HETEROCYCLIC COMPOUNDS. I. REACTIONS OF *o*-AMINO-CARBOXAMIDE WITH β-DIKETONES: SYNTHESIS OF IMIDAZO[1,5-a]PYRIMIDINE AND PYRAZOLO[1,5-a]PYRIMIDINE DERIVATIVES [1]

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Abstract-Treatment of 5-aminoimidazole-4-carboxamide hydrochloride (1) and 5-aminopyrazole-4-carboxamide hemisulfate (2) with β-diketones furnished 2,4-disubstituted imidazo[1,5-a]pyrimidine-8-carboxamide (7) and 5,7-disubstituted pyrazolo[1,5-a]pyrimidine-3-carboxamide (8) respectively. The ^{1}H nmr and ^{13}C nmr spectra of these compounds and the X-ray crystallography of compound 7a are discussed.

The purine derivatives and analogues constitute a class of important chemotherapeutic agents since the introduction of purine-6-(1*H*, 9*H*)-thione (6-mercaptopurine, 6-MP) by Elion and Hitchings[2] in 1952, which is still widely used in clinics for the treatment of lymphoblastic leukemia.[3] In the hope of obtaining more effective anticancer agents, medicinal chemists have continued to synthesize novel purine analogues with greater specificity.[4] Recently, due to an appreciation of the important effect of the purine receptor on the cardiovascular system and the discovery of the mechanism of action of adenosine analogues related to the adenosine

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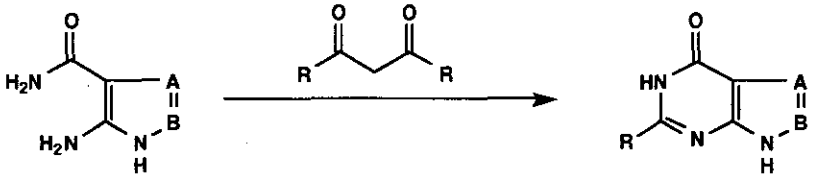
receptors, several analogs of purine were synthesized and tested.[5] In a course of our synthetic program on the purine analogs,[6] we were interested in preparing 2-substituted hypoxanthine and its nucleoside analogous for pharmacological evaluation. Meanwhile, a recent synthetic study on the reactions of *o*-amino-carboxamide with β-diketones, we found that a treatment of *o*-aminobenzenesulfonamide with 2,4-pentanedione furnished a good yield of 3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide.[7] A literature survey indicated that a reaction of anthranilamide with 2,4-pentanedione in the 6% ethanolic hydrogen chloride led to the synthesis of 2-methylquinazolin-4(3*H*)-one in quantitative yield *via* a similar retro-aldol type reaction.[8]



1. A = N, B = CH
2. A = CH, B = N

3. A = N, B= CH
4. A = CH, B = N

R = CH_3, CF_3, C_6H_5

At the outset, we reasoned that an analogous reaction between 5-aminoimidazole-4-carboxamide hydrochloride (1) and 2,4-pentanedione would afford compound (3). However, when compound

5. A = N, B = CH
6. A = CH, B = N

7. A=N, B=CH
8. A=CH, B=N

a. R = CH_3 ; b. R = CF_3 ; c. R = C_6H_5

(1) was treated with 2,4-pentanedione at room temperature, a quantitative amount of product was obtained and the mass spectrum (70 ev) of this product illustrated the molecular ion peak at *m/z* = 190 (relative intensity 100%), the fragment ion peak 174 being M^+-16, which initially appeared to be the double Schiff base product (5 a) instead of the expected compound (3 a). The

