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Synthesis of novel tricyclic pyrimidine-fused 5,6-dihydrobenzodiazepines via a Pictet–Spengler-like cyclization

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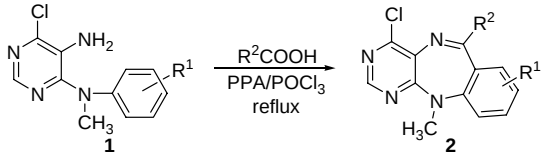
Abstract—Novel pyrimidine-fused 5,6-dihydrobenzodiazepines were prepared via a Pictet–Spengler-like cyclization. It was based on the intramolecular electrophilic substitution of the phenyl ring of 5-amino-6-chloro-4-(*N*-methylanilino)pyrimidine **1** by the iminium intermediate formed with an aldehyde in one pot. The products may be further transformed by subsequent nucleophilic substitution of the chloro atom. This strategy may provide an efficient method to access a library of compounds based on privileged substructures that are of interest in drug discovery.

1. Introduction

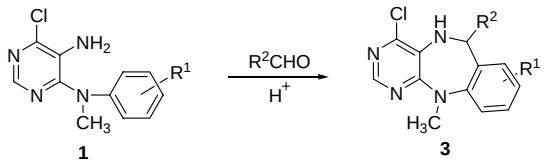
Heterocyclic compounds are often considered privileged structures in medicinal chemistry[1,2] due to their various biological effects. Benzodiazepines represent a class of heterocycles with important activities in the central nervous system and medicinal chemistry efforts in this field have led to the discovery of several CNS drugs. For example, clozapine, olanzapine and quetiapine are used in the clinic for treating schizophrenia, while clonazepam, diazepam, lorazepam, nitrazepam, and oxazepam are used as anti-anxiety drugs. In addition, there are numerous reports of heterocyclic scaffolds containing the benzodiazepine moiety, which show additional biological activities.[3–5]

Another class of heterocycles has often been used as scaffolds in medicinal chemistry are pyrimidines. Consequently, synthetic methodologies for synthesis of novel pyrimidines or pyrimidine-fused compounds are of particular interests to organic and medicinal chemists. For example, synthetic methods have been reported for the efficient syntheses of purines,[6] pyrrolopyrimidines,[7] pyrazolopyrimidines,[8] pyrimidopyrimidines,[9] imidazopyrimidines[10] and furopyrimidines.[11] Recently, we reported a new methodology for the synthesis of pyrimidine-fused benzodiazepines **2**, which entailed an intramolecular Friedel–Crafts type reaction (Scheme 1).[12]



Scheme 1.

As part of our on-going efforts to develop new synthetic methods to prepare novel heterocyclic scaffolds, we envisioned that a Pictet–Spengler-like cyclization[13] of pyrimidine **1** with an aldehyde in place of the carboxylic acid should lead to tricyclic 4-chloro-5,6-dihydropyrimido[4,5-*b*][1,4]benzodiazepines **3** (Scheme 2). This methodology could be complementary to the recently reported one for pyrimido[4,5-*b*][1,4]benzodiazepines.[12] To the best of our knowledge, this is the first approach to fuse pyrimidine with a benzodiazepine by a Pictet–Spengler-like cyclization.[14] Herein, the detailed results from our investigation including exploration of the scope of the cyclization are described.



Scheme 2.

Keywords: Aldehyde; Benzodiazepines; Pyrimidines.
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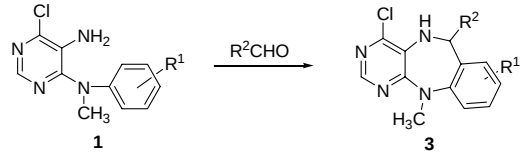
Table 1. Syntheses of 4-chloro-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepines

