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SYNTHESIS OF NOVEL ANGULAR AND LINEAR FUSED [5-6-5] HETEROCYCLES BY THE REACTION OF METHYL CYANO-(3-CYANO-4,5-DIHYDRO-2(3*H*)-FURANYLIDENE)ACETATE WITH HYDRAZINES AND DIMETHYLFORMAMIDE DIMETHYL ACETAL

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Abstract – A convenient and efficient method for the synthesis of novel angular and linear fused [5-6-5] three heterocycles is described. Methyl cyano-(3-cyano-4,5-dihydro-2(3*H*)-furanylidene)acetate (**1**) was reacted with an excess of hydrazine monohydrate to give 3,4'-bipyrazole **5**. Compound **5** was condensed with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) to yield angular dipyrazolopyrimidine **6**. On the other hand, pyrazoles **3b-d** were obtained by reaction of **1** with hydrazines. Compounds **3b-d** were reacted with hydrazine monohydrate, pyrazolopyridines **7a-c** were taken. Compounds **7a-c** were condensed with DMFDMA to give linear pyrazolotriazolopyridines **8a-c**.

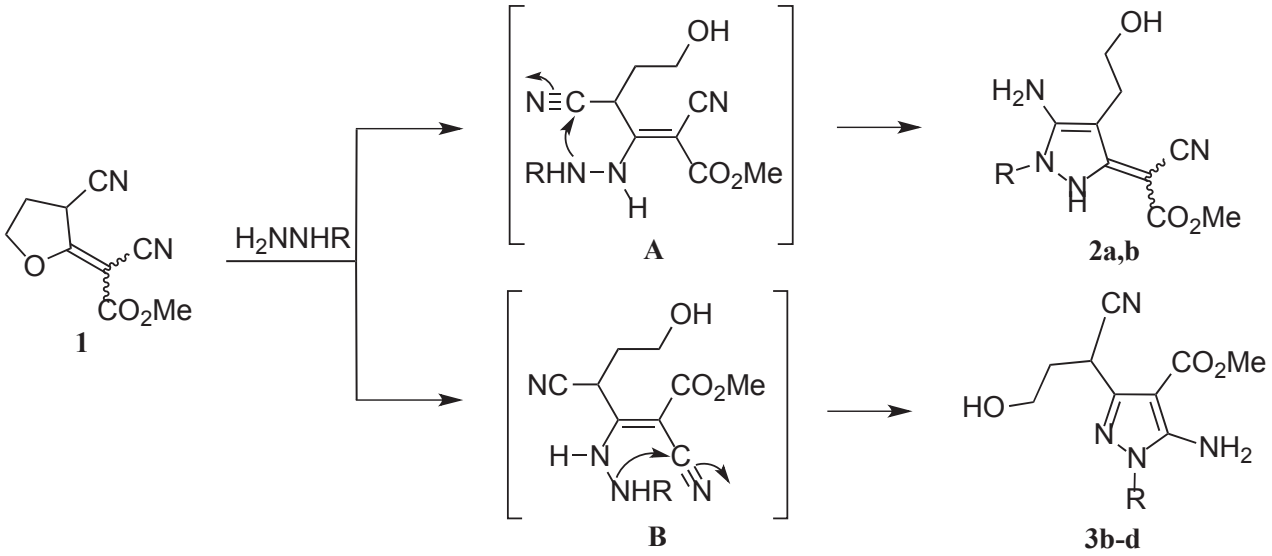
INTRODUCTION

Fused [5-6-5] three heterocyclic compounds are used as intermediates for synthesizing bioactive substances and biologically active substances.[1] For this reason, syntheses of various fused [5-6-5] heterocyclic compounds have been carried out.[2] In particular, many angular fused [5-6-5] heterocyclic compounds containing nitrogen atom are reported to exhibit IκB kinase inhibitory activity,[3] xanthine oxidase inhibition,[4] Janus kinase 1 and Janus kinase 2 inhibitory activity,[5] and adenosine A_1, and A_{2a} receptor inhibitor,[6] adenosine A_3 receptor affinity[7] and inhibitory activity.[8] On the other hand, it has been reported that a linear fused [5-6-5] heterocyclic compound containing nitrogen atom has antiviral action.[9] Therefore, efficient synthesis of angular type and linear type nitrogen-containing fused [5-6-5] heterocyclic compounds was carried out using compound **1** of the starting material already reported in our previous literature.[10]

RESULTS AND DISCUSSION

When **1** as a starting material was reacted with hydrazine monohydrate in 1,2-dichlorobenzene, ring opening reaction of **1** and then cyclization reaction of intermediate progressed, pyrazole **2a** (80%) was obtained, unlike the report by Patzel *et al*.[11] The product **2a** gave satisfactory spectroscopic date consistent with their assigned structure (experimental section). The IR spectra of **2a** display bands in the range of 3272-3583 cm^{-1} due to a primary amino group, two secondary amino groups, and hydroxyl group, and a band of 2169 cm^{-1} due to a conjugated cyano group, and a band of 1644 cm^{-1} due to a ester carbonyl group.

When compound **1** is reacted with methylhydrazine in 1,2-dichlorobenzene at room temperature for 24 h, pyrazole **2b** is formed in 66%. Furthermore, when compound **1** and methylhydrazine are reacted in 1,4-dioxane at room temperature for 24 h, 16% of pyrazole **2b** and 79% of the pyrazole **3b** were obtained, and when compound **1** was reacted with phenylhydrazine and/or 4-methoxyphenylhydrazine hydrochloride/triethylamine, the corresponding pyrazoles **3c,d** were synthesized, respectively. The IR spectra of **3b-d** display bands in the range of 3226-3533 cm^{-1} due to a primary amino group and a hydroxyl group, and a band of near 2248 cm^{-1} due to a non-conjugated cyano group. The ^{1}H NMR spectrum of **3b-d** in DMSO-d_6 exhibits two two-proton singlet near δ 2.05 and 3.55 due to the 3-hydroxypropyl methylene protons, and a one-proton singlet near δ 4.53 assignable to the 3-hydroxypropyl 1-methine proton, D_2O exchangeable three two-protons singles δ 3.35, 5.97, 9.36 due to the secondary amino protons. The ^{13}C NMR spectrum of **3b-d** shows a signal δ 27 due to the 3-hydroxypropyl 1-methine carbon, and two signals near δ 34 and 58 due to the two methylene carbons of 3-hydroxypropyl group. The formation of **2a,b** and **3b-d** can be explained by the mechanism shown in Scheme 1. Therefore, the reaction between compound **1** and hydrazines probably results in an intermediate by ring opening of tetrahydrofuran of compound **1**, pyrazole **2a,b** are formed by an intramolecular cyclization reaction of between the cyano group at the 4-position of the intermediate and the hydrazinyl group. It is also considered that pyrazole **3b-d** are formed by an intramolecular cyclization reaction between the cyano group at the 2-position of the intermediate and the hydrazinyl group. The reason why the compound **2** or **3** is selectively formed is that the steric structure of the intermediate is determined by the steric bulkiness of the substituent R of the hydrazine. That is, when the substituent is a small functional group, since the steric hindrance between the substituent R of the intermediate and the cyano group at the 4-position is small, **2** is produced via intermediate **A**. When the substituent R is bulky, it is considered that **3** is formed through a ring closure reaction with the cyano group at the 2-position via the intermediate **B** because of the steric hindrance with the cyano group at the 4-position of the intermediate.



