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Synthesis and in vitro activity of 6-amino-2,9-diarylpurines for *Mycobacterium tuberculosis*

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ABSTRACT

A mild method was developed to synthesize 6-amino-2-phenolic-9-alkyl and 9-arylpurines. The new compounds were screened for antibacterial activity against *Mycobacterium tuberculosis* strain $H_{37}Rv$. The 9-tolyl derivatives with a dimethylamino or a piperidine substituent in C6 and the 3-hydroxyphenyl or 4-hydroxyphenyl substituent in C2 were highly active against the bacilli.

1. Introduction

The *Mycobacterium tuberculosis*, the microorganism responsible for tuberculosis, is considered the leading cause of death worldwide.[1] It is estimated that at least one-third of the world's population is infected with a latent form of this organism and about 10% of these individuals will develop the active form of the disease during their lifetime.[2] The co-infection with HIV is especially lethal and serves as a trigger to convert latent tuberculosis into an active transmissible infection. The current therapy requires treatment with a combination of drugs, over 6–9 months and results in an overall cure rate of approximately 85%.[2] The emergence of multidrug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) caused an urgency in the search for new antitubercular agents.[3]

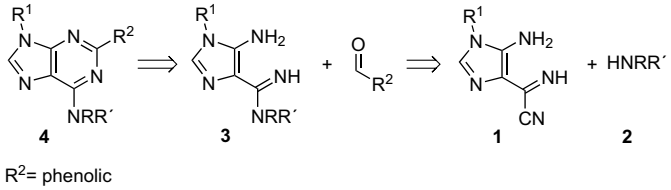
It is well known that invasive pathogens, as *Mycobacterium tuberculosis*, require iron as an essential element for numerous biochemical processes. They obtain iron from the host by small molecule iron chelators known as siderophores and using the cellular Fe-siderophore uptake system.[4] During last decade some purine derivatives were identified as promising new drug candidates against *Mycobacterium tuberculosis*.[5] The research was mainly focussed on nucleoside analogues as siderophore biosynthesis inhibitors[6] and on purine derivatives having different substituents in N9, C2, C6 and C8 of the purine ring. For non nucleoside analogues, it has been demonstrated that the identity of the substituents on C6, C8 and N9 are crucial for activity.[7] Compounds with an aryl, a small alkyl or a proton as the N9 substituent were essentially inactive, whereas 9-benzyl-6-(2-furyl)purines were highly potent. The target of this non nucleoside analogues and the mechanism of action is still unknown.

The substituents incorporated in C2 of the purine ring, in the non nucleoside series, were limited to hydrogen and chlorine atoms.[7a] As far as we know, no further research was carried out to explore the effect of different substituents in this position of the purine core.

This observation prompted us to design new purine derivatives with potential antituberculosis activity combining the purine moiety with phenolic residues, which are known as excellent iron chelators.

As far as we know a phenolic substituent was never introduced in C2 of the purine ring and the 6-amino-2,9-diarylpurines were never evaluated as antituberculosis agents. Herein we report the synthesis of new 6-amino-2-phenolic-purines **4** and their antimycobacterial activity.

Having established compounds **4** as the target molecules, the disconnection analysis (Scheme 1) shows that the compounds **3** are convenient precursors to the purine **4**.



Scheme 1. Disconnection analysis of the target molecule **4**.

During last decade, a renewed interest in the development of new synthetic methods to incorporate convenient substituents in the

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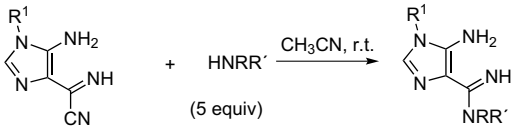
purine nucleus has emerged,[8] mainly due to the biological importance of these compounds.[9] In our research group we developed an efficient method to obtain 6-aminopurines **4** (R^2=H)[8l] by reaction of the intermediate **3** with dimethylformamide diethyl acetal in acetonitrile. The precursors **1** are not commercially available and were synthesized from diaminomaleonitrile in three consecutive steps.[10]

In order to prepare 6-amino-2-phenolic-purines **4** we combined imidazoles **3** with phenolic aldehydes that incorporate one and two hydroxyl groups. New compounds **3** were synthesized using the reaction conditions previously established. The condensation of imidazoles **3** with phenolic aldehydes was carefully studied.

2. Results and discussion

The new substituted 4-amidinoimidazoles **3** were obtained by reaction of imidazoles **1a–c** with 5 equiv of secondary amines in acetonitrile (Scheme 2). The imidazoles **3a–i** gradually precipitated from the reaction medium and were isolated in good yield (64–89%). Compound **3e** was previously isolated from the reaction of **1a** with a large excess of gaseous dimethylamine in chloroform.[8l] In the present work, **3e** was obtained under mild experimental conditions from the reaction of **1a** and 1.5 equiv of aqueous dimethylamine in acetonitrile.



1 a R^1=4-$CH_3C_6H_4$
b R^1=C_6H_5
c R^1=CH_3

2

3

Compound **1**	Compound **2**	Reaction time	Product	Yield %
1a	piperidine	2h	**3a**	85 [a]
	morpholine	24h	**3b**	84
	thiomorpholine	24h	**3c**	89
	pyrrolidine	1h	**3d**	60
	$HNMe_2$	**2** (1.5 equiv), 48h	**3e**	74 [a]
1b	piperidine	24h	**3f**	64
	morpholine	5h	**3g**	78
1c	piperidine	24h	**3h**	68
	morpholine	24h	**3i**	66

[a] Compounds **3a** and **3e** were isolated previously (reference 8l) in 67 and 87% yield, respectively.

Scheme 2. Synthesis of compounds **3**.

The ^{1}H NMR data obtained for these new substituted imidazoles **3** is in good agreement with that previously reported.[8l] A careful study using NMR heteronuclear correlation techniques (HMQC and HMBC) also confirmed the structure assignment. Typically, in the ^{1}H NMR spectra of these compounds, the proton H2 appears as a singlet in the range δ 7.0–7.4 ppm and the carbon C2 at $\delta\sim$128–132 ppm. The infrared spectra confirmed the absence of the stretching vibration of the cyano group.

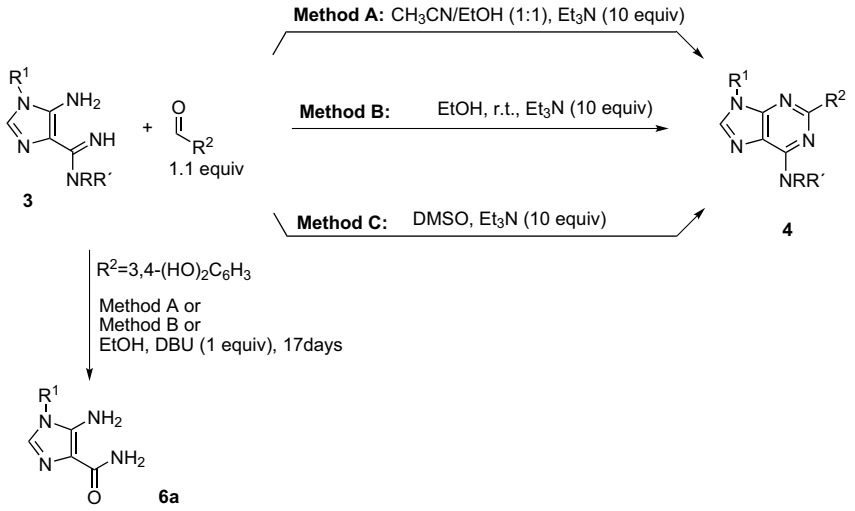
In order to prepare the new purines **4**, imidazoles **3** were reacted with salicylaldehyde and 4-hydroxybenzaldehyde in a mixture of acetonitrile and ethanol in basic medium. (Scheme 3, Table 1, method A). The products **4** precipitated as off white solids from a dark reaction medium and were isolated in moderate to good yields (48–85%).

When similar experimental conditions were applied to the reaction of **3a** with 3,4-dihydroxibenzaldehyde, extensive degradation of the reaction medium occurred. The TLC analysis of the reaction mixture after 25 days at 8 °C showed a complex mixture and the absence of purine. A small amount of a solid precipitated from the reaction mixture and was identified as compound **6a** (5%). The structure of compound **6a** was assigned mainly on the basis of NMR data. The ^{1}H NMR spectrum shows a singlet at δ=7.30 ppm, typical of the H2 proton of substituted imidazoles. The amino group in position 5 of the imidazole ring corresponds to a broad singlet at δ=5.69 ppm and the NH_2 of the amide group appears as two very broad singlets at δ=6.76 and 6.90 ppm.