elemental analysis for this product is consistent with an empirical composition of $C_9H_{10}N_4O$. However, the ^1H nmr spectrum of the product revealed two singlets at δ 2.51 and 2.65 for methyl groups, two deuterium oxide exchangeable NH at δ 7.22 and 7.61, the imidazole CH at δ 8.33, and the chemical shift at δ 6.79 which is corresponding to another aromatic CH. On the basis of uv, ^1H and ^{13}C nmr spectral data, the structure of this product could not only be 5,7-dimethylimidazo[5,4-b]diazocin-9(8*H*)-one (5a) but also be 2,4-dimethylimidazo[1,5-a]pyrimidine-8-carboxamide (7a). A literature perusal revealed that the synthesis of diazocine ring system remains a challenge and limited in organic medicinal chemistry.[9] Only few 1,5-benzodiazocines have been prepared because they are considered as homologues of 1,4-benzodiazepine drugs.[10] Thus, to further confirm the structure of the isolated product, a nice crystal of the product was prepared and subjected to X-ray crystallography and illustrated the structure as 9a. (Figure 1) Interestingly, when 1 was reacted with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione or dibenzoylmethane at room temperature, the reaction did not proceed. Only at elevated temperature, 2,4-ditrifluoromethylimidazo[1,5-a]pyrimidine-8-carboxamide (7b) and 2,4-diphenylimidazo[1,5-a]pyrimidine-8-carboxamide (7c) could be obtained in 50% and 51% yields respectively after column chromatography.

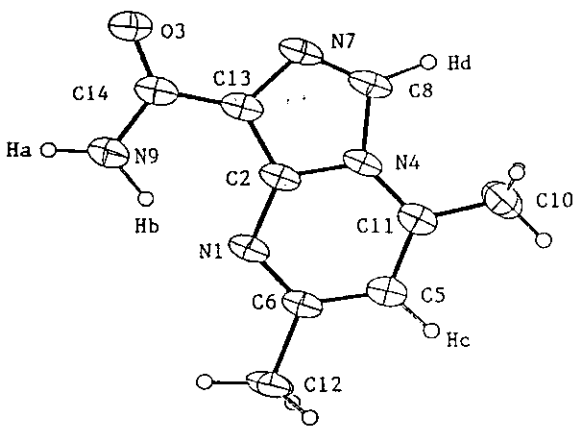
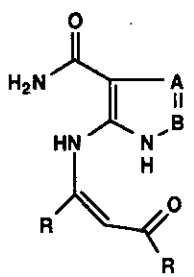


Figure 1. Perspective view and atom labelling of the X-ray structure of compound (7a)

To ascertain the general applicability of this facile reaction between 5-member ring heterocycle containing *o*-amino-carboxamide and β-diketone, when 5-aminopyrazole-4-

carboxamide hemisulfate (2) was treated with 2,4-pentanedione in methanol at room temperature, 5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide (8a) was obtained in 73 % yield as well instead of 4a. Similarly, the reactions of 2 with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione or dibenzoylmethane were performed at elevated temperature affording 5,7-ditrifluoromethylpyrazolo[1,5-a]pyrimidine-3-carboxamide (8b) and 5,7-diphenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (8c) in 76% and 89% yields respectively.

These reactions were probably involved an initial Schiff base formation to give enaminoketone intermediates (9) and (10) following by an intramolecular 1,2-nucleophilic addition of the imidazole or pyrazole ring nitrogen to the carbonyl group of the α,β-unsaturated ketone and subsequently an elimination of one mole of water. We presumed that the formation of (7) and (8) rather than purine derivatives (3 and 4) and/or 5:8 fused 1,5-diazocines (5 and 6) might be due to the nitrogen atom of carboxamide moiety existing as tautomeric enol form in imidazole and pyrazole ring system instead of existing as a tautomeric keto form as that observed in anthranilamide. In a recent communication on the ^1H nmr spectra of AICA-riboside and its derivatives,[6] we revealed that the two protons of the amino group in carboxamide moiety existed as two singlets instead of one singlet. This would lend some support to the fact that the lone pair electrons of the nitrogen atom on the carboxamide moiety in 1 and 2 were delocalized to form the enol form. It would bestow a positive charge on the nitrogen atom which decrease the

