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Synthesis of some diazino-fused tricyclic systems via Suzuki cross-coupling and regioselective nitrene insertion reactions

Pál Tapolcsányi,[a] Gábor Krajsovszky,[a] Rómeó Andó,[a] Péter Lipcsey,[a] Gyula Horváth,[b] Péter Mátyus,[a,*] Zsuzsanna Riedl,[c] György Hajós,[c] Bert U. W. Maes[d] and Guy L. F. Lemière[d]

[a]*Department of Organic Chemistry, Semmelweis University, Högyes E. u. 7., Budapest 1092, Hungary*
[b]*IVAX Institute for Drug Research, Ltd., H-1045 Budapest, Berlini u. 47-49, Hungary*
[c]*Chemical Research Center, Institute of Chemistry, Hungarian Academy of Sciences, P.O. Box 17, H-1525 Budapest, Hungary*
[d]*Department of Chemistry, University of Antwerp (RUCA), Groenenborgerlaan 171, B-2020 Antwerpen, Belgium*

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Abstract—Suzuki coupling of 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one, 6-chloro-1,3-dimethyluracil and 2-chloropyrazine with protected aminoaryl boronic acids resulted in the corresponding pivaloylaminophenyl diazines which were transformed to diazino-fused indole and cinnoline derivatives. Suzuki coupling of 5-amino-6-chloro-1,3-dimethyluracil with 2-formylphenyl boronic acid afforded a novel pyrimidoisoquinoline ring system in a one-pot reaction.

1. Introduction

In our recent papers we reported on the synthesis of pyridazinoindole and pyridazinoisoquinoline ring systems via Suzuki coupling of a halopyridazin-3(2*H*)-one with substituted aryl boronic acids.[1] Apart from these studies, application of the Suzuki[2,3] reaction in combination with ring closure reactions for the synthesis of diazino-fused ring systems has hardly been explored. In order to investigate the scope and limitations of this approach, we now describe Suzuki reactions of various halodiazines including pyridazine, pyrimidine and pyrazine derivatives with properly functionalized aryl boronic acids, and the subsequent ring closure reactions of the aryldiazines obtained.

Although, Suzuki arylation of 5-bromo-2-methyl-6-phenylpyridazin-3(2*H*)-one was recently performed by Ravina et al.[1d] with various aryl boronic acids to prepare 5-aryl-6-phenylpyridazin-3(2*H*)-ones, no further transformation of these compounds to pyridazino-fused ring systems has been described so far.

2. Results and discussion

In our experiment, Suzuki reaction of 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one (**1**) with *o*-pivaloylaminophenyl boronic acid (**2a**) smoothly gave the corresponding arylated 5-pivaloylaminophenyl derivative **3** (Scheme 1). This compound, after removal of the pivaloyl protecting group, afforded the amine **4**. The latter compound could be successfully transformed to the azide **6** via diazonium salt **5**. Next, heating the azide in *o*-dichlorobenzene, led to the formation of a tricyclic ring system, and 3-methyl-1-phenyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-one (**7**) could be isolated as the single product. It is suspected that this reaction involves the formation of a nitrene intermediate, the ring closure of which may occur with the involvement of C-4 position of the pyridazinone ring or the *ortho*-position of the 6-phenyl group. The latter route was a priori thought to be less likely, because of the formation of a seven-membered ring in that case. The NMR spectra of **7** were in full agreement with the 6–5–6 fused ring system, and excluded the formation of a 7-membered product unambiguously. Thus, the lack of a singlet in the ^{1}H NMR spectrum corresponding with a hydrogen atom at C-4 in **6** (C-4a in **7**) as well as the presence of two intense peaks at 128.0 and 128.3 ppm, each corresponding to the two equivalent carbon atoms of the phenyl group in the ^{13}C NMR spectrum, prove the pattern of fusion of compound **7**.

Next, we turned to uracil derivatives. As a starting material, the easily available, and functionalizable 6-chloro-1,3-dimethyluracil (**8**) was chosen. Although, much attention has been paid to the chemistry of uracils, there have been published so far only a few examples[4] for the Suzuki arylation of uracil derivatives. In the first series of experiments, the synthetic methodology leading to the pyridazino[4,5-*b*]indole ring system was adapted to 6-chloro-1,3-dimethyluracil (**8**). We found that Suzuki

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* Corresponding author. Tel./fax: 1-217-08-51;
e-mail: matypet@szerves.sote.hu.

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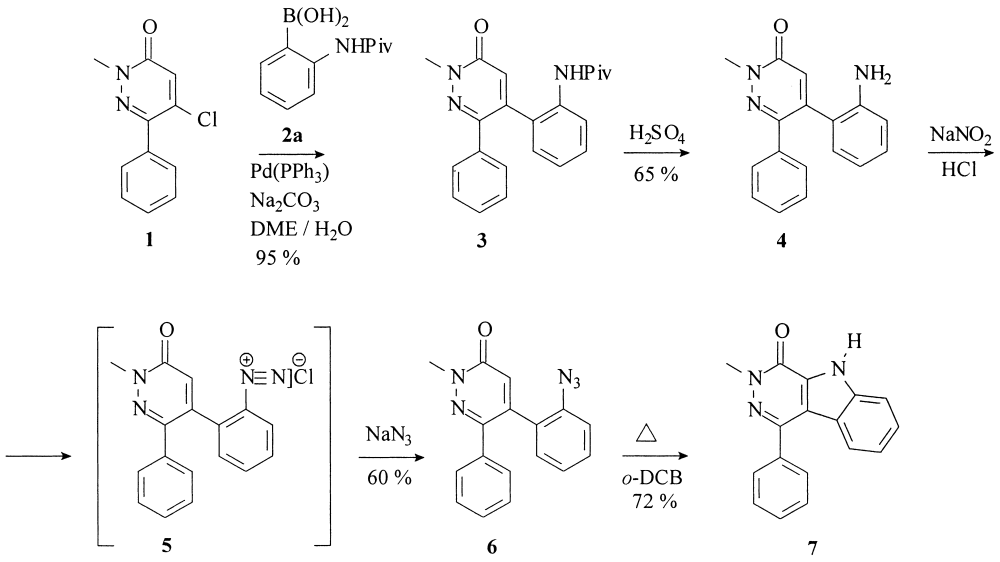


