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UNEXPECTED REACTION OF 2-HYDRAZINOPERIMIDINE WITH MALEIC ANHYDRIDE: SYNTHESES OF (8-AMINO-9-OXO-9,10-DIHYDRO-8*H*-IMIDAZO[1,2-*a*]PERIMIDIN-10-YL)ACETIC ACID AND ITS AZOMETHINE DERIVATIVES

Anton V. Dolzhenko, Wai-Keung Chui,* and Anna V. Dolzhenko

Department of Pharmacy, Faculty of Science, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore. E-mail: phacwk@nus.edu.sg

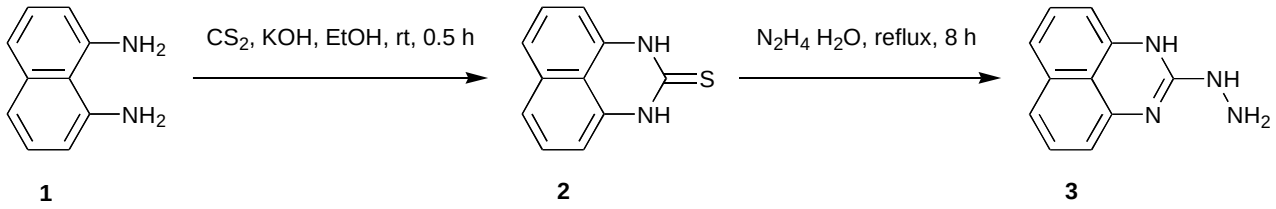
Abstract – The reaction of 2-hydrazinoperimidine (**3**) and maleic anhydride in mild conditions afforded the formation of an unexpected product, namely (8-amino-9-oxo-9,10-dihydro-8*H*-imidazo[1,2-*a*]perimidin-10-yl)acetic acid (**5**). The possible mechanism of this reaction is discussed. Schiff bases (**9a-f**) were prepared from **5** using corresponding aldehydes. The structures of the prepared compounds were established with spectral analysis including NOESY 2D experiments.

INTRODUCTION

2-Hydrazinoperimidine (**3**) has been shown to be a valuable synthon in heterocyclic chemistry. Hydrazine (**3**) was reported to be used for the synthesis of pyrazolylperimidine[1,2] and preparation of perimidines fused with *s*-triazole[3-8] or *as*-triazine rings.[8] It is well known that maleic anhydride undergoes three general types of reactions: condensation with dienes across its double bond to give Diels-Alder adducts, addition to the double bond with formation of succinic anhydride derivatives, and reaction at one of the carbonyl groups with (usually) concomitant cleavage of the anhydride system. Our laboratory has been working on the reactions of maleic anhydrides with N,X-binucleophiles that lead to the formation of azaheterylacetic acids *via* N-acylation and Michael addition.[9,10] In continuation of this investigation, we describe herein the conversion of 2-hydrazinoperimidine (**3**) to the imidazo[1,2-*a*]perimidine (**5**) together with the synthesis of the azomethine derivatives of compound (**5**).