Some reactions were carried out using ethanol as solvent in order to increase the solubility of the reagents (Scheme 3, Table 1, method B) and the products **4** were isolated in moderate yields.

When 3,4-dihydroxybenzaldehyde was reacted with **3b** in ethanol using DBU as base, compound **6a** was again the only product isolated in 7% yield from a very complex reaction mixture.

Methods A and B failed to generate the purines **4** with a dihydroxyphenyl substituent in C2 of the purine ring and this led us to analyse some of the reaction mixtures by ^{1}H NMR, as the reaction proceeded. The reaction mixture of **3b** and salicylaldehyde was analysed after 10 days at 8 °C (Scheme 4). The spectrum showed a mixture of purine **4e** and the corresponding dihydropurine **5e** in a 1:2 molar ratio. This assignment was based on the typical signals of H8 of the purines **4** ($\delta_{H8}\sim$8.54 ppm) and the singlet at δ=5.55 ppm, which can be assigned to H2 of dihydropurine **5e**. Compound **5e** evolved to the purine **4e**, in DMSO solution, in the

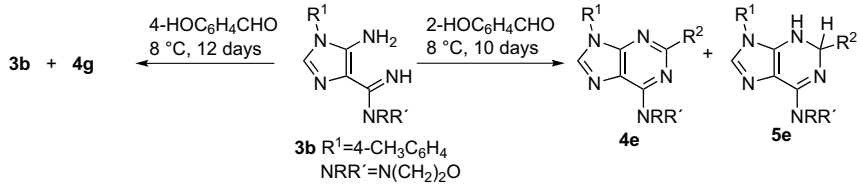


Scheme 3. General approaches to the synthesis of purines **4**.

Table 1
Reaction conditions to generate purines **4** and imidazole **6a**

Reagent	R^2 (aldehyde)	Method/reaction conditions	Product	Yield (%)
3a	2-HOC_6H_4	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), 8 °C, 10 days	**4a**	65
	3-HOC_6H_4	B: EtOHEt_3N (10 equiv), rt, 26 days	**4b**	65
	4-HOC_6H_4	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), 8 °C, 24 days	**4c**	53
		B: EtOH, Et_3N (10 equiv), rt, 30 days	**4c**	69
	3,4-$(HO)_2C_6H_3$	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), 8 °C, 25 days	**6a**	5
		C: DMSO, Et_3N (10 equiv), 40 °C, 45 days	**4d**	46
		C: DMSO, Et_3N (10 equiv), 11 °C, 48 days	**4d**[a]	
3b	2-HOC_6H_4	C:DMSO, Et_3N (10 equiv), rt, 8 days	**4e**	79
	4-HOC_6H_4	C: DMSO, Et_3N (10 equiv), rt, 30 days	**4g**	84
	3-HOC_6H_4	B: EtOH, Et_3N (10 equiv), rt, 26 days	**4f**	63
	3,4-$(HO)_2C_6H_3$	B: EtOH, DBU (1 equiv), rt, 17days	**6a**	7
		C: DMSO, Et_3N (10 equiv), rt, 41 days	**4h**[b]	
		C: DMSO, Et_3N (10 equiv), rt, 54 days	**4h**[c]	32
		C: DMSO, Et_3N (10 equiv), rt, 18 days	**4h**[d]	
3c	2-HOC_6H_4	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), 11 °C, 20 days	**4i**	85
	3-HOC_6H_4	B: EtOH, Et_3N (10 equiv), rt, 30 days	**4j**	66
	4-HOC_6H_4	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), 8 °C, 30 days	**4k**	56
		C: DMSO, Et_3N (10 equiv), 11 °C, 48 days	**4k**	80
	3,4-$(HO)_2C_6H_3$	C: DMSO, Et_3N (10 equiv), 8 °C, 42 days	**4l**[e]	
		C: DMSO, Et_3N (10 equiv), rt, 46 days	**4l**[e]	40
		C: DMSO, Et_3N (10 equiv), 40 °C, 51 days	**4l**	45
3d	2-HOC_6H_4	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), 11 °C, 31 days	**4m**	81
	3-HOC_6H_4	B: EtOH, Et_3N (10 equiv), rt, 20 days	**4y**	54
	4-HOC_6H_4	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), 11 °C, 37 days	**4n**	71
3e	2-HOC_6H_4	B: EtOH, Et_3N (10 equiv), rt, 13 days	**4o**	66
	3-HOC_6H_4	B: EtOH, Et_3N (10 equiv), rt, 8 days	**4p**	34
	4-HOC_6H_4	C: DMSO, Et_3N (10 equiv), rt, 18 days	**4q**	61
3f	2-HOC_6H_4	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), rt, 6 days	**4r**	70
	4-HOC_6H_4	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), rt, 27 days	**4s**	47
3g	2-HOC_6H_4	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), rt, 24 days	**4t**	72
	4-HOC_6H_4	C: DMSO, Et_3N (10 equiv), rt, 30 days	**4u**	82
	3,4-$(HO)_2C_6H_3$	C: DMSO, Et_3N (10 equiv), rt, 30 days	**4v**	33
		C: DMSO, Et_3N (10 equiv), rt, 10 days	**4v**[e]	
3h	4-HOC_6H_4	A: CH_3CN/EtOH (1:1), Et_3N (10 equiv), 11 °C, 41 days	**4w**	48
3i	4-HOC_6H_4	C: DMSO, Et_3N (10 equiv), 11 °C, 42 days	**4x**	80
	3,4-$(HO)_2C_6H_3$	C: DMSO (0.4 mL), Et_3N (10 equiv), 40 °C, 15 days	**4z**	72

[a] Isolated as a mixture of **4d** and starting material in a 1:1 ratio.
[b] Isolated as a mixture of **4h** and starting material in a 2:1 ratio.
[c] Isolated as a mixture of **4h** and starting material in a 4:1 ratio.
[d] Isolated as a mixture of **4h** and starting material in a 1:1 ratio.
[e] The crude product was contaminated with traces of the starting material.



Scheme 4. Composition of the reaction mixture by ^{1}H NMR: **4e**/**5e** (1:2 molar ratio) and **3b**/**4g** (1:4 molar ratio).

NMR tube. The reaction mixture of **3b** with 4-hydroxybenzaldehyde was also analysed by ^{1}H NMR after 12 days at 8 °C. The spectrum showed a mixture of the product **4g** and starting material **3b** in a 4:1 molar ratio.

These results indicate that both reactions are very slow. The reaction of **3b** with salicylaldehyde to generate the corresponding dihydropurine **5e** and purine **4e** is slightly faster than the reaction of **3b** with 4-hydroxybenzaldehyde. The phenolic hydroxyl group in the 2-position of the salicylaldehyde is probably involved in an intramolecular H-bonding with the carbonyl oxygen, activating it for nucleophilic attack. Elimination of water from the adduct will also contribute to accelerate this reaction.

The evolution of dihydropurine **5e** to purine **4e** is very slow under the reaction conditions A or B leading to moderate yields of the product. In DMSO solution this evolution occurred without competitive degradation. These observations prompted us to use DMSO as solvent in order to reduce degradation of the reaction medium, improve the solubility of reagents and tentatively decrease the reaction time.

When the imidazoles **3** were reacted with 2-hydroxy or 4-hydroxybenzaldehydes in DMSO, the purines **4** were obtained in good to excellent yield (Scheme 3, Table 1, method C) after 10–54 days, usually at room temperature.

The reaction of imidazole **3a** with 3,4-dihydroxybenzaldehyde was also carried out under these reaction conditions. After 48 days at 11 °C a mixture of purine **4d** and starting material **3a** was isolated in a 1:1 ratio. This is evidence that the reaction rate between imidazoles **3a** and 3,4-dihydroxybenzaldehyde is slower than that observed for 4-hydroxy or 2-hydroxybenzaldehydes. However, purine **4** is formed, and in order to increase the reaction rate, imidazoles **3** were combined with 3,4-dihydroxybenzaldehyde, in DMSO, at room temperature or at 40 °C. Extensive degradation occurred at 40 °C however the products were obtained as pure solids, in moderate yields, after dry flash

chromatography using dichloromethane as solvent, (Scheme 3, Table 1, method C).

All the compounds were fully characterised by analytical and spectroscopic techniques including heteronuclear correlation techniques (HMBC and HMQC). Typically, the ^{1}H NMR spectra of purines **4** show a singlet at $\delta\sim$8.0–8.6 ppm assigned to H8. The three bond interactions observed in the HMBC spectra between H8 and C4 and C5 identifies these carbon atoms at $\delta\sim$149–152 ppm and $\delta\sim$117–119 ppm respectively. The C2 carbon appears around $\delta\sim$158 ppm and was unequivocally assigned from the three-bonds interaction with the *ortho* protons of the substituent in position 2 of the purine ring.