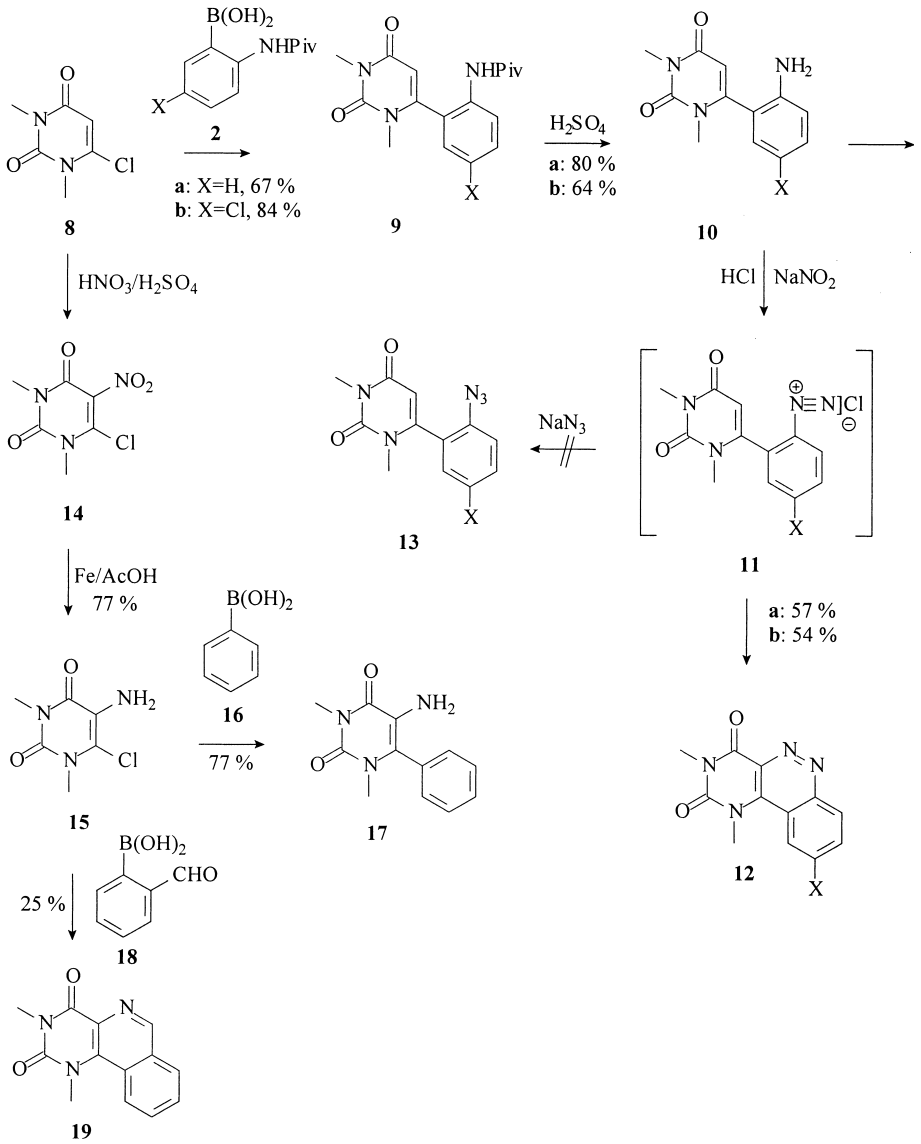
Scheme 1.

reaction of **8** with *o*-pivaloylaminophenyl boronic acid (**2a**) and even with the chloro-substituted derivative (**2b**) smoothly afforded the pivaloylaminouracils **9a** and **9b**, respectively, in acceptable yields (Scheme 2). After deprotection, the aminophenyluracils **10a** and **10b**, respectively, were diazotized. The diazonium salts **11a** and **11b** thus obtained were treated with NaN_3 in order to prepare the azido compounds **13a** and **13b**. At this stage of transformations, quite unexpectedly, an intramolecular azo-coupling occurred to give pyrimido[5,4-*c*]cinnoline derivatives **12a**, and **12b**, respectively, and the nucleophilic substitution reaction was not observed. The ^{1}H NMR spectra of the products indicated that ring closure did indeed proceed, since the singlet of H-5 at 5.74 ppm in the starting amino compounds **10a**, **10b**, could not be detected any more. The mass spectral data and the elemental analysis were in accordance with the formation of pyrimidocinnoline ring system **12**. The pyrimido[5,4-*c*]cinnoline ring system is itself known,[5] but its derivatives have been obtained in a conceptually different way utilizing cinnoline building blocks.