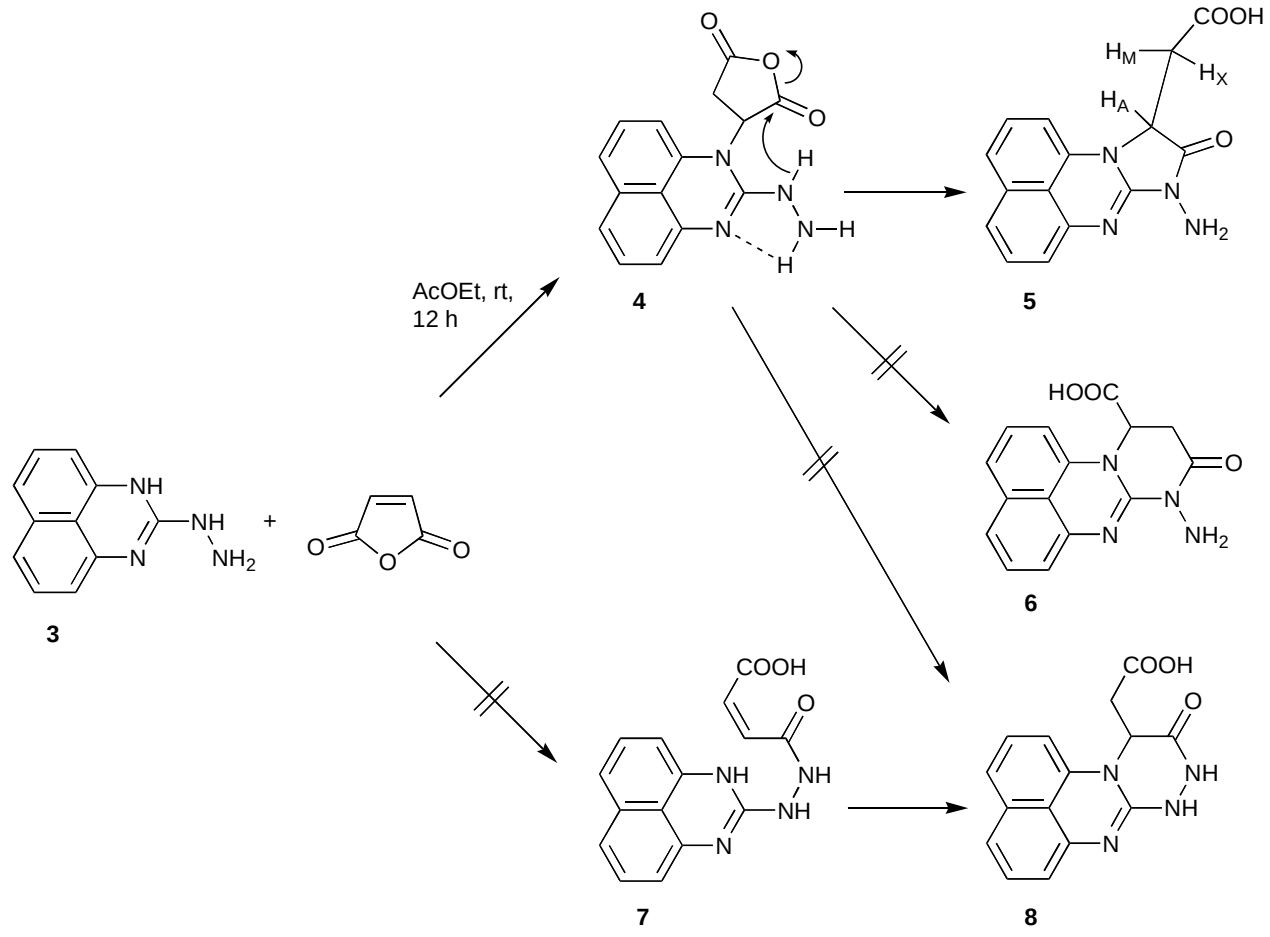
RESULTS AND DISCUSSION

2-Hyrdazinoperimidine (**3**) was prepared from 1,8-naphthalenediamine (**1**) according to Scheme 1, using methods reported in the literature.[1,11]



Scheme 1

The reaction between **3** and maleic anhydride was carried out in ethyl acetate at room temperature and resulted in the formation of compound (**5**) (Scheme 2).



Scheme 2

The structure of compound (**5**) was elucidated by IR and NMR spectral data. The ^{1}H NMR spectrum of compound (**5**) showed three doublet of doublets: signals of the geminal diastereotopic methylene protons at 3.00 and 3.28 ppm and signal of the vicinal methine proton at 4.78 ppm. At the same time, the broad COOH signal at 12.40 ppm suggested the opening of the anhydride ring. These findings together with the ^{13}C NMR signals of CH_2 at 30.3 ppm and CH at 54.1 ppm, indicated the formation of compound (**5**). The singlet of the two protons at 5.08 ppm in ^{1}H NMR spectrum of the compound (**5**) gave the evidence that NH_2 group of

2-hyrdazinoperimidine (**3**) was not affected in the reaction and confirm the structure (**5**). The possible attack of NH_2 group in an intermediate (**4**) was probably prevented by intramolecular hydrogen bond stabilization. The NOESY 2D spectra of compound (**5**) showed cross-peaks for the signal of perimidine ring at 6.44 ppm and signals at 3.28 and 4.78 ppm that confirmed the annulation of imidazole ring and the structure (**5**) (Figure).