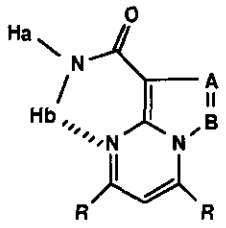


9. A = N, B = CH
10. A = CH, B = N

nitrogen atom basicity of the carboxamide. This would thus prevent the nitrogen atom of the carboxamide from conducting an either 1,2-addition to form 1,5-diazocines (5 and 6) or 1,4-addition to give purine derivatives (3 and 4). It shall be noted that the mass spectrum of

compound (7) and (8) at 70 ev was characterized by a fragment ion peak at M^+-16, indicative of having a similar pathway of fragmentation via an initial elimination of NH_2 from its parent ion. The ^1H nmr spectrum of 7 and 8 illustrated that the two protons on the nitrogen atom of the carboxamide moiety were chemically nonequivalent and split as two singlets. As can be seen

Table 1 Proton resonance data [a] for the carboxamide protons of 7 and 8



7. A = N, B = CH; 8. A = CH, B = N

Compounds		Solvent	NH_a	NH_b	Downfield shift [b]	Downfield Shift [c]
7 a,	R=CH_3	$CDCl_3$	5.58	7.78		2.10
7 a,	R=CH_3	DMSO-d_6	7.22	7.61	1.64	0.39
7 b,	R=CF_3	$CDCl_3$	5.96	7.34		1.38
7 b,	R=CF_3	DMSO-d_6	7.60	7.70	1.64	0.10
8 a,	R=CH_3	$CDCl_3$	5.69	7.93		2.24
8 a,	R=CH_3	DMSO-d_6	7.43	7.57	1.74	0.14
8 b,	R=CF_3	$CDCl_3$	6.11	7.39		1.28
8 b,	R=CF_3	DMSO-d_6	7.38	7.77	1.27	0.39

[a] In parts per million. Chemical shift was measured using 5% solutions (w/v) after it had been ascertained that there was no concentration dependence. b. Downfield shift= δ NH_a (DMSO-d_6) - δ NH_a ($CDCl_3$). c. Downfield shift= δ NH_b ($CDCl_3$) - δ NH_a ($CDCl_3$).

from Table 1, the NH_b proton of the carboxamide, while shifted downfield with respect to that of NH_a proton when 7a,b and 8a,b were measured in deuteriochloroform, experienced little downfield shift on changing solvent to DMSO-d_6. The chemical shift difference between NH_a and NH_b of 7a,b and 8a,b is in a range from 1.28 to 2.10 ppm in deuteriochloroform and from 0.14 to 0.39 ppm in DMSO-d_6. The great chemical shift difference between H_a and H_b using deuteriochloroform as solvent must mean that the NH_b proton is already intramolecularly hydrogen bonded to the ring nitrogen and anisotropic effect as described above. On the other hand, the downfield shift of the NH_a proton among 7a,b and 8a,b in DMSO-d_6 with respect to those NH_a of 7a,b and 8a,b in deuteriochloroform is in a range from 1.27 to 1.74 ppm. This may be due to the solute-solvent hydrogen bonding in DMSO-d_6 solution, i.e., the formation of a NH_a---OS bond. It is in agreement with the fact that the formation of hydrogen bonds generally cause a downfield shift of the resonance signal of the proton involved.[11] However, the hydrogen bonding between NH_b and the ring nitrogen atom is effected to a certain extent by the substituent on the ring system, e.g. the chemical shift of NH_b at δ 7.34 in 7b and at δ 7.39 in 8b in deuteriochloroform are more upfield shift than those of NH_b in the corresponding 7a (δ 7.70) and 8a (δ, 7.77) respectively. This can be ascribed to the inductive effect of the trifluoro group which make the corresponding nitrogen atom more electron deficient and thus reduce the ring currency and the strength of hydrogen bonding. Thus, the reduced hydrogen bonding between NH_b and the ring nitrogen atom would allow the solvent to compete the hydrogen bonding formation and cause the NH_b downfield shift in DMSO-d_6. It shall be noted further that the ^{13}C nmr spectrum of 7b showed two quartets at δ 119.26 (J_{CF}=272.6 Hz) and δ 120.06 (q J_{CF}=273.6 Hz) for CF_3 groups and the other two quartets at δ 130.82 (q, J_{CF}=38.25 Hz) and δ 144.00 (q, J_{CF}=38.6 Hz) for C-4 and C-2 carbons. These coupling constants are in agreement with literature data.[12] The same phenomena was also observed in that of 8b.