a: R = H, **b**: R = Me, **c**: R = Ph, **d**: R = 4-$MeOC_6H_4$

Scheme 1

Table 1. Synthesis of pyrazoles **2a,b** and **3b-d** by reaction of **1** and hydrazines

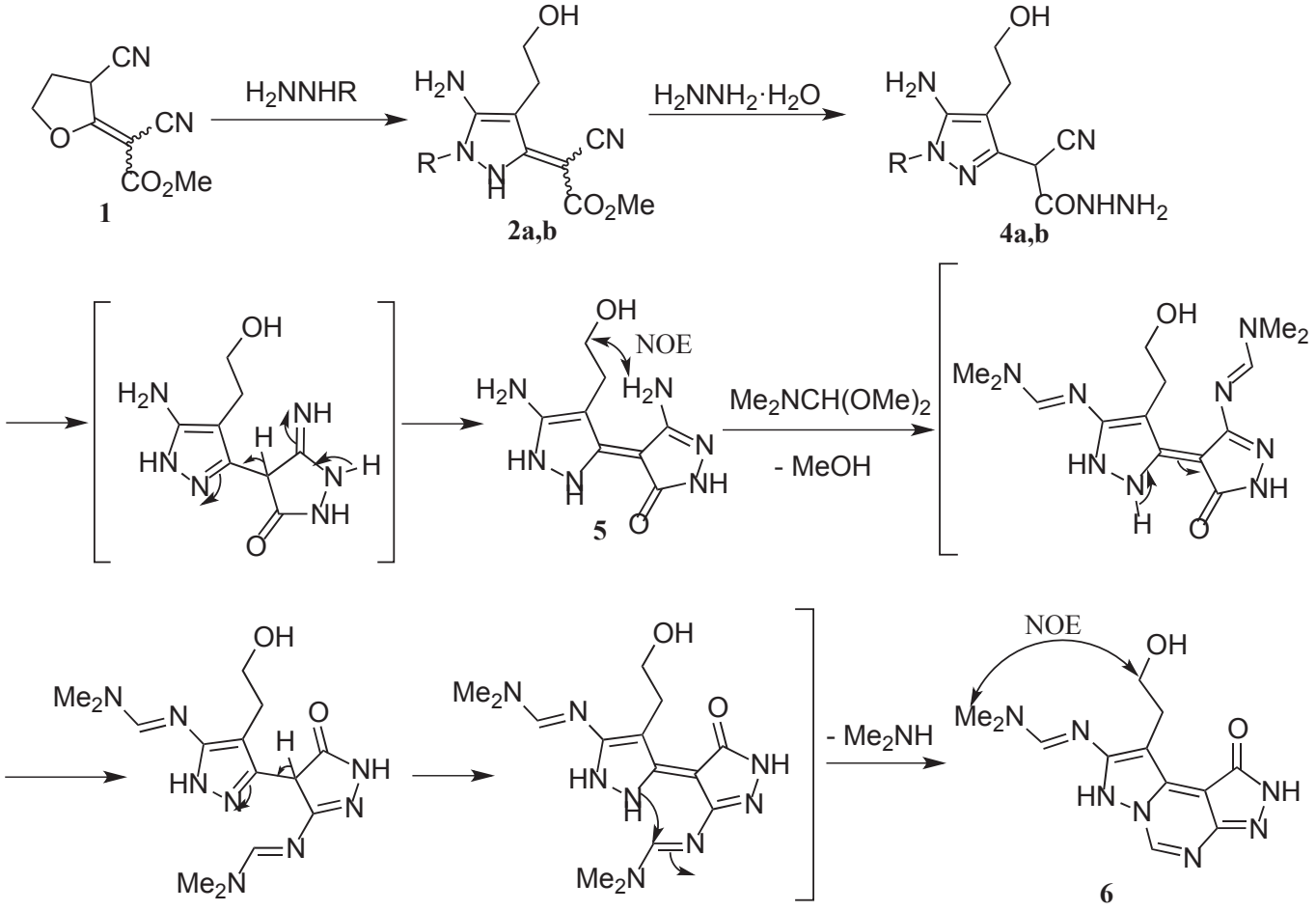
Entry	$RHNNH_2$	Solvent	Temp. Time	Product	Yield (%)
1	$H_2NNH_2 \cdot H_2O$	1,2-dichlorobenzene	rt, 24 h	**2a**	80
2	$H_2NNH_2 \cdot H_2O$	1,4-dioxane	rt, 24 h	**2a**	67
3	$MeHNNH_2$	1,2-dichlorobenzene	rt, 24 h	**2b**	66
4	$MeHNNH_2$	1,4-dioxane	rt, 24 h	**2b/3b**	15/79[a)]
5	$PhHNNH_2$	1,2-dichlorobenzene	rt, 24 h	**3c**	90
6	$PhHNNH_2$	1,4-dioxane	rt, 24 h	**3c**	95
7	4-$MeOC_6H_4HNNH_2 \cdot HCl$ / Et_3N	1,2-dichlorobenzene	rt, 24 h	**3d**	83
8	4-$MeOC_6H_4HNNH_2 \cdot HCl$ / Et_3N	1,4-dioxane	rt, 24 h	**3d**	86

a) Isolated yield.

Reaction of **2a** with hydrazine monohydrate gave 3,4'-bipyrazole **5**, but hydrazide **4a** cannot be isolated. The IR spectra of **5** show bands 3455, 3415, 3339, 3138 cm^{-1} due to a primary amino group, two secondary amino groups, and a hydroxyl group, 1637 cm^{-1} due to an amide carbonyl group. The ^1H NMR spectrum of **5** in DMSO-d_6 exhibits D_2O exchangeable three two-protons singles δ 3.35, 5.97, 9.36 due to the secondary amino protons. The ^{13}C NMR spectrum of **5** shows a signal δ 168.2 due to the carbonyl carbon. The stereochemistry of **5** was assigned by mean of NOE between the 3-amino proton of

pyrazolone and methylene protons at the 2-position of 2-hydroxyethyl group. In the NOESY spectra of **5**, the NOE showed that these groups are located on the same side of the 2-hydroxyethyl group.