3. Biological activity

3.1. Antibacterial activity against *M. tuberculosis*

All the new 2-phenolic-6-aminopurines **4** were screened for antimycobacterial activity on the *M. tuberculosis* strain H_{37}Rv according to procedures previously published by the TAACF organization.[11]

The results, summarized in Table 2, show that most of the 6-amino-2,9-diarylpurines **4** are active against *Mycobacterium tuberculosis* and the activity depends on the substituents present in C2, C6 and N9 of the purine ring. Purines **4b** (IC_{90}=3.543 μg/mL) and **4q** (IC_{90}=4.721 μg/mL) are highly active and they both have the 4-tolyl group in the N9 position. The phenyl and in particular the methyl group in this position, lead to weakly active or inactive structures, with a marginal dependence on the nature of the remaining substituents of the purine ring. For compound **4d**, with a piperidinyl substituent in the 6-position, the highest activity is associated with the presence of the 3-hydroxyphenyl group in the 2-position. A poor activity was registered for compound **4c** (IC_{90}>100 μg/mL and IC_{50}=16.118 μg/mL), with 4-hydroxyphenyl substituent in the 2-position, and compound **4d**, with a 3,4-dihydroxyphenyl substituent in this position, proved to be moderately active (IC_{90}=19.41 μg/mL).

Table 2
Antibacterial activity against *M. tuberculosis* strain H_{37}R and cytotoxic activity against VERO cells of compounds **4**

Compound	IC_{90} (μg/mL)	IC_{50} (μg/mL)	EC_{50} (μg/mL)	SI
4a	>100	>100	nd	nd
4b	3.543	1.227	5.106	1.441
4c	>100	16.118	nd	nd
4d	19.41	9.03	nd	nd
4e	>100	>100	nd	nd
4f	10.649	3.839	nd	nd
4g	>100	7.564	nd	nd
4h	>100	39.946	nd	nd
4i	>100	>100	nd	nd
4j	>100	18.493	nd	nd
4k	>100	39.344	nd	nd
4l	12.129	7.671	nd	nd
4m	>100	>100	nd	nd
4y	>100	1.654	nd	nd
4n	>100	>100	nd	nd
4o	>100	>100	nd	nd
4p	>100	42.044	nd	nd
4q	4.721	2.61	11.516	2.439
4r	>100	>100	nd	nd
4s	>100	>100	nd	nd
4t	>100	>100	nd	nd
4u	17.811	4.961	nd	nd
4v	29.407	7.976	nd	nd
4w	>100	>100	nd	nd
4x	>100	>100	nd	nd
4z	>100	29.821	nd	nd

In summary, the presence of an aromatic group in N9 (4-tolyl) and hydroxyl groups in the 3- or 4-position of the aryl substituent R^2, present in C2, seems to enhance the antitubercular activity. However, an alkyl group in N9 or a 2-hydroxylphenyl group in C2 have the opposite effect. Compounds having in C2 the substituents 3-hydroxyphenyl or 4-hydroxyphenyl can be highly active (**4b** and **4q**) or weakly active (**4c** or **4p**) and it is difficult to establish a clear correlation between the nature of the substituents in the purine scaffold and the antitubercular activity. Compounds having in C2 the substituent 3,4-dihydroxyphenyl are, in general, weakly active (**4d**, **4h**, **4l**, **4v** and **4x**)

3.2. Cytotoxicity

The two most active compounds were further evaluated for their cytotoxicity (EC_{50}) on mammalian VERO cell lines,[11] by TAACF, and showed a low selectivity index.

4. Conclusions

This work describes a simple method to synthesize novel 9-alkyl and 9-aryl-2-phenolic-6-aminopurines which proved to be active against *Mycobacterium tuberculosis*.

The potency depends on the substituents present in N9, C2 and C6 of the purine core. The presence of a 4-tolyl group in N9 and a 3-hydroxy or 4-hydroxyphenyl in C2 combined with a secondary amine (piperidine or dimethylamine) in C6 proved to be important features for activity but a clear structure–activity correlation pattern could not be identified. New substituents were incorporated in the purine scaffold leading to different derivatives **4**. Compounds **4b** and **4g** were identified as highly active against *M. tuberculosis* with a low level of cytotoxicity.

Further structural modifications of the identified hit are in progress in order to enhance the efficacy of the new compounds.

5. Experimental

5.1. General techniques

The 5-amino-1-aryl-4-(cyanoformimidoyl) imidazoles **1a–c** used in this work were prepared according to previously described procedures.[10] NMR spectra were recorded with a Varian Unity Plus (300 MHz) or with a Bruker Avance II NMR spectrometer (400 MHz), including the ^{1}H and ^{13}C correlation spectra (HMQC and HMBC). IR spectra were recorded with a FT-IR Bomem MB 104 using Nujol mulls and NaCl cells. The reactions were monitored by thin-layer chromatography (TLC) with the use of silica gel 60 F_{254} (Merck). The melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Elemental analysis were performed with a LECO CHNS-932 instrument.

5.2. General procedure for synthesis of imidazoles 3

The secondary amine—1.5 to 5 equiv was added to a green suspension of **1** in acetonitrile and the resulting solution was kept under stirring, at room temperature. An off-white solid precipitated from the solution and the reaction was monitored by TLC. When the TLC showed absence of the starting material, the solid suspension was filtered and washed with acetonitrile and diethyl ether to give compounds **3**.

*5.2.1. 4-[Imino(piperidin-1-yl)methyl]-1-(p-tolyl)-1H-imidazol-5-amine **3a***

Compound **3a** (0.53 g, 1.87 mmol, 85%), was obtained as an off-white solid from [5-amino-1-(*p*-tolyl)-1*H*-imidazol-4-yl](imino)acetonitrile **1a** (0.49 g, 2.20 mmol) and piperidine (1.1 mL, 10.98 mmol).[Lit. 8l]

*5.2.2. 4-[Imino(morpholin-4-yl)methyl]-1-(p-tolyl)-1H-imidazol-5-amine **3b***

Compound **3b** (0.43 g, 1.51 mmol, 84%), was obtained as a white solid from [5-amino-1-(*p*-tolyl)-1*H*-imidazol-4-yl](imino)acetonitrile **1a** (0.41 g, 1.80 mmol) and morpholine (0.78 mL, 9.00 mmol). Mp 203–205 °C; IR (Nujol mull) 3365, 3285, 3122, 1626, 1592, 1519 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.36 (s, 3H), 3.33 (br s, 4H), 3.66 (t, J=4.8 Hz, 4H), 4.0–7.20 (br s, 3H), 7.33 (s, 1H), 7.35 (s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 47.2, 66.1, 114.2, 124.6, 130.0, 130.1, 132.3, 137.6, 139.5, 163.0. Anal. Calcd for $C_{15}H_{19}N_5O$ (285.34): C, 63.14; H, 6.71; N, 24.54. Found: C, 63.20; H, 6.63; N, 24.49.

*5.2.3. 4-[Imino(thiomorpholin-4-yl)methyl]-1-(p-tolyl)-1H-imidazol-5-amine **3c***

Compound **3c** (0.43 g, 1.41 mmol, 89%), was obtained as an off-white solid from [5-amino-1-(*p*-tolyl)-1*H*-imidazol-4-yl](imino)-acetonitrile **1a** (0.36 g, 1.60 mmol) and thiomorpholine (0.82 mL, 8.00 mmol). Mp 204–206 °C; IR (Nujol mull) 3358, 3281, 3125, 1622, 1588, 1518 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.36 (s, 3H), 2.64 (m, 4H), 3.65 (m, 4H), 5.43 (s, 2H), 7.35 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.7, 26.4, 49.3, 113.6, 124.8, 130.2, 130.7, 132.2, 137.8, 139.4, 162.1. Anal. Calcd for $C_{15}H_{19}N_5S$ (301.41): C, 59.77; H, 6.35; N, 23.24; S, 10.64. Found: C, 59.84; H, 6.35; N, 23.18; S, 10.77.