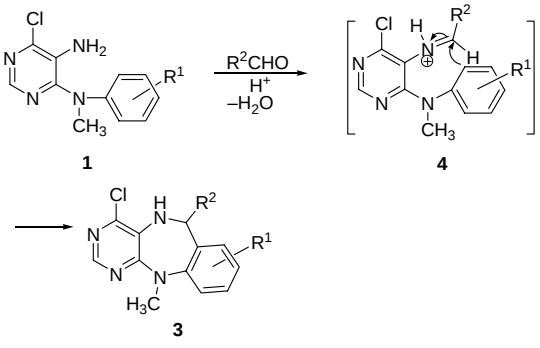


Pyrimidines	R^1	R^2	Products	Yield (%)	Time
1.1	H	$CH_3CH_2CH_2$	**3.1**	65	27 h
1.1	H	CH_3CH_2	**3.2**	47	34 h
1.1	H	Ph	**3.3**	65	48 h
1.1	H	4′-CH_3–C_6H_4	**3.4**	44	24 h
1.1	H	4′-F–C_6H_4	**3.5**	88	29 h
1.1	H	4′-NO_2–C_6H_4	**3.6**	97	16 h
1.2	*p*-CH_3	$CH_3CH_2CH_2$	**3.7**	72	24 h
1.2	*p*-CH_3	CH_3CH_2	**3.8**	57	17 h
1.2	*p*-CH_3	Ph	**3.9**	72	26 h
1.2	*p*-CH_3	4′-CH_3–C_6H_4	**3.10**	46	17 h
1.2	*p*-CH_3	4′-F–C_6H_4	**3.11**	75	35 h
1.2	*p*-CH_3	4′-NO_2–C_6H_4	**3.12**	97	18 h
1.3	*m*-CH_3	$CH_3CH_2CH_2$	**3.13**	81	23 h
1.3	*m*-CH_3	CH_3CH_2	**3.14**	74	21 h
1.3	*m*-CH_3	Ph	**3.15**	71	24 h
1.3	*m*-CH_3	4′-CH_3–C_6H_4	**3.16**	45	17 h
1.3	*m*-CH_3	4′-F–C_6H_4	**3.17**	91	21 h
1.3	*m*-CH_3	4′-NO_2–C_6H_4	**3.18**	99	22 h
1.4	*p*-F	Ph	**3.19**	19	6 days

2. Result and discussion

The starting pyrimidines **1** were readily prepared by a known two-step process from commercially available 5-nitro-4,6-dichloro-pyrimidine and *N*-methylanilines in high yields.[12] Initially, the cyclization reactions of pyrimidine **1.1** (R^1=H) with various aldehydes were investigated. These reactions proceeded smoothly to yield products **3.1**–**3.6** in the presence of excess amount of trifluoroacetic acid in refluxing acetonitrile (Table 1).

A plausible mechanism similar to Pictet–Spengler type reactions was proposed as shown in Scheme 3. It was envisioned that the cyclization reaction proceeded through an iminium intermediate **4** formed between the amino group of pyrimidine **1** and an aldehyde under acid-catalyzed conditions. Iminium **4** underwent an intramolecular electrophilic substitution of the adjacent electron-rich phenyl ring of the anilino moiety to yield the seven-membered ring of the final cyclized product. This is an unusual case since most



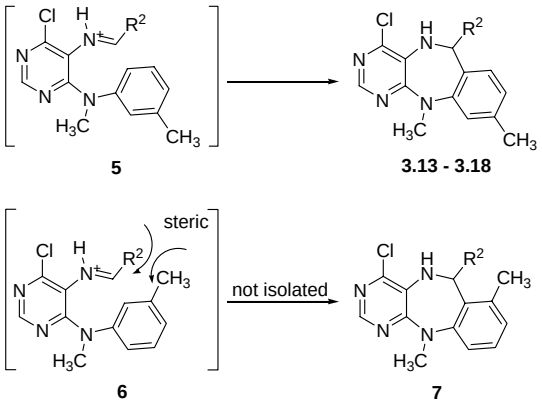
Scheme 3.

Pictet–Spengler reactions in the literature involve an aliphatic amine instead of an aromatic one.

As shown in Table 1, the desired cyclization products were obtained in moderate to excellent yields (44–95%). Higher yields were isolated when electron-withdrawing groups were present in aromatic aldehydes (**3.5**, **3.6**), which may be attributed to their higher reactivity towards imine formation and stabilization effect on the imine intermediates. The scope of the cyclization was further expanded to various pyrimidine derivatives (**1.2**–**1.4**) and the results were also listed in Table 1.