An X-ray crystallographic study of compound (7a) (Figure 1) was carried out, and the determined structure is in agreement with our ^1H nmr structural assignments. Single crystals[13] of 7a were grown from DMF. The X-ray diffraction data were collected at 21°C with a Rigaku AFC5R(RU-300) rotating anode X-ray diffractometer by using the ω-2θ scan mode with graphite-monochromated CuKα(λ = 1.5418Å) radiation. Cell parameters were determined by least

squares refinement, the setting angles of 25 accurately centered reflections ($50^{o}<2\theta<75^{o}$) being used. Throughout data collection the intensities of three standard reflections ([0,-2,4],[0,-2,-4],[-2,-1,-2]) were monitored every 2 hours and this indicated no significant crystal decomposition. The intensity data were corrected for Lorentz and polarization effects and for absorption by a procedure based on azimuthal ψ-scan from reflections [-2,1,0],[-2,1,-1] and [-3,0,-1].[14] Reflections with $F > 3\sigma(F)$ were used for structure solution and refinement.

The structure was solved by the direct methods using the program SHELXS-86.[15] Full-matrix least squares refinement was carried out on positional and anisotropic thermal parameters of all non-hydrogen atoms by using the NRCVAX package.[16] The function minimized was $\Sigma w(|Fo|-|Fc|)$, where $w = [\sigma^2(F_o)+0.0001(F_o)^2]^{-1}$. Positions of the hydrogen atoms were all located in difference Fourier map and also included in the refinement with isotropic temperature factors. In the last stage least-squares calculation, goodness of fit = 2.06, $(\Delta\rho)_{max}$ = 0.16 e Å-3, $(\Delta/\sigma)_{max}$=0.001. Final atom coordinates, bond lengths and bond angles are listed in Tables 2-4. Tabulations of hydrogen atomic coordinates, anisotropic thermal parameters, structure factors are available from the author Y.-C. Liaw. Figure 1 shows a perspective view and atom labelling of the crystal structure. All the non-hydrogen atoms lie in the same plane. N9 of the amide group donates a strong intramolecular hydrogen bond (2.905(4) Å) to N1 of the base. Two molecules form a dimer by two intermolecular hydrogen bonds (2.907(4) Å) between their amide groups. (Figure 2) Base-base stacking (average 3.42 Å) along a axis and hydrophobic interactions stabilize the crystal packing. (Figure 3A and 3B) Thus, hydrogen bond existing between Hb and N1 in compound (7a) confirmed our ^{1}H nmr studies.

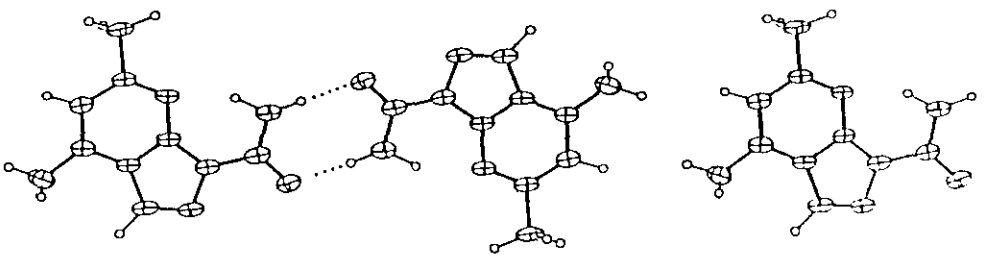


Figure 2. An ORTEP drawing shows the intermolecular H-Bond within dimer (left) and the hydrophobic interactions between dimers which maintain the extension along 2B±A directions.

