Synthesis A. Shirsale et al. Paper

A Convenient and Concise Metal-Free Approach to Functionalized Bicyclic Pyrimidinones from Oxazine-2,6-diones

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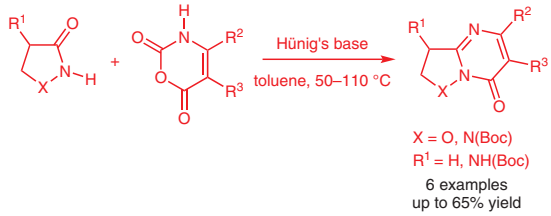

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Abstract The synthesis of previously unreported pyrazolo-pyrimidinones and isoxazolo-pyrimidinones are achieved via metal-free coupling of oxazine-2,6-diones with pyrazolidinone and isoxazolidinone, respectively. The synthesis provides easy access to a variety of novel 2-dimensional building blocks that can be derivatized to generate a range of drug- and agro-like molecules.

Key words isoxazolidinone, pyrazolidinone, oxazine-2,6-dione, metal-free coupling

Quinazolinones are privileged heterocycles found in several natural products and biologically active compounds in both fused and stand-alone heterocyclic structures (Figure 1).[1] Luotonin A represents one such example from quinazolinone family of natural product, which is isolated from Chinese herbal medicinal plant *Peganum nigellastrum*.[1]

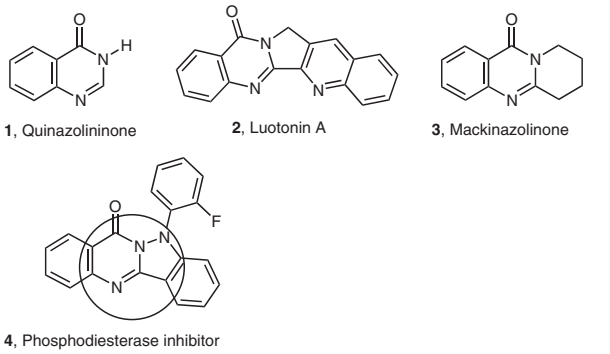


Figure 1 Biologically relevant heterocycles with fused pyrimidinone

Combination of novel heterocycles with divergent functional groups represents a powerful technique in finding novel active ingredients (AIs) for drug and agrochemical use. One such example is the discovery of indazolo-quinazolinone **4**, which is a combination of indazole with quinazolininone and is a potent inhibitor of phosphodiesterase.[2]

Furthermore, such heterocycles with additional handle for derivatization unfold opportunities to expedite the process of finding new leads for drug discovery and agrochemical development. Pyrazolone, pyrimidinone, and isoxazole have been long proven privileged heterocycles, which have shown relevant biological activities for agrochemical targets (Figure 2).[3] As part of our ongoing hit discovery program for the agrochemical development we were interested in the synthesis of fused pyrazolo-pyrimidinone and isoxazolo-pyrimidinone heterocycles, which could be easily

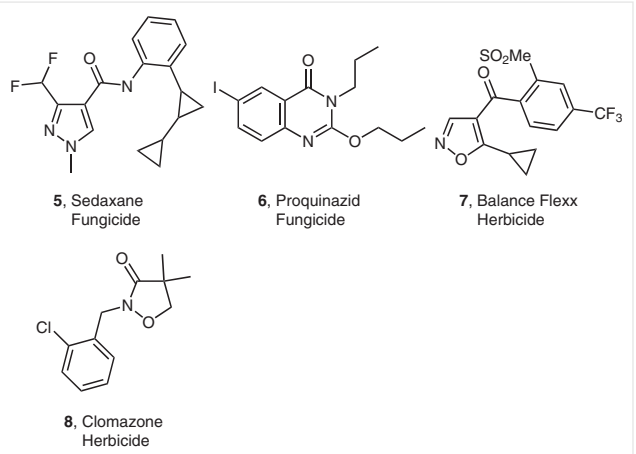


Figure 2 Commercially available agrochemicals with isoxazole, pyrimidinone, and pyrazole motives

derivatized to generate a library of agrolike targets. However, to the best of our knowledge bicyclic pyrimidinones **9** and **10** where R^2 and R^3 are not fused with additional phenyl ring or have handles for derivatization such as **11** have never been reported in literature (Figure 3).