*5.2.4. 4-[Imino(pyrrolidin-1-yl)methyl]-1-(p-tolyl)-1H-imidazol-5-amine **3d***

Compound **3d** (0.66 g, 2.44 mmol, 60%), was obtained as an orange solid from [5-amino-1-(*p*-tolyl)-1*H*-imidazol-4-yl](imino)-acetonitrile **1a** (0.94 g, 4.16 mmol) and pyrrolidine (1.73 mL, 20.78 mmol). Mp 185–187 °C; IR (Nujol mull) 3432, 3345, 3109, 1597, 1577, 1551, 1518 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.38 (t, J=6.3 Hz, 4H), 2.36 (s, 3H), 3.54 (t, J=6.3 Hz, 4H), 6.11 (s, 3H), 7.26 (s, 1H), 7.36 (s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 24.9, 47.6, 114.7, 124.3, 128.2, 130.1, 132.6, 137.3, 141.8, 158.9. Anal. Calcd for $C_{15}H_{19}N_5$ (269.34): C, 66.89; H, 7.11; N, 26.00. Found: C, 67.17; H, 7.00; N, 25.91.

*5.2.5. 5-Amino-N,N-dimethyl-1-(p-tolyl)-1H-imidazole-4-carboximidamide **3e***

Compound **3e.**HCN (1.09 g; 4.04 mmol, 74%), was obtained as an off-white solid from [5-amino-1-(*p*-tolyl)-1*H*-imidazol-4-yl](imino)-acetonitrile **1a** (1.23 g; 5.47 mmol) and a 40% aquous solution of dimethylamine (1.04 mL; 8.20 mmol).[Lit. 8l]

*5.2.6. 4-[Imino(piperidin-1-yl)methyl]-1-phenyl-1H-imidazol-5-amine **3f***

Compound **3f** (0.27 g, 1.02 mmol, 64%), was obtained as an off-white solid from (5-amino-1-phenyl-1*H*-imidazol-4-yl)(imino)-acetonitrile **1b** (0.35 g, 1.64 mmol) and piperidine (0.8 mL, 8.20 mmol). Mp 130–132 °C; IR (Nujol mull) 3353, 3286, 3119, 1624, 1591, 1550, 1515 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.56 (s, 6H), 3.31(br s, 4H), 4.50–6.50 (brs, 3H), 7.39 (s, 1H), 7.40–7.60 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 24.4, 25.5, 47.5, 115.1, 124.6, 127.9, 129.7, 129.8, 135.0, 139.0, 163.3. Anal. Calcd for $C_{15}H_{19}N_5$ 0.4H_2O (276.54): C, 65.17; H, 7.17; N, 25.34. Found: C, 65.28; H, 6.94; N, 25.24.

*5.2.7. 4-[Imino(morpholin-4-yl)methyl]-1-phenyl-1H-imidazol-5-amine **3g***

Compound **3g** (0.29 g, 1.08 mmol, 78%), was obtained as a white solid from (5-amino-1-phenyl-1*H*-imidazol-4-yl)(imino)acetonitrile **1b** (0.29 g, 1.64 mmol) and morpholine (0.6 mL, 6.90 mmol). Mp 181–183 °C; IR (Nujol mull) 3357, 3290, 3123, 1627, 1594, 1518 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 3.33 (br s, 4H), 3.67 (t, J=4.8 Hz, 4H), 5.59 (s, 2H), 7.06 (s, 1H), 7.39 (s, 1H), 7.40–7.60 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 47.1, 66.1, 114.8, 124.6, 127.9, 129.4, 129.7, 134.9, 139.4, 163.3. Anal. Calcd for $C_{14}H_{17}N_5O$ (271.32): C, 61.98; H, 6.32; N, 25.81. Found: C, 62.07; H, 6.21; N, 25.68.

*5.2.8. 4-(Imino(piperidin-1-yl)methyl)-1-methyl-1H-imidazol-5-amine **3h***

Compound **3h** (0.47 g, 2.30 mmol, 68%), was obtained as a white solid from (5-amino-1-methyl-1*H*-imidazol-4-yl)(imino)acetonitrile **1c** (0.50 g, 3.38 mmol) and piperidine (1.7 mL, 16.92 mmol). Mp 133–135 °C; IR (Nujol mull) 3332, 3109; 1606, 1578, 1522 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.57 (br s, 6H), 3.40–3.43 (m, 7H), 4.80–6.80 (s, 3H), 7.24 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 29.7, 45.8, 46.5, 54.6, 113.8, 130.7, 163.2. Anal. Calcd for $C_{10}H_{17}N_5$ (207.28): C, 57.95; H, 8.27; N, 33.79. Found: C, 57.80; H, 8.30; N, 33.90.

*5.2.9. 4-[Imino(morpholin-4-yl)methyl]-1-methyl-1H-imidazol-5-amine **3i***

Compound **3i** (0.21 g, 0.99 mmol, 66%), was obtained as an off-white solid from (5-amino-1-methyl-1*H*-imidazol-4-yl)(imino)-acetonitrile **1c** (0.22 g, 1.50 mmol) and morpholine (0.7 mL, 7.50 mmol). Mp 191–193 °C; IR (Nujol mull) 3338, 3311, 3235, 3185, 3111, 1613, 1584, 1555, 1512 cm^{-1}; ^1H NMR (300 MHZ, DMSO-d_6), δ (ppm): 3.24 (t, J=4.2 Hz, 4H), 3.38 (s, 3H), 3.64 (t, J=4.2 Hz, 4H), 5.46 (s, 2H), 6.92 (s, 1H), 7.09 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 29.7, 47.1, 66.0, 114.2, 130.4, 139.7, 163.8. Anal. Calcd for $C_9H_{15}N_5O$ (209.25): C, 51.66; H, 7.23; N, 33.47. Found: C, 51.60; H, 6.97; N, 33.46.

5.3. Synthesis of compound 6a

To a stirred suspension of **3b** (0.12 g, 0.42 mmol) in ethanol was added the 3,4-dihydroxybenzaldehyde (0.078 g, 1.3 equiv) and one equiv of DBU, at room temperature. A dark brown homogeneous solution was obtained. A solid started to precipitate after two days from a very complex mixture (evidence by TLC). After 17 days the solid in suspension was filtered and washed with diethyl ether and identified as compound **6a** (0.006 g, 0.028 mmol, 7%). Mp 238.1–239.0 °C. IR (Nujol mull) 3409, 3326, 3138, 1666 (C=O), 1655; ^1H NMR (300 MHZ, DMSO-d_6), δ (pm): 2.36 (s, 3H), 5.69 (s, 2H), 6.76 (br s, 1H), 6.90 (br s, 1H), 7.30 (s, 1H), 7.36 (s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.60, 112.89, 124.44, 129.64, 130.19, 132.07, 137.66, 142.61, 166.73. Anal. Calcd for $C_{11}H_{12}N_4O$ (216.23): C, 61.11; H, 5.59; N, 25.91. Found: C, 61.31; H, 5.57; N, 25.63.

5.4. General procedure for the synthesis of purines 4

5.4.1. Method A

To a stirred suspension of **3** in a mixture of acetonitrile/ethanol (1:1), 1.1 equiv of aldehyde and 10 equiv of triethylamine were added, at room temperature. A yellow solution developed and an off-white solid started to precipitate from solution after 10–41 days. When the TLC indicated absence of starting material, the reaction mixture was concentrated in the rotary evaporator and addition of acetonitrile led to a suspension that was filtered. The solid was washed with acetonitrile and diethyl ether and identified as compound **4**.

5.4.2. Method B

To a stirred suspension of **3** in ethanol, 1.1 equiv of aldehyde and 10 equiv of triethylamine were added, at room temperature. A yellow solution developed and an off-white solid started to precipitate from solution after 8–30 days. When the TLC indicated absence of starting material, the reaction mixture was concentrated

in the rotary evaporator and addition of acetonitrile led to a suspension that was filtered. The solid was washed with acetonitrile and diethyl ether and identified as compound **4**.

5.4.3. Method C

To a stirred suspension of **3** in DMSO, 1.1 equiv of aldehyde and 10 equiv of triethylamine were added, at room temperature. An orange solution was formed and the reaction was kept at room temperature or at 40 °C until TLC show the absence of starting material. The triethylamine was removed under reduced pressure and cold water was added to the solution. The crude product was filtered and washed abundantly with water and diethyl ether. The crude product was analysed by ^{1}H NMR and was purified by dry flash cromathography, when necessary, using dichloromethane as solvent.

