387	75	
6g		223–224	385	74	

in the region of 11.15–11.94 and 9.72–9.81 ppm, respectively. Furthermore, aromatic protons and aliphatic protons were observed in the expected regions around 7.11–8.85 and 1.25–4.02 ppm, respectively. The ^{1}H NMR spectrum of **6a** showed two sets of signals in ^{1}H NMR with an approximate ratio of 71:29 (~2.5:1) due to the two possible stereoisomers (Fig. 1). Additional support for the structures of **6a**–**6g** was provided by ^{13}C NMR spectra, which provided the right number of carbons at the expected ppms. These results are in agreement with the proposed structures (see Experimental section).

Scheme 1 shows that in the presence of TEA as a catalyst (pathway B), the reaction proceeds from cyclocondensation, the precursors cyclized rapidly to 8,9-dihydro-7*H*-purine-6-carboxamide **7a**–**7g**. It seems practical to assume that a comparable cyclization may occur with the phenylurea derivative **5** in the presence of a base. The rapid 6e-cyclocondensation followed by oxidative cyclization in the presence of molecular oxygen from air led to the aromatic target compounds **7a**–**7g** [34]. The structure of products was characterized by FT-IR, NMR and mass spectrometry (see Table 3 and supporting data). The IR spectrum of compounds **7a**–**7g** revealed the presence of stretching OH absorption at 3429–3493 cm^{-1} and vibration for NH bands at 3233–3380 cm^{-1}. Furthermore, absorption bands in the 1662–1748 cm^{-1} region corresponding to C=O stretching bands and absorption bands in the 1584–1600 cm^{-1} region indicate the presence of C=N stretching bands. The absence of CN groups is consistent with cyclization. The NMR spectra of **7a**–**7g** were recorded in DMSO at 25 °C. The ^{1}H NMR spectra showed a singlet at δ 12.85–13.16 ppm (1H) due to the NH proton of the imidazol-2-one ring (Scheme 2) which is consistent with the literature reports in this regard (δ 9–13 ppm) [35, 36]. The OH proton appeared as a broad singlet signal at δ 11.97–12.09 ppm. The amide protons of 6-carboxamido group have different chemical shifts which is typical for the amide group in 8,9-dihydro-7*H*-purine-6-carboxamide. The amide protons

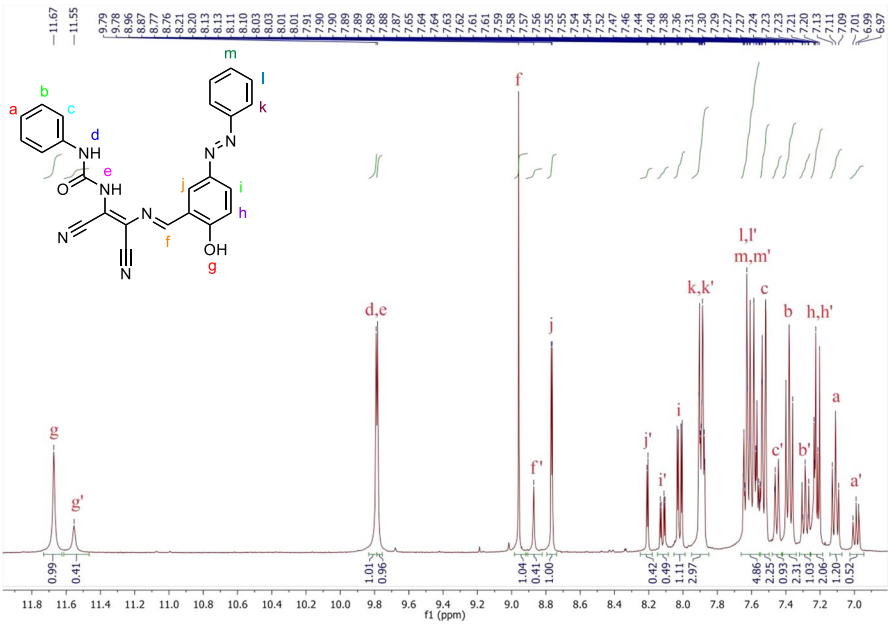


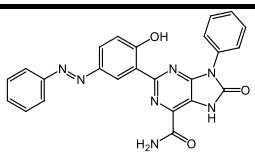
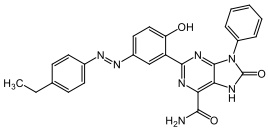
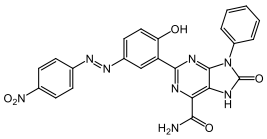
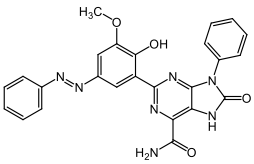
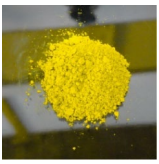
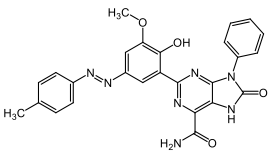
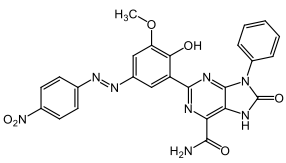
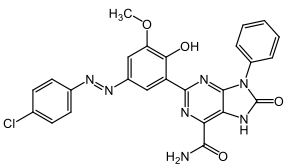
Fig. 1 ^{1}H NMR of 6a indicates a mixture of two isomers with a ratio of 71:29