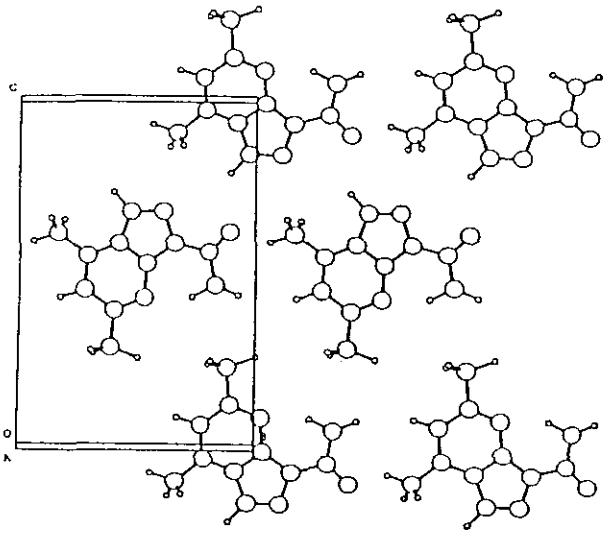


Figure 3A (left). The hydrophobic interactions between interlaced.

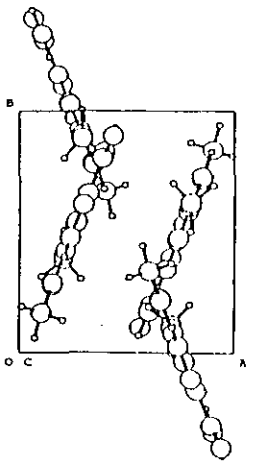


Figure 3B (right). A perspective drawing shows intermolecular stacking.

Table 2. Atomic coordinates and isotropic thermal parameters (Biso). E. S. Ds. refer to the last digit printed.

	x	y	z	Biso*
N 1	0.2373(3)	0.0288 (3)	0.08076(13)	3.9(1)
C 2	0.2317(3)	0.0382 (3)	-0.01577(16)	3.7(1)
O 3	0.0625(3)	0.3956 (2)	-0.11226(13)	5.7(1)
N 4	0.2840(3)	-0.0803 (3)	-0.07271(13)	3.9(1)
C 5	0.3475(4)	-0.2245 (4)	0.06113(18)	4.3(1)
C 6	0.2929(3)	-0.1004 (3)	0.11734(16)	3.9(1)
N 7	0.2018(3)	0.1089 (3)	-0.16826(14)	4.8(1)
C 8	0.2617(4)	-0.0277 (4)	-0.16551(17)	4.7(2)
N 9	0.1025(4)	0.3307 (4)	0.04187(16)	5.4(1)
C10	0.3982(6)	-0.3357 (5)	-0.10068(25)	5.9(2)
C11	0.3445(4)	-0.2136 (3)	-0.03539(17)	4.1(1)
C12	0.2943(6)	-0.1150 (5)	0.22336(19)	5.5(2)
C13	0.1803(3)	0.1552 (3)	-0.07631(16)	4.0(1)
C14	0.1116(4)	0.3025 (3)	-0.05215(18)	4.4(1)

*Biso is defined as one third of the trace of the orthogonalised Bij tensor

Table 3. Bond lengths (Å)

N(1)-C(2)	1.367(3)	N(7)-C(8)	1.291(5)
N(1)-C(6)	1.318(4)	N(7)-C(13)	1.378(3)
C(2)-N(4)	1.388(3)	C(10)-C(11)	1.487(4)
C(2)-C(13)	1.390(4)	C(13)-C(14)	1.447(4)
O(3)-C(14)	1.230(3)	N(9)-C(14)	1.357(4)
N(4)-C(8)	1.397(3)	C(6)-C(12)	1.504(3)
N(4)-C(11)	1.364(4)	C(5)-C(11)	1.368(4)
C(5)-C(6)	1.425(4)		

Table 4. Bond Angle(°)