It was anticipated that the reaction of 2-hyrdazinoperimidine (**3**) with maleic anhydride under the mild conditions would have formed hydrazide (**7**). Subsequent intramolecular Michael addition would have furnished the 1,2,4-triazino[4,3-*a*]perimidinylacetic acid (**8**). The anticipated pathway was based on reported cyclizations of maleic acid monoamides derived from maleic anhydride.[12] However, the NH_2 protons singlet observed in ^{1}H NMR spectrum ruled out this reaction pathway. The theoretically possible formation of the compound (**6**) from the transient adduct (**4**) was excluded based on NOESY 2D data.

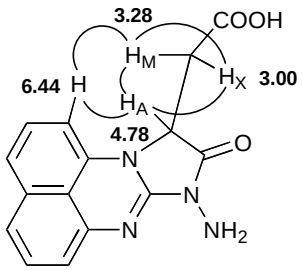
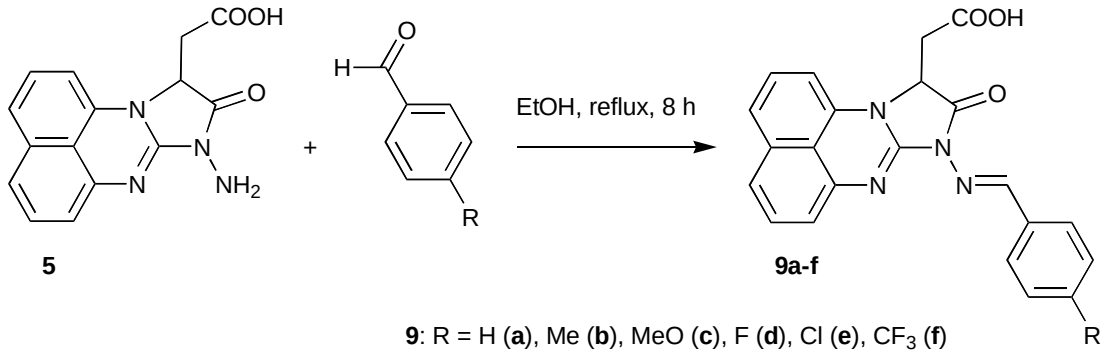


Figure. Key NOE correlations of the amino acid (**5**)

The reaction of the amino acid (**5**) with several aldehydes was found to afford the corresponding Schiff bases (**9a-f**) (Scheme 3). The ^{1}H NMR and IR spectra of the azomethine compounds (**9a-f**) showed no signals due to NH_2 protons observed in the spectra of **5**.



Scheme 3

In conclusion, the reaction of 2-hyrdazinoperimidine (**3**) with maleic anhydride was found to proceed with high regioselectivity, giving a new type of *N*-amino heterocycle, (8-amino-9-oxo-9,10-dihydro-8*H*-imidazo[1,2-*a*]perimidin-10-yl)acetic acid (**5**). Compound (**5**) was successfully condensed with arylaldehydes to afford azomethine derivatives (**9a-f**).

EXPERIMENTAL

General Methods. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. IR spectra were performed on a JASCO FT-IR-430 spectrophotometer in KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer, using DMSO-d_6 as a solvent and TMS as an internal reference. The assignments were made using the reported data,[13] DEPT135, COSY and NOESY 2D spectral data. The asterisk indicates that assignments may be reversed.

2-Mercaptoperimidine (2)

To the solution of 1,8-naphthalenediamine (**1**) (20.6 g, 0.13 mol) and carbon disulfide (9.0 mL, 0.15 mol) in ethanol (100 mL) solid potassium hydroxide (50 mg) was added with stirring. After 15 min the precipitate of **2** was filtered, washed with ethanol, dried and used without further purification. Yield 25.5 g (98 %); mp > 360 °C (lit.,[11] mp > 300 °C).