appear at the region of δ 8.03–8.63 ppm as two separate NH peaks due to the rotation inhibition around the partial double bond, and because of the anisotropic effect, H_f appears in the lower field (Scheme 2). Furthermore, deuterium (D_2O) NMR data showed that there are three different exchangeable NH protons which confirm the 8,9-dihydro-7*H*-purine-6-carboxamide structure (Fig. 2). The ^{13}C NMR spectra of **7a–7g** are in agreement with the proposed structures. In ^{13}C NMR of **7e**, two kinds of carbon appeared in the aliphatic region, the signal at δ 56.2 ppm is attributed to O–CH_3, the C=O and C=N signals appeared at δ 141.3–165.6 ppm and other aromatic carbons appeared at δ 102.3–132.6 ppm (see Experimental section).

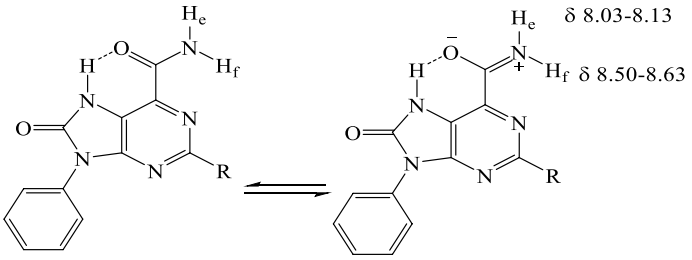
Antibacterial activity

The in vitro antibacterial activity of compounds **6a**–**6g** and **7a**–**7g** was evaluated against Gram-negative and Gram-positive bacteria including: *Micrococcus luteus* (*M. luteus*), *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*Ps. aeruginosa*) by zone inhibition method (mm). The results of preliminary antibacterial testing of the compounds are reported in Table 4. Tetracycline and Ampicillin were used as standard drugs, and DMSO was used as a negative control. The examination of antibacterial screening data showed that the compound importance antibacterial activity against *Micrococcus luteus* is: **6d > 6b > 6a > 6f > 6g = 6e > 6c** and **7e > 7g > 7b > 7a > 7f > 7c = 7d**.

Table 3 Physical properties of target *azo*- purine-6-carboxamides **7a–7g**

Entry	Compounds	M.p. (°C)	λ_{max} (in DMSO)	Yield%	Color
7a		> 320	352	88	
7b		> 320	351	92	
7c		> 320	365	78	
7d		> 320	356	87	
7e		> 320	355	85	
7f		> 320	364	75	
7g		> 320	358	82	

Antibacterial activity depends on the nature of the bacterial strain, the chelating ability of the Schiff base and the solubility of the compounds [37]. The morphology of the cell wall is a key factor that influences the activity of antibacterial agents. In this study, all compounds show more strong antibacterial activity against Gram-positive bacteria, namely *M. luteus* and *S. aureus* compared with



Scheme 2 Rotation inhibition around the partial double bond in 6-carboxamido group

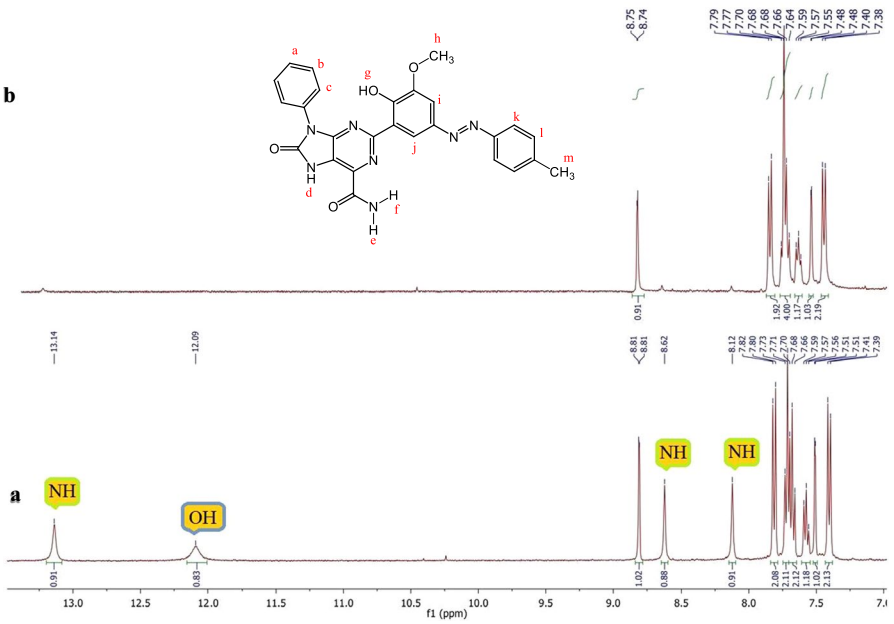


Fig. 2 **a** ^{1}H NMR spectra of compound **7e** **b** D_2O exchange

Gram-negative bacteria. This may be due to the nature of the bacteria cell wall. Gram-negative bacteria have an outer lipid membrane, and this usually poses a barrier to the degree of diffusion of antibiotics and antibacterial agents.