C(2)-N(1)-C(6)	116.3(2)	N(4)-C(11)-C(5)	116.1(3)
N(1)-C(2)-N(4)	122.3(2)	N(4)-C(11)-C(10)	118.9(3)
N(1)-C(2)-C(13)	131.2(3)	C(5)-C(11)-C(10)	125.0(3)
N(4)-C(2)-C(13)	106.5(2)	O(3)-C(14)-N(9)	121.9(3)
C(2)-N(4)-C(8)	105.4(2)	O(3)-C(14)-C(13)	122.7(2)
C(2)-N(4)-C(11)	121.8(2)	N(9)-C(14)-C(13)	115.4(3)
C(8)-N(4)-C(11)	132.8(2)	N(4)-C(8)-N(7)	111.7(3)
C(6)-C(5)-C(11)	120.5(3)	C(8)-N(7)-C(13)	107.6(2)
C(2)-C(13)-N(7)	108.7(3)	C(5)-C(6)-C(12)	119.8(3)
N(1)-C(6)-C(5)	123.0(2)	C(2)-C(13)-C(14)	128.3(2)
N(1)-C(6)-C(12)	117.2(3)	N(7)-C(13)-C(14)	123.1(2)

It would appear that this investigation provided an approach toward the synthesis of novel *fused purine homologues.*

EXPERIMENTAL

General Methods: Melting points were obtained on an electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 983 G spectrophotometer. *Uv spectra were recorded on a Beckman UA 50 spectrometer.* ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a either Jeol FX-100 or Jeol JNM-EX400 spectrometer from National Taiwan Normal University or on a Bruker Model AM 300WB spectrometer from National Taiwan University, Taipei, and are reported in parts per million with DMSO-$\underline{d}_6$ as internal standard on a δ scale. EI mass spectra was recorded on Jeol JMS-D100 mass spectrometer from National Taiwan University. *Elemental analyses were carried out either on a Heraeus* Elemental Analyzer in Cheng-Kong University, Tainan, or on a Perkin-Elmer 240 Elemental Analyzer in National Taiwan University, Taipei.

2,4-Dimethylimidazo[1,5-$\underline{a}$]pyrimidine-8-carboxamide (7a)

To a suspension of 4-aminoimidazole-5-carboxamide hydrochloride *(5.0 g, 0.03 mol) in methanol* (50 ml) was added 2,4-pentanedione (7.7 ml, 0.12 mol). The mixture was stirred at room temperature for 8 h. The light green solid was collected by filtration and the filtrate was concentrated *in vacuo* to give light green solid which was collected by filtration again. The solid was combined together and recrystallized from DMF to furnish 5.14 g (88%) of $\underline{7a}$, mp > 300 °C [lit.,[17] 305-307°C]; ir (KBr): 3353, 3147, 3077, 1666, 1619, 1517, 956, 850 cm^{-1}; uv λ_{max} nm (ε x 10^4): (H_2O, pH 1) 316 (0.67), 282 (0.54), 271 (0.52); (MeOH) 339 (0.51), 289 (0.58), 279 (0.53); (H_2O,

pH 13) 338 (0.46), 289 (0.54), 279 (0.52); ^{1}H nmr (300 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 6.79 (s, 1H, CH), 7.22 (s, 1H, NH_a), 7.61 (s, 1H, NH_b), 8.33 (s, 1H, CH); ^{1}H nmr (400 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 5.58 (s, 1H, NH_a), 6.42 (s, 1H, Ar-H), 7.78 (s, 1H, NH_b), 7.98 (s, 1H, Ar-H); ^{13}C nmr (DMSO-d_6): δ 16.92, 24.42, 109.34, 120.84, 123.80, 138.19, 141.88, 159.39, 163.12; ms: m/z 190 (M^+, 100%), 174 (M^+-16, 74%), 162 (M^+-28, 25%); Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.83; H, 5.30; N, 29.48.

2,4-Ditrifluoromethylimidazo[1,5-a]pyrimidine-8-carboxamide (7b)