On the other hand, when pyrazole **2b** was reacted with hydrazine monohydrate, hydrazide **4b** was obtained. Furthermore, **4b** was reacted with hydrazine monohydrate, but **4b** decomposed and no expected 3,4'-bipyrazole was produced. The IR spectra of **4b** display bands in the range of 3264-3437 cm^{-1} due to an amino group and a hydroxyl group, 2245 cm^{-1} due to a non-conjugated cyano group, and 1679 cm^{-1} due to a carbonyl group. The ^1H NMR spectrum of **4b** in DMSO-d_6 exhibits D_2O exchangeable a proton single δ 4.68 due to the secondary amino proton, and D_2O exchangeable two two-protons singles δ 5.02, 9.16 due to the primary amino protons. The ^{13}C NMR spectrum of **4b** shows a signal δ 163.5 due to the carbonyl carbon.



Scheme 2

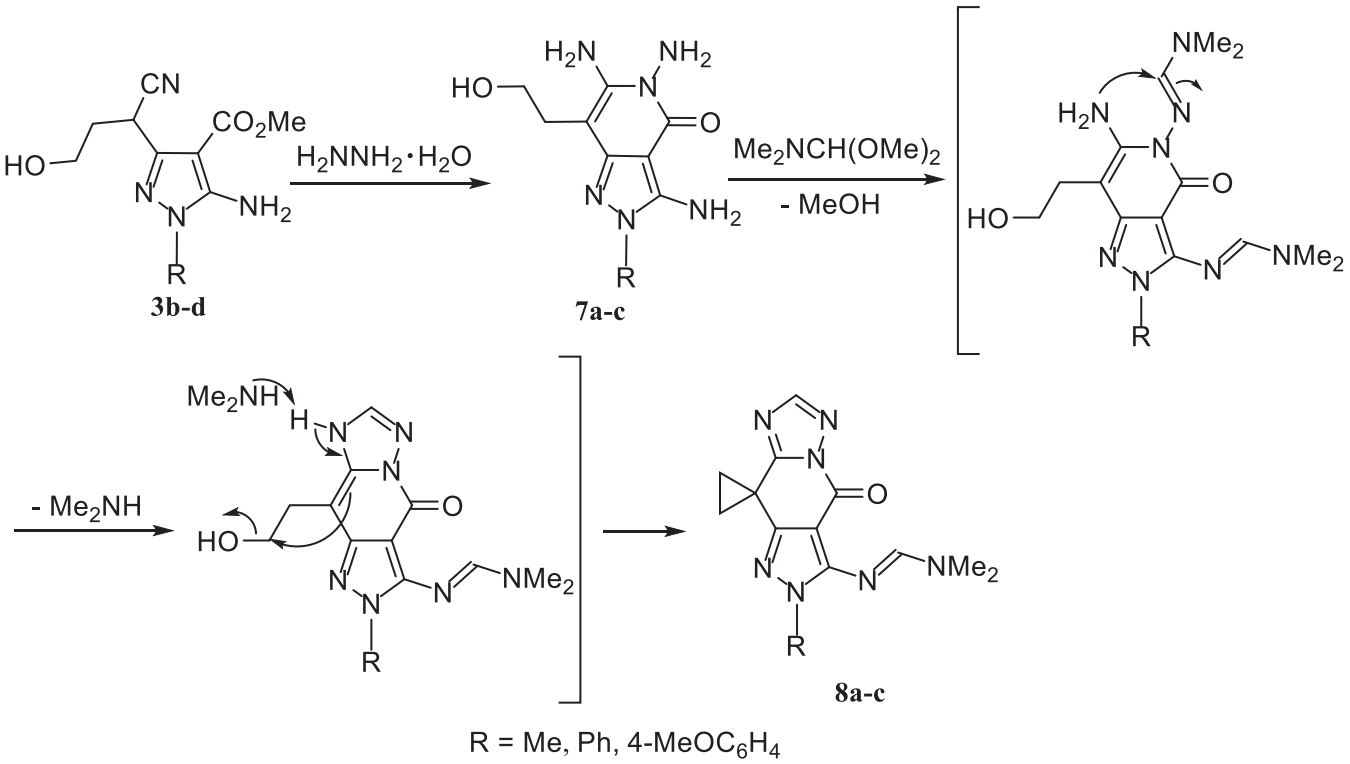
Reaction of **1** with 2.3 equiv. of hydrazine monohydrate in 1,2-dichlorobenzene at room temperature for 27 h gave 3,4'-bipyrazole **5** (79%). When 3,4'-bipyrazole **5** was reacted with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA),[12] angular type dipyrazolepyridazine **6** was given. The IR spectra of **6**

display bands of 3410, 3233 cm^{-1} due to two animo groups and a hydroxyl group, and 1627 cm^{-1} due to an amide carbonyl group. The ^1H NMR spectrum of **6** in DMSO-*d*$_6$ exhibits two three-protons singlet δ 3.00 and 3.09 due to the two methyl groups, a one-proton singlet δ 8.27 due to the olefin proton of (dimethylamino)methylene group, and a one-proton singlet δ 8.80 due to the 5-methine proton. The ^{13}C NMR spectrum of **6** shows two signals near δ 37.0 due to the methyl carbon of dimethylamino group, and a signal δ 140 due to the 5-methine carbon and a signal δ 154.8 due to the olefin carbon of (dimethylamino)methylene group. The stereochemistry of **6** was assigned by mean of NOE between the methyl protons, and 2-hydroxyethyl methylene protons at the 2-position. In the NOESY spectra of **6**, the NOE showed the dimethylamino group are located on the same side of the 2-hydroxyethyl group.

3,4'-Dipyrazole **5** and DMFDMA to produce dipyrazolepyridazine **6** is described in Scheme 2. Compound **5** reacts with DMFDMA, the two amino groups of **5** condense with DMFDMA, respectively, and the axis of dipyrazole rotates due to the movement of protons of pyrazole, closing with proton migration to construct pyrimidine ring, **6** is formed.

Reaction of pyrazoles **3b-d** with hydrazine monohydrate yielded the corresponding pyrazolopyridines **7a-c**. The IR spectra of **7a-c** display bands in the range of 3210-3462 cm^{-1} due to a primary amino group and a hydroxyl group, and near 1657 cm^{-1} due to an amide carbonyl group. The ^1H NMR spectrum of **7a-c** in DMSO-*d*$_6$ exhibits D_2O exchangeable three two-protons singlet near δ 5.05, 5.64, 6.03 attributable to the primary amino protons. The ^{13}C NMR spectrum of **7a-c** shows a signal near δ 159.5 due to the amide carbonyl carbon.