In a second series of experiments, uracil (**8**) was transformed into the known 5-amino-6-chloro-1,3-dimethyluracil[6] (**15**) via nitration and subsequent reduction. The presence of the amino group in **15** also offered an easy transformation to a polycyclic system after coupling with a boronic acid possessing a complementary functionality. The coupling reaction between *ortho*-substituted halo arene and *ortho*-substituted arylboronic acid, has been challenging per se, moreover, the approach might be of great preparative value providing an efficient route to a novel ring system. To test the reactivity of **15**, the Suzuki coupling reaction was carried out first with unsubstituted phenylboronic acid (**16**), which resulted in the formation of the new 5-amino-6-phenyluracil **17**. Under similar conditions, treatment of **15** with *o*-formylphenyl boronic acid afforded a novel pyrimido[5,4-*c*]isoquinoline ring system, and no intermediate could de isolated. The ^{1}H and ^{13}C NMR spectra of the product prove the structure of **19**: the singlet of H-6 at 9.13 ppm and the peak of C-6 at 149.2 ppm were of diagnostic value.

The different behavior of the aminophenyl substituted pyridazine and pyrimidine derivatives in the diazotization and subsequent ring closure procedures prompted us to examine the reactivity of the third diazine, pyrazine. Suzuki coupling of 2-chloropyrazine (**20**) with some aryl boronic acids are known[7] but it has not been described with *o*-pivaloylaminophenyl boronic acid (**2a**). Treatment of 2-chloropyrazine with **2a** led to the formation of **21** (Scheme 3). Deprotection to the amine **22**, and its diazotization were also carried out. The subsequent aza transfer reaction smoothly proceeded following the transformation of the pyridazine analog, and led to the expected azidophenylpyrazine **24**. Upon its heating in *o*-dichlorobenzene for cyclization, however, the pyrazino[1,2-*b*]indazole **25** was isolated as main product, and the expected pyrazino[2,3-*b*]indol **26** (prepared in an independent way[8]) was only detected as a side-product (**25**/**26**=94:6, by ^{1}H NMR). The NMR chemical shift data of **25** were in agreement with the structure. Furthermore, saturation at the signal of H-1 caused a positive nOe on H-10, whereas upon saturation of H-10, an intensity enhancement was observed on the signals of H-1 and H-9, providing supporting evidence for this constitution. Formation of the pyrazino[1,2-*b*]indazole **25** can be easily interpretated. Obviously, the ring-nitrogen atom in the pyrazine intermediate is more nucleophilic than the C-3 position, therefore the cyclization occurred with the involvement of the nitrogen atom.[9]

In conclusion, various halodiazines underwent Suzuki coupling with pivaloylaminophenyl boronic acid to afford the respective pivaloylaminophenyldiazines. Removal of the pivaloyl group followed by diazotization gave diazonium salts, which may be transformed to tricyclic systems by (i) nucleophilic substitution with azide ion followed by ring closure, or (ii) an intramolecular azo coupling process. An aminohalodiazine underwent with



Scheme 2.

o-formylphenyl boronic acid Suzuki coupling and condensation in a one-pot procedure to give the respective tricyclic ring system.

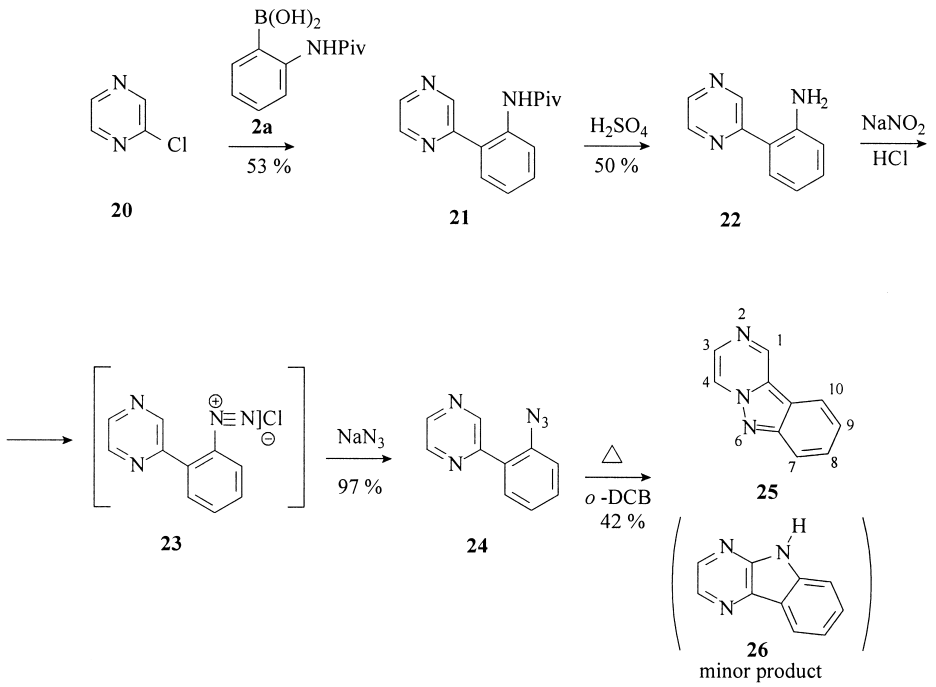
3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 200 spectrometer in $CDCl_3$ or in DMSO-d_6 with TMS as the internal standard. Chemical shifts are given in ppm and *J* values in Hz. Melting points were determined in a Kofler apparatus and are uncorrected. IR spectra were obtained as potassium bromide pellets or as liquid films between two potassium bromide pellets with a Perkin–Elmer 1600 FT-IR spectrophotometer. Elemental analyses were performed on a Carlo Erba Elemental Analyzer Model 1012 apparatus. Flash chromatography was carried out on Kieselgel 60 (Merck), 0.040–0.063 mm. Starting compounds were synthesized by literature procedures cited: 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one[10] (**1**), 6-chloro-1,3-dimethyluracil[11] (**8**), 6-chloro-1,3-dimethyl-5-nitrouracil[12] (**14**), 2-pivaloylaminophenyl boronic acids[13] (**2a**, **2b**) and tetrakis(triphenylphosphine)palladium[14] or were obtained from commercial sources: phenyl boronic acid (**16**) (Fluka), 2-formylphenyl boronic acid (**18**) (Aldrich), and chloropyrazine (**20**) (Aldrich).