*5.4.4. 2-(6-(Piperidin-1-yl)-9-p-tolyl-9H-purin-2-yl)phenol **4a***

Method A: Compound **4a** (0.12 g, 0.30 mmol, 65%), was obtained as an off-white solid from **3a** (0.13 g, 0.46 mmol) and salicylaldehyde (65 μL, 0.51 mmol). Mp 169–171 °C; IR (Nujol mull) 3106, 1698, 1589, 1574, 1513 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.71 (s, 6H), 2.42 (s, 3H, CH_3), 4.29 (s, 4H), 6.85 (d, J=7.8 Hz, 1H), 6.89 (t, J=7.8 Hz, 1H), 7.31 (dt, J=7.8, 1.8 Hz, 1H), 7.45 (d, J=8.1 Hz, 2H), 7.67 (d, J=8.1 Hz, 2H), 8.32 (dd, J=7.8, 1.8 Hz, 1H), 8.53 (s, 1H), 13.51 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.7, 24.2, 25.7, 46.2, 117.2, 118.0, 118.7, 119.3, 123.7, 128.9, 130.2, 132.1, 132.1, 137.9, 139.3, 148.8, 152.5, 158.1, 159.5. Anal. Calcd for $C_{23}H_{23}N_5O$ (385.46): C, 71.67; H, 6.01; N, 18.17. Found: C, 71.66; H, 5.95; N, 18.05.

*5.4.5. 3-(6-(Piperidin-1-yl)-9-p-tolyl-9H-purin-2-yl)phenol **4b***

Method B: Compound **4b** (0.11 g, 0.38 mmol, 65%), was obtained as an off-white solid from **3a** (0.16 g, 0.58 mmol) and 3-hydroxybenzaldehyde (0.08 g, 0.64 mmol). Mp 194–196 °C; IR (Nujol mull) 3105, 1659, 1611, 1574, 1515 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.65 (s, 6H), 2.40 (s, 3H), 4.28 (s, 4H), 6.81 (d, J=8.1 Hz, 1H), 7.23 (t, J=8.1 Hz, 1H), 7.43 (d, J=8.1 Hz, 2H), 7.79 (d, J=8.1 Hz, 4H), 8.51 (s, 1H), 9.20 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 24.3, 25.7, 45.6, 114.5, 116.8, 118.4, 118.6, 123.3, 129.1, 129.9, 132.6, 137.0, 138.9, 139.7, 151.3, 153.0, 157.3, 157.5. Anal. Calcd for $C_{23}H_{23}N_5O$ (385.46): C, 71.67; H, 6.01; N, 18.17. Found: C, 71.60; H, 5.80; N, 18.03.

*5.4.6. 4-(6-(Piperidin-1-yl)-9-p-tolyl-9H-purin-2-yl)phenol **4c***

Method A: Compound **4c** (0.10 g, 0.26 mmol, 53%), was obtained as an off-white solid from **3a** (0.14 g, 0.49 mmol) and 4-hydroxybenzaldehyde (0.07 g, 0.54 mmol).

Method B: A first crop of compound **4c** (0.11 g, 0.29 mmol, 49%), was obtained as an off-white solid from **3a** (0.16 g, 0.58 mmol) and 4-hydroxybenzaldehyde (0.08 g, 0.64 mmol). A second crop of compound **4c** (0.04 g, 0.10 mmol, 20%) was obtained as an off-white solid by addition of acetonitrile and water to the resulting mother liquor. Mp 243–245 °C; IR (Nujol mull) 3382, 3102, 1601, 1574, 1525, 1513 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.65 (s, 6H), 2.40 (s, 3H), 4.30 (s, 4H), 6.82 (d, J=8.4 Hz, 2H), 7.42 (d, J=8.4 Hz, 2H), 7.80 (d, J=8.4 Hz, 2H), 8.17 (d, J=8.4 Hz, 2H), 8.46 (s, 1H), 9.74 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 24.3, 25.7, 45.6, 114.9, 117.9, 123.1, 129.3 (2C), 129.9, 132.7, 136.9, 138.3, 151.4, 153.0, 157.8, 159.1. Anal. Calcd for $C_{23}H_{23}N_5O$ 0.1H_2O (387.26): C, 71.35; H, 6.00; N, 18.10. Found: C, 71.20; H, 6.25; N, 18.41.

*5.4.7. 4-(6-(piperidin-1-yl)-9-p-tolyl-9H-purin-2-yl)benzene-1,2-diol **4d***

Method C: The crude product **4d** (0.20 g) was obtained as a brown solid from **3a** (0.15 g, 0.54 mmol) and 3,4-dihydroxybenzaldehyde (0.08 g, 0.59 mmol). The solid was purified by dry flash chromatography on silica gel using 300 mL of dichloromethane as solvent to give **4d** (0.10 g, 0.25 mmol, 46%) as an off-white solid. Mp 233–235 °C; IR (Nujol mull) 3138, 1710, 1575, 1525 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.60–1.65 (m, 6H), 2.40 (s, 3H), 4.30 (s, 4H), 6.77 (d, J=8.4 Hz, 1H), 7.42 (d, J=8.1 Hz, 2H), 7.67 (dd, J=8.4, 2.1 Hz, 1H), 7.70–7.80 (m, 3H), 8.44 (s, 1H), 9.12 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.7, 24.4, 25.8, 45.6, 115.3 (2C), 117.9, 119.7, 123.3, 129.8, 129.9, 132.8, 136.9, 138.4, 144.8, 147.4, 151.4, 153.0, 157.9. Anal. Calcd for $C_{23}H_{23}N_5O_2$ 1.1H_2O (421.26): C, 65.60; H, 5.99; N, 16.63. Found: C, 65.60; H, 5.74; N, 16.41.

*5.4.8. 2-(6-Morpholino-9-p-tolyl-9H-purin-2-yl)phenol **4e***

Method C: Compond **4e** (0.13 g, 0.35 mmol, 79%), was obtained as a white solid from **3b** (0.13 g, 0.44 mmol) and salicylaldehyde (52 μL, 0.49 mmol) after triethylamine elimination under reduce pressure and addition of acetonitrile to the suspension. Mp 207–209 °C; IR (Nujol mull) 3234, 1598, 1576, 1509 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.42 (s, 3H), 3.79 (s, 4H), 4.30 (s, 4H), 6.85 (d, J=7.8 Hz, 1H), 6.89 (t, J=7.8 Hz, 1H), 7.31 (t, J=7.8 Hz, 1H), 7.45 (d, J=8.1 Hz, 2H), 7.65 (d, J=8.1 Hz, 2H), 8.32 (dd, J=7.8, 1.2 Hz, 1H), 8.54 (s, 1H), 13.32 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 45.5, 66.1, 117.2, 118.2, 118.6, 119.1, 123.7, 129.0, 130.2, 131.9, 132.1, 137.9, 139.7, 148.7, 152.7, 158.0, 159.4.Anal. Calcd for $C_{22}H_{21}N_5O_2$ 0.35H_2O (393.73): C, 67.10; H, 5.52; N, 17.80. Found: C, 66.99; H, 5.64; N, 17.43.

*5.4.9. 3-(6-Morpholino-9-p-tolyl-9H-purin-2-yl)phenol **4f***

Method B: Compound **4f** (0.27 g, 0.70 mmol, 63%), was obtained as a white solid from **3b** (0.32 g, 1.12 mmol) and 3-hydroxybenzaldehyde (0.16 g, 1.23 mmol). Mp 257–259 °C; IR (Nujol mull) 3337, 3121, 1605, 1581, 1524 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.41 (s, 3H), 3.78 (s, 4H), 4.43 (s, 4H), 6.82 (d, J=8.1 Hz, 1H), 7.24 (t, J=8.1 Hz, 1H), 7.44 (d, J=8.1 Hz, 2H), 7.78 (s, 1H), 7.79 (d, J=8.1 Hz, 3H), 8.56 (s, 1H), 9.46 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 45.3, 66.2, 114.5, 116.9, 118.6, 118.6, 123.4, 129.2, 129.9, 132.5, 137.2, 139.4, 139.5, 151.4, 153.2, 157.3, 157.5. Anal. Calcd for $C_{22}H_{21}N_5O_2$ 0.2H_2O (391.03): C, 67.59; H, 5.48; N, 17.92. Found: C, 67.88; H, 5.74; N, 17.57.

*5.4.10. 4-(6-Morpholino-9-p-tolyl-9H-purin-2-yl)phenol **4g***

Method C: Compound **4g** (0.24 g, 0.63 mmol, 84%), was obtained as an off-white solid from **3b** (0.21 g, 0.75 mmol) and 4-hydroxybenzaldehyde (0.10 g, 0.83 mmol). Mp 258–260 °C; IR (Nujol mull) 3382, 3124, 1597, 1575, 1521 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.40 (s, 3H), 3.77 (s, 4H), 4.30 (s, 4H), 6.82 (d, J=8.7 Hz, 2H), 7.42 (d, J=8.4 Hz, 2H), 7.79 (d, J=8.4 Hz, 2H), 8.19 (d, J=8.7 Hz, 2H), 8.50 (s, 1H), 9.83 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 45.2, 66.3, 115.0, 118.1, 123.2, 129.1, 129.4, 129.9, 132.7, 137.0, 138.9, 151.5, 153.2, 157.8, 159.3. Anal. Calcd for $C_{22}H_{21}N_5O_2$ 0.79H_2O (401.65): C, 65.80; H, 5.63; N, 17.45. Found: C, 65.78; H, 5.83; N, 17.44.