2-Hydrazinoperimidine (3)

The suspension of 2-mercaptoperimidine (**2**) (5.0 g, 0.025 mol) in 25 mL (0.5 mol) of 99 % hydrazine hydrate was heated under reflux for 8 h. After cooling the precipitate of **3** was filtered, washed with methanol and recrystallized from DMF/water. Yield 4.4 g (89%); mp 193-195 °C (lit.,[1] mp 188-191 °C).

(8-Amino-9-oxo-9,10-dihydro-8H-imidazo[1,2-a]perimidin-10-yl)acetic acid (5)

The mixture of maleic anhydride (1.96 g, 0.01 mol) and 2-hydrazinoperimidine (**3**) (3.96 g, 0.02 mol) in ethyl acetate (50 mL) was stirred for 12 h at rt. The precipitation was filtered, washed with ethyl acetate and recrystallized from DMF/water to afford the pure product (**5**). Yield 1.71 g (72 %); mp 274 °C (decomp).

IR (KBr, ν, cm^{-1}): 3310 (NH st), 3178 (NH st), 3051 (CH st), 2919 (CH st), 2716 (CH st), 1770 (COOH st), 1707 (C=O st), 1642 (C=N st), 1617 (NH δ), 1597, 1504, 1467, 1450, 1408, 1256, 819.

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.00 (1H, dd, J_{AX} = 2.3 Hz, J_{MX} = 17.7 Hz, H_X), 3.28 (1H, dd, J_{AM} = 5.3 Hz, J_{MX} = 17.7 Hz, H_M), 4.78 (1H, dd, J_{AM} = 5.3 Hz, J_{AX} = 2.3 Hz, H-10), 5.08 (2H, s, NH_2), 6.44 (1H, d, J = 6.8 Hz, H-1), 6.81 (1H, d, J = 7.2 Hz, H-6), 7.14-7.26 (3H, m, H-2, H-3 and H-4), 7.30 (1H, t, J = 7.7 Hz, H-5), 12.40 (1H, br. s, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 30.3 (CH_2), 54.1 (C-10), 100.8 (C-1), 114.4 (C-6), 118.7 (C-3), 119.2 (C-4), 119.8 (C-3a[1]), 127.4 (C-2), 128.7 (C-5), 134.7* (C-3a), 134.8* (C-6a), 143.0 (C-11a), 150.6 (C-7a), 169.5 (C=O), 170.2 (COOH).

Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.75; H, 3.98; N, 18.77.

Azomethine derivatives of (8-amino-9-oxo-9,10-dihydro-8H-imidazo[1,2-a]perimidin-10-yl)acetic acid (9a-f)

The mixture of (8-amino-9-oxo-9,10-dihydro-8*H*-imidazo[1,2-*a*]perimidin-10-yl)acetic acid (0.60 g, 0.002 mol) and appropriate arylaldehyde (0.002 mol) in ethanol (20 mL) was heated under reflux for 8 h. The precipitation was filtered, washed with ethanol and recrystallized from DMF/water to afford the pure products (**9a-f**).

[8-(Phenylmethylene)amino-9-oxo-9,10-dihydro-8H-imidazo[1,2-a]perimidin-10-yl]acetic acid (9a)

Yield 88%; mp 276-277 °C (decomp).

IR (KBr, ν, cm^{-1}): 3050 (CH st), 2923 (CH st), 2720 (CH st), 1757 (COOH st), 1703 (C=O st), 1642 (C=N st), 1598, 1505, 1465, 1448, 1354, 1211, 816, 761, 705, 691.