3.2. General procedure for the Suzuki cross-coupling reaction

A mixture of the diazine (441 mg, 2 mmol) and tetrakis-(triphenylphosphine)palladium (120 mg, 0.1 mmol) in dimethoxyethane (12 mL, distilled from $SnCl_2$) was stirred for 20 min at room temperature under argon atmosphere. The appropriate boronic acid (2.5 mmol) and Na_2CO_3 solution (2 mL, 2 M) were added and the mixture was refluxed for 8 h. The reaction mixture was poured onto ice-water (30 mL) and extracted with chloroform



Scheme 3.

(3×30 mL), the extract was dried over anh. Na_2SO_4, filtered and evaporated to dryness. The residue was subjected to column chromatography on silica gel or recrystallized.

3.3. General procedure for the hydrolysis of the pivaloylamino derivatives

Sulfuric acid solution (20%, 35 mL) was added to the appropriate pivaloylanilide (2 mmol) and refluxed for 3 h. After cooling, the pH of the mixture was adjusted to 8 by addition of aqueous (25%) ammonia. The mixture was then extracted with chloroform (3×50 mL), dried over Na_2SO_4, filtered and evaporated to dryness.

3.4. General procedure for the diazotization and azidation

The appropriate amine (5 mmol) was dissolved in concentrated hydrochloric acid (40 mL) and cooled to 0°C with stirring. Aqueous $NaNO_2$ solution (0.73 g, 10.62 mmol of $NaNO_2$ in 27 mL of water) was added dropwise at such a rate that the temperature of the mixture did not exceed 5°C. The mixture was stirred at this temperature for 1.5 h. A solution of NaN_3 (0.644 g, 10.62 mmol) and sodium acetate trihydrate (9.52 g, 70 mmol) in water (24 mL) was then added at 0–5°C and the mixture was stirred for an additional 1 h at this temperature. (Caution: potential explosion hazard!). Then the mixture was neutralized with saturated Na_2CO_3 solution and extracted with dichloromethane (3×50 mL), dried over Na_2SO_4, filtered and evaporated without heating. The product decomposed in air and was therefore stored under argon in a refrigerator.

3.5. General procedure for the ring closure of the azides

A solution of the appropriate azide (1 mmol) in *o*-dichlorobenzene (10 mL) was refluxed for 1 h, the solvent was then removed under reduced pressure, and the residue was recrystallized.

3.5.1. *N*-[2-(1-Methyl-6-oxo-3-phenyl-1,6-dihydropyridazin-4-yl)phenyl]pivalamide (3). The crude product obtained according to the general procedure (1.2) was purified by flash chromatography using ethyl acetate-petroleum ether (4:1) mixture as the eluent and crystallized from a mixture of diisopropyl ether and petroleum ether to yield the title compound (692 mg, 95%) as white prisms; mp 261–262°C; R_f (EtOAc): 0.55; ν_{max}: 3330, 2966, 1682, 1646, 1572, 1491, 1440, 1167, 997, 897, 762 cm^{-1}; δ_H ($CDCl_3$): 7.47 (d, J=8.2 Hz, 1H, H-3′), 7.10–7.40 (m, 8H, phenyl, H-4′, -5′ and -6′), 6.95 (s, 1H, H-5), 6.88 (br s, 1H, NH), 3.93 (s, 3H, 2-CH_3), 1.10 (s, 9H, C(CH_3)$_3$); δ_C ($CDCl_3$): 176.3 (O*C*C(CH_3)$_3$), 159.8 (C-6), 145.4 and 143.0 (C-3 and -2′), 134.4 and 134.3 (C-4 and -1″), 130.0, 129.83, 129.80, 129.23 (C-1′), 129.16 (C-5′), 128.4 and 128.3 (C-2″, -3″, -5″, and -6″), 125.5 (C-3′), 124.4 (C-5), 40.4 (N–CH_3), 39.4 (*C*(CH_3)$_3$), 27.3 (C(*C*H_3)$_3$). Anal. calcd for $C_{22}H_{23}N_3O_2$ (361.44): C, 73.11; H, 6.41; N, 11.63. Found: C, 73.05; H, 6.41, N, 11.59.

3.5.2. 5-(2-Aminophenyl)-2-methyl-6-phenylpyridazin-3(2*H*)-one (4). The crude product obtained according to the general procedure (1.3) was recrystallized from a mixture of ethyl acetate and petroleum ether to yield the title compound (360 mg, 65%) as pale yellow needles; mp 193–194°C; R_f (EtOAc): 0.40; ν_{max}: 3298, 1658, 1571, 1491, 1308, 1158, 949, 753 cm^{-1}; δ_H ($CDCl_3$): 7.07–7.26 (m, 5H, phenyl), 7.14 (dd, J=8.2, 7.6 Hz, 1H, H-4′), 6.99 (s, 1H, H-4), 6.88 (d, J=7.6 Hz, 1H, H-6′), 6.71 (t, J=7.6 Hz, 1H, H-5′), 6.59 (d, J=8.2 Hz, 1H, H-3′), 3.91 (s, 3H, 2-CH_3), 3.51 (s, 2H, NH_2); δ_C ($CDCl_3$): 160.2 (C-3), 146.3 and 144.0 and 143.1 (C-5, -6, and -2′), 135.2 (C-1″), 130.1 and 129.9 and 129.8 and 128.7 (C-4, -4′, -6′, and -4″), 128.3 and 128.0 (C-2″, -3″, -5″, and -6″), 121.4 (C-1′), 118.6

and 116.0 (C-3′ and -5′), 40.2 (2-CH_3). Anal. calcd for $C_{17}H_{15}N_3O$ (277.33): C, 73.63; H, 5.45; N, 15.15. Found: C, 73.82; H, 5.41, N, 15.10.