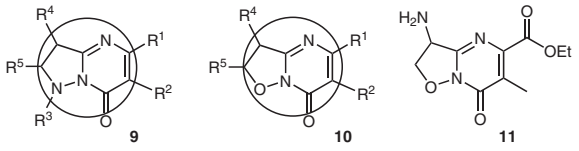
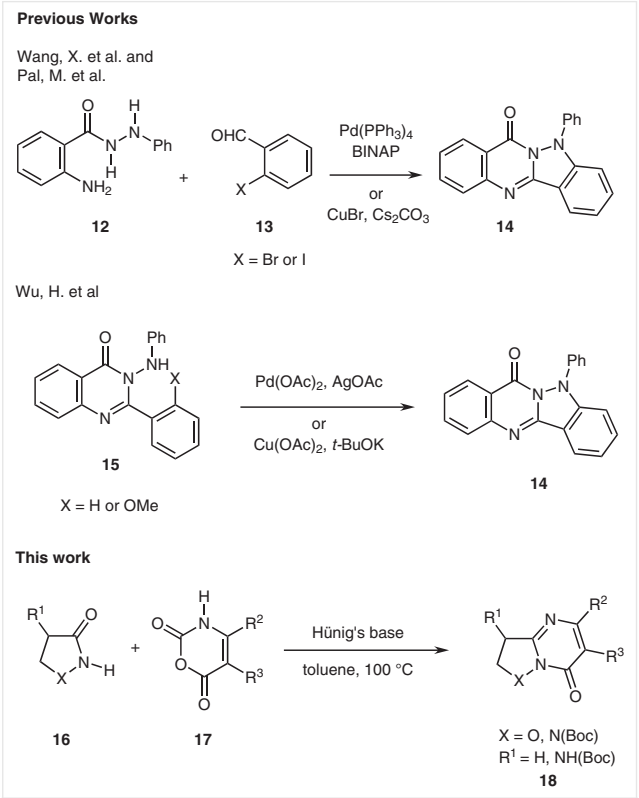


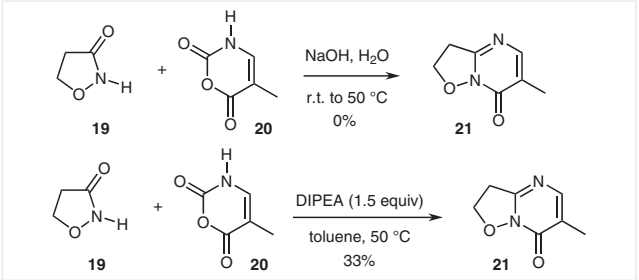
Figure 3 Fused hybrid bicyclic pyrimidinones

Only few approaches are reported in literature for the construction of central core of fused bicyclic pyrimidinone **9**. Pal, Wang, and Wu have independently reported the synthesis of indazoloquinazolinone derivatives from isatoic anhydride.[2,4] Pal's and Wang's method rely on the metal-catalyzed (Pd or Cu) coupling of *o*-halobenzaldehyde with benzohydrazide while Wu has reported two approaches, first involving dual-metal-catalyzed intramolecular oxidative C–H amination and second featuring Cu-catalyzed C–OMe bond cleavage and intramolecular amination of 3-anilino-2-phenylquinazolin-4-one (**15**) (Scheme 1). The current work utilizes the dual reactivity of oxazine-2,6-dione and base-catalyzed coupling of Boc-protected pyrazolidinone in the absence of any metal. It gives access to non-flat and non-aromatic substitutions/fusions on R^2, R^3 and opportunity to vary functional group diversification on nitrogen atom after Boc deprotection, which was not possible with earlier methods. It is noteworthy that previous methods suffer from the drawback that they cannot be used for the synthesis of such stand-alone bicyclic pyrimidinone structures like **11**.



Scheme 1 Strategies for the synthesis of central core of 2,3-dihydropyrazolo[1,5-*a*]pyrimidin-7-one

Preliminary investigation started with the exploration of model coupling reaction of oxazine-2,6-dione **20** and the in situ generated sodium salt of isoxazolidin-3-one **19** in the presence of water.[5] But the reaction led only to decomposition and no isolable product was obtained. We were delighted to learn that the reaction proceeded smoothly in the presence of Hünig's base (diisopropylethylamine, DIPEA) and toluene at 50 °C to furnish 2,3-dihydroisoxazolo[2,3-*a*]pyrimidin-7-one **21** in 33% yield (Scheme 2).