When pyrazolopyridines **7a-c** were reacted with DMFDMA, the corresponding linear type pyrazolotriazolopyridines **8a-c** was formed. The IR spectra of **8a-c** display a band near 1706 cm^{-1} due to an amide carbonyl group. The ^1H NMR spectrum of **8a-c** in DMSO-*d*$_6$ exhibits two two-protons singlet near δ 2.08 as singnable to the methylene protons of cyclopropane, two three-protons singlet δ 3.05 and 3.18 due to the two methyl groups, a one-proton singlet near δ 7.98 due to the 7-methine proton, and a one-proton singlet δ 9.17 due to the olefin proton of (dimethylamino)methylene group. The ^{13}C NMR spectrum of **8a-c** shows a signal near δ 25.0 due to the methylene carbon and two signals near δ 34.3, 40.8 due to the dimethylamino carbon, and a signal near δ 152.5 due to the 7-methine carbon, and a signal near δ 155.0 due to the amide carbonyl carbon, and a signal near δ 159.6 due to the olefin carbon of the (dimethylamino)methylene group. The stereochemistry of **8a-c** was assigned by mean of NOE between the methyl proton, and 2-proton of pyrazole. In the NOESY spectra of **8a-c**, the NOE showed the dimethylamino group are located on the same side of the 2-substituent of pyrazole.



Scheme 3

Table 2. Synthesis of pyrazolotriazolopyridines **8a-c** by the reaction of **3b-d** with hydrazine monohydrate and DMFDMA

Entry	Substrate	R	Product	Yield (%)
1	**3b**	Me	**7a**	37
2	**3c**	Ph	**7b**	32
3	**3d**	4-$MeOC_6H_4$	**7c**	74

Entry	Substrate	R	Product	Yield (%)
1	**7a**	Me	**8a**	31
2	**7b**	Ph	**8b**	32
3	**7c**	4-$MeOC_6H_4$	**8c**	30

The formation of linear pyrazolotriazolopyridines **8a-c** could be explained by the proposed mechanism presented in Scheme 3. Condensation occurs with compounds **7a-c** and 2 equiv. of DMFDMA, dimethylamine and methanol are eliminated, and a triazole ring is constructed. As the removed dimethylamine withdraws hydrogen at 1-position of the triazole, whereby cyclopropane is formed, forming **8a-c**.

In conclusion, when we treated methyl cyano(3-cyano-4,5-dihydro-2(3*H*)-furanylidene)acetate (**1**) with hydrazine monohydrate, the domino reaction proceeds and 3,4'-bipyrazole **5** is formed, then DMFDMA to form angular dipyrazolopyrimidine **6**. On the other hand, **1** was reacted with hydrazines, hydrazine

monohydrate and then DMFDMA to obtain linear triazolopyrazolopyridines **8a-c**. We have developed a new method for synthesizing fused [5-6-5] heterocyclic compounds of angular type and linear type.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a JASCO FT/IR-4100 spectrometer and Thermo Fisher Scientific Nicolet iS5 FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-A500 spectrometer at 500.00 and 125.65 MHz, and JEOL JNM-ECZ R spectrometer 600.17 and 150.91 MHz, respectively. The ^{1}H and ^{13}C chemical shifts (δ) are reported in part per million (ppm) relative to TMS at internal standard. Positive (+) FAB MS spectra were obtained on a JEOL JMS-700T spectrometer. Elemental analyses were performed on YANACO MT-6 CHN analyzer. The starting compound **1** was prepared in this laboratory according to the procedure reported in literature.[10]

General procedure for the preparation of pyrazole 2 from 1 and hydrazines. A solution of **1** (0.96 g, 5 mmol), hydrazine monohydrate (0.33 g, 6.5 mmol) and/or methylhydrazine (0.23 g, 5 mmol) in 1,2-dichlorobenzene (20 mL) was stirred at rt for 24 h. The obtained solid was isolated by filtration, washed with EtOH (5 mL), dried and recycryzallized from MeOH to give pyrazole **2a** (0.90 g, 80%) and **2b** (0.79 g, 66%).

Methyl [5-Amino-4-(2-hydroxyethyl)-1*H*-pyrazol-3(2*H*)-ylidene]-2-cyanoacetate (2a) Colorless prisms, mp 145-147 °C (dec.) (MeOH); IR (KBr): ν 3583, 3543, 3382, 3327, 3272 (NH, OH), 2169 (CN), 1644 (CO) cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$): δ 2.40-2.43 (m, 0.5H, 2-hydroxyethyl 1-H), 2.61 (t, *J* = 6.7 Hz, 1.5H, 2-hydroxyethyl 1-H), 3.38-3.42 (m, 0.5H, 2-hydroxyethyl 2-H), 3.46 (t, *J* = 6.7 Hz, 1.5H, 2-hydroxyethyl 2-H), 3.52 (s, 2.25H, CO_2CH_3), 3.70 (s, 0.75H, CO_2CH_3), 4.46 (br s, 0.75H, OH), 4.61 (br s, 0.25H, OH), 4.82 (br s, 0.25H, NH_2), 5.44 (s, 0.25H, 2-H), 5.89 (br s, 1.5H, NH_2), 11.4 (br s, 1.75H, 3NH) ppm; ^{13}C NMR (DMSO-*d*$_6$): δ 24.4, 25.3 (2-hydroxyethyl C-1), 36.4 (C-*C*H-CN), 49.1 (C=*C*-CN), 49.5, 53.2 (CO_2CH_3), 61.1, 61.2 (2-hydroxyethyl C-2), 90.2, 97.7 (pyrazole C-3), 116.1, 122.5 (CN), 138.9 (pyrazole C-4), 147.4 (pyrazole C-5), 148.1 (pyrazole C-4), 151.6 (pyrazole C-5), 165.5, 169.0 (CO) ppm; FAB(+) MS: *m/z* 225 $[M+H]^+$. Anal. Calcd for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99. Found: C, 48.11; H, 5.38; N, 24.96.

Methyl [5-Amino-4-(2-hydroxyethyl)-1-methyl-1*H*-pyrazol-3(2*H*)-ylidene]-2-cyanoacetate (2b) Pale yellow prisms, mp 170-171 °C (dec.) (MeOH); IR (KBr): ν 3384, 3327, 3274, 3202 (NH, OH), 2183 (CN), 1670 (CO) cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$): δ 2.42 (t, *J* = 6.7 Hz, 1.5H, 2-hydroxyethyl 1-H), 2.62 (t, *J* = 6.7 Hz, 0.5H, 2-hydroxyethyl 1-H), 3.37-3.41 (m, 0.5H, 2-hydroxyethyl 2-H), 3.42-3.48 (m, 1.5H, 2-hydroxyethyl 2-H), 3.46 (s, 0.75H, NCH_3), 3.49 (s, 2.25H, NCH_3), 3.53 (s, 0.75H, CO_2CH_3), 3.70 (s, 2.25H, CO_2CH_3), 4.44 (br s, 0.25H, OH), 4.60 (br s, 0.75H, OH), 5.04 (br s, 1.5H, NH_2), 5.41 (s, 0.75H,

2-H), 6.26 (br s, 0.5H, NH_2), 11.47 (br s, 0.25H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 24.6, 25.6 (2-hydroxyethyl C-1), 33.3, 34.3 (NCH_3), 36.3 (C-*C*H-CN), 49.4 (C=*C*-CN), 49.5, 53.2 (CO_2CH_3), 61.0 (2-hydroxyethyl C-2), 90.3, 97.9 (pyrazole C-3), 116.1, 122.5 (CN), 137.9 (pyrazole C-4), 145.6 (pyrazole C-5), 148.0 (pyrazole C-4), 152.1 (pyrazole C-5), 165.5, 168.6 (CO) ppm; FAB(+) MS: *m/z* 239 $[M+H]^+$. Anal. Calcd for $C_{10}H_{14}N_4O_3 \cdot 0.15\ H_2O$: C, 49.85; H, 5.98; N, 23.25. Found: C, 49.86; H, 6.04; N, 23.25.