It is believed that Schiff bases form a chelate with the bacterial strain by making hydrogen bondings through the phenolic and azomethine group with the active centers of cell constituents thus resulting in interference with normal cell process. Therefore, any factor that influences the rate of hydrogen bond formation also affects the antibacterial power. In general, it can be said that compounds **7e**, **7b** and **6b** can better form hydrogen bonds because of their electron donor substituents and hence have higher antibacterial activity. On the other hand,

Table 4 Antimicrobial activity of compounds **6a**–**6g** and **7a**–**7g**

Entry	Compound	Conc. in DMSO µg per 0.1 mL	Antimicrobial activity (zone of inhibition in mm)			
			M. luteus	*S. aureus*	*E. coli*	*Ps. aeruginosa*
1	**6a**	100	13	5	4	6
2	**6b**	100	15	8	–	2
3	**6c**	100	6	2	–	–
4	**6d**	100	18	10	8	6
5	**6e**	100	9	15	6	4
6	**6f**	100	12	8	5	7
7	**6g**	100	9	8	9	11
8	**7a**	100	15	10	4	6
9	**7b**	100	16	12	5	5
10	**7c**	100	8	6	0	3
11	**7d**	100	8	14	2	8
12	**7e**	100	22	12	6	8
13	**7f**	100	12	5	2	2
14	**7g**	100	18	15	5	10
13	Tetracycline	100	25	21	21	19
14	Ampicillin	100	27	22	8	0
15	DMSO	100	–	–	–	–

compounds with NO_2 substituent as a strong electron-withdrawing group (**7f**, **7c**, **6f**, **6g**, **6c**) have less antibacterial activity.

It is interesting to note that compounds **7a**–**7g** compared with **6a**–**6g** showed greater penetration power to the membranous wall of the bacteria. This increase in antibacterial activity may be due to the presence of the purine heterocyclic ring in the structure of compounds **7a**–**7g**, which its antibacterial properties have already been reported [38, 39].

Conclusion

Here, we have been successfully synthesized eight symmetric DAMN-functionalized Schiff bases in good yields via a simple reaction between DAMN and azo-coupled to o-vanillin or salicylaldehyde precursors. In continuation, a facile synthesis of new 8,9-dihydro-7*H*-purine-6-carboxamide was reported via an efficient two-component reaction of azo dyes and 1-(2-amino-1,2-dicyanovinyl)-3-phenylurea in the presence of triethylamine as catalyst. The simplicity, easy execution, simple workup and good yields together with the use of easily accessible starting materials are characteristics of this process. The antibacterial activities of all newly synthesized compounds showed significantly strong activity against *Gram*-positive bacteria, namely *M. luteus* and *S. aureus*. Compounds **7a**–**7g** compared with **6a**–**6g** showed greater penetration power to the membranous wall of the bacteria.

Experimental

Materials and apparatus

The diaminomaleonitrile (DAMN) was purchased from Merck and used without further modification. The azo dyes **3a**–**3i** have been prepared from our reported method [40]. The structure of products has been well characterized by FT-IR, UV–Vis, NMR and mass spectrometry. The NMR spectra were obtained in DMSO-d_6 at 25 °C on a Bruker Avance spectrometer, operating at 400 MHz and 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR). The internal standard for the ^{1}H and ^{13}C NMR spectra was TMS. Chemical shifts (δ) are reported in ppm, and the coupling constants (J) are given in Hertz (Hz). Elemental analysis was made by a Carlo-Erba EA1110 CNNO-S analyzer and agreed with the calculated values. The FT-IR spectra for the samples were obtained using Shimadzu FT-IR-8900 spectrophotometer by using KBr pellets. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected.

Synthesis of 1-(2-amino-1,2-dicyanovinyl)-3-phenylurea 5

The DAMN **4** (1.08 g, 10 mmol) was dissolved in acetonitrile (10 mL) in an ice bath, and the solution was stirred vigorously for 5 min. Then, phenyl isocyanate (1.09 mL, 10 mmol) was added and the mixture stirred at 0 °C for 10 min. The reaction was then stirred for a further 24 h at room temperature to give the phenylurea derivative **5**. The product was collected by filtration and washed with acetonitrile. Yield: 89%, m.p. 182–185 °C (reported 180–210) [41]; FT-IR (KBr, υ/cm^{-1}): 3452 and 3354 (NH_2 stretch), 3262 (N–H stretch), 3017 (aromatic C–H stretch), 2219 (CN), 1689 (C=O stretch), 1604 (C=C stretch), 1550, 1512, 1377 (CH_2 bend), 752 (aromatic C–H out-of-plane bending). Anal. Calcd. for $C_{11}H_9N_5O$ (%): C, 58.14; H, 3.99; N, 30.82. Found: C, 58.19; H, 3.95; N, 30.87.