3.5.3. 5-(2-Azidophenyl)-2-methyl-6-phenylpyridazin-3-(2*H*)-one (6). The crude product obtained according to the general procedure (1.4) was not further purified. Yield: 910 mg (60%); R_f (EtOAc): 0.60; ν_{max}: 2938, 2434, 2131, 1664, 1569, 1492, 1442, 1277, 1152, 998, 952, 883, 758, 697; δ_H ($CDCl_3$): 7.10–7.50 (m, 8H, phenyl, H-4′, -5′, -6′), 7.02 (d, J=8.0 Hz, 1H, H-3′), 6.90 (s, 1H, H-4), 3.91 (s, 3H, 2-CH_3).

3.5.4. 3-Methyl-1-phenyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-one (7). The crude product obtained according to the general procedure (1.5) was recrystallized from a mixture of methanol and chloroform to yield the title compound (270 mg, 72%) as gray needles; mp 294°C; R_f (EtOAc): 0.55; ν_{max}: 3139, 1653, 1527, 1386, 1329, 1021, 741 cm^{-1}; δ_H ($CDCl_3$ and MeOD-d_4): 7.70–7.72 (m, 2H, H-2′ and -6′), 7.64 (d, J=8.4 Hz, 1H, H-6), 7.54–7.56 (m, 3H, H-3′, -4′ and -5′), 7.42–7.50 (m, 2H, H-7 and -9), 7.13 (m, 1H, H-8), 3.97 (s, 3H, 3-CH_3); δ_C ($CDCl_3$ and MeOD-d_4): 154.8 (C-4), 145.4 and 139.5 and 135.8 and 131.4 (C-1, -4a, -5a and C-1′), 128.3 and 128.0 (C-2′, -6′, -3′ and -5′), 128.8 and 126.7 and 121.7 and 120.9 (C-6, -7, -9, and -4′), 120.7 and 116.7 (C-9a and -9b), 112.3 (C-8), 38.1 (3-CH_3). Anal. calcd for $C_{17}H_{13}N_3O$ (275.31): C, 74.17; H, 4.76; N, 15.26. Found: C, 74.18; H, 4.73, N, 15.21.

3.5.5. *N*-[2-(1,3-Dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)phenyl]pivalamide (9a). The crude product obtained according to the general procedure (1.2) was recrystallized from *n*-butanol to yield the title compound (423 mg, 67%) as yellow prisms; mp 172–173°C; R_f ($CHCl_3$/MeOH, 40:1): 0.28; ν_{max}: 3350, 2962, 1652, 1620, 1438, 1371, 1166, 1008, 830, 763, 551 cm^{-1}; δ_H ($CDCl_3$): 8.02 (d, J=8.2 Hz, 1H, H-6′), 7.51 (m, 1H, H-5′), 7.18–7.31 (m, 2H, H-3′ and -4′), 5.72 (s, 1H, H-5), 3.42 (s, 3H, N–CH_3), 3.13 (s, 3H, N–CH_3), 1.21 (s, 9H, $C(CH_3)_3$); δ_C ($CDCl_3$): 176.6 (O*C*$C(CH_3)_3$), 162.1 (C-6), 152.5 and 151.5 (C-2, and -1′), 134.7 (C-4), 131.2 and 128.4 and 125.3 and 123.9 (C-2′, -3′, -4′, -5′ and -6′), 102.7 (C-5), 39.7 (*C*$(CH_3)_3$), 33.7 and 28.2 (1-CH_3 and 3-CH_3), 27.4 (C(*C*$H_3)_3$); Anal. calcd for $C_{17}H_{21}N_3O_3$ (315.37): C, 64.75; H, 6.71; N, 13.32. Found: C, 64.70; H, 6.77; N, 13.11.

3.5.6. *N*-[4-Chloro-2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)phenyl]pivalamide (9b). The crude product obtained according to the general procedure (1.2) was recrystallized from *n*-butanol to yield the title compound (587 mg, 84%) as yellow prisms; mp 193–194°C; R_f ($CHCl_3$/MeOH, 40:1): 0.30; ν_{max}: 3301, 2962, 1707, 1655, 1508, 1398, 1366, 1286, 1248, 1205, 1159, 1090, 1018, 971, 883, 822 cm^{-1}; δ_H ($CDCl_3$): 7.96 (dd, J=8.8, 1.9 Hz, 1H, H-6′), 7.46 (dd, J=8.8, 2.4 Hz 1H, H-5′), 7.34 (br s, 1H, NH), 7.23 (d, J=2.4 Hz, 1H, H-3′), 5.68(s, 1H, H-5), 3.39(s, 3H, N–CH_3), 3.13(s, 3H, N–CH_3), 1.20(s, 9H, $C(CH_3)_3$), δ_C ($CDCl_3$): 176.7 (O*C*$C(CH_3)_3$), 161.9 (C-6), 152.2 (C-2), 150.1 (C-4), 133.4 (C-1′), 131.2 and 128.2 (C-3′ and -5′), 130.7 (C-4′), 126.7 (C-2′), 125.4 (C-6′), 102.9 (C-5), 39.7 (*C*$(CH_3)_3$), 33.7 and 28.2 (1-CH_3 and 3-CH_3), 27.3 (C(*C*$H_3)_3$). Anal. calcd for $C_{17}H_{20}ClN_3O_3$ (349.82): C, 58,37; H, 5.76; N, 12.01. Found: C, 58.34; H, 5.64; N, 11.66.