General procedure for the preparation of pyrazole 3b-d, from 1 and hydrazines. A solution of **1** (0.96 g, 5 mmol), and/or methylhydrazine (0.23 g, 5 mmol) and/or phenylhydrazine (0.54 g, 5 mmol) and/or 4-methoxyphenylhydrazine hydrochloride (0.88 g, 5 mmol) and Et_3N (0.51 g, 5 mmol) (in the case of **3d**) in 1,4-dioxane (20 mL) was stirred at rt for 24 h. After removal of the solvent *in vacuo,* cold water was added to the residue. The obtained mixture was extracted with CH_2Cl_2, dried over by Na_2SO_4, and concentrated *in vacuo*.

(A) The residue was recrystallized from CH_2Cl_2/petroleum ether to take **3b** (0.94 g, 79%) and **3d** (1.41 g, 86%).

(B) The residue was purified by column chromatography on aluminum oxide with CH_2Cl_2 as eluent to afford **3c** (1.43 g, 95%).

Methyl 5-Amino-3-(1-cyano-3-hydroxypropyl)-1-methyl-1*H*-pyrazole-4-carboxylate (3b) Colorless prisms, mp 176-178 °C (CH_2Cl_2/petroleum ether); IR (KBr): ν 3488, 3428, 3312 (NH, OH), 2250 (CN), 1682 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.96-2.08 (m, 2H, 3-hydroxypropyl 2-H), 3.51-3.56 (m, 2H, 3-hydroxypropyl 3-H), 3.53 (s, 3H, NCH_3), 3.72 (s, 3H, CO_2CH_3), 4.46 (dd, *J* = 2.7, 6.1 Hz, 1H, 3-hydroxypropyl 1-H), 4.68 (s, 1H, OH), 6.32 (s, 2H, NH_2) ppm; ^{13}C NMR (DMSO-d_6): δ 26.7 (3-hydroxypropyl C-1), 34.2 (NCH_3), 34.5 (3-hydroxypropyl C-2), 50.3 (CO_2CH_3), 57.8 (3-hydroxypropyl C-3), 91.0 (C-4), 119.8 (CN), 145.0 (C-3), 150.9 (C-5), 163.2 (CO) ppm; FAB(+) MS: *m/z* 239 $[M+H]^+$. Anal. Calcd for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.21; H, 5.98; N, 23.51.

Methyl 5-Amino-3-(1-cyano-3-hydroxypropan-1-yl)-1-phenyl-1*H*-pyrazole-4-carboxylate (3c) Red oil; IR (neat): ν 3444, 3342, 3226 (NH, OH), 2247 (CN), 1688 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.02-2.14 (m, 2H, 3-hydroxypropyl 2-H), 3.56-3.60 (m, 2H, 3-hydroxypropyl 3-H), 3.78 (s, 3H, CO_2CH_3), 4.55-4.58 (m, 1H, 3-hydroxypropyl 1-H), 4.73 (t, 1H, *J* = 5.2 Hz, OH), 6.43 (s, 2H, NH_2), 7.42-7.46 (m, 1H, aryl H), 7.52-7.57 (m, 4H, aryl H) ppm; ^{13}C NMR (DMSO-d_6): δ 26.9 (3-hydroxypropyl C-1), 34.3 (3-hydroxypropyl C-2), 50.6 (CO_2CH_3), 57.7 (3-hydroxypropyl C-3), 91.7 (C-4), 119.6 (CN), 124.0, 127.8, 129.4, 137.3 (C aryl), 146.9 (C-3), 150.6 (C-5), 163.3 (CO) ppm; FAB(+) MS: *m/z* 301 $[M+H]^+$. Anal. Calcd for $C_{15}H_{16}N_4O_4 \cdot 0.25\ H_2O$: C, 59.10; H, 5.46; N, 18.38. Found: C, 59.03; H, 5.48; N, 17.91.

Methyl 5-Amino-3-(1-cyano-3-hydroxypropan-1-yl)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carboxy-

late (3d) Colorless needles, mp 128-129 °C (dec.) (CH_2Cl_2/petroleum ether); IR (KBr): ν 3534, 3377, 3289 (NH, OH), 2245 (CN), 1691 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.00-2.14 (m, 2H, 3-hydroxypropyl 2-H), 3.56-3.58 (m, 2H, 3-hydroxypropyl 3-H), 3.77 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 4.53-4.56 (m, 1H, 3-hydroxypropyl 1-H), 4.72 (t, 1H, J = 5.2 Hz, OH), 6.28 (s, 2H, NH_2), 7.07-7.10 (m, 2H, aryl H), 7.40-7.43 (m, 2H, aryl H) ppm; ^{13}C NMR (DMSO-d_6): δ 26.9 (3-hydroxypropyl C-1), 34.3 (3-hydroxypropyl C-2), 50.5 (CO_2CH_3), 55.4 (OCH_3), 57.8 (3-hydroxypropyl C-3), 91.4 (C-4), 114.6 (C aryl), 119.6 (CN), 126.1, 130.0 (C aryl), 146.4 (C-3), 150.7 (C-5), 158.8 (C aryl), 163.3 (CO) ppm; FAB(+) MS: *m/z* 331 $[M+H]^+$. Anal. Calcd for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.20; H, 5.49; N, 16.94.

General procedure for the preparation of pyrazole 4b from 2b and hydrazine hydrate. The mixture of **2b** (0.71 g, 3 mmol) and hydrazine monohydrate (0.15 g, 3 mmol) in 1,2-dichlorobenzene (10 mL) was stirred at rt for 3 h. The obtained solid was isolated by filtration, and washed with CH_2Cl_2, dried and recrystallized from MeOH to give **4b** (0.64 g, 89%).