The effect of R^1 substituents on the reactivity of pyrimidine **1** was explored by varying its position and changing the electronegativity. *para*- and *meta*-Methyl substitutions of the anilino phenyl in pyrimidine **1.2** were well tolerated and the desired cyclized products **3.7**–**3.18** were isolated in good to excellent yields. However, a *para*-fluoro substitution (pyrimidine **1.4**) led to a significant decrease in the reaction rate and only 19% of the desired product **3.19** was isolated after 6 days of reaction. These results were consistent with the reaction mechanism that entailed an intramolecular electrophilic substitution of the anilino phenyl ring by iminium ion intermediate **4**. Therefore, when R^1 is an electron-donating group (e.g., CH_3) the phenyl group is more reactive towards an electrophile; while the phenyl group has reduced electron density leading to lower reactivity when R^1 is an electron-withdrawing group (e.g., F). Conversely, when an aromatic aldehyde containing an electron-withdrawing group on its phenyl ring should increase the electro-deficiency of the carbonyl, thereby facilitate imine formation. For instance, **3.6**, **3.12**, **3.18** (R^2=4′-NO_2–C_6H_4) were isolated with excellent yields. It was noteworthy that when R^1 was an *m*-CH_3 two possible regioisomers could be formed. However, only

one regioisomer was isolated (products **3.13–3.18**) suggesting that this reaction could be highly regioselective when a non-symmetrical phenyl ring was present in pyrimidines **1**. This observation may be attributed to the difference in steric effects between the two regioisomers as shown in Scheme 4.

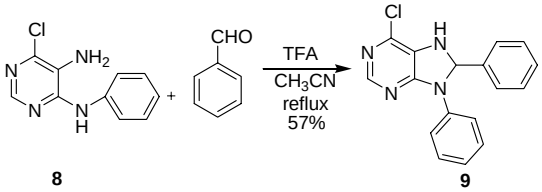


Scheme 4.

When aromatic aldehydes were used regioisomers **7** was not even detected by LC–MS; while the molecular ions of isomers **7** could barely be observed on LC–MS when aliphatic aldehydes were employed. However, the amount was too small to be isolated.

Given the success of this cyclization reaction of pyrimidines **1** with various aldehydes, it was logical to attempt to further expand the scope of this cyclization reaction to ketones. Unfortunately, all attempts on the reactions between **1.1** and various ketones, such as acetone, butan-2-one and acetophenone, failed to generate the desired products.

To investigate whether the 4-anilino group had to be blocked (currently with a methyl group in pyrimidines **1.1–1.4**), the reaction of pyrimidine **8** and benzaldehyde was conducted under the above condition (Scheme 5). No desired cyclization product was observed instead only the dihydropurine compound **9** was obtained in 57% yield. The formation of compound **9** was presumably due to the nucleophilic attack on the iminium ion by the 4-amino group that was more nucleophilic compared to the phenyl ring and the formation of a five-membered ring system was kinetically more favored compared to that of a seven-membered ring system.



Scheme 5.

3. Conclusion

In conclusion, an efficient method was developed for the construction of a novel heterocyclic scaffold, 5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepines. This new method complements the existing chemistries for the preparation of benzodiazepine derivatives. The resulting 4-chloro-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepines may be suitable for further manipulations such as nucleophilic substitution reactions of the 4-chloro group to yield products with more diversity. Therefore, this new reaction is applicable to the preparation of large libraries of novel scaffolds that are of interest in drug discovery.

4. Experimental

4.1. General

The starting compound **1** were prepared by a modified procedure reported by us.[12] Phosphoryl oxychloride was freshly distilled. All other commercial reagents were used as received without additional purification. Melting point was uncorrected. Mass spectra and HPLC (ELSD) data was recorded on an 1100 LC/MS system (Agilent Technology Corporation) with Alltech ELSD 2000, using a 4.6×50 mm Column (CenturySIL C-18 AQ^+, 5μ) with a linear gradient 30–90% (v/v) acetonitrile–water with 0.035% trifluoro-acetic acid over 8 min with a flow rate of 3.5 mL/min. Analytical TLC was performed using 2.5×5 cm plated coated with a 0.25 mm thickness of silica gel 60 F_{254}. Column chromatography was performed using silica gel G (200–300 mesh). All ^1H NMR spectra (300 MHz) are reported as follows: chemical shifts in ppm downfield from TMS as internal standard (δ scale) and $CDCl_3$ or DMSO-d_6 as the solvent. Multiplicities are indicated as the following: multiplicity [s=singlet, d=doublet, t=triplet, m=multiplet, integration and coupling constant (Hz)]. All ^{13}C NMR spectra (75 MHz) were determined with complete proton decoupling and reported in ppm.