*5.4.11. 4-(6-Morpholino-9-p-tolyl-9H-purin-2-yl)benzene-1,2-diol **4h***

Method C: The crude product (0.23 g) was obtained as a brown solid from **3b** (0.18 g, 0.63 mmol) and 3,4-dihydroxybenzaldehyde (0.10 g, 0.69 mmol). The solid was purified by dry flash chromatography on silica gel using 400 mL of dichloromethane as solvent to give **4h** (0.08 g, 0.20 mmol, 32%). Mp 270–272 °C; IR (Nujol mull) 3296, 1710, 3226, 1590, 1569, 1524 cm-1; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.41 (s, 3H), 3.78 (s, 4H), 4.31 (s, 4H), 6.77 (d, J=8.1 Hz, 1H), 7.43 (d, J=8.4 Hz, 2H), 7.68 (dd, J=8.1, 2.1 Hz, 1H), 7.78 (d, J=2.1 Hz, 1H), 7.79 (d, J=8.4 Hz, 2H), 8.50 (s, 1H), 9.03 (s, 1H), 9.19 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 45.3, 66.3, 115.25, 115.28, 118.1, 119.8, 123.3, 129.6, 129.9, 132.7, 137.0, 138.9, 144.8, 147.5, 151.5, 153.1, 157.9. Anal. Calcd for $C_{22}H_{21}N_5O_3$ 0.3H_2O (408.83): C, 64.64; H, 5.29; N, 17.14. Found: C, 64.63; H, 5.23; N, 17.16.

5.4.12. 2-(6-Thiomorpholino-9-p-tolyl-9H-purin-2-yl)phenol ***4i***

Method A: Compound **4i** (0.13 g, 0.32 mmol, 85%), was obtained as a white solid from **3c** (0.11 g, 0.38 mmol) and salicylaldehyde (60.9 μL, 0.57 mmol, 1.5 equiv). Mp 203–205 °C; IR (Nujol mull) 3234, 1588, 1567, 1525, 1509 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.42 (s, 3H), 2.80 (s, 4H), 4.60 (s, 4H), 6.86 (d, J=8.3 Hz, 1H), 6.91 (t, J=8.3 Hz, 1H), 7.32 (dt, J=8.3, 1.8 Hz, 1H), 7.45 (d, J=8.7 Hz, 2H), 7.66 (d, J=8.7 Hz, 2H), 8.32 (dd, J=8.3, 1.8 Hz, 1H), 8.56 (s, 1H), 13.31 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 26.5, 47.9, 117.2, 118.2, 118.7, 119.2, 123.8, 129.0, 130.2, 131.9, 132.1, 138.0, 139.7, 148.8, 152.5, 158.0, 159.4. Anal. Calcd for $C_{22}H_{21}N_5OS$ $0.5H_2O$ (412.50): C, 64.08; H, 5.34; N, 16.99; S, 7.77. Found: C, 64.00; H, 5.56; N, 16.99; S, 7.66.

5.4.13. 3-(6-Thiomorpholino-9-p-tolyl-9H-purin-2-yl)phenol ***4j***

Method B: Compound **4j** (0.16 g, 0.40 mmol, 66%), was obtained as an off-white solid from **3c** (0.18 g, 0.62 mmol) and 3-hydroxybenzaldehyde (0.08 g, 0.67 mmol). Mp 267–269 °C; IR (Nujol mull) 3325, 3166, 1664, 1560, 1582, 1525 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.40 (s, 3H), 2.77 (s, 4H), 4.61 (s, 4H), 6.82 (d, J=7.8 Hz, 1H), 7.24 (t, J=7.8 Hz, 1H), 7.43 (d, J=7.8, 2H), 7.77 (s, 1H), 7.79 (d, J=7.8 Hz, 3H), 8.54 (s, 1H), 9.48 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 26.5, 47.5, 114.5, 116.9, 118.6 (2C), 123.4, 129.2, 129.9, 132.5, 137.2, 139.4, 139.5, 151.4, 152.9, 157.3, 157.6. Anal. Calcd for $C_{22}H_{21}N_5OS$ H_2O (421.50): C, 62.71; H, 5.46; N, 16.60; S, 7.60. Found: C, 62.48; H, 5.59; N, 16.25; S, 7.68.

5.4.14. 4-(6-Thiomorpholino-9-p-tolyl-9H-purin-2-yl)phenol ***4k***

Method A: Compound **4k** (0.09 g, 0.23 mmol, 56%), was obtained as an off-white solid from **3c** (0.12 g, 0.41 mmol) and 4-hydroxybenzaldehyde (0.06 g, 0.45 mmol).

Method C: Compound **4k** (0.14 g, 0.35 mmol, 80%), was obtained as an off-white solid from **3c** (0.13 g, 0.44 mmol) and 4-hydroxybenzaldehyde (0.06 g, 0.48 mmol). Mp 264–266 °C; IR (Nujol mull) 3112, 1595, 1573, 1526, 1509 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.40 (s, 3H), 2.77 (s, 4H), 4.60 (s, 4H), 6.82 (d, J=8.0 Hz, 2H), 7.43 (d, J=8.4 Hz, 2H), 7.80 (d, J=8.4 Hz, 2H), 8.17 (d, J=8.0 Hz, 2H), 8.51 (s, 1H), 9.81 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 26.5, 47.5, 115.04, 118.10, 123.2, 129.1, 129.4, 129.9, 132.6, 137.0, 138.9, 151.5, 152.9, 157.8, 159.3. Anal. Calcd for $C_{22}H_{21}N_5OS$ $0.38H_2O$ (408.90): C, 64.41; H, 5.31; N, 17.08; S, 7.81. Found: C, 64.41; H, 5.40; N, 16.80; S, 7.68.

5.4.15. 4-(6-Thiomorpholino-9-p-tolyl-9H-purin-2-yl)benzene-1,2-diol ***4l***

Method C: The crude product **4l** (0.16 g) was obtained as a brown solid from **3c** (0.16 g, 0.53 mmol) and 3,4-dihydroxybenzaldehyde (0.08 g, 0.58 mmol). The solid was purified by dry flash chromatography on silica gel using 300 mL of dichloromethane as solvent to give **4l** (0.10 g, 0.24 mmol, 45%) as a white solid. Mp 275–277 °C; IR (Nujol mull) 3136, 1618, 1572, 1526 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.41 (s, 3H), 2.76 (m, 4H), 4.60 (s, 4H), 6.73 (d, J=8.4 Hz, 1H), 7.43 (d, J=8.1 Hz, 2H), 7.70 (dd, J=8.4, 2.1 Hz, 1H), 7.79 (d, J=8.1 Hz, 3H), 8.53 (s, 1H), 9.05 (s, 1H), 9.23 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 36.2, 44.5, 115.27 (2C), 118.3, 119.8, 123.3, 129.5, 129.9, 132.6, 137.1, 139.1, 144.9, 147.6, 151.6, 152.8, 158.0. Anal. Calcd for $C_{22}H_{21}N_5O_2S$ $1.5H_2O$ (446.50): C, 59.19; H, 5.38; N, 15.69; S, 7.17. Found: C, 59.37; H, 5.30; N, 15.63; S, 7.03.

5.4.16. 2-(6-(Pyrrolidin-1-yl)-9-p-tolyl-9H-purin-2-yl)phenol ***4m***

Method A: Compound **4m** (0.12 g, 0.33 mmol, 81%), was obtained as a white solid from **3d** (0.11 g, 0.41 mmol) and salicylaldehyde (48 μL, 0.45 mmol). Mp 235–237 °C; IR (Nujol mull) 3102, 1603, 1590, 1557, 1525, 1515 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.01 (s, 4H), 2.41 (s, 3H), 3.72 (s, 2H), 4.15 (s, 2H), 6.86 (d, J=7.7 Hz, 1H), 6.87 (t, J=7.7 Hz, 1H), 7.30 (dt, J=7.7, 1.2 Hz, 1H), 7.44 (d, J=8.4 Hz, 2H), 7.74 (d, J=8.4 Hz, 2H), 8.30 (dd, J=7.7, 1.2 Hz, 1H), 8.53 (s, 1H), 13.94 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 23.7, 25.8, 47.3, 48.9, 117.3, 118.3, 118.5, 119.2, 123.4, 128.7, 130.1, 132.0, 132.3, 137.5, 139.9, 149.0, 151.1, 158.3, 159.7. Anal. Calcd for $C_{22}H_{21}N_5O$ $0.3H_2O$ (376.84): C, 70.14; H, 5.74; N, 18.60. Found: C, 70.39; H, 5.75; N, 18.61.