3.5.7. 6-(2-Aminophenyl)-1,3-dimethyluracil (10a). The crude product obtained according to the general procedure (1.3) was recrystallized from acetonitrile to yield the title compound (370 mg, 80%) as brownish yellow prisms; R_f ($CHCl_3$/MeOH, 40:1): 0.24; mp 175–176°C; ν_{max}: 3411, 3343, 3239, 1691, 1645, 1460, 1428, 1367, 1258, 1005, 816, 755; δ_H ($CDCl_3$): 7.27 (m, 1H, H-4′), 7.04 (d, J=7.6 Hz, 1H, H-6′), 7.75–7.87 (m, 2H, H-3′ and -5′), 5.74 (s, 1H, H-5), 3.84 (br s, 2H, NH_2), 3.40 (s, 3H, N–CH_3), 3.20 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 162.4 (C-4), 152.7 (C-2), 143.4 (C-2′), 131.4 and 128.8 (C-4′ and -6′), 118.7 and 116.0 (C-6, -1′, -3′, -5′), 102.7 (C-5), 33.0 and 28.0 (1-CH_3 and 3-CH_3). Anal. calcd for $C_{12}H_{13}N_3O_2$ (231.25): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.61; H, 5.67; N, 17.85.

3.5.8. 6-(2-Amino-5-chlorophenyl)-1,3-dimethyluracil (10b). The crude product obtained according to the general procedure (1.3) was recrystallized from acetonitrile to yield the title compound (340 mg, 64%) as yellow prisms; mp 221–222°C; R_f ($CHCl_3$/MeOH, 40:1): 0.17; ν_{max}: 3422, 3350, 3246, 1694, 1648, 1483, 1010, 823 cm^{-1}; δ_H ($CDCl_3$): 7.25 (dd, J=8.6, 2.2 Hz, 1H, H-4′), 7.05 (d, J=2.2 Hz, 1H, H-6′), 6.74 (d, J=8.6 Hz, 1H, H-3′), 5.74 (s, 1H, H-5), 3.85 (br s, 2H, NH_2), 3.40 (s, 3H, N–CH_3), 3.21 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 162.5 (C-4), 152.5 (C-2), 151.1 (C-6), 141.8 (C-2′), 131.3 and 128.4 (C-4′ and -6′), 123.6 (C-5′), 119.9 (C-1′), 117.5 (C-3′), 103.0 (C-5), 33.1 and 28.1 (1-CH_3 and 3-CH_3). Anal. calcd for $C_{12}H_{12}ClN_3O_2$ (265.70): C, 54,25; H, 4.55; N, 15.81. Found: C, 54.55; H, 4.57; N, 15.94.

3.5.9. 1,3-Dimethylpyrimido[5,4-*c*]cinnoline-2,4(1*H*,3*H*)-dione (12a). The crude product obtained according to the general procedure for diazotization and azidation (1.4) was recrystallized from *n*-butanol to yield white prisms (690 mg, 57 %); R_f ($CHCl_3$/MeOH, 9:1): 0.55; mp 257–258°C; ν_{max}: 1718, 1673, 1512, 1457, 1375, 1063, 786 cm^{-1}; δ_H ($CDCl_3$): 8.74 (d, J=8.0 Hz, 1H, H-7), 8.50 (d, J=8.0 Hz, 1H, H-10), 8.04 (t, 1H, J=8.0 Hz, H-9), 7.89 (t, 1H, J=8.0 Hz, H-8), 4.06 (s, 1H, 3-CH_3), 3.63 (s, 1H, 1-CH_3); δ_C ($CDCl_3$): 159.8 (C-4), 151.8 (C-2 and -6a), 137.2 (C-10b), 132.5 and 131.6 and 130.9 (C-8, -9 and -10), 124.1 (C-7 and -4a), 115.0 (C-10a), 38.2 (1-CH_3), 29.2 (3-CH_3). Anal. calcd for $C_{12}H_{10}N_4O_2$ (242.24): C, 59,50; H, 4.16; N, 23.13. Found: C, 59.47; H, 4.17; N, 22.84.

Preparation of the title compound was repeated without addition of sodium azide, as follows: 6-(2-Aminophenyl)-1,3-dimethyluracil (**10a**) (5 mmol) was dissolved in concentrated hydrochloric acid (40 mL) and cooled to 0°C with stirring. Aqueous $NaNO_2$ solution (0.73 g, 10.62 mmol of $NaNO_2$ in 27 mL of water) was added dropwise at such a rate that the temperature of the mixture did not exceed 5°C. The mixture was stirred at this temperature for 1.5 h. Then the mixture was neutralized with saturated Na_2CO_3 solution and extracted with dichloromethane (3×50 mL), dried over Na_2SO_4, filtered, evaporated and recrystallized from *n*-butanol. This procedure gave the same result as the above described method.