Path A: general procedure for the synthesis of DAMN-based Schiff bases derivatives 6a–6g

In a 25-mL round bottom flask, corresponding premade azo dyes **3a**–**3i** (1 mmol) were dissolved in 10 mL of MeOH and a few drops of AcOH were added. The mixture was stirred at 40 °C for 5 min, and then, phenylurea **5** (1 mmol) was added and the mixture stirred at reflux condition for further 25 min. After completion of the reaction, product was collected by filtration, washed with MeOH and recrystallized from DMF/H_2O.

1-(1,2-dicyano-2-((-2-hydroxy-5-(phenyldiazenyl)benzylidene)amino)vinyl)-3-phenylurea 6a

Orange powder, Yield: 86%, m.p. 199–200 °C, EtOH; FT-IR (KBr, cm^{-1}): 3316 (NH), 3064 (aromatic C–H), 2224 (CN), 1664 (C=O), 1599 (C=N), 1556 (C=C), 1488 (N=N), 1352 (C=C), 1237 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): Isomer 115a: 11.67 (br, 1H, H_g), 9.79 (m, 2H, H_d, H_e), 8.96 (s, 1H, H_f), 8.77 (d, J = 2.6 Hz, 1H, H_j), 8.02 (dd, J = 8.9, 2.5 Hz, 1H, H_i), 7.91–7.87 (m, 2H, H_k), 7.65–7.56 (m, 3H, H_l, H_m), 7.53 (d, J = 7.7 Hz, 2H, H_c), 7.38 (t, J = 7.9 Hz, 2H, H_b), 7.24–7.20 (m, 1H, H_h), 7.11 (t, J = 7.4 Hz, 1H, H_a). Isomer 115a': 11.55 (br, 1H, $H_{g'}$), 9.79 (m, 2H, H_d, H_e), 8.87 (s, 1H, H_f'), 8.21 (d, J = 2.5 Hz, 1H, H_j'), 8.12 (dd, J = 8.8, 2.5 Hz, 1H, H_i'), 7.91–7.87 (m, 1H, $H_{k'}$), 7.65–7.56 (m, 2H, $H_{l'}$, $H_{m'}$), 7.45 (d, J = 7.8 Hz, 1H, H_c'), 7.29 (t, J = 7.9 Hz, 1H, H_b'), 7.24–7.20 (m, 1H, $H_{h'}$), 6.99 (t, J = 7.3 Hz, 1H, $H_{a'}$). ^{13}C NMR (100 MHz, DMSO) δ (ppm): 163.8, 162.8, 157.4, 152.8, 152.4, 149.4, 145.8, 139.9, 138.5, 131.6, 130.2, 130.0, 129.9, 129.6, 129.2, 126.7, 126.4, 124.2, 123.9, 123.1, 122.9, 122.8, 121.7, 119.3, 118.9, 118.4, 118.2, 116.2, 113.7, 112.8. HRMS-ESI (m/z) calcd. for $C_{24}H_{17}N_7O_2$ [M^+] 435.1444, found 435.1449.

1-(1,2-dicyano-2-((5-((4-ethylphenyl)diazenyl)-2-hydroxybenzylidene)amino) vinyl)-3-phenylurea 6b

Orange powder, Yield: 88%, m.p. 221–222 °C, EtOH; FT-IR (KBr, cm^{-1}): 3445 (OH), 3344 and 3236 (NH), 2964 and 2931 (aliphatic C–H), 2225 (CN), 1663 (C=O), 1599 (C=N), 1538 (C=C), 1494 (N=N), 1345(C=C), 1232(C–O). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.63 (br, 1H, H_g), 9.80–9.78 (m, 2H, H_d, H_e), 8.95 (s, 1H, H_f), 8.74 (d, J = 2.5 Hz, 1H, H_j), 8.00 (dd, J = 8.9, 2.6 Hz, 1H, H_i), 7.83 (d, J = 8.3 Hz, 2H, H_k), 7.53 (d, J = 7.7 Hz, 2H, H_c), 7.46 (d, J = 8.5 Hz, 2H, H_l), 7.38 (t, J = 7.9 Hz, 2H, H_b), 7.20 (d, J = 8.9 Hz, 1H, H_h), 7.11 (t, J = 7.3 Hz, 1H, H_a), 2.72 (q, J = 7.6 Hz, 2H, H_m), 1.25 (t, J = 7.6 Hz, 3H, H_n). ^{13}C NMR (100 MHz, DMSO) δ (ppm): 163.6, 157.4, 152.8, 147.9, 145.3, 138.5, 130.2, 129.6, 129.3, 129.3, 129.2, 126.5, 126.4, 123.0, 122.9, 119.3, 118.9, 118.9, 118.1, 116.2, 28.5, 15.8. HRMS-ESI (m/z) calcd. for $C_{26}H_{21}N_7O_2$ [M^+] 463.1757, found 463.1750.