5.4.17. 3-(6-(Pyrrolidin-1-yl)-9-p-tolyl-9H-purin-2-yl)phenol ***4y***

Method B: Compound **4y** (0.09 g, 0.26 mmol, 54%), was obtained as an off-white solid from **3d** (0.13 g, 0.48 mmol) and 3-hydroxybenzaldehyde (0.07 g, 0.53 mmol). Mp 227–229 °C; IR (Nujol mull) 3163, 3122, 1584, 1523, 1510 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.00 (s, 4H), 2.40 (s, 3H), 3.81 (s, 2H), 4.12 (s, 2H), 6.81 (dd, J=7.8, 1.8 Hz, 1H), 7.23 (t, J=7.8 Hz, 1H), 7.43 (d, J=7.8 Hz, 2H), 7.82 (d, J=7.8 Hz, 4H), 8.49 (s, 1H), 9.43 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 23.7, 25.8, 46.9, 48.4, 114.6, 116.7, 118.6, 118.9, 123.0, 129.0, 129.9, 132.8, 136.8, 139.2, 139.8, 150.6, 152.4, 157.2, 157.8. Anal. Calcd for $C_{22}H_{21}N_5O$ (371.44): C, 71.14; H, 5.70; N, 18.85. Found: C, 71.15; H, 5.92; N, 19.18.

5.4.18. 4-(6-(Pyrrolidin-1-yl)-9-p-tolyl-9H-purin-2-yl)phenol ***4n***

Method A: Compound **4n** (0.11 g, 0.29 mmol, 71%), was obtained as an off-white solid from **3d** (0.11 g, 0.41 mmol) and 4-hydroxybenzaldehyde (0.06 g, 0.45 mmol). Mp 260–262 °C; IR (Nujol mull) 3069, 1596, 1581, 1526, 1510 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.95 (s, 4H), 2.38 (s, 3H), 3.76 (s, 2H), 4.06 (s, 2H), 6.83 (d, J=8.7 Hz, 2H), 7.38 (d, J=8.1 Hz, 2H), 7.81 (d, J=8.1 Hz, 2H), 8.22 (d, J=8.7 Hz, 2H), 8.39 (s, 1H), 9.74 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 23.6, 25.8, 46.9, 48.3, 114.9, 118.4, 122.7, 129.3, 129.5, 129.8, 132.9, 136.6, 138.6, 150.7, 152.4, 158.0, 159.1. Anal. Calcd for $C_{22}H_{21}N_5O$ $0.44H_2O$ (379.36): C, 69.67; H, 5.77; N, 18.47. Found: C, 69.66; H, 5.96; N, 16.26.

5.4.19. 2-(6-(Dimethylamino)-9-p-tolyl-9H-purin-2-yl)phenol ***4o***

Method B: Compound **4o** (0.06 g, 0.18 mmol, 66%), was obtained as an off-white solid from **3e** (0.07 g, 0.28 mmol) and salicylaldehyde (33 μL, 0.30 mmol), after addition of water to the crude mixture, instead of acetonitrile. Mp 212–215 °C; IR (Nujol mull) 1698, 1560, 1512 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.42 (s, 3H), 3.40–4.00 (br s, 6H), 6.87 (d, J=8.8 Hz, 1H), 6.89 (t, J=8.8 Hz, 1H), 7.31 (dt, J=8.0, 1.8 Hz, 1H), 7.45 (d, J=8.4 Hz, 2H), 7.70 (d, J=8.4 Hz, 2H), 8.33 (dd, J=8.0, 1.8 Hz, 1H), 8.54 (s, 1H), 13.70 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 38.0, 117.2, 118.2, 118.5, 119.2, 123.5, 128.8, 130.1, 131.9, 132.1, 137.6, 139.3, 148.8, 153.3, 157.9, 159.5. Anal. Calcd for $C_{20}H_{19}N_5O$ (345.40): C, 69.55; H, 5.54; N, 20.28. Found: C, 69.79; H, 5.77; N, 20.41.

5.4.20. 3-(6-(Dimethylamino)-9-p-tolyl-9H-purin-2-yl)phenol ***4p***

Method B: Compound **4p** (0.04 g, 0.10 mmol, 34%), was obtained as an off-white solid from **3e** (0.07 g, 0.30 mmol) and 3-hydroxybenzaldehyde (0.04 g, 0.34 mmol). Mp 184–186 °C; IR (Nujol mull) 3333, 3106, 1647, 1585, 1530 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ (ppm): 2.40 (s, 3H), 3.56 (s, 6H), 6.82 (dd, J=8.1, 1.5 Hz, 1H), 7.23 (t, J=8.1 Hz, 1H), 7.43 (d, J=8.1 Hz, 2H), 7.80 (s, 1H), 7.79 (d, J=8.1 Hz, 3H), 8.51 (s, 1H), 9.48 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 38.0, 114.6, 116.8, 118.6, 118.8, 123.2, 129.1, 129.9, 132.7, 137.0, 138.9, 139.7, 151.0, 154.2, 157.3, 157.5. Anal. Calcd for $C_{20}H_{19}N_5$ $0.5H_2O$ (354.40): C, 67.79; H, 5.65; N, 19.77. Found: C, 67.63; H, 5.78; N, 19.58.

5.4.21. 4-(6-(Dimethylamino)-9-p-tolyl-9H-purin-2-yl)phenol ***4q***

Method C: Compound **4q** (0.12 g, 0.34 mmol, 61%), was obtained as an off-white solid from **3e** (0.14 g, 0.56 mmol) and 4-hydroxybenzaldehyde (0.07 g, 0.62 mmol). Mp 228–230 °C; IR (Nujol mull) 3423, 3177, 1601, 1586, 1565, 1519 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6), δ (ppm): 2.39 (s, 3H), 3.54 (s, 6H), 6.82 (dd, J=7.0, 2.0 Hz, 2H),

7.41 (d, J=8.0 Hz, 2H), 7.80 (d, J=8.0 Hz, 2H), 8.20 (dd, J=7.0, 2.0 Hz, 2H), 8.45 (s, 1H), 9.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 20.6, 37.8, 114.09, 118.24, 123.0, 129.30, 129.31, 129.9, 132.8, 136.8, 138.3, 151.1, 154.1, 157.6, 159.2. Anal. Calcd for $C_{20}H_{19}N_5O$ 0.8H_2O (359.80): C, 66.78; H, 5.73; N, 19.48. Found: C, 66.80; H, 6.01; N, 19.50.

5.4.22. 2-(9-Phenyl-6-(piperidin-1-yl)-9H-purin-2-yl)phenol ***4r***

Method A: Compound **4r** (0.14 g, 0.38 mmol, 70%), was obtained as a white solid from **3f** (0.15 g, 0.55 mmol) and salicylaldehyde (64 μL, 0.61 mmol). Mp 164–166 °C; IR (Nujol mull) 3115, 1731, 1605, 1563, 1516 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.71 (s, 6H), 4.29 (s, 4H), 6.86 (d, J=8.0 Hz, 1H), 6.90 (t, J=8.0 Hz, 1H), 7.31 (td, J=8.0, 1.5 Hz, 1H), 7.53 (t, J=7.5 Hz, 1H), 7.66 (t, J=7.5 Hz, 2H), 7.81 (d, J=7.5 Hz, 2H), 8.33 (dd, J=8.0, 1.5 Hz, 1H), 8.58 (s, 1H), 13.50 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 24.1, 25.7, 46.0, 117.2, 118.0, 118.6, 119.3, 123.8, 128.1, 128.9, 129.7, 132.0, 134.5, 139.2, 148.8, 152.4, 158.1, 159.4. Anal. Calcd for $C_{22}H_{21}N_5O$ (371.44): C, 71.14; H, 5.70; N, 18.85. Found: C, 71.19; H, 5.72; N, 18.94.