3.5.10. 9-Chloro-1,3-dimethylpyrimido[5,4-*c*]cinnoline-2,4(1*H*,3*H*)-dione (12b). 6-(2-Amino-5-chlorophenyl)-1,3-dimethyluracil (**10b**) (5 mmol) was dissolved in concentrated hydrochloric acid (40 mL) and cooled to 0°C with stirring. Aqueous $NaNO_2$ solution (0.73 g, 10.62 mmol of $NaNO_2$ in 27 mL of water) was added dropwise at such a rate that the temperature of the mixture did not exceed 5°C. The mixture was stirred at this temperature for 1.5 h. Then the mixture was neutralized with saturated Na_2CO_3 solution and extracted with dichloromethane (3×50 mL), dried over Na_2SO_4, filtered, evaporated and recrystallized from *n*-butanol to yield pale yellow prisms (747 mg, 54%); mp 218–219°C; R_f ($CHCl_3$/MeOH, 9:1): 0.63; ν_{max}: 1721, 1668, 1502, 1441, 1363, 1286, 1246, 1216, 1084, 847; δ_H ($CDCl_3$): 8.58 (d, J=9.0 Hz, 1H, H-7), 8.46 (d, J=1.5 Hz, 1H, H-10), 7.93 (dd, J=9.0, 1.5 Hz, 1H, H-8), 4.04 (s, 3H, N–CH_3), 3.57 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 159.3 (C-4), 151.3, 149.9, 137.3, 136.3, 133.4 and 132.8 (C-8 and -10), 130.2, 123.3 (C-7), 115.8 (C-10a), 38.0 and 29.2 (1-CH_3 and 3-CH_3); Anal. calcd for $C_{12}H_9ClN_4O_2$ (276.78): C, 52.09; H, 3.28; N, 20.25; Cl, 12.81. Found: C, 52.22; H, 3.26; N, 20.20 Cl, 12.80.

3.5.11. 5-Amino-6-chloro-1,3-dimethyluracil (15). 6-Chloro-5-nitro-1,3-dimethyluracil (880 mg, 4 mmol) was dissolved in acetic acid (99.5 %) (20 mL), iron powder (2.4 g) was added and stirred at 25°C for 4 h. The reaction mixture was then poured onto ice-water (100 g), neutralised with Na_2CO_3, extracted with ethyl acetate (5×50 mL), dried over Na_2SO_4 and evaporated to give yellow prisms (588 mg, 77%); R_f (EtOAc): 0.70; mp 120–122°C (lit.[4a] 118–120°C, lit.[4b] 120–121°C); ν_{max}: 3459, 3363, 1651, 1570, 1480, 1415, 1338, 1085; δ_H ($CDCl_3$): 3.71 (br s, 2H, NH_2), 3.55 (s, 3H, N–CH_3), 3.39 (s, 3H, N–CH_3), δ_C ($CDCl_3$): 158.4 (C-4), 149.4 (C-2), 121.7 and 119.7 (C-5 and -6), 33.3 (1-CH_3), 28.7 (3-CH_3).

3.5.12. 5-Amino-6-phenyl-1,3-dimethyluracil (17). The crude product obtained according to the general procedure (1.2) was purified by flash chromatography (EtOAc/$CHCl_3$, 5:95) to yield orange prisms (360 mg, 77%); mp 104–107°C; R_f (EtOAc/$CHCl_3$, 1:1): 0.50; ν_{max}: 3449, 3347, 1682, 1623, 1575, 1482, 1439, 1354, 1309, 1188, 1084, 785, 722, 697, 541. δ_H ($CDCl_3$): 7.40–7.60 (m, 3H, H-3′, -4′, -5′), 7.33 (d, J=7.8 Hz, 2H, H-2′ and -6′), 3.47 (s, 3H, N–CH_3), 3.15 (br s, 2H, NH_2), 3.09 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 160.2 (C-4), 150.6 (C-2), 131.0 and 129.8 and 128.9 (C-6, -1′, -2′, -3′, -4′, -5′ and -6′), 119.7 (C-5), 34.1 (N–CH_3), 28.5 (N–CH_3). Anal. calcd for $C_{12}H_{13}N_3O_2$ (231.25): C, 62.33; H, 5.57; N, 18.19. Found: C, 61.98; H, 5.57; N, 18.29.

3.5.13. 1,3-Dimethylpyrimido[5,4-*c*]isoquinoline-2,4(1*H*,3*H*)-dione (19). The crude product obtained according to the general procedure (1.2) was subjected to flash chromatography (EtOAc/$CHCl_3$, 1:1), and crystallized from a mixture of acetone and methanol to yield yellow needles (120 mg, 25%); mp 283–284°C; R_f (EtOAc/$CHCl_3$, 1:1): 0.26; ν_{max}: 1693, 1654, 1483, 1335, 1287, 1070, 776; δ_H ($CDCl_3$): 9.13 (s, 1H, H-6); 8.42 (m, 1H) and 8.10 (m, 1H): (H-7 and -10), 7.83 (m, 2H, H-8 and -9), 3.95 (s, 3H, N–CH_3): 3.55 (s, 3H, N–CH_3), δ_C ($CDCl_3$): 161.1 (C-4), 152.5 (C-2), 149.1 (C-6), 136.6 (C-10b), 131.5 (C-4a), 130.3, 130.0, 128.8, 127.0 and 126.0 (C-6a and -10a), 124.8, 39.5 (N–CH_3), 28.9 (N–CH_3). Anal. calcd for $C_{13}H_{11}N_3O_2$ (241.25): C, 64.72; H, 4.60; N, 17.42. Found: C, 64.74; H, 4.46; N, 17.46.