1-(1,2-dicyano-2-((2-hydroxy-5-((4-nitrophenyl)diazenyl)benzylidene)amino) vinyl)-3-phenylurea 6c

Orange powder, Yield: 78%, m.p. 233–234 °C, EtOH; FT-IR (KBr, cm^{-1}): 3444 (OH), 3319 and 3236 (NH), 2226 (CN), 1662 (C=O), 1605 (C=N), 1547 (C=C), 1491 (N=N), 1343 (C=C), 1236 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.94 (br, 1H, H_g), 9.79 (s, 2H, H_e, H_d), 8.94 (s, 1H, H_f), 8.85 (d, J = 2.5 Hz, 1H, H_j), 8.48 (d, J = 9 Hz, 2H, H_l), 8.09–8.06 (m, 3H, H_k, H_i), 7.53 (d, J = 7.8 Hz, 2H, H_c), 7.38 (t, J = 7.9 Hz, 2H, H_b), 7.24 (d, J = 9 Hz, 1H, H_h), 7.11 (t, J = 7.4 Hz, 1H, H_a). ^{13}C NMR (100 MHz, DMSO) δ (ppm): 164.9, 163.8, 155.8, 155.7, 149.3,

148.6, 138.4, 129.9, 129.6, 129.2, 126.8, 125.7, 125.6, 125.2, 123.8, 123.7, 122.7, 119.3, 119.1, 116.0. HRMS-ESI (*m/z*) calcd. for $C_{24}H_{16}N_8O_4$ [M^+] 480.1295, found 480.1289.

1-(2-((5-((4-chlorophenyl)diazenyl)-2-hydroxy-3-methoxybenzylidene) amino)-1,2-dicyanovinyl)-3-phenylurea **6d**

Orange powder, Yield: 78%, m.p. 233–34 °C, EtOH; FT-IR (KBr, cm^{-1}): 3321 (NH), 3074 (aromatic C–H), 2949 (aliphatic C–H), 2226 (CN), 1659 (C=O), 1602 (C=N), 1552 (C=C), 1485 (N=N), 1289 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.15 (br, 1H, H_g), 9.8 (s, 1H, H_d), 9.74 (s, 1H, H_e), 8.97 (s, 1H, H_f), 8.47 (d, J = 2.2 Hz, 1H, H_j), 7.91 (d, J = 8.7 Hz, 2H, H_l), 7.69 (d, J = 8.6 Hz, 2H, H_k), 7.62 (d, J = 2.2 Hz, 1H, H_i), 7.52 (d, J = 7.7 Hz, 2H, H_c), 7.38 (t, J = 7.9 Hz, 2H, H_b), 7.11 (t, J = 7.5 Hz, 1H, H_a), 4.00 (s, 3H, H_h).^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 157.2, 154.7, 152.8, 150.9, 150, 144.7, 139.9, 136, 130.1, 129.6, 129.2, 127.5, 124.5, 124.5, 122.7, 119.1, 118.9, 117.8, 114.7, 107.5, 56.8. HRMS-ESI (*m/z*) calcd. for $C_{25}H_{18}ClN_7O_3$ [M^+] 499.1160, found 499.1169.

1-(2-((5-((4-bromophenyl)diazenyl)-2-hydroxy-3-methoxybenzylidene) amino)-1,2-dicyanovinyl)-3-phenylurea **6e**

Light brown powder, Yield: 81%, m.p. 250–252 °C, EtOH; FT-IR (KBr, cm^{-1}): 3316 (NH), 3074 (aromatic C–H), 2949 (aliphatic C–H), 2226 (CN), 1660 (C=O), 1603 (C=N), 1574, 1552 (C=C), 1485 (N=N), 1354 (C=C), 1288 (C–O).^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.16 (br, 1H, H_g), 9.80 (s, 1H, H_d), 9.75 (s, 1H, H_e), 8.98 (s, 1H, H_f), 8.48 (d, J = 2.2 Hz, 1H, H_j), 7.84 (s, 4H, H_k, H_l), 7.63 (d, J = 2.1 Hz, 1H, H_i), 7.52 (d, J = 7.9 Hz, 2H, H_c), 7.38 (t, J = 7.9 Hz, 2H, H_b), 7.12 (t, J = 7.3 Hz, 1H, H_a), 4.00 (s, 3H, H_h). ^{13}C NMR (100 MHz, DMSO) δ (ppm): 157.2, 152.8, 149.8, 149.3, 145.2, 138.4, 133.1, 133.0, 133.0, 129.6, 129.2, 124.7, 124.7, 122.6, 119.3, 118.9, 118.2, 116.1, 112.8, 107.5, 56.7. HRMS-ESI (*m/z*) calcd. for $C_{25}H_{18}BrN_7O_3$ [M^+] 543.0655, found 543.0645.