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.08 (1H, dd, J_{AX} = 2.6 Hz, J_{MX} = 17.8 Hz, H_X), 3.42 (1H, dd, J_{AM} = 5.0 Hz, J_{MX} = 17.8 Hz, H_M), 4.93 (1H, dd, J_{AM} = 5.0 Hz, J_{AX} = 2.6 Hz, H-10), 6.53 (1H, dd, J = 6.6, 1.3 Hz, H-1), 6.86 (1H, d, J = 7.2 Hz, H-6), 7.19-7.35 (5H, m, H-2, H-3, H-4, H-5 and H-4'), 7.52-7.61 (2H, m, H-3' and H-5'), 7.93 (2H, dd, J = 7.5, 1.5 Hz, H-2' and H-6'), 9.47 (1H, s, CH=N), 12.18 (1H, br. s, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 30.9 (CH_2), 54.3 (C-10), 101.3 (C-1), 115.1 (C-6), 119.0 (C-3), 119.7 (C-4), 119.8 (C-3a[1]), 127.5 (C-2), 128.1 (C-2' and C-6'), 128.8 (C-5), 129.0 (C-3' and C-5'), 131.9 (C-4'), 133.0 (C-1'), 134.5* (C-3a), 134.7* (C-6a), 142.5 (C-11a), 148.5 (C-7a), 159.7 (CH=N), 167.7 (C=O), 170.3 (COOH).

Anal. Calcd for $C_{22}H_{16}N_4O_3$: C, 68.74; H, 4.20; N, 14.58. Found: C, 68.62; H, 4.06; N, 14.41.

[8-(4-Methylphenylmethylene)amino-9-oxo-9,10-dihydro-8H-imidazo[1,2-a]perimidin-10-yl]acetic acid (9b)

Yield 92%; mp 295 °C (decomp).

IR (KBr, ν, cm^{-1}): 3052 (CH st), 2920 (CH st), 2727 (CH st), 1752 (COOH st), 1714 (C=O st), 1643 (C=N st), 1602, 1506, 1467, 1451, 1256, 1180, 816, 761, 702, 655, 516.

^{1}H NMR (300 MHz, DMSO-d_6): δ 2.40 (3H, s, Me), 3.07 (1H, dd, J_{AX} = 2.6 Hz, J_{MX} = 17.7 Hz, H_X), 3.42 (1H, dd, J_{AM} = 5.0 Hz, J_{MX} = 17.7 Hz, H_M), 4.92 (1H, dd, J_{AM} = 5.0 Hz, J_{AX} = 2.6 Hz, H-10), 6.52 (1H, dd, J = 6.4, 1.5 Hz, H-1), 6.86 (1H, d, J = 7.2 Hz, H-6), 7.17-7.28 (3H, m, H-2, H-3 and H-4), 7.32 (1H, t, J = 7.7 Hz, H-5), 7.37 (2H, d, J = 7.9 Hz, H-3' and H-5'), 7.81 (2H, d, J = 7.9 Hz, H-2' and H-6'), 9.38 (1H, s, CH=N), 12.77 (1H, s, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 21.1 (Me), 30.9 (CH_2), 54.2 (C-10), 101.2 (C-1), 115.0 (C-6), 118.9 (C-3), 119.6 (C-4), 119.8 (C-3a[1]), 127.5 (C-2), 128.1 (C-2' and C-6'), 128.8 (C-5), 129.6 (C-3' and C-5'),

130.3 (C-1'), 134.4* (C-3a), 134.7* (C-6a), 142.1 (C-4'), 142.5 (C-11a), 148.6 (C-7a), 160.1 (CH=N), 167.6 (C=O), 170.2 (COOH).

Anal. Calcd for $C_{23}H_{18}N_4O_3$: C, 69.34; H, 4.55; N, 14.06. Found: C, 69.30; H, 4.48; N, 13.96.

[8-(4-Methoxyphenylmethylene)amino-9-oxo-9,10-dihydro-8H-imidazo[1,2-a]perimidin-10-yl]acetic acid (9c)

Yield 85%; mp 292 °C (decomp).

IR (KBr, ν, cm^{-1}): 3053 (CH st), 2938 (CH st), 2838 (CH st), 1747 (COOH st), 1707 (C=O st), 1643 (C=N st), 1621, 1597, 1506, 1465, 1450, 1441, 1257, 1210, 816, 762.