To a suspension of 4-aminoimidazole-5-carboxamide hydrochloride (0.64 g, 3.94 mmol) in anhydrous methanol (45 ml) was added 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (2.2 ml, 15.8 mmol). The mixture was refluxed in an oil bath under nitrogen for 24 h. The reaction mixture was applied to column chromatography [silica gel, 2.5 x 17 cm, 230-400 mesh; solvent system, chloroform/methanol= 95/5]. The fraction (Rf=0.39) was collected and evaporated *in vacuo* to furnish 0.59 g (50%) of 7b. An analytical sample was recrystallized from toluene. mp 170-173°C; ^{1}H nmr (400 MHz, DMSO-d_6): δ 7.60 (s, 1H, NH_a), 7.70 (s, 1H, NH_b), 8.02 (s, 1H, =CH), 8.86 (s, 1H, =CH); ^{1}H nmr (400 MHz, $CDCl_3$): δ 5.96 (s, 1H, NH_a), 7.34 (s, 1H, =CH), 7.36 (s, 1H, NH_b), 8.36 (s, 1H, =CH); ^{13}C nmr (100.4 MHz, DMSO-d_6): δ 119.26 (q, J_{CF}=272.6 Hz, CF_3), 120.06 (q, J_{CF}=273.6 Hz, CF_3), 126.20, 126.99, 130.82 (q, J_{CF}=38.25 Hz), 136.26, 144.00 (q, J_{CF}=38.55 Hz), 162.07; ms: m/z 298 (M^+, 50%), 282 (M^+-16, 16%), 270 (M^+-28, 30%), 262 (M^+-36, 20%), 243 (M^+-55, 10%), 216 (M^+-82, 40%); Anal. Calcd for $C_9H_4F_6N_4O.H_2O$: C, 34.19; H, 1.19; N, 17.72. Found: C, 34.29; H, 1.92; N, 17.52.

2,4-Diphenylimidazo[1,5-a]pyrimidine-8-carboxamide (7c)

To a suspension of 4-aminoimidazole-5-carboxamide hydrochloride (0.34 g, 2.09 mmol) in anhydrous ethanol (50 ml) was added dibenzoylmethane (0.47 g, 2.1 mmol). The mixture was refluxed in an oil bath under nitrogen for 48 h. The solid was collected by filtration and washed with ethanol (10 ml). The filtrate was applied to column chromatography [silica gel, 2.5 x 15 cm, 230-400 mesh; solvent system, chloroform/methanol= 95/5]. The fraction (Rf=0.19) was collected and evaporated *in vacuo*. The solid was combined together to furnish 0.33 g (51%) of 7c. An analytical sample was recrystallized from toluene. mp 169°C (dec.); ^{1}H nmr (300 MHz, DMSO-d_6): δ 7.39 (br s, 1H, NH_a), 7.59-7.69 (m, 6H, Ar-H), 7.74 (br s, 1H, NH_b), 7.96-7.99 (m, 2H, Ar-H), 8.32 (m,

2H, Ar-H), 8.35 (s, 1H, =CH); ^{13}C nmr (75 MHz, DMSO-d_6): δ 106.28, 122.70, 124.24, 127.46, 128.64, 128.93, 129.31, 130.73, 131.00, 131.30, 135.99, 138.88, 143.89, 155.43, 162.91; ms: m/z 314 (M^+, 100%), 298 (M^+-16, 45%), 286 (M^+-28, 35%), 258 (M^+-56, 20%), 232 (M^+-82, 20%); Anal. Calcd for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.49; H, 4.37; N, 17.51.

5,7-Dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide (8a)

To a suspension of 3-aminopyrazole-4-carboxamide hemisulfate (4.24 g, 24.2 mmol) in anhydrous methanol (160 ml) was added 2,4-pentanedione (10 ml, 96.8 mmol). The mixture was stirred at room temperature for 48 h and evaporated *in vacuo* to dryness. The residue was recrystallized from ethanol to furnish 4.48 g (97%) of 8a. mp 244-247°C; ir (KBr): 3485, 3365, 3189, 3061, 1668 (C=O), 1625, 1593, 1564, 1482, 1362, 1280, 1242, 1199, 1110, 1078, 940, 909 cm^{-1}; uv λ_{max} nm (ε x 10^4): (H_2O, pH 1) 269 (1.13), 239 (2.24); (MeOH) 305 (0.56), 237 (1.84); (H_2O, pH 13) 304 (0.56), 238 (1.85); ^{1}H nmr (400 MHz, DMSO-d_6): δ 2.59 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 7.06 (s, 1H, =C-H), 7.43 (s, 1H, NH_a), 7.57 (s, 1H, NH_b), 8.44 (s, 1H, =C-H); ^{1}H nmr (400 MHz, $CDCl_3$): δ 2.57 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 5.69 (s, 1H, NH_a), 6.65 (s, 1H, =C-H), 7.93 (s, 1H, NH_b), 8.44 (s, 1H, =C-H); ^{13}C nmr (75 MHz, DMSO-d_6): δ 16.41, 24.30, 109.93, 145.16, 145.44, 146.99, 161.39, 162.91; ms: m/z 190 (M^+, 40%), 174 (M^+-16, 100%), 146 (M^+-44); Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.49; H, 5.22; N, 29.51.