1-(1,2-dicyano-2-((2-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)benzylidene) amino)vinyl)-3-phenylurea **6f**

Orange powder, Yield: 75%, m.p. 225 °C, EtOH; FT-IR (KBr, cm^{-1}): 3446 (OH), 2225 (CN), 1658 (C=O), 1600 (C=N), 1553 (C=C), 1460 (N=N), 1343 (C=C), 1263 (C–O). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.41 (br, 1H, H_g), 9.80 (s, 1H, H_d), 9.76 (br, 1H, H_e), 8.97 (s, 1H, H_f), 8.56 (d, J = 2.2 Hz, 1H, H_j), 8.48 (d, J = 9 Hz, 2H, H_l), 8.07 (d, J = 8.9 Hz, 2H, H_k), 7.66 (d, J = 2.1 Hz, 1H, H_i), 7.52 (d, J = 8 Hz, 2H, H_c), 7.38 (t, J = 7.9 Hz, 2H, H_b), 7.11 (t, J = 7.4 Hz, 1H, H_a), 4.01 (s, 3H, H_h). ^{13}C NMR (100 MHz, DMSO) δ (ppm): 156.9, 149.3, 138.4, 129.6, 125.7, 125.6, 123.9, 119.3, 116.0, 56.8. (The product shows low solubility in any appropriate solvents to allow for structural characterization using ^{13}C NMR.). HRMS-ESI (*m/z*) calcd. for $C_{25}H_{18}N_8O_5$ [M^+] 510.1400, found 510.1411.

1-(1,2-dicyano-2-((2-hydroxy-3-methoxy-5-((3-nitrophenyl)diazenyl)benzylidene) amino)vinyl)-3-phenylurea **6g**

Yellow powder, Yield: 74%, m.p. 223–224 °C, EtOH; FT-IR (KBr, cm^{-1}): 3447 (OH), 3331 (NH), 3088 (aromatic C–H), 2986 (aliphatic C–H), 2225 (CN), 1666 (C=O), 1600 (C=N), 1556 (C=C), 1458(N=N), 1351(C=C), 1265(C–O). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.30 (br, 1H, H_g), 9.81 (s, 1H, H_d), 9.72 (br, 1H, H_e), 8.96 (s, 1H, H_f), 8.60 (t, J = 2.1 Hz, 1H, H_k), 8.54 (d, J = 2.3 Hz, 1H, H_j), 8.40 (d, J = 8.2 Hz, 1H, H_n), 8.35 (d, J = 8.4 Hz, 1H, H_l), 7.92 (t, J = 8.1 Hz, 1H, H_m),7.68 (d, J = 2.3 Hz, 1H, H_i), 7.52 (d, J = 7.8 Hz, 2H, H_c), 7.37 (t, J = 7.9 Hz, 2H, H_b), 7.11 (t, J = 7.3 Hz, 1H, H_a), 4.02 (s, 3H, H_h). ^{13}C NMR (100 MHz, DMSO) δ (ppm): 155.4, 152.8, 150.1, 149.2, 144.6, 139.9, 131.6, 129.9, 129.6, 129.2, 127.5, 126.8, 125.5, 122.8, 122.7, 119.8, 119.2, 118.9, 116.1, 114.7, 107.6, 90.8, 56.9. HRMS-ESI (*m*/*z*) calcd. For $C_{25}H_{18}N_8O_5$ [M^+] 510.1400, found 510.1407.

Path B: general procedure for the synthesis of azo-8,9-dihydro-7H-purine-6-carboxamide 7a–7g

In a 25-mL round bottom flask, corresponding premade azo dyes **3a**–**3i** (1 mmol) were dissolved in 10 mL of MeOH and a few drops of triethylamine were added. The mixture was stirred at 40 °C for 5 min, and then, phenylurea **5** (1 mmol) was added and the mixture stirred at reflux condition for further 25 min. Thin-layer chromatography (TLC) was used to monitor the progress of the reaction (EtOAc/*n*-hexane 3:6). After completion of the reaction, the product was collected by filtration, washed with MeOH and recrystallized from DMF/H_2O.

2-(2-hydroxy-5-(phenyldiazenyl)phenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide **7a**

Orange powder, Yield: 88%, m.p. > 320 °C; FT-IR (KBr, υ/cm^{-1}): 3443 (OH), 3237 (NH), 1742 (C=O), 1689 (C=O), 1584 (C=N), 1488 (N=N). ^{1}H NMR (500 MHz, DMSO-*d*6) δ: 12.85 (s, 1H, H_d), 11.97 (s, 1H, Hg), 9.07 (s, 1H, Hj), 8.50 (s, 1H, H_f), 8.05 (s, 1H, H_e), 7.88–7.84 (m, 3H, Hi, Hk), 7.72 (d, J = 7.8 Hz, 2H, Hc), 7.65 (t, J = 7.8 Hz, 2H, Hb), 7.59–7.50 (m, 4H, Ha, Hl, Hm), 7.07(d, J = 8.8 Hz, 1H, Hh). ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 165.6, 161.8, 154.4, 152.5, 151.9, 145.6, 133.4, 132.6, 131.2, 129.8, 129.8, 129.8, 129.7, 129.0, 128.0, 126.9, 123.7, 122.7, 119.6, 119.1. HRMS-ESI (*m*/*z*) calcd. For $C_{24}H_{17}N_7O_3$ [M^+] 451.1393, found 451.1399.