4.2. General procedure for 4-chloro-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepines

5-Amino-6-chloro-4-*N*-methyl-anilino-pyrimidine (**1**) (0.85 mmol), the appropriate aldehyde or its derivatives (1.275 mmol) and TFA (0.8 mL) were dissolved in CH_3CN (10.0 mL), and stirred under reflux for 16–48 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc (15 mL), and washed with saturated $NaHCO_3$ (3×15 mL). The water layer was extracted with EtOAc (3×10 mL). The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash chromatography (elution with EtOAc/petroleum ether=1:10 for the compound **3.6**, **3.12**, **3.18**, elution with EtOAc/petroleum ether=1:30 for the others).

4.2.1. 4-Chloro-11-methyl-6-propyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.1). Yellow oil, yield: 65%, ES-MS: 289.2 [$(M+1)^+$]. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.29–7.34 (m, 1H), 7.03–7.17 (m, 3H), 4.54–4.59 (m, 1H), 4.48 (d, J=4.2 Hz, 1H), 3.49 (s, 3H), 1.97–2.07 (m, 2H), 1.39–1.54 (m, 2H), 1.02

(t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.9, 145.8, 145.6, 142.5, 135.5, 128.4, 128.1, 126.0, 123.8, 122.3, 57.3, 40.0, 35.1, 20.1, 13.9. Anal. Calcd for $C_{15}H_{17}ClN_4$: C, 62.39; H, 5.93; N, 19.40. Found C, 62.37; H, 5.69; N, 19.40.

4.2.2. 4-Chloro-11-methyl-6-ethyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepin (3.2). Yellow oil, yield: 47%, ES-MS: 275.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.29–7.34 (m, 1H), 7.03–7.16 (m, 3H), 4.52 (d, J=3.9 Hz, 1H), 4.41–4.48 (m, 1H), 3.49 (s, 3H), 1.98–2.14 (m, 2H), 1.05 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.0, 145.9, 145.6, 142.6, 135.4, 128.5, 128.1, 126.1, 123.9, 122.4, 59.4, 40.1, 26.1, 11.5.

4.2.3. 4-Chloro-11-methyl-6-phenyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.3). Yellow oil, yield: 65%, ES-MS: 323.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.31–7.40 (m, 4H), 7.24–7.27 (m, 2H), 7.16 (d, J=7.8 Hz, 1H), 7.06 (td, J=7.5, 0.9 Hz, 1H), 6.95 (dd, J=7.5 Hz, 1H), 5.82 (d, J=4.2 Hz, 1H), 4.97 (d, J=3.9 Hz, 1H), 3.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.3, 146.4, 146.0, 143.0, 140.1, 135.7, 129.0, 128.8, 128.0, 127.8, 127.7, 126.3, 124.0, 122.8, 60.8, 39.7. Anal. Calcd for $C_{18}H_{15}ClN_4$: C, 66.98; H, 4.68; N, 17.36. Found C, 67.02; H, 4.95; N, 17.07.

4.2.4. 4-Chloro-11-methyl-6-(4′-methyl-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.4). Yellow oil, yield: 44%, ES-MS: 337.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.32–7.38 (m, 1H), 7.14–7.20 (m, 5H), 7.04 (td, J=7.2, 1.2 Hz, 2H), 6.92 (dd, J=7.5, 1.5 Hz, 1H), 5.84 (d, J=3.9 Hz, 1H), 4.91 (d, J=3.3 Hz, 1H), 3.32 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.3, 146.4, 146.0, 142.9, 137.5, 136.9, 135.9, 129.4, 128.9, 128.2, 127.6, 126.4, 123.9, 122.7, 60.5, 39.9, 21.1.