2-(5-Amino-4-(2-hydroxyethyl)-1-methyl-1*H*-pyrazol-3-yl)-2-cyanoacetohydrazide (4b) Colorless prisms, mp 176-177 °C (dec.) (MeOH); IR (KBr): ν 3437, 3394, 3311, 3265 (NH, OH), 2245 (CN), 1679 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.36-2.45 (m, 2H, 2-hydroxyethyl 1-H), 3.38-3.39 (m, 2H, 2-hydroxyethyl 2-H), 3.44 (s, 3H, NCH_3), 4.33 (br s, 1H, OH), 4.68 (s, 1H, NH), 4.86 (s, 1H, 2-H), 5.02 (br s, 2H, NH_2), 9.16 (br s, 2H, NH_2) ppm; ^{13}C NMR (DMSO-d_6): δ 26.0 (2-hydroxyethyl C-1), 34.8 (NCH_3), 36.4 (C-2), 61.6 (2-hydroxyethyl C-2), 98.2 (pyrazolone C-3), 117.6 (CN), 139.2 (pyrazole C-4), 146.2 (pyrazole C-5), 163.5 (CO) ppm; FAB(+) MS: *m/z* 239 $[M+H]^+$. Anal. Calcd for $C_9H_{14}N_6O_2$: C, 45.37; H, 5.92; N, 35.27. Found: C, 45.21; H, 5.92; N, 35.06.

General procedure for the preparation of 3,4'-bipyrazole 5, from 1 and/or 2a and hydrazine hydrate.

Procedure A: The mixture of **1** (0.96 g, 5 mmol) and hydrazine monohydrate (0.33 g, 6.5 mmol) in 1,2-dichlorobenzene (20 mL) was stirred at rt for 27 h. The obtained solid was isolated by filtration, and washed with CH_2Cl_2, dried and recrystallized from MeOH to give **5** (0.88 g, 79%).

Procedure B: The mixture of **2a** (0.67 g, 3 mmol) and hydrazine monohydrate (0.15 g, 3 mmol) in 1,2-dichlorobenzene (10 mL) was stirred at rt for 3 h. After work-up as described above, **5** was obtained. (0.53 g, 79%).

(4*Z*)-5-Amino-4-[5-amino-1,2-dihydro-4-(2-hydroxyethyl)-3*H*-pyrazol-3-ylidene]-2,4-dihydro-3*H*-pyrazol-3-one (5) Colorless needles, mp 243-244 °C (dec.) (MeOH); IR (KBr): ν 3455, 3415, 3339, 3138 (NH, OH), 1637 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.48 (t, J = 6.3 Hz, 2H, 2-hydroxyethyl 1-H), 3.35 (br s, 2H, NH_2), 3.50 (t, J = 6.3 Hz, 2H, 2-hydroxyethyl 2-H), 4.46 (br s, 2H, NH, OH), 5.97 (br s, 2H, NH_2), 9.36 (br s, 2H, 2NH) ppm; ^{13}C NMR (DMSO-d_6): δ 25.8 (2-hydroxyethyl C-1), 60.6

(2-hydroxyethyl C-2), 80.2 (pyrazolone C-4), 99.4 (pyrazole C-4), 136.4 (pyrazole C-5), 151.0 (pyrazole C-3), 156.6 (pyrazolone C-5), 168.2 (CO) ppm; FAB(+) MS: *m/z* 225 $[M+H]^+$. Anal. Calcd for $C_8H_{12}N_6O_2$: C, 42.85; H, 5.39; N, 37.48. Found: C, 42.82; H, 5.49; N, 37.23.

General procedure for the preparation of dipyrazolopyrimidine 6, from 5 and DMFDMA. A mixture of **5** (0.22 g, 1 mmol) and *N,N*-dimethylformamide dimethyl acetal (0.30 g, 2.5 mmol) in EtOH (10 ml) was refluxed for 6 h. After removal of the solvent *in vacuo*, Et_2O was added to the residue. The precipitate was isolated by filtration, washed with Et_2O dried and recrystallized from MeOH to afford **6** (0.22 g, 76%).

(*E*)-*N'*-[2,7-Dihydro-9-(2-hydroxyethyl)-1-oxo-1*H*-dipyrazolo[1,5-*c*:4',3'-*e*]pyrimidin-8-yl]-*N*,*N*-dimethylmethanimidamide (6) Colorless prisms, mp >300 °C (MeOH); IR (KBr): ν 3410, 3233 (NH, OH), 1627 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.00 (s, 3H, NCH_3), 3.02 (t, *J* = 6.9 Hz, 2H, 2-hydroxyethyl 1-H), 3.09 (s, 3H, NCH_3), 3.62 (t, *J* = 6.9 Hz, 2H, 2-hydroxyethyl 2-H), 5.15 (br s, 1H, OH), 8.27 (s, 1H, olefin H), 8.80 (s, 1H, 5-H), 10.89 (br s, 1H, NH), 12.28 (br s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 25.9 (2-hydroxyethyl C-1), 33.9, 39.8 (NCH_3), 61.5 (2-hydroxyethyl C-2), 89.2 (C-9b), 100.8 (C-9), 134.6 (C-9a), 140.1 (C-5), 144.9 (C-3a), 153.8 (CO), 154.8 (N=*C*HN(CH_3)$_2$), 162.4 (C-8) ppm; FAB(+) MS: *m/z* 290 $[M+H]^+$. Anal. Calcd for $C_{12}H_{15}N_7O_2$: C, 49.82; H, 5.23; N, 33.89. Found: C, 49.72; H, 5.22; N, 33.67.

General procedure for the preparation of pyrazolopyridines 7a-c, from 3b-d and hydrazine hydrate. A solution of **3b-d** (3 mmol) and hydrazine monohydrate (5 mL) was stirred at rt for 24 h. The cold water was added to the obtained mixture. The precipitate was isolated by filtration, washed with water, dried and recrystallized from MeOH to take **7a** (0.26 g, 37%), **7b** (0.29 g, 32%), and **7c** (0.73 g, 74%).

3,5,6-Triamino-7-(2-hydroxyethyl)-2-methy-2*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-one (7a) Colorless needles, mp 246-247 °C (dec.) (MeOH); IR (KBr): ν 3443, 3416, 3307, 3234, 3194, 3165 (NH, OH), 1648 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.51 (t, *J* = 6.9 Hz, 2H, 2-hydroxyethyl 1-H), 3.46 (dd, *J* = 6.9, 12.3 Hz, 2H, 2-hydroxyethyl 2-H), 3.48 (s, 3H, NCH_3), 4.63 (t, *J* = 5.1 Hz, 1H, OH), 4.99 (s, 2H, NH_2), 5.52 (s, 2H, NH_2), 5.97 (s, 2H, NH_2) ppm; ^{13}C NMR (DMSO-d_6): δ 28.8 (2-hydroxyethyl C-1), 34.4 (NCH_3), 60.9 (2-hydroxyethyl C-2), 81.5 (C-7), 91.7 (C-3a), 145.5 (C-6), 146.8 (C-3), 149.7 (C-7a), 159.1 (CO) ppm; FAB(+) MS: *m/z* 239 $[M+H]^+$. Anal. Calcd for $C_9H_{14}N_6O_3$: C, 45.37; H, 5.92; N, 35.27. Found: C, 45.36; H, 5.87; N, 35.31.