2-(5-((4-ethylphenyl)diazenyl)-2-hydroxyphenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide **7b**

Orange powder, Yield: 92%, m.p. > 320 °C; FT-IR (KBr, υ/cm^{-1}): 3449 (OH), 3233 (NH), 2964 (aliphatic C–H), 1742 (C=O), 1663 (C=O), 1597 (C=N). ^{1}H NMR

(400 MHz, DMSO-d_6) δ: 12.88 (s, 1H, H_d), 12.09 (s, 1H, H_g), 9.11 (d, J = 2.6 Hz, 1H, H_j), 8.63 (s, 1H, H_f), 8.13 (s, 1H, H_e), 7.89 (dd, J = 8.8, 2.6 Hz, 1H, H_i), 7.82 (d, J = 8.1 Hz, 2H, H_k), 7.73 (d, J = 7.9 Hz, 2H, H_c), 7.67 (t, J = 7.7 Hz, 2H, H_b), 7.57 (t, J = 7.3 Hz, 1H, H_a), 7.44 (d, J = 8.2 Hz, 2H, H_l), 7.09 (d, J = 8.8 Hz, 1H, H_h), 2.72 (q, J = 7.6 Hz, 2H, H_m), 1.25 (t, J = 7.6 Hz, 3H, H_n). ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 165.6, 161.6, 154.4, 153.2, 151.9, 150.7, 147.6, 145.6, 133.4, 132.6, 129.8, 129.2, 129.1, 129.1, 127.9, 126.9, 123.7, 122.9, 119.6, 119.1, 28.5, 15.8. HRMS-ESI (m/z) calcd. For $C_{26}H_{21}N_7O_3$ [M^+] 479.1706, found 479.1713.

2-(2-hydroxy-5-((4-nitrophenyl)diazenyl)phenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide **7c**

Orange powder, Yield: 78%, m.p. > 320 °C; FT-IR (KBr, υ/cm^{-1}): 3321 and 3283 (NH), 3062 (aromatic C–H), 2926 and 2875 (aliphatic C–H), 2223 (CN), 1659 (C=O), 1609 (C=N), 1233 and 1194 (C–O). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.07 (s, 1H, H_d), 12.08 (s, 1H, H_g), 9.22 (s, 1H, H_j), 8.62 (s, 1H, H_f), 8.44 (d, J = 8.6 Hz, 2H, H_k), 8.10 (s, 1H, H_e), 8.06(d, J = 8.7 Hz, 2H, H_l), 7.96 (dd, J = 8.8, 2.5 Hz, 1H, H_i), 7.72 (d, J = 7.8 Hz, 2H, H_c), 7.67 (t, J = 7.9 Hz, 2H, H_b), 7.56 (t, J = 7.3 Hz, 1H, H_a), 7.13(d, J = 8.7 Hz, 1H, H_h). The product was too insoluble for analysis by ^{13}C NMR spectroscopy. HRMS-ESI (m/z) calcd. For $C_{24}H_{16}N_8O_5$ [M^+] 496.1244, found 496.1239.

2-(2-hydroxy-3-methoxy-5-(phenyldiazenyl)phenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide **7d**

Yellow powder, Yield: 87%, m.p. > 320 °C; FT-IR (KBr, υ/cm^{-1}): 3429 (OH), 3333 and 3265(NH), 3063 (aromatic C–H), 2937 (aliphatic C–H), 1734 (C=O), 1680 (C=O), 1600 (C=N), 1120 (C–O). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.14 (s, 1H, H_d), 12.01 (s, 1H, H_g), 8.75 (s, 1H, H_j), 8.51 (s, 1H, H_f), 8.08 (s, 1H, H_e), 7.85 (d, J = 7.6 Hz, 2H, H_k), 7.70 (d, J = 7.9 Hz, 2H, H_c), 7.64 (t, J = 7.7 Hz, 2H, H_b), 7.58–7.49 (m, 4H, H_a, H_l, H_m), 7.45 (s, 1H, H_i), 3.86 (s, 3H, H_h). ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 165.5, 164.8, 154.5, 153.2, 152.9, 152.5, 151.8, 150.0, 149.9, 147.6, 144.6, 132.6, 131.1, 129.8, 129.8, 129.0, 129.0, 126.8, 122.7, 118.9, 56.2. HRMS-ESI (m/z) calcd. For $C_{25}H_{19}N_7O_4$ [M^+] 481.1499, found 481.1490.