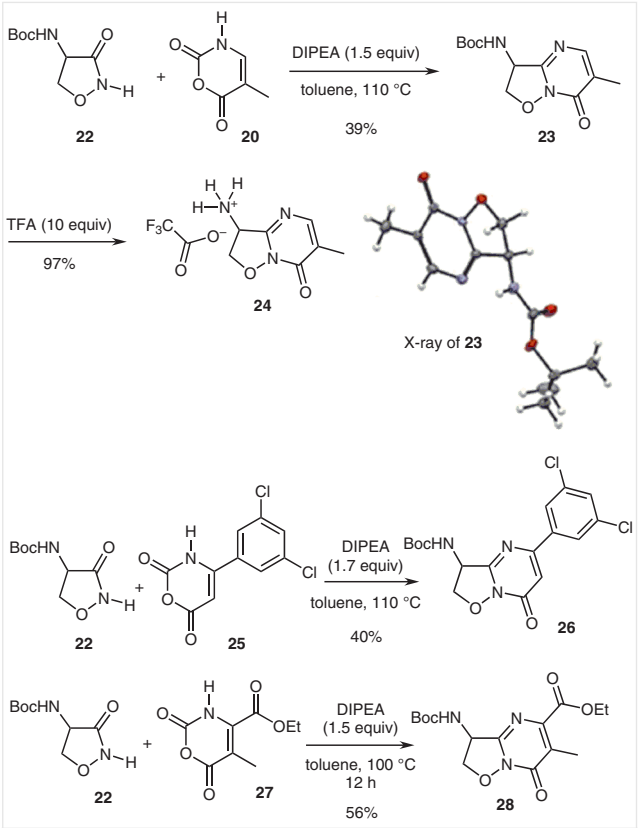


Scheme 2 Model coupling reaction

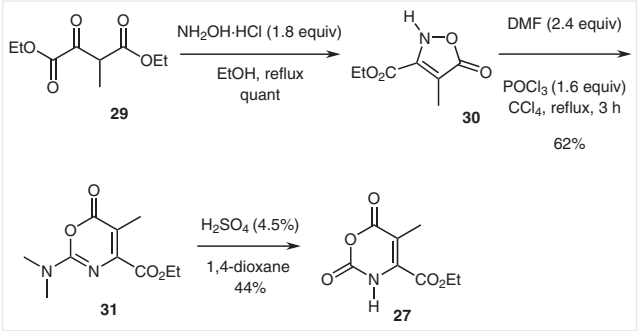
The coupling reaction proceeds smoothly using amino-substituted isoxazolidin-3-one **22** as well to form bicyclic heterocycle **23** in 39% yield (Scheme 3). X-ray crystallographic data of compound **23** confirmed the regioselective addition and the formation of bicyclic structure. The reaction was found to be general for both isoxazolidin-3-one as well as different oxazine-2,6-diones. For instance, the coupling reaction of isoxazole **22** and aryl-substituted oxazine-2,6-dione **25** proceeds under similar conditions to form amino-substituted heterocycle **26** in 40% yield.

Coupling of isoxazolidinone **22** and ester-substituted dihydroisoxazole **27** also proceeded efficiently to form 2-D amino ester bicyclic building block **28** in 56% yield (Scheme 3). The starting material anhydride **27** can be prepared following the literature procedure by Beccalli et al.[6,7] (Scheme 4).

We next turned our attention towards the coupling reaction of pyrazolidinone **32**[8] and oxazine-2,6-dione **33**. To our delight, the reaction proceeded smoothly to furnish pyrazolo[1,5-*a*]pyrimidin-7-one **34** in 40% yield. N-Boc deprotection of **34** using 2,2,2-trifluoroacetic acid (TFA) leads to the formation of pyrazolo[1,5-*a*]pyrimidin-7-one



Scheme 3 1-D and 2-D building blocks of dihydroisoxazolopyrimidinone

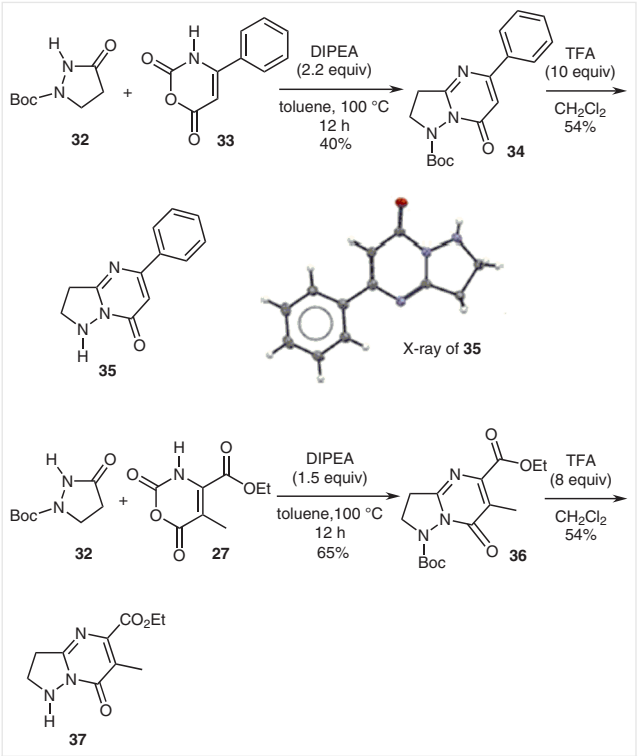


Scheme 4 Synthesis of ester-substituted oxazine-2,6-dione **27**

35, which could be derivatized for S_NAr, alkylation, or acylation reactions for expedited library synthesis.

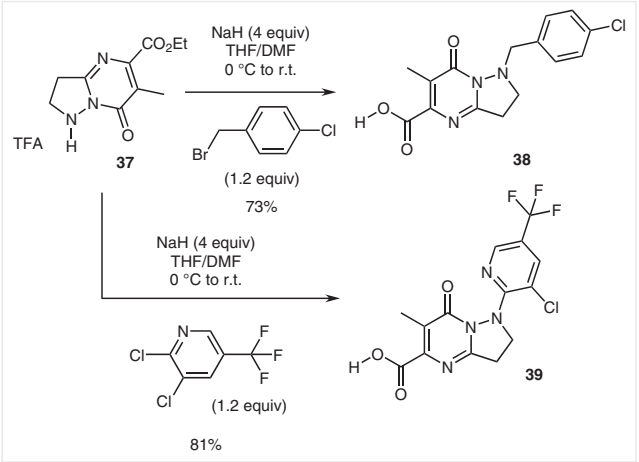
The structure of pyrazolopyrimidinone **35** was further confirmed using X-ray crystallography. Ester-substituted oxazine-2,6-dione **27** also underwent reaction with pyrazolidinone **32** under similar condition to form pyrazolopyrimidinone **36** in 65% yield (Scheme 5).