4.2.5. 4-Chloro-11-methyl-6-(4′-fluoro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.5). Yellow oil, yield: 88%, ES-MS: 341.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.35–7.40 (m, 1H), 7.16–7.23 (m, 3H), 6.97–7.10 (m, 4H), 5.74 (d, J=3.0 Hz, 1H), 4.96 (d, J=3.3 Hz, 1H), 3.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0 (d, J=245.0 Hz, 1C), 151.2, 146.5, 145.8, 143.1, 136.1, 136.1, 135.4, 129.2, 127.9 (d, J=5.7 Hz, 2C), 127.7, 124.1, 122.8, 115.5 (d, J=21.8 Hz, 2C), 60.3, 39.7.

4.2.6. 4-Chloro-11-methyl-6-(4′-nitro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.6). Orange solid, yield: 97%, ES-MS: 368.1 [$(M+1)^+$]. Mp 174.5–175.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, J=8.7 Hz, 2H), 8.00 (s, 1H), 7.41–7.46 (m, 1H), 7.35 (d, J=8.4 Hz, 2H), 7.20–7.16 (m, 3H), 5.60 (d, J=5.7 Hz, 1H), 5.19 (d, J=5.7 Hz, 1H), 3.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.1, 148.3, 147.2, 146.8, 145.7, 143.5, 134.5, 129.8, 128.4, 126.8, 126.6, 124.5, 123.8, 123.1, 60.8, 39.1. Anal. Calcd for $C_{18}H_{14}ClN_5O_2$: C, 58.78; H, 3.84; N, 19.04. Found C, 58.86; H, 3.74; N, 18.93.

4.2.7. 4-Chloro-8,11-dimethyl-6-propyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.7). Yellow oil, yield: 72%, ES-MS: 303.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.12 (d, J=8.4 Hz, 1H), 7.04 (d, J=8.4 Hz, 1H), 6.94 (d, J=1.8 Hz, 1H), 4.45–4.54 (m, 2H), 3.47 (s, 3H), 2.32 (s, 3H), 1.96–2.04 (m, 2H), 1.36–1.53 (m, 2H), 1.00 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.1, 145.9, 143.0, 142.5, 135.2, 133.5, 128.9, 128.0, 126.7, 122.2, 57.5, 40.0, 35.2, 20.7, 20.2, 13.9.

4.2.8. 4-Chloro-8,11-dimethyl-6-ethyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.8). Yellow oil, yield: 57%, ES-MS: 289.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.11 (d, J=8.1 Hz, 1H), 7.04 (d, J=8.1 Hz, 1H), 6.93 (s, 1H), 4.49 (s, 1H), 4.37–4.41 (m, 1H), 3.47 (s, 3H), 2.32 (s, 3H), 1.98–2.12 (m, 2H), 1.05 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.0, 145.8, 142.8, 142.4, 134.9, 133.4, 128.8, 127.8, 126.7, 122.1, 59.4, 39.9, 26.0, 20.6, 11.4.

4.2.9. 4-Chloro-8,11-dimethyl-6-phenyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.9). Yellow oil, yield: 72%, ES-MS: 337.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.27–7.39 (m, 3H), 7.23–7.26 (m, 2H), 7.16 (dd, J=8.7 Hz, 1.5 Hz, 1H), 7.05 (d, J=8.7 Hz, 1H), 6.79 (d, J=1.5 Hz, 1H), 5.73 (d, J=3.9 Hz, 1H), 4.98 (d, J=3.9 Hz, 1H), 3.23 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.5, 146.5, 143.3, 142.9, 140.2, 135.3, 133.8, 129.5, 128.6, 128.5, 127.8, 127.6, 126.3, 122.7, 60.9, 39.7, 20.8.

4.2.10. 4-Chloro-8,11-dimethyl-6-(4′-methyl-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.10). Yellow oil, yield: 46%, ES-MS: 351.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.12–7.19 (m, 4H), 7.06 (d, J=8.1 Hz, 2H), 6.75 (s, 1H), 5.76 (d, J=3.6 Hz, 1H), 4.91 (d, J=3.6 Hz, 1H), 3.28 (s, 3H), 2.36 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.5, 146.4, 143.3, 142.9, 137.3, 137.0, 135.5, 133.7, 129.4, 129.3, 128.2, 127.9, 126.3, 122.6, 60.6, 39.8, 21.1, 20.8.