3,5,6-Triamino-7-(2-hydroxyethyl)-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-one (7b) Colorless prisms, mp 198-200 °C (dec.) (MeOH/diethylether) IR (KBr): ν3424, 3309, 3209 (NH, OH), 1656 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.57 (t, *J* = 6.9 Hz, 2H, 2-hydroxyethyl 1-H), 3.51 (dd, *J* = 6.9, 12.0 Hz, 2H, 2-hydroxyethyl 2-H), 4.63 (t, *J* = 5.1 Hz, 1H, OH), 5.07 (s, 2H, NH_2), 5.71 (s, 2H, NH_2), 6.14 (s, 2H, NH_2), 7.30-7.32 (m, 1H, aryl H), 7.46-7.49 (m, 2H, aryl H), 7.56-7.58 (m, 2H, aryl H) ppm; ^{13}C NMR

(DMSO-d_6): δ 28.8 (2-hydroxyethyl C-1), 60.8 (2-hydroxyethyl C-2), 80.8 (C-7), 92.9 (C-3a), 123.5, 127.1, 129.8, 139.1 (C aryl), 146.5 (C-6), 146.7 (C-3), 150.8 (C-7a), 159.8 (CO) ppm; FAB(+) MS: *m/z* 301 $[M+H]^+$. Anal. Calcd for $C_{14}H_{16}N_6O_2 \cdot 0.15H_2O$: C, 55.49; H, 5.42; N, 27.73. Found: C, 55.50; H, 5.42; N, 27.85.

3,5,6-Triamino-7-(2-hydroxyethyl)-2-(4-methoxyphenyl)-2*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-one (7c) Colorless prisms, mp 206-207 °C (dec.) (EtOH); IR (KBr): ν 3462, 3401, 3360, 3333 (NH, OH), 1664 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.61 (t, J = 7.0 Hz, 2H, 2-hydroxyethyl 1-H), 3.55 (dd, J = 7.0, 11.9 Hz, 2H, 2-hydroxyethyl 2-H), 3.81 (s, 3H, OCH_3), 4.62 (t, J = 5.2 Hz, 1H, OH), 5.08 (s, 2H, NH_2), 5.68 (s, 2H, NH_2), 5.99 (s, 2H, NH_2), 7.04-7.07 (m, 2H, aryl H), 7.47-7.50 (m, 2H, aryl H) ppm; ^{13}C NMR (DMSO-d_6): δ 28.2 (2-hydroxyethyl C-1), 55.4 (OCH_3), 60.3 (2-hydroxyethyl C-2), 80.5 (C-7), 92.0 (C-3a), 114.4, 124.9, 131.4 (C aryl), 145.6 (C-3), 145.9 (C-6), 149.9 (C-7a), 157.9 (C aryl), 159.0 (CO) ppm; FAB(+) MS: *m/z* 331 $[M+H]^+$. Anal. Calcd for $C_{15}H_{18}N_6O_3$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.56; H, 5.49; N, 25.30.

General procedure for the preparation of pyrazolotriazolopyridines 8a-c, from 7a-c and DMFDMA. A solution of **7a-c** (1 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (0.48 g, 4 mmol) in DMF (5 mL) was stirred at 80 °C for 2 h. After removal of the solvent under reduced pressure, cold water was added to the residue. The resulting mixture was extracted with CH_2Cl_2 (30 mL). The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with CH_2Cl_2 eluent as the eluent to afford **8a** (0.09 g, 31%), **8b** (0.11 g, 32%) and **8c** (0.11 g, 30%).

***N'*-[2,4-Dihydro-2-methyl-4-oxo-spiro[cyclopropane-1,9-pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]-pyridin]-3-yl]-*N*,*N*-dimethylmethanimidamide (8a)** Pale yellow needles, mp 213-214 °C (dec.) (CH_2Cl_2/petroleum ether); IR (KBr): ν 1695 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.98-2.06 (m, 4H, cyclopropane $2CH_2$), 3.09 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 3.71(s, 3H, 2-CH_3), 7.96 (s, 1H, 7-H), 9.27 (s, 1H, olefin H) ppm; ^{13}C NMR ($CDCl_3$): δ 18.5 (C-9), 24.9 (cyclopropane CH_2), 34.1(NCH_3), 34.8 (2-CH_3), 40.9 (NCH_3), 97.4 (C-3a), 152.5 (C-7), 153.0 (C-9a), 153.8 (CO), 155.5 (C-3), 159.5 (N=*C*HN(CH_3)$_2$), 161.3 (C-8a) ppm; FAB(+) MS: *m/z* 286 $[M+H]^+$. Anal. Calcd for $C_{13}H_{15}N_7O$: C, 54.73; H, 5.30; N, 34.37. Found: C, 54.54; H, 5.32; N, 34.18.

***N'*-[2,4-Dihydro-2-phenyl-4-oxo-spiro[cyclopropane-1,9-pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]-pyridin]-3-yl]-*N*,*N*-dimethylmethanimidamide (8b)** Pale yellow needles, mp 226-227 °C (dec.) (CH_2Cl_2/petroleum ether) IR (KBr): ν 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.09-2.13 (m, 4H, cyclopropane $2CH_2$), 3.04 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 7.30-7.31 (m, 1H, aryl H), 7.41-7.43 (m, 2H, aryl H), 7.77-7.79 (m, 2H, aryl H), 7.99 (s, 1H, 7-H), 9.12 (s, 1H, olefin H) ppm; ^{13}C NMR ($CDCl_3$): δ 18.6 (C-9), 25.1 (cyclopropane CH_2), 34.4, 40.9 (NCH_3), 98.3 (C-3a), 124.6, 127.2, 128.5, 139.2 (C

aryl), 152.6 (C-7), 154.0 (C-9a), 154.3 (C-3), 155.7 (CO), 159.7 (N=*C*HN(CH_3)$_2$), 161.3 (C-8a) ppm; FAB(+) MS: *m/z* 348 $[M+H]^+$. Anal. Calcd for $C_{18}H_{17}N_7O$: C, 62.24; H, 4.93; N, 28.23. Found: C, 62.35; H, 4.99; N, 28.31.