To showcase the utility of the two-dimensional pyrazolo-pyrimidinone building block, the free 'N' was derivatized via alkylation and S_NAr substitution reactions to generate



Scheme 5 Synthesis of pyrazolo[1,5-*a*]pyrimidin-7-ones **35** and **37**

carboxylic acid building blocks, which could potentially be further derivatized to generate library of agro- and drug-like targets (Scheme 6).



Scheme 6 Synthesis of pyrazolo[1,5-*a*]pyrimidin-7-one carboxylic acids **38** and **39**

In conclusion, we have developed a one-step synthesis to construct bicyclic pyrazolo-pyrimidinones and isoxazolo-pyrimidinones via coupling of oxazine-2,6-diones with pyrazolidione and isoxazolidinone, respectively. The sequence provides easy access to unknown drug- and agro-

like heterocyclic building blocks, which can be derivatized to generate library of compounds that will expedite the lead generation process in agrochemical- and drug discovery.

All reactions were performed under N_2 atmosphere. Analytical grade solvents were used without any further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II-400 spectrometer using $CHCl_3$ as internal standard. LCMS was recorded in Spectra were recorded on a Mass Spectrometer from Agilent Technologies (6410 Triple Quadruple Mass Spectrometer) equipped with an electrospray source [Polarity: Positive and Negative Polarity Switch, Capillary: 4.00 kV, Fragmentor: 100.00 V, Gas Temperature: 350 °C, Gas Flow: 11 L/min, Nebulizer Gas: 45 psi, Mass range: 110–1000 Da, DAD Wavelength range: 210–400 nm. Column: KINETEX EVO C18, length 50 mm, diameter 4.6 mm, particle size 2.6 µm. Column oven temperature 40 °C. Solvent gradient: A: H_2O with 0.1% formic acid/MeCN (95:5 v/v). B: MeCN with 0.1% formic acid. Gradient: 0 min 90% A, 10% B; 0.9–1.8 min 0% A, 100% B, 2.2–2.5 min 90% A, 10% B. Flow rate 1.8 mL/min]. Chemical shift values are given in ppm (δ) relative to $CHCl_3$ (7.27 ppm), DMSO (2.54 ppm) and coupling constants *J* are given in hertz (Hz). IR spectra were recorded on Shimadzu DRS Prestige 21 spectrophotometer. Column chromatographic purifications were performed on a CombiflashRf (Teledyne Isco) with silica gel using the mobile phase indicated.

5-Methyl-3*H*-1,3-oxazine-2,6-dione (20)

Compound **20** was prepared according to the literature report.[9]

To a mixture of NaOCl solution (4.99%, 10 mL) and NaOH (1.6 g, 40 mmol) cooled at 0 °C was added dropwise a precooled (0 °C) solution of 3-methylpyrrole-2,5-dione (3.55 g, 32 mmol) in H_2O (14 mL). The reaction mixture was then stirred at the same temperature for 4 h to obtain a clear solution. After completion of reaction (monitored by TLC), dilute H_2SO_4 was added until pH 3 to form a white precipitate, which was filtered and dried to obtain the desired product as a white solid; yield: 1.8 g (44%); mp 115–117 °C.

IR (KBr): 2970, 2910, 2162, 1753, 1172, 813, 549 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.67–1.87 (m, 3 H), 7.38–7.55 (m, 1 H), 11.16–11.47 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 148.9, 141.6, 103.1, 11.9.

MS (ESI): *m*/*z* = 125.8 (M – H).

6-Methyl-2,3-dihydroisoxazolo[2,3-*a*]pyrimidin-7-one (21)

To a solution of isoxazolidin-3-one (**19**; 0.070 g, 0.80 mmol) in toluene (3 mL) was added DIPEA (0.155 g, 1.2 mmol, 1.5 equiv) at r.t. The reaction mixture was stirred for 5 min and to it was added 5-methyl-3*H*-1,3-oxazine-2,6-dione (**20**; 0.152 g, 1.2 mmol, 1.5 equiv) at once and the mixture was stirred at 50 °C for 2 h. After completion of the reaction (TLC monitoring), the reaction mass was concentrated on a rotavap and the crude product thus obtained was purified by column chromatography to obtain the desired product **21** as a yellow solid; yield: 0.040 g (33%); mp 122–124 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.05–2.17 (m, 3 H), 3.46–3.59 (m, 2 H), 4.64–4.81 (m, 2 H), 7.61–7.75 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 147.8, 123.4, 68.4, 31.8, 12.0.

HRMS-ESI: *m*/*z* calcd for $C_7H_8N_2O_2$ (M + H): 153.0664; found: 153.0653.

tert-Butyl *N*-(6-Methyl-7-oxo-2,3-dihydroisoxazolo[2,3-*a*]pyrimidin-3-yl)carbamate (23)

To a solution of *tert*-butyl *N*-(3-oxoisoxazolidin-4-yl)carbamate (**22**; 3.88 g, 19.2 mmol) in toluene (50 mL) was added DIPEA (3.7 g, 28.8 mmol, 1.5 equiv). The reaction mass was stirred for 10 min and to it was added 5-methyl-3*H*-1,3-oxazine-2,6-dione (**20**; 2.44 g, 19.2 mmol, 1 equiv). The reaction mass was then heated at 100 °C overnight. The TLC indicated consumption of starting material. The reaction mass was diluted with H_2O and extracted with EtOAc (3 × 25 mL), the combined organic layers were dried (Na_2SO_4), and concentrated to obtain the crude product, which was purified by column chromatography to obtain the desired product **23** as a white solid; yield: 2.0 g (39%); mp 188–190 °C.