3.5.14. *N*-[2-(Pyrazin-2-yl)phenyl]pivalamide (21). The crude product obtained according to the general procedure (1.2) was subjected to flash chromatography (EtOAc/$CHCl_3$, 5:95) to yield colorless oil (270 mg, 53%); R_f (EtOAc/$CHCl_3$, 1:9): 0.40; ν_{max}: 3342, 2962, 1682, 1584, 1528, 1478, 1440, 1309, 1164, 1073, 1021, 923, 849, 756; δ_H ($CDCl_3$): 11.6 (br s, 1H, NH), 9.07 (s, 1H, H-3), 8.64 (d, 1H, H-6′), 8.63 (s, 2H, H-5 and -6), 7.72 (dd, J=7.7, 1.4 Hz, 1H, H-3′), 7.48 (td, J=7.7, 1.4 Hz, 1H, H-5′), 7.21 (t, J=7.7 Hz, 1H, H-4′), 1.31 (s, 9H, $C(CH_3)_3$); δ_C ($CDCl_3$): 177.4(*C*OC(CH_3)$_3$), 153.5(C-2), 144.5 and 142.3 and 141.1(C-3, -5 and -6), 138.3(C-1′), 131.1 and 128.6(C-3′ and -5′), 123.6 and 122.4(C-4′ and -6′), 122.9(C-2′), 40.1(CO*C*(CH_3)$_3$, 27.6(COC(*C*H_3)$_3$. Anal. calcd for $C_{15}H_{17}N_3O$ (255.32): C, 70.56; H, 6.71; N, 16.46. Found: C, 70.27; H, 6.79; N, 16.35.

3.5.15. 2-(2-Aminophenyl)pyrazine (22). The crude product obtained according to the general procedure (1.3) was subjected to flash chromatography (EtOAc/$CHCl_3$, 1:4) to yield yellow needles (171 mg, 50%); mp 80–81°C; R_f (EtOAc/$CHCl_3$, 5:95): 0.20; ν_{max}: 3376, 3268, 3156, 3082, 3038, 2924, 2764, 2684, 2342, 1614, 1514, 1482, 1442, 1402, 1354, 1332, 1304, 1260, 1190, 1164, 1140, 1074, 1042, 1018, 954, 926, 844, 764, 698; δ_H ($CDCl_3$): 8.99 (d, J=1.2 Hz, 1H, H-3), 8.52 (dd, J=2.6, 1.6 Hz, 1H, H-5), 8.43 (d, J=2.6 Hz, 1H, H-6), 7.60 (dd, J=2.6, 1.4 Hz, 1H, H-6′), 7.22 (td, J=7.3, 1.4 Hz, 1H, H-4′), 6.75–6.85 (m, 2H, H-3′ and -5′), 5.70 (br s, 2H, NH_2), δ_C ($CDCl_3$ and DMSO-d_6): 154.1(C-2), 146.7 (C-2′), 143.1 and 141.5 and 140.7 (C-3, -5, -6), 130.5 and 128.5 (C-4′ and -6′), 117.9 and 117.3 and 117.1 (C-1′, -3′ and -5′). Anal. calcd for $C_{10}H_9N_3$ (171.20): C, 70.16; H, 5.30; N, 24.54. Found: C, 69.81; H, 5.23; N, 24.55.

3.5.16. 2-(2-Azidophenyl)pyrazine (24). The crude product obtained according to the general procedure (1.4) was not further purified (955 mg, 97%); R_f ($CHCl_3$/MeOH, 9:1): 0.85; ν_{max}: 3442, 2130, 2096, 1600, 1580, 1492, 1462, 1446, 1396, 1288, 1152, 1072, 1016, 766, 742; δ_H ($CDCl_3$): 9.03 (s, 1H, H-3), 8.67 (s, 1H, H-5), 8.53 (s, 1H, H-6), 7.73 (dd, J=8.4, 1.7 Hz, 1H, H-6′), 7.50 (td, J=8.0, 1.7 Hz, 1H, H-4′), 7.29 (m, 2H, H-3′ and -5′).

3.5.17. Pyrazino[1,2-*b*]indazole (25). The crude product obtained according to the general procedure was filtered through silicagel, eluted first with $CHCl_3$ (50 mL), then ethyl acetate (250 mL). The ethyl acetate fraction was evaporated to dryness to yield gray crystals (71 mg, 42%), which were further purified by flash chromatography using ethyl acetate/chloroform (1:9) as the eluent (65 mg, 38%) and recrystallized from methanol to get white needles; mp 146–147°C; R_f (EtOAc/$CHCl_3$, 1:9): 0.25; ν_{max}: 3055, 3010, 1725, 1588, 1510, 1427, 1333, 1273, 1204, 1154, 990, 889, 811, 752; δ_H (DMSO-d_6): 9.82 (d, J=1.4 Hz, 1H, H-1), 9.06 (dd, J=4.7, 1.5 Hz, 1H, H-3), 8.44 (d, J=8.2 Hz, 1H, H-10), 8.34 (d, J=4.7 Hz, 1H, H-4), 7.93 (d, J=8.6 Hz, 1H, H-7), 7.67 (dd, J=8.3, 6.8 Hz, 1H, H-8), 7.44 (dd, J=7.6, 7.5 Hz, 1H, H-9); δ_C (DMSO-d_6): 148.8 (C-6a), 144.1

(C-1), 134.7 (C-4), 130.3 (C-10b), 129.2 (C-8), 122.5 (C-9), 121.7 (C-3), 120.6 (C-10), 116.3 (C-7), 115.1 (C-10a). Anal. calcd for $C_{10}H_7N_3$ (169.19): C, 70.99; H, 4.17; N, 24.84. Found: C, 71.12; H, 4.15; N, 24.62.

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