5,7-Ditrifluoromethylpyrazolo[1,5-a]pyrimidine-3-carboxamide (8b)

To a suspension of 3-aminopyrazole-4-carboxamide hemisulfate (0.21 g, 1.2 mmol) in anhydrous methanol (20 ml) was added 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (0.7 ml, 4.8 mmol). The mixture was refluxed in an oil bath under nitrogen for 46 h. The mixture was applied to column chromatography [silica gel, 1 x 19 cm; solvent system, chloroform]. The fraction (Rf=0.69) was collected by filtration and evaporated *in vacuo* to give 0.27 g (76%) of 8b. An analytical sample was recrystallized from toluene. mp 219-221°C; ^{1}H nmr (400 MHz, DMSO-d_6): δ 7.38 (br s, 1H, NH_a), 7.77 (br s, 1H, NH_b), 8.28 (s, 1H, =CH), 8.94 (s, 1H, =CH); ^{1}H nmr (400 MHz, $CDCl_3$): δ 6.11 (s, 1H, NH_a), 7.39 (s, 1H, NH_b), 7.57 (s, 1H, =CH), 8.90 (s, 1H, =CH); ^{13}C nmr (100.4 MHz, DMSO-d_6): δ 105.15, 108.78, 118.87 (q, J_{CF}=273.5 Hz, CF_3), 120.02 (q, J_{CF}=273.5 Hz, CF_3), 135.51 (q, J_{CF}=36.7 Hz), 145.35, 147.19 (q, J_{CF}= 38.5 Hz), 148.12, 161.39; ms: m/z 298 (M^+, 46%), 282 (M^+-16, 100%), 262 (M^+-36, 28%), 254 (M^+-

44), 212 (M^+-86); Anal. Calcd for $C_9H_4F_6N_4O$: C, 36.26; H, 1.35; N, 18.79. Found: C, 36.23; H, 0.99; N, 18.73.

5,7-Diphenylpyrazolo[1,5-a]pyrimidine-3-carboxamide (8c)

To a suspension of 3-aminopyrazole-4-carboxamide hemisulfate (0.1 g, 0.57 mmol) in anhydrous ethanol (20 ml) was added dibenzoylmethane (0.13 g, 0.58 mmol). The mixture was refluxed in an oil bath under nitrogen for 20 h. To the mixture was then added water (15 ml) to afford precipitate. The light green solid was then collected by filtration and washed with chloroform and ether (1:1, 20 ml) to give 0.16 g (89%) of 8c. An analytical sample was recrystallized from ethanol. mp 272-274°C; ^{1}H nmr (300 MHz, DMSO-d_6): δ 7.32 (s, 1H, NH_a), 7.55-7.66 (m, 6H, Ar-H), 7.73 (s, 1H, NH_b), 7.96 (s, 1H, =CH), 8.14-8.22 (m, 2H, Ar-H), 8.37-8.40 (m, 2H, Ar-H), 8.58 (s, 1H, =CH); ^{13}C nmr (75 MHz, DMSO-d_6): δ 105.41, 106.18, 127.31, 127.71, 128.35, 128.75, 128.98, 129.91, 130.10, 131.20, 131.31, 132.91, 135.82, 146.18, 146.54, 147.47, 157.48, 162.72; ms: m/z 314 (M^+, 70%), 298 (M^+-16, 100%), 269 (M^+-44), 258 (M^+-56), 242 (M^+-62); Anal. Calcd for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.32; H, 4.66; N, 17.52.

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