IR (KBr): 3358, 1687, 1670, 1531, 1170, 964 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 5.64 (br d, *J* = 5.87 Hz, 1 H), 5.45 (br d, *J* = 6.72 Hz, 1 H), 4.96 (br t, *J* = 8.31 Hz, 1 H), 4.44 (t, *J* = 8.68 Hz, 1 H), 2.09 (s, 3 H), 1.44 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 150.0, 147.9, 124.6, 80.2, 76.2, 74.4, 52.9, 27.2, 12.1.

HRMS-ESI: *m*/*z* calcd for $C_{12}H_{17}N_3O_4$ (M + H): 268.1297; found: 268.1290.

For details of X-ray crystal data of **23**, see ref. 10.

(6-Methyl-7-oxo-2,3-dihydroisoxazolo[2,3-*a*]pyrimidin-3-yl)ammonium 2,2,2-Trifluoroacetate (24)

To a solution of **23** (0.410 g, 1.53 mmol) in CH_2Cl_2 (7 mL) was added TFA (1.74 g, 15.3 mmol, 10 equiv) and the reaction mixture was stirred at r.t. overnight. TLC of the reaction mass indicated consumption of the starting material. The reaction mixture was then concentrated and the desired product **24** was isolated as its TFA salt off-white solid; yield: 0.420 g (97%); mp 110–112 °C.

IR (KBr): 2985, 2675, 1662, 1535, 1207, 1174, 1132, 840 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.95–2.06 (m, 3 H), 4.64 (dd, *J* = 9.72, 5.44 Hz, 1 H), 4.93 (t, *J* = 8.93 Hz, 1 H), 5.27 (dd, *J* = 7.64, 5.69 Hz, 1 H), 7.94 (s, 1 H), 8.61–9.10 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.8, 149.6, 148.7, 125.1, 72.1, 52.1, 12.7.

^{19}F NMR (377 MHz, DMSO-d_6): δ = –73.62.

HRMS-ESI: *m*/*z* calcd for $C_7H_{10}N_3O_2$ (M + H): 168.0768; found: 168.0764.

tert-Butyl *N*-[5-(3,5-Dichlorophenyl)-7-oxo-2,3-dihydroisoxazolo[2,3-*a*]pyrimidin-3-yl]carbamate (26)

To a solution of *tert*-butyl *N*-(3-oxoisoxazolidin-4-yl)carbamate (**22**; 2.21 g, 10.9 mmol) in toluene (30 mL) was added DIPEA (2.4 g, 18.6 mmol, 1.7 equiv). After stirring for 10 min, 4-(3,5-dichlorophenyl)-3*H*-1,3-oxazine-2,6-dione (**25**; 1.7 g, 10.9 mmol, 1 equiv) was added and the reaction mixture was heated at 100 °C for 14 h. After completion of the reaction (TLC monitoring), the reaction mass was concentrated under reduced pressure and purified by column chromatography to obtain the desired product **26** as a off-white solid; yield: 1.72 g (40%); mp 198–201 °C.

IR (KBr): 3345, 1682, 1599, 1520, 1443, 1371 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.10 (s, 2 H), 7.80–7.90 (m, 1 H), 7.76 (t, *J* = 1.65 Hz, 1 H), 7.23 (s, 1 H), 5.58 (br d, *J* = 8.44 Hz, 1 H), 4.95 (t, *J* = 8.74 Hz, 1 H), 4.40 (br t, *J* = 8.07 Hz, 1 H), 3.38–3.44 (m, 1 H), 3.12–3.32 (m, 1 H), 1.44 (s, 8 H), 1.38 (br s, 1 H), 1.29 (br s, 2 H), 1.10 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.5, 155.5, 155.1, 154.0, 139.4, 135.2, 130.2, 125.9, 110.2, 79.8, 73.6, 54.5, 28.5.

HRMS-ESI: *m*/*z* calcd for $C_7H_{10}N_3O_2$ (M + H): 398.0674; found: 398.0667.

Ethyl 4-Methyl-5-oxo-2*H*-isoxazole-3-carboxylate (30)

Prepared as reported in the literature.[7]

To a solution of diethyl 2-methyl-3-oxobutanedioate (**29**; 3 g, 0.014 mol) in EtOH (30 mL) was added $NH_2OH{\cdot}HCl$ (1.74 g, 0.025 mol). The reaction mass was heated at 78 °C for 14 h. After completion of the reaction (TLC monitoring), the mixture was directly concentrated under reduced pressure. The residue was triturated 3 times with petroleum ether to obtain the desired product **30** as a white solid; yield: 2.5 g (quant); mp 68–70 °C.

IR (KBr): 3610, 3116, 1728, 1398, 1238 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.30 (t, *J* = 7.09 Hz, 3 H), 1.91 (s, 3 H), 4.32 (q, *J* = 7.09 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 159.9, 153.5, 153.2, 62.0, 14.3, 7.0.