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.07 (1H, dd, J_{AX} = 2.6 Hz, J_{MX} = 17.8 Hz, H_X), 3.41 (1H, dd, J_{AM} = 5.0 Hz, J_{MX} = 17.8 Hz, H_M), 3.86 (3H, s, OMe), 4.92 (1H, dd, J_{AM} = 5.0 Hz, J_{AX} = 2.6 Hz, H-10), 6.52 (1H, dd, J = 6.7, 1.5 Hz, H-1), 6.85 (1H, dd, J = 7.2, 0.8 Hz, H-6), 7.11 (2H, d, J = 8.6 Hz, H-3' and H-5'), 7.18-7.28 (3H, m, H-2, H-3 and H-4), 7.31 (1H, t, J = 7.7 Hz, H-5), 7.88 (2H, d, J = 8.6 Hz, H-2' and H-6'), 9.27 (1H, s, CH=N), 12.76 (1H, s, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 30.9 (CH_2), 54.3 (C-10), 55.4 (OMe), 101.2 (C-1), 114.5 (C-3' and C-5'), 115.0 (C-6), 118.9 (C-3), 119.6 (C-4), 119.8 (C-3a^1), 125.4 (C-1'), 127.4 (C-2), 128.7 (C-5), 130.0 (C-2' and C-6'), 134.5* (C-3a), 134.7* (C-6a), 142.6 (C-11a), 148.6 (C-7a), 160.5 (CH=N), 162.2 (C-4'), 167.6 (C=O), 170.2 (COOH).

Anal. Calcd for $C_{23}H_{18}N_4O_4$: C, 66.66; H, 4.38; N, 13.52. Found: C, 66.58; H, 4.30; N, 13.35.

[8-(4-Fluoromethylphenylmethylene)amino-9-oxo-9,10-dihydro-8H-imidazo[1,2-a]perimidin-10-yl]-acetic acid (9d)

Yield 90%; mp 290 °C (decomp).

IR (KBr, ν, cm^{-1}): 3068 (CH st), 2896 (CH st), 2717 (CH st), 1746 (COOH st), 1719 (C=O st), 1647 (C=N st), 1601, 1503, 1464, 1452, 1233 (CF st), 1179, 818, 771, 699, 654.

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.08 (1H, dd, J_{AX} = 2.6 Hz, J_{MX} = 17.8 Hz, H_X), 3.42 (1H, dd, J_{AM} = 5.0 Hz, J_{MX} = 17.8 Hz, H_M), 4.93 (1H, dd, J_{AM} = 5.0 Hz, J_{AX} = 2.6 Hz, H-10), 6.53 (1H, dd, J = 6.8, 1.3 Hz, H-1), 6.86 (1H, d, J = 6.8 Hz, H-6), 7.18-7.29 (3H, m, H-2, H-3 and H-4), 7.32 (1H, t, J = 8.1 Hz, H-5), 7.40 (2H, dd, J = 8.9, 8.6 Hz, H-3' and H-5'), 8.01 (2H, dd, J = 8.6, 5.7 Hz, H-2' and H-6'), 9.48 (1H, s, CH=N), 12.69 (1H, br. s, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 30.9 (CH_2), 54.2 (C-10), 101.3 (C-1), 115.1 (C-6), 116.2 (d, J = 22.3 Hz, C-2' and C-6'), 119.0 (C-3), 119.7 (C-4), 119.8 (C-3a^1), 127.5 (C-2), 128.8 (C-5), 129.7 (d, J = 2.9 Hz, C-1'), 130.5 (q, J = 9.4 Hz, C-3' and C-5'), 134.4* (C-3a), 134.7* (C-6a), 142.5 (C-11a), 148.5 (C-7a), 158.4 (CH=N), 164.1 (d, J = 250.0 Hz, C-4'), 167.7 (C=O), 170.2 (COOH).

Anal. Calcd for $C_{22}H_{15}FN_4O_3$: C, 65.67; H, 3.76; N, 13.92. Found: C, 65.55; H, 3.56; N, 13.64.

[8-(4-Chlorophenylmethylene)amino-9-oxo-9,10-dihydro-8H-imidazo[1,2-a]perimidin-10-yl]acetic acid (9e)

Yield 94%; mp 298 °C (decomp).

IR (KBr, ν, cm^{-1}): 3053 (CH st), 2930 (CH st), 2825 (CH st), 1756 (COOH st), 1705 (C=O st), 1644 (C=N st), 1596, 1466, 1449, 1215, 1088 (CCl st), 815, 760.