4.2.11. 4-Chloro-8,11-dimethyl-6-(4′-fluoro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.11). Yellow solid, yield: 75%, ES-MS: 355.1 [$(M+1)^+$]. Mp 153.7–155.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.16–7.22 (m, 3H), 7.00–7.07 (m, 3H), 6.81 (d, J=1.5 Hz, 1H), 5.66 (d, J=4.8 Hz, 1H), 4.96 (d, J=4.8 Hz, 1H), 3.22 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0 (d, J=245.0 Hz, 1C), 151.4, 146.6, 143.2, 143.1, 136.1, 135.0, 133.9, 129.6, 128.5, 127.8 (d, J=8.0 Hz, 2C), 127.4, 122.8, 115.5 (d, J=21.8 Hz, 2C), 60.4, 39.6, 20.7. Anal. Calcd for $C_{19}H_{16}ClFN_4$: C, 64.32; H, 4.55; N, 15.79. Found C, 64.14; H, 4.49; N, 15.52.

4.2.12. 4-Chloro-8,11-dimethyl-6-(4′-nitro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.12). Orange solid, yield: 97%, ES-MS: 382.1 [$(M+1)^+$]. Mp 225.6–227.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, J=8.7 Hz, 2H), 7.98 (s, 1H), 7.34 (d, J=8.1 Hz, 2H), 7.23 (d, J=8.1 Hz, 1H), 7.06 (d, J=8.1 Hz, 1H), 7.00 (s, 1H), 5.53 (d, J=5.7 Hz, 1H), 5.18 (d, J=6.0 Hz, 1H), 3.07 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.3, 148.4,

147.1, 146.8, 143.4, 142.9, 134.4, 134.2, 130.2, 129.0, 126.6, 123.7, 123.0, 60.8, 39.0, 20.7.

4.2.13. 4-Chloro-9,11-dimethyl-6-propyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.13). Yellow oil, yield: 81%, ES-MS: 303.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.01 (d, J=7.8 Hz, 1H), 6.96 (s, 1H), 6.88 (dd, J=7.8, 1.2 Hz, 1H), 4.51–4.56 (m, 1H), 4.45–4.46 (m, 1H), 3.48 (s, 3H), 2.34 (s, 3H), 1.94–2.06 (m, 2H), 1.33–1.55 (m, 2H), 0.99 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.0, 145.8, 145.5, 142.5, 138.2, 132.6, 128.2, 125.9, 124.5, 122.9, 57.0, 40.0, 35.2, 21.2, 20.1, 13.9.

4.2.14. 4-Chloro-9,11-dimethyl-6-ethyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.14). Yellow oil, yield: 74%, ES-MS: 289.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.01 (d, J=7.5 Hz, 1H), 6.96 (s, 1H), 6.88 (d, J=7.5 Hz, 1H), 4.49–4.50 (m, 1H), 4.38–4.45 (m, 1H), 3.48 (s, 3H), 2.34 (s, 3H), 1.98–2.14 (m, 2H), 1.05 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.0, 145.8, 145.4, 142.5, 138.2, 132.4, 128.1, 126.1, 124.5, 122.9, 59.1, 40.0, 26.2, 21.2, 11.5. Anal. Calcd for $C_{15}H_{17}ClN_4$: C, 62.39; H, 5.93; N, 19.40. Found C, 62.56; H, 6.12; N, 19.22.

4.2.15. 4-Chloro-9,11-dimethyl-6-phenyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.15). Yellow oil, yield: 71%, ES-MS: 337.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.30–7.38 (m, 3H), 7.24–7.27 (m, 2H), 6.98 (s, 1H), 6.86 (d, J=7.8 Hz, 1H), 6.82 (d, J=7.8 Hz, 1H), 5.78 (d, J=3.9 Hz, 1H), 4.95 (d, J=3.9 Hz, 1H), 3.27 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.3, 146.3, 145.8, 142.9, 140.4, 139.0, 132.8, 128.7, 128.1, 127.7, 127.6, 126.3, 124.7, 123.4, 60.5, 39.7, 21.2.