MS (ESI): *m*/*z* = 169.8 (M – H).

Ethyl 2-(Dimethylamino)-5-methyl-6-oxo-1,3-oxazine-4-carboxylate (31)

Prepared as reported in the literature.[7]

To a mixture of DMF (2.08 mL, 0.026 mol) and CCl_4(38 mL) was added $POCl_3$(1.73 mL, 0.018 mol) dropwise at 0 °C. The reaction mass was stirred for 30 min at 0 °C and then at r.t. for 15 min. The reaction mass was again cooled to 0 °C and solid ethyl 4-methyl-5-oxo-2*H*-isoxazole-3-carboxylate (**30**; 2 g, 0.011 mol) was added. The reaction mixture was stirred for 1 h at 0 °C, for 1 h at r.t., and finally heated for 4 h at 80 °C. After completion of the reaction (TLC monitoring) the mixture was cooled using ice-water bath and quenched with sat. aq $NaHCO_3$(30 mL) under cooling condition. The mixture was then extracted with CH_2Cl_2 (3 × 70 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude mixture thus obtained was purified by column chromatography to obtain the desired product **31** as a white solid; yield: 1.65 g (62%); mp 56–58 °C.

IR (KBr): 2981, 2945, 1730, 1020, 866, 756, 729 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33–1.45 (m, 3 H), 1.92–2.07 (m, 3 H), 2.96–3.26 (m, 6 H), 4.26–4.48 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 160.8, 157.3, 153.9, 103.3, 61.4, 36.9, 35.7, 13.6, 10.6.

MS (ESI): *m*/*z* = 226.8 (M + H).

Ethyl 5-Methyl-2,6-dioxo-3*H*-1,3-oxazine-4-carboxylate (27)

To a solution of ethyl 2-(dimethylamino)-5-methyl-6-oxo-1,3-oxazine-4-carboxylate (**31**; 1 g, 0.004 mol) in 1,4-dioxane (46 mL) was added 4.5% H_2SO_4(prepared by diluting 1 mL of concd $H_2SO_4$to 22 mL with H_2O) and the reaction mixture was heated at 100 °C for 1 h. After completion of the reaction (TLC monitoring), the mixture was cooled to r.t. The reaction mass was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with H_2O and aq $NaHCO_3$, and dried (Na_2SO_4). Evaporation of the solvent afforded a crude mixture, which was purified by column chromatography to obtain the desired product **27** as a white solid; yield: 0.39 g (44%); mp 90–92 °C.

IR (KBr): 3109, 2985, 1726, 1396 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34–1.53 (m, 3 H), 2.21–2.38 (m, 3 H), 4.39–4.55 (m, 2 H), 8.56–8.77 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 159.9, 146.6, 136.2, 111.3, 63.7, 13.5, 11.3.

MS (ESI): *m*/*z* = 199.8 (M + H).

Ethyl 3-(*tert*-Butoxycarbonylamino)-6-methyl-7-oxo-2,3-dihydroisoxazolo[2,3-*a*]pyrimidine-5-carboxylate (28)

To a solution of *tert*-butyl *N*-(3-oxoisoxazolidin-4-yl)carbamate (**22**; 2.44 g, 12.1 mmol) in toluene (40 mL) was added DIPEA (2.34 g, 18.1 mmol, 1.5 equiv). After stirring for 10 min, ethyl 5-methyl-2,6-dioxo-3*H*-1,3-oxazine-4-carboxylate (**27**; 2.4 g, 12.1 mmol, 1 equiv) was added and the reaction mixture was heated at 100 °C for 14 h. After completion of the reaction (TLC monitoring), the reaction mass was concentrated under reduced pressure and purified by column chromatography to obtain the desired product **28** as a off-white solid; yield: 2.29 g (56%); mp 140–142 °C.

IR (KBr): 3352, 3315, 2978, 1712, 1514, 1236, 1166 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38–1.43 (m, 3 H), 1.43–1.48 (m, 9 H), 2.24–2.33 (m, 3 H), 4.39–4.46 (m, 2 H), 4.46–4.51 (m, 1 H), 4.93–5.15 (m, 1 H), 5.31–5.60 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 154.7, 154.4, 149.9, 147.8, 126.5, 80.8, 75.4, 61.9, 53.8, 27.8, 13.7, 11.7.

HRMS-ESI: *m*/*z* calcd for $C_{15}H_{21}N_3O_6$ (M + H): 340.1508; found: 340.1493.

4-Phenyl-3*H*-1,3-oxazine-2,6-dione (33)

Prepared as per the literature protocol.[7]

To a mixture of ethyl 3-oxo-3-phenylpropanoate (10 g, 52.026 mmol) and methyl carbamate (3.9 g, 52.026 mmol, 1 equiv) was added $POCl_3$ (30 mL, 318.6 mmol). The reaction mixture was heated at 90 °C for 3 h. After completion of the reaction (monitored by TLC and LCMS), the excess of $POCl_3$ was evaporated on a rotavap under reduced pressure. The solid was then washed with toluene (3 × 25 mL), then Et_2O (3 × 25 mL), and finally with EtOH (3 × 25 mL) to obtain the desired product **33** a off-white solid, which was used as such in the next step; yield: 5.8 g (59%); mp 209–211 °C.