***N'*-[2,4-Dihydro-2-(4-methoxyphenyl)-4-oxo-spiro[cyclopropane-1,9-pyrazolo[3,4-*d*][1,2,4]triazolo-[1,5-*a*]pyridin]-3-yl]-*N*,*N*-dimethylmethanimidamide (8c)** Pale yellow needles, mp 205-207 °C (dec.) (CH_2Cl_2/petroleum ether); IR (KBr): ν 1709 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.11 (s, 4H, cyclopropane 2CH_2), 3.03 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 3.84 (s, 3H, OCH_3), 6.92-6.96 (m, 2H, aryl H), 7.64-7.68 (m, 2H, aryl H), 7.99 (s, 1H, 7-H), 9.12 (s, 1H, olefin H) ppm; ^{13}C NMR ($CDCl_3$): δ 18.5 (C-9), 24.9 (cyclopropane CH_2), 34.3, 40.7 (NCH_3), 55.5 (OCH_3), 98.0 (C-3a), 113.6, 125.9, 132.3 (C aryl), 152.5 (C-7), 153.7 (C-3), 153.9 (C-9a), 155.6 (CO), 158.6 (C aryl), 159.5 (N=*C*HN(CH_3)$_2$), 161.2 (C-8a) ppm; FAB(+) MS: *m/z* 378 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}N_7O_2$: C, 60.47; H, 5.07; N, 25.98. Found: C, 64.41; H, 5.14; N, 26.07.

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REFERENCES

1. (a) S. Xiao, C. Chen, H. Li, K. Lin, and W. Zhou, *Org. Process Res. Dev.*, 2015, **19**, 373; (b) B. E. Maryanoff, S. O. Nortey, J. F. Gardocki, R. P. Shank, and S. P. Dodgson, *J. Med. Chem*., 1987, **30**, 880.
2. S. Hilton and S. Rossiter, 'Comprehensive Heterocyclic Chemistry III: Three Heterocyclic Rings Fused (5-6-5)' Vol 12, ed. by K. Jones, Elsevier, 2008, p 711.
3. J. Kempson, J. Guo, J. Das, R. V. Moquin, S. H. Spergel, S. H. Watterson, C. M. Langevine, A. J. Dyckman, M. Pattoli, J. R. Burke, X. Yang, K. M. Gillooly, K. W. McIntyre, L. Chen, J. H. Dodd, M. McKinnon, J. C. Barrish, and W. J. Pitts, *Bioorg. Med. Chem. Lett*., 2009, **19**, 2646.
4. K. Nepali, G. Singh, A. Turan, A. Agarwal, S. Sapra, R. Kumar, U. C. Banerjee, P. K. Verma, N. K. Satti, M. K. Gupta, O. P. Suri, and K. L. Dhar, *Bioorg. Med. Chem*., 2011, **19**, 1950.
5. (a) M. Zak, R. Mendonca, M. Balazs, K. Barrett, P. Bergeron, W. S. Blair, C. Chang, G. Deshmukh, J. DeVoss, P. S. Dragovich, C. Eigenbrot, N. Ghilardi, P. Gibbons, S. Gradl, C. Hamman, E. J. Hanan, E. Harstad, P. R. Hewitt, C. A. Hurley, T. Jin, A. Johnson, T. Johnson, J. R. Kenny, M. F. T. Koehler, P. B. Kohli, J. J. Kulagowski, S. Labadie, J. Liao, M. Liimatta, Z. Lin, P. J. Lupardus, R. J. Maxey, J. M. Murray, R. Pulk, M. Rodriguez, S. Savage, S. Shia, M. Steffek, S. Ubhayakar, M. Ultsch, A. Abbema, S. I. Ward, L. Xiao, and Y. Xiao, *J. Med. Chem*., 2012, **55**, 6176; (b) C. A.

Hurley, W. S. Blair, R. J. Bull, C. Chang, P. H. Crackett, G. Deshmukh, H. J. Dyke, R. Fong, N. Ghilardi, P. Gibbons, P. R. Hewitt, A. Johnson, T. Johnson, J. R. Kenny, P. B. Kohli, J. J. Kulagowski, M. Liimatta, P. J. Lupardus, R. J. Maxey, R. Mendonca, R. Narukulla, R. Pulk, S. Ubhayakar, A. Abbema, S. I. Ward, B. Waszkowycz, and M. Zak, *Bioorg. Med. Chem. Lett*., 2013, **23**, 3592; (c) S. V. Epps, B. Fiamengo, J. Edmunds, A. Ericsson, K. Frank, M. Friedman, D. George, J. George, E. Goedken, B. Kotecki, G. Martinez, P. Merta, M. Morytko, S. Shekhar, B. Skinner, K. Stewart, J. Voss, G. Wallace, L. Wang, L. Wang, and N. Wishart, *Bioorg. Med. Chem. Lett*., 2013, **23**, 693.

6. (a) P. G. Baraldi, S. Manfredini, D. Simoni, L. Zappaterra, C. Zocchi, S. Dionisotti, and E. Ongini, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2539; (b) E. Ongini, *Drug Dev. Res*., 1997, **42**, 63; (c) P. G. Baraldi, B. Cacciari, R. Romagnoli, G. Spalluto, A. Monopoli, E. Ongini, K. Varani, and P. A. Borea, *J. Med. Chem*., 2002, **45**, 115; (d) W. Guba, M. Nettekoven, B. Püllmann, C. Riemer, and S. Schmitt, *Bioorg. Med. Chem. Lett*., 2004, **14**, 3307; (e) P. G. Baraldi, G. Saponaro, M. A. Tabrizi, S. Baraldi, R. Romagnoli, A. R. Moorman, K. Varani, P. A. Borea, and D. Preti, *Bioorg. Med. Chem*., 2012, **20**, 1046.
7. S. L. Cheong, A. V. Dolzhenko, S. Paoletta, E. P. R. Lee, S. Kachler, S. Federico, K.-N. Klotz, A. V. Dolzhenko, G. Spalluto, S. Moro, and G. Pastorin, *Bioorg. Med. Chem*., 2011, **19**, 6120.
8. (a) P. G. Baraldi, A. Bovero, F. Fruttarolo, R. Romagnoli, M. A. Tabrizi, D. Preti, K. Varani, P. A. Borea, and A. R. Moorman, *Bioorg. Med. Chem*., 2003, **11**, 4161; (b) T. Okamura, Y. Kurogi, K. Hashimoto, S. Sato, H. Nishikawa, K. Kiryua, and Y. Nagao, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3775; (c) S. L. Cheong, S. Federico, G. Venkatesan, P. Paira, Y.-M. Shao, G. Spalluto, C. W. Yap, and G. Pastorin, *Bioorg. Med. Chem. Lett*., 2011, **21**, 2898.
9. B. Golankiewicz, T. Ostrowski, G. Anddrei, R. Snoeck, and E. D. Clercq, *J. Med. Chem*., 1994, **37**, 3187.
10. K. Yamagata, Y. Hashimoto, and M. Yamazaki, *Liebigs Ann. Chem*., 1994, 791.
11. M. Paätzel and J. Liebscher, *J. Heterocycl. Chem*., 1991, **28**, 1257.
12. (a) P. F. Schuda, C. B. Ebner, and T. M. Morgan, *Tetrahedron Lett.*, 1986, **27**, 2567; (b) W. Kantlehner, E. Haug, and H. Haben, *Liebigs Ann. Chem.*, 1982, 298; (c) E. E. Garcia and R. I. Fryer, *J. Heterocycl. Chem*., 1974, **11**, 219.