2-(2-hydroxy-3-methoxy-5-(p-tolyldiazenyl)phenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide **7e**

Orange powder, Yield: 85%, m.p. > 320 °C; FT-IR (KBr, υ/cm^{-1}): 3447 (OH), 3237 (NH), 2932 (aliphatic C–H), 1748 (C=O), 1666 (C=O), 1597 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 13.14 (s, 1H, H_d), 12.09 (s, 1H, H_g), 8.81(d, J = 2.3 Hz, 1H, H_j), 8.62 (s, 1H, H_f), 8.12 (s, 1H, H_e), 7.81 (d, J = 8.1 Hz, 2H, H_k), 7.72 (d, J = 7.4 Hz, 2H, H_c), 7.68 (t, J = 7.7 Hz, 2H, H_b), 7.57 (t, J = 7.2 Hz, 1H, H_a), 7.51 (d, J = 2.3 Hz, 1H, H_i), 7.40 (d, J = 8.1 Hz, 2H, H_l), 3.89 (s, 3H, H_h), 2.42 (s, 3H, H_m). ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ: 165.6, 154.5, 153.2, 152.6,

151.9, 150.5, 150.1, 144.6, 141.3, 132.6, 130.4, 129.8, 129.1, 126.9, 122.9, 122.8, 122.4, 119.0, 116.0, 102.3, 56.2, 21.5. HRMS-ESI (*m*/*z*) calcd. For $C_{26}H_{21}N_7O_4$ [M^+] 495.1655, found 495.1664.

2-(2-hydroxy-3-methoxy-5-((4-nitrophenyl)diazenyl)phenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide **7f**

Orange powder, Yield: 75%, m.p. > 320 °C; FT-IR (KBr, υ/cm^{-1}): 3457 (OH), 3094 (aromatic C–H), 2928 (aliphatic C–H), 1744 (C=O), 1678 (C=O), 1600 (C=N), 1528 and 1349 (NO_2). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.16 (s, 1H, H_d), 11.99 (s, 1H, H_g), 8.79 (s, 1H, H_j), 8.52 (s, 1H, H_f), 8.03 (s, 1H, H_e), 7.89 (d, J = 8.3 Hz, 2H, H_k), 7.71 (d, J = 7.9 Hz, 2H, H_c), 7.67–7.63 (m, 4H, H_b, H_l), 7.55 (t, J = 7.4 Hz, 1H, H_a), 7.51 (s, 1H, H_i), 3.88 (s, 3H, H_h). The product was too insoluble for analysis by ^{13}C NMR spectroscopy. HRMS-ESI (*m*/*z*) calcd. For $C_{25}H_{18}N_8O_6$ [M^+] 526.1349, found 526.1358.

2-(5-((4-chlorophenyl)diazenyl)-2-hydroxy-3-methoxyphenyl)-8-oxo-9-phenyl-8,9-dihydro-7H-purine-6-carboxamide **7g**

Yellow powder, Yield: 82%, m.p. > 320 °C; FT-IR (KBr, υ/cm^{-1}: 3423 (OH),), 3332 (NH), 3263(NH), 1740(C=O), 1680 (C=O), 1598 (C=N), 1461 (N=N). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.31 (s, 1H, H_d), 11.97 (s, 1H, H_g), 8.84(s, 1H, H_j), 8.53–7.48 (m, 12H, H_a, H_b, H_c, H_e, H_f, H_i, H_k, H_l), 3.87 (s, 3H, H_h). The product was too insoluble for analysis by ^{13}C NMR spectroscopy. HRMS-ESI (*m*/*z*) calcd. For $C_{25}H_{18}ClN_7O_4$ [M^+] 515.1109, found 515.1102.

Determination of antibacterial activity

A colony of each standard test organism was sub-cultured in order to obtain fresh bacteria on the nutrient agar plates at 37 °C for 18 h. For preparations of suspensions of microorganisms (0.5 McFarland), one to two colonies from each plate were dissolved in isotonic saline solution. Then, Mueller–Hinton agar (Merck) plates were prepared according to manufacturers' instructions in order to evaluate the antibacterial activities of compounds. The sterile Mueller–Hinton agar plates were inoculated with the bacteria. 0.01 g of test samples was dissolved in 1 mL dimethyl sulfoxide (DMSO) to obtain a stock solution. A concentration of 100 µg/0.1 mL of each sample was prepared. 0.1 mL of prepared samples was dropped into each respective labeled well aseptically. The inoculated plates were left on the table for 1 h to allow each sample to diffuse into the agar. For comparison, Erythromycin and Tetracycline were used as positive control and DMSO as a negative control. The plates were incubated overnight at 37 °C, and zones of inhibition were measured in millimeters. All the tests were performed in triplicate, and the average was taken as the final reading. The bacterial strains isolated from clinical specimens were used in the study.

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