IR (KBr): 3143, 3111, 1768, 1755, 1693, 1485, 1371, 993, 763, 565 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.77–7.80 (m, 2 H), 7.48–7.63 (m, 4 H), 6.01 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.1, 156.8, 149.5, 132.2, 129.1, 127.4, 92.0.

HRMS-ESI: *m*/*z* calcd for $C_{10}H_7NO_3$ (M + H): 190.0504; found: 190.0514.

***tert*-Butyl 7-Oxo-5-phenyl-2,3-dihydropyrazolo[1,5-*a*]pyrimidine-1-carboxylate (34)**

To a solution of *tert*-butyl 3-oxopyrazolidine-1-carboxylate (**32**; 0.2 g, 1 mmol) in toluene (5 mL) was added DIPEA (0.258 g, 2 mmol, 2.2 equiv) at r.t. under stirring followed by the addition of 4-phenyl-3*H*-1,3-oxazine-2,6-dione (**33**; 0.189 g, 1 mmol, 1 equiv). The reaction mixture was stirred overnight at 100 °C. After completion of the reaction (TLC monitoring), the mixture was concentrated under reduced pressure and was directly loaded on a silica gel column for purification to obtain the desired product **34** as an off-white solid; yield: 0.14 g (40%); mp 147–149 °C.

IR (KBr): 2978, 2353, 1734, 1687, 1670, 1606, 1292, 1157, 1080 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47–1.58 (m, 9 H), 3.16–3.33 (m, 2 H), 4.11–4.25 (m, 2 H), 6.73–6.81 (m, 1 H), 7.37–7.51 (m, 3 H), 7.83–7.96 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 158.3, 156.7, 154.5, 135.6, 130.1, 128.4, 126.6, 108.2, 84.2, 48.4, 31.7, 27.5.

HRMS-ESI: *m*/*z* calcd for $C_{17}H_{19}N_3O_3$ (M + H): 314.1504; found: 314.1489.

5-Phenyl-2,3-dihydro-1*H*-pyrazolo[1,5-*a*]pyrimidin-1-ium-7-one 2,2,2-Trifluoroacetate (35)

To a solution of *tert*-butyl 7-oxo-5-phenyl-2,3-dihydropyrazolo[1,5-*a*]pyrimidine-1-carboxylate (**34**; 2.03 g, 6.48 mmol) in CH_2Cl_2 (40 mL) was added TFA (7.4 g, 64.8 mmol, 10 equiv) slowly at 10 °C and the reaction mass was stirred at r.t. overnight. After completion of the reaction (TLC and LCMS), CH_2Cl_2 was evaporated on a rotavap under reduced pressure. The solid gummy mass was then triturated 3–4 times with Et_2O to afford **35** as a off-white solid; yield: 1.16 g (54%); mp 189–191 °C.

IR (KBr): 3215, 1643, 1492, 1386, 945, 779, 694 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.25–3.38 (m, 2 H), 3.41–3.55 (m, 2 H), 6.72–6.87 (m, 1 H), 7.13–7.29 (m, 1 H), 7.38–7.52 (m, 3 H), 7.95–8.09 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.8, 158.0, 156.6, 136.1, 130.1, 128.6, 126.6, 105.8, 42.8, 32.5.

^{19}F NMR (377 MHz, DMSO-d_6): δ = –73.43.

HRMS-ESI: *m*/*z* calcd for $C_{12}H_{12}N_3O$ (M + H): 214.0975; found: 214.0981.

For details of X-ray crystal data of **35**, see ref. 10.

O^1-*tert*-Butyl *O*^{5}-Ethyl 6-Methyl-7-oxo-2,3-dihydropyrazolo[1,5-*a*]pyrimidine-1,5-dicarboxylate (36)

To a solution of *tert*-butyl 3-oxopyrazolidine-1-carboxylate (**32**; 1.5 g, 8.1 mmol) in toluene (25 mL) was added DIPEA (1.55 g, 12 mmol, 1.5 equiv). The reaction mixture was stirred for 10 min followed by the addition of ethyl 5-methyl-2,6-dioxo-3*H*-1,3-oxazine-4-carboxylate (**27**; 1.6 g, 8.1 mmol, 1 equiv) and stirred overnight at 100 °C. After completion of the reaction (TLC monitoring), the reaction mass was concentrated under reduced pressure, and the crude mass thus obtained was purified by column chromatography to obtain the desired product **36** as a yellow solid; yield: 1.7 g (65%); mp 124–126 °C.

IR (KBr): 2985, 1739, 1718, 1676, 1373, 1301, 1236, 1161, 846 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37–1.45 (m, 3 H), 1.45–1.55 (m, 9 H), 2.26–2.37 (m, 3 H), 3.18–3.29 (m, 2 H), 4.07–4.22 (m, 2 H), 4.36–4.48 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 157.0, 155.8, 154.0, 147.0, 125.3, 84.4, 61.8, 48.5, 31.4, 27.4, 13.7, 11.7.

HRMS-ESI: *m*/*z* calcd for $C_{15}H_{21}N_3O_5$ (M + H): 324.1559; found: 324.1558.