4.2.16. 4-Chloro-9,11-dimethyl-6-(4′-methyl-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.16). Yellow oil, yield: 45%, ES-MS: 351.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.11–7.16 (m, 4H), 6.98 (s, 1H), 6.85 (d, J=8.4 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.80 (d, J=3.3 Hz, 1H), 4.89 (d, J=3.3 Hz, 1H), 3.30 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.3, 146.3, 145.8, 142.9, 138.8, 137.4, 137.1, 133.0, 129.4, 128.2, 127.6, 126.4, 124.6, 123.3, 60.2, 39.9, 21.2, 21.1.

4.2.17. 4-Chloro-9,11-dimethyl-6-(4′-fluoro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.17). Yellow oil, yield: 91%, ES-MS: 355.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.19–7.23 (m, 2H), 7.98–7.06 (m, 3H), 6.87 (s, 2H), 5.70 (d, J=4.2 Hz, 1H), 4.94 (d, J=4.2 Hz, 1H), 3.25 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0 (d, J=245.0 Hz, 1C), 151.3, 146.4, 145.6, 143.1, 139.1, 136.3, 132.4, 127.9, 127.8 (d, J=3.4 Hz, 2C), 127.7, 124.7, 123.5, 115.5 (d, J=21.8 Hz, 2C), 60.0, 39.6, 21.2.

4.2.18. 4-Chloro-9,11-dimethyl-6-(4′-nitro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.18). Orange solid, yield: 99%, ES-MS: 382.1 [$(M+1)^+$]. Mp 82.4–88.7 °C (no clear melting point observed). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, J=8.4 Hz, 2H), 7.99 (s, 1H), 7.34 (d, J=8.4 Hz, 2H), 7.07 (d, J=7.2 Hz, 1H), 6.98 (s, 1H), 6.96 (d, J=7.5 Hz, 1H), 5.56 (d, J=5.4 Hz, 1H), 5.17 (d, J=5.4 Hz, 1H), 3.09 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.2, 148.6, 147.1, 146.7, 145.5, 143.4, 139.9, 131.6, 128.2, 126.9, 126.1, 125.1, 123.7, 123.6, 60.5, 39.0, 21.3.

4.2.19. 4-Chloro-8-fluoro-11-methyl-6-phenyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.19). 5-Amino-6-chloro-4-*N*-methyl anilinopyrimidine (**1.4**) (200 mg, 0.85 mmol), the benzaldehyde (0.14 mL, 1.275 mmol) and TFA (0.8 mL) were dissolved in CH_3CN (10.0 mL), and stirred under reflux for 6 days. The reaction mixture was concentrated in vacuo, diluted with EtOAc (15 mL), and washed with saturated $NaHCO_3$ (3×15 mL). The water layer was extracted with EtOAc (3×10 mL). The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash chromatography to give **3.19** (55 mg, 19%) as a yellow oil (elution with EtOAc/petroleum ether=1:30). Yield: 19%, ES-MS: 341.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.36–7.43 (m, 3H), 7.28–7.33 (m, 2H), 7.11–7.16 (m, 1H), 7.02 (td, J=8.7, 3.0 Hz, 1H), 6.60–6.63 (dd, J=8.7, 3.0 Hz, 1H), 5.87 (d, J=3.3 Hz, 1H), 4.87 (d, J=3.0 Hz, 1H), 3.28 (s, 3H).

4.2.20. 6-Chloro-8,9-diphenyl-8,9-dihydro-7*H*-purine (9). 6-Chloro-4-*N*-phenylpyrimidine-4,5-diamine (**8**) (200 mg, 0.91 mmol), benzaldehyde (0.14 mL, 1.275 mmol) and TFA (0.8 mL) were dissolved in CH_3CN (10.0 mL), and stirred under reflux for 23 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc (15 mL), and washed with saturated $NaHCO_3$ (3×15 mL). The water layer was extracted with EtOAc (3×10 mL). The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash chromatography to give **9** (160 mg, 57%) as a yellow solid (elution with EtOAc/petroleum ether=1:10). ES-MS: 309.1 [$(M+1)^+$]. Mp 72.4–75.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93 (s, 1H), 7.28–7.31 (m, 5H), 7.12–7.15 (m, 2H), 6.91–6.97 (m, 3H), 5.61 (d, J=4.5 Hz, 1H), 5.13 (d, J=4.8 Hz, 1H).

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