5.4.23. 4-(9-Phenyl-6-(piperidin-1-yl)-9H-purin-2-yl)phenol ***4s***

Method A: Compound **4s** (0.08 g, 0.21 mmol, 47%), was obtained as an off-white solid from **3f** (0.15 g, .55 mmol) and 4-hydroxybenzaldehyde (0.06 g, 0.48 mmol). Mp 253–255 °C; IR (Nujol mull) 3141, 1612, 1595, 1574, 1561, 1517 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.65 (s, 6H), 4.30 (s, 4H), 6.83 (d, J=8.7 Hz, 2H), 7.46 (t, J=7.5 Hz, 1H), 7.63 (t, J=7.5 Hz, 2H), 7.95 (d, J=7.5 Hz, 2H), 8.18 (d, J=8.7 Hz, 2H), 8.51 (s, 1H), 9.78 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 24.4, 25.7, 45.6, 115.0, 118.0, 123.2, 127.3, 129.2, 129.3, 129.5, 135.3, 138.3, 151.4, 153.1, 159.2. Anal. Calcd for $C_{22}H_{21}N_5O$ 0.2H_2O (375.04): C, 70.48; H, 5.71; N, 18.69. Found: C, 70.46; H, 5.89; N, 18.43.

5.4.24. 2-(6-Morpholino-9-phenyl-9H-purin-2-yl)phenol ***4t***

Method A: Compound **4t** (0.14 g, 0.37 mmol, 72%), was obtained as a white solid from **3g** (0.14 g, 0.52 mmol) and salicylaldehyde (62 μL, 0.57 mmol). Mp 201–203 °C; IR (Nujol mull) 3106, 1741, 1605, 1567, 1518 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 3.81 (s, 4H), 4.25 (s, 4H), 6.86 (d, J=7.5 Hz, 1H), 6.90 (t, J=8.0 Hz, 1H), 7.32 (td, J=8.0, 1.8 Hz, 1H), 7.54 (t, J=7.5 Hz, 1H), 7.66 (t, J=7.5 Hz, 2H), 7.79 (d, J=7.2 Hz, 2H), 8.34 (dd, J=8.0, 1.8 Hz, 1H), 8.61 (s, 1H), 13.31 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 45.3, 66.1, 117.2, 118.2, 118.6, 119.1, 123.8, 128.2, 129.0, 129.8, 132.1, 134.4, 139.6, 148.7, 152.7, 158.0, 159.4. Anal. Calcd for $C_{21}H_{19}N_5O_2$ 0.33H_2O (379.35): C, 66.49; H, 5.19; N, 18.47. Found: C, 66.62; H, 5.04; N, 18.55.

5.4.25. 4-(6-Morpholino-9-phenyl-9H-purin-2-yl)phenol ***4u***

Method C: Compound **4u** (0.24 g, 0.65 mmol, 82%), was obtained as an off-white solid from **3g** (0.22 g, 0.80 mmol) and 4-hydroxybenzaldehyde (0.11 g, 0.88 mmol) after elimination of triethylamine under reduced pressure and water addition. Mp 262–264 °C; IR (Nujol mull) 3535, 3090, 1595, 1579, 1518 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 3.78 (s, 4H), 4.31 (s, 4H), 6.83 (d, J=6.9 Hz, 2H), 7.47 (t, J=8.1 Hz, 1H), 7.63 (t, J=8.1 Hz, 2H), 7.94 (d, J=8.1 Hz, 2H), 8.19 (d, J=6.9 Hz, 2H), 8.56 (s, 1H), 9.78 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 45.2, 66.3, 115.0, 118.2, 123.2, 127.5, 129.1, 129.4, 129.6, 135.2, 138.9, 151.5, 153.2, 157.8, 159.3. Anal. Calcd for $C_{21}H_{19}N_5O_2$ H_2O (391.41): C, 64.45; H, 5.37; N, 17.90. Found: C, 64.37; H, 5.52; N, 17.80.

5.4.26. 4-(6-Morpholino-9-phenyl-9H-purin-2-yl)benzene-1,2-diol ***4v***

Method C: The crude product **4v** (0.24 g), was obtained as a brown solid from **3g** (0.19 g, 0.71 mmol) and 3,4-dyhydroxybenzaldehyde (0.11 g, 0.78 mmol). The solid was purified by dry flash chromatography on silica gel using 300 mL of dichloromethane as solvent to give **4v** (0.09 g, 0.23 mmol, 33%). Mp 291–293 °C; IR (Nujol mull) 3321, 1577, 1515 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 3.78 (m, 4H), 4.31 (s, 4H), 6.78 (d, J=8.1 Hz, 1H), 7.48 (t, J=8.4 Hz, 1H), 7.64 (t, J=8.4 Hz, 2H), 7.70 (dd, J=8.1, 1.8 Hz, 1H), 7.79 (d, J=1.8 Hz, 1H), 7.94 (d, J=8.4 Hz, 2H), 8.54 (s, 1H), 13.32 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 20.6, 45.5, 66.1, 117.2, 118.2, 118.6, 119.1, 123.7, 129.0, 130.2, 131.9, 132.1, 137.9, 139.7, 148.7, 152.7, 158.0, 159.4. Anal. Calcd for $C_{21}H_{19}N_5O_3$ 0.34H_2O (393.53): C, 63.78; H, 4.98; N, 17.72. Found: C, 63.77; H, 5.00; N, 17.78.

5.4.27. 4-(9-Methyl-6-morpholino-9H-purin-2-yl)phenol ***4x***

Method C: Compound **4x** (0.10 g, 0.31 mmol, 80%), was obtained as an off-white solid from **3i** (0.11 g, 0.39 mmol) and 4-hydroxybenzaldehyde (0.05 g, 0.43 mmol). Mp 247–249 °C; IR (Nujol mull) 3420, 3175, 1610, 1573, 1516 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 3.74 (s, 4H), 3.75 (s, 3H), 4.25 (s, 4H), 6.83 (d, J=9.0 Hz, 2H), 8.09 (s, 1H), 8.24 (d, J=8.7 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 29.3, 45.1, 66.3, 114.9, 117.6, 129.30, 129.33, 140.7, 152.2, 152.9, 157.1, 159.1. Anal. Calcd for $C_{16}H_{17}N_5O_2$ 1.8H_2O (343.74): C, 55.91; H, 5.99; N, 20.38. Found: C, 55.92; H, 5.75; N, 20.18.

5.4.28. 4-(9-methyl-6-morpholino-9H-purin-2-yl)benzene-1,2-diol ***4z***

Method C: Compound **4z** (0.10 g, 0.32 mmol, 72%), was obtained as an off-white solid from **3i** (0.13 g, 0.44 mmol) and 3,4-dihydroxybenzaldehyde (0.07 g, 0.48 mmol). Mp 264–266 °C; IR (Nujol mull) 3459, 3219, 3114, 1579, 1529 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 3.75 (s, 4H), 3.76 (s, 3H), 4.25 (s, 4H), 6.77 (d, J=8.1 Hz, 1H), 7.73 (dd, J=8.1, 2.4 Hz, 1H), 7.85 (d, J=2.4 Hz, 1H), 8.09 (s, 1H), 9.09 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 29.4, 45.1, 66.3, 115.2 (2C), 117.6, 119.7, 129.8, 140.7, 144.8, 147.3, 152.2, 152.9, 157.3. Anal. Calcd for $C_{16}H_{17}N_5O_3$ 0.27H_2O (332.20): C, 57.86; H, 5.28; N, 21.09. Found: C, 57.86; H, 5.33; N, 20.82.

5.4.29. 4-(9-Methyl-6-(piperidin-1-yl)-9H-purin-2-yl)phenol ***4w***

Method A: Compound **4w** (0.09 g, 0.29 mmol, 48%), was obtained as an off-white solid from **3h** (0.13 g, 0.61 mmol) and 4-hydroxybenzaldehyde (0.08 g, 0.67 mmol) after triethylamine elimination under reduce pressure and addition of acetonitrile to the solution. Mp 270 °C (dec); IR (Nujol mull) 3210, 3125, 1596, 1568, 1516 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 1.60 (s, 6H), 3.75 (s, 3H), 4.24 (s, 4H), 6.83 (d, J=8.4 Hz, 2H), 8.04 (s, 1H), 8.22 (d, J=8.4 Hz, 2H), 9.73 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6), δ (ppm): 25.7, 24.4, 29.3, 45.5, 114.9, 117.4, 129.3, 129.5, 140.1, 152.0, 152.9, 157.1, 159.0. Anal. Calcd for $C_{17}H_{19}N_5O$ 0.38H_2O (316.21): C, 64.59; H, 6.26; N, 22.16. Found: C, 64.59; H, 6.21; N, 21.97.

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