Ethyl 6-Methyl-7-oxo-2,3-dihydro-1*H*-pyrazolo[1,5-*a*]pyrimidin-1-ium-5-carboxylate 2,2,2-Trifluoroacetate (37)

To the solution of *O*^{1}-*tert*-butyl *O*^{5}-ethyl 6-methyl-7-oxo-2,3-dihydropyrazolo[1,5-*a*]pyrimidine-1,5-dicarboxylate (**36**; 1.5 g, 4.6 mmol) in CH_2Cl_2 (20 mL) at 10 °C was added dropwise TFA (4.2 g, 37 mmol, 8 equiv) at r.t. and the reaction mixture was stirred at r.t. for 12 h. After completion of the reaction, the reaction mass was concentrated under reduced pressure. The gummy residue obtained was triturated with Et_2O to obtain a yellow solid, which was then dried under high vacuum and isolated as the TFA salt **37**; yellow solid; yield: 0.84 g (54%); mp 80–82 °C.

IR (KBr): 3163, 2983, 1726, 1712, 1649, 1230 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.21–1.34 (m, 3 H), 1.93–2.14 (m, 3 H), 3.16–3.30 (m, 2 H), 3.40–3.50 (m, 2 H), 4.22–4.36 (m, 2 H), 6.96–7.29 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.4, 158.8, 155.5, 147.9, 120.3, 61.3, 43.1, 31.9, 14.0, 11.3.

^{19}F NMR (377 MHz, DMSO-d_6): δ = –74.11.

HRMS-ESI: *m*/*z* calcd for $C_{10}H_{14}N_3O_3$ (M + H): 224.1030; found: 224.1036.

1-[(4-Chlorophenyl)methyl]-6-methyl-7-oxo-2,3-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic Acid (38)

To a suspension of NaH (0.043 g, 1.8 mmol, 4 equiv) in anhyd THF (2 mL) was added dropwise at 0 °C, a solution of ethyl 6-methyl-7-oxo-2,3-dihydro-1*H*-pyrazolo[1,5-*a*]pyrimidin-1-ium-5-carboxylate 2,2,2-trifluoroacetate (**37**; 0.15 g, 0.44 mmol) in DMF (0.5 mL). After stirring the reaction mass for 10 min, a solution of 1-(bromomethyl)-4-chlorobenzene (0.109 g, 0.53 mmol, 1.2 equiv) in THF (0.5 mL) was added dropwise, which led to precipitation of the reaction mass. To the same reaction mass was added THF (6 mL) and DMF (1.5 mL) and stirring was continued for 1 h at r.t. The reaction mixture was then acidified with aq 2 N HCl and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to obtain the crude product, which was triturated with Et_2O to isolate the desired product **38** as a yellow solid; yield: 0.104 g (73%); mp 164–166 °C.

IR (KBr): 2353, 1712, 1680, 1664, 1554, 1384, 1217, 1168 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.10 (s, 3 H), 3.09 (br t, *J* = 7.52 Hz, 2 H), 3.40 (br t, *J* = 7.70 Hz, 2 H), 4.22 (s, 2 H), 7.37–7.47 (m, 4 H), 13.21–14.01 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5, 157.6, 156.9, 149.0, 134.4, 132.2, 130.7, 128.1, 120.5, 56.0, 47.2, 29.4, 11.1.

HRMS-ESI: *m*/*z* calcd for $C_{15}H_{14}ClN_3O_3$ (M + H): 320.0802; found: 320.0792.

1-[3-Chloro-5-(trifluoromethyl)-2-pyridyl]-6-methyl-7-oxo-2,3-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic Acid (39)

To a suspension of NaH (0.043 g, 1.8 mmol, 4 equiv) in anhyd THF (2 mL) at 0 °C was added dropwise a solution of ethyl 6-methyl-7-oxo-2,3-dihydro-1*H*-pyrazolo[1,5-*a*]pyrimidin-1-ium-5-carboxylate 2,2,2-trifluoroacetate (**38**; 0.15 g, 0.44 mmol) in DMF (0.5 mL). After stirring the reaction mixture for 10 min, 2,3-dichloro-5-(trifluoromethyl)pyridine (0.115 g, 0.53 mmol, 1.2 equiv) was added dropwise, followed by the addition of THF (6 mL) and DMF (1.5 mL). The reaction mass was stirred for 1 h at r.t., then acidified with aq 2 N HCl, and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to obtain a crude mass. Trituration with Et_2O and cooling to 0 °C afforded the desired product **39** as an off-white solid; yield: 0.135 g (81%); mp 185–187 °C.

IR (KBr): 2922, 1734, 1672, 1554, 1323, 1136, 1051 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.04 (s, 3 H), 3.20–3.44 (m, 8 H), 4.16 (br t, *J* = 7.40 Hz, 2 H), 8.58–8.61 (m, 1 H), 8.65 (s, 1 H), 13.39–13.88 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5, 157.7, 156.9, 156.2, 149.7, 142.5, 136.5, 123.8, 123.0, 122.7, 121.4, 121.1, 119.9, 51.3, 30.3, 11.1.

HRMS-ESI: *m*/*z* calcd for $C_{14}H_{10}ClF_3N_4O_3$ (M + H): 375.0472; found: 375.0465.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609364.

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(10) CCDC 1818542 (**23**) and 1818638 (**35**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.