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.07 (1H, dd, J_{AX} = 2.6 Hz, J_{MX} = 17.7 Hz, H_X), 3.42 (1H, dd, J_{AM} = 5.0 Hz, J_{MX} = 17.7 Hz, H_M), 4.93 (1H, dd, J_{AM} = 5.0 Hz, J_{AX} = 2.6 Hz, H-10), 6.53 (1H, dd, J = 6.4, 1.5 Hz, H-1), 6.87 (1H, d, J = 7.2 Hz, H-6), 7.17-7.29 (3H, m, H-2, H-3 and H-4), 7.32 (1H, t, J = 7.7 Hz, H-5), 7.63 (2H, d, J = 8.3 Hz, H-2' and H-6'), 7.96 (2H, d, J = 8.3 Hz, H-3' and H-5'), 9.54 (1H, s, CH=N), 12.79 (1H, s, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 30.9 (CH_2), 54.2 (C-10), 101.3 (C-1), 115.1 (C-6), 119.0 (C-3), 119.7 (C-4), 119.8 (C-3a^1), 127.5 (C-2), 128.8 (C-5), 129.1* (C-2' and C-6'), 129.7* (C-3' and C-5'), 132.0 (C-1'), 134.4* (C-3a), 134.7* (C-6a), 136.4 (C-4'), 142.4 (C-11a), 148.6 (C-7a), 157.7 (CH=N), 167.6 (C=O), 170.2 (COOH).

Anal. Calcd for $C_{22}H_{15}ClN_4O_3$: C, 63.09; H, 3.61; N, 13.38. Found: C, 62.98; H, 3.60; N, 13.46.

[8-(4-Trifluoromethylphenylmethylene)amino-9-oxo-9,10-dihydro-8H-imidazo[1,2-a]perimidin-10-yl]-acetic acid (9f)

Yield 89%; mp 299 °C (decomp).

IR (KBr, ν, cm^{-1}): 3053 (CH st), 2934 (CH st), 1755 (COOH st), 1705 (C=O st), 1645 (C=N st), 1602, 1466, 1450, 1326 (CF_3 st), 1177, 1133, 1067, 815, 759.

^{1}H NMR (300 MHz, DMSO-d_6): δ 3.09 (1H, dd, J_{AX} = 2.6 Hz, J_{MX} = 17.8 Hz, H_X), 3.43 (1H, dd, J_{AM} = 4.9 Hz, J_{MX} = 17.8 Hz, H_M), 4.94 (1H, dd, J_{AM} = 4.9 Hz, J_{AX} = 2.6 Hz, H-10), 6.54 (1H, dd, J = 6.4, 1.5 Hz, H-1), 6.89 (1H, d, J = 7.5 Hz, H-6), 7.20-7.31 (3H, m, H-2, H-3 and H-4), 7.33 (1H, t, J = 7.7 Hz, H-5), 7.93 (2H, d, J = 8.0 Hz, H-3' and H-5'), 8.15 (2H, d, J = 8.0 Hz, H-2' and H-6'), 9.73 (1H, s, CH=N), 12.76 (1H, br. s, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 30.9 (CH_2), 54.2 (C-10), 101.4 (C-1), 115.1 (C-6), 119.1 (C-3), 119.8 (C-4), 119.9 (C-3a^1), 123.8 (q, J = 272.4 Hz, CF_3), 125.9 (q, J = 3.9 Hz, C-3' and C-5'), 127.5 (C-2), 128.6 (C-2' and C-6'), 128.8 (C-5), 131.1 (q, J = 31.8 Hz, C-4'), 134.4* (C-3a), 134.7* (C-6a), 137.1 (C-1'), 142.4 (C-11a), 148.4 (C-7a), 156.4 (CH=N), 167.9 (C=O), 170.3 (COOH).

Anal. Calcd for $C_{23}H_{15}F_3N_4O_3$: C, 61.07; H, 3.34; N, 12.38. Found: C, 60.92; H, 3.12; N, 12.22.

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