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Regioselective aluminium chloride induced heteroarylation of pyrrolo[1,2-*b*]pyridazines: its scope and application☆

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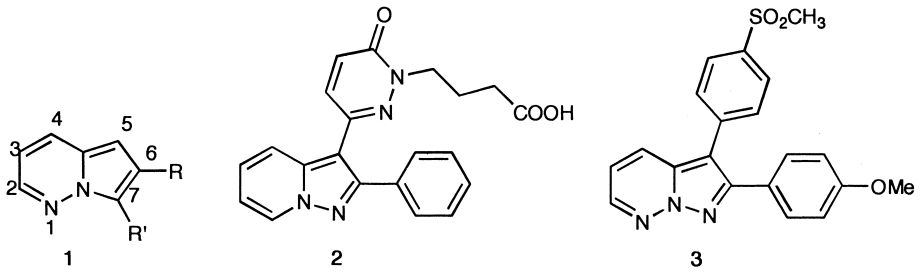
Abstract—We describe a detailed study on the novel synthesis of 6,7-disubstituted pyrrolo[1,2-*b*]pyridazines through $AlCl_3$ induced C–C bond formation reactions. A wide variety of 6-aryl substituted azolopyridazines was reacted with 3,6-dichloropyridazine to give 7-pyridazinyl substituted pyrrolopyridazines regioselectively in good to excellent yield. The mechanism and regiochemistry of the reaction along with applications of the methodology are discussed. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The pyridazine nucleus, which has been known for more than a century, is of considerable interest because of its many synthetic[1] and biological uses.[2] This six membered heterocycle has been found to be an integral part of many polynuclear heterocycles. An example of this class is pyrrolo[1,2-*b*]pyridazine or 5-azaindolizine **1** (Fig. 1). Several nitrogen heterocycles related to **1** have attracted particular attention due to their potential therapeutic usefulness.[3–9] Amongst them adenosine A_1 receptor antagonist **2** (FK 838),[4] anti-inflammatory agent **3**[6] and anti-platelet agent[8] (KC-764) are of particular interest (Fig. 1). Compound **2** has been described as a potent and selective non-xanthine adenosine A_1 receptor antagonist related to both diuretic and antihypertensive effects, whereas **3** has been developed as a highly selective cyclooxygenase-2 (COX-2) inhibitor for pain management. Several derivatives of **1** have been reported as inhibitors of lipid peroxidation,[9a] hydroxymethylglutaryl (HMG) CoA reductase[9b] and secretory phospholipase A2 (s PLA2)[9c] along with their antimicrobial activity.[2b,9d]

As part of our continuing interest in the development of various diaryl heterocycles[10] for biological testing in different therapeutic areas,[10c] we decided to explore the biological and pharmacological properties of a combinatorial library based on the scaffold of pyrrolopyridazines **1**. We thought that due to the structural similarity with the pyrazolopyridine nucleus of **2** this could be an alternative template for the development of potent and water soluble adenosine A_1 receptor antagonists. We therefore postulated that introduction of an aryl group and a pyridazinone moiety (in which the double bond and carbonyl group of acrylolylamide were mimicked by a ring system)[4] at position 6 and 7 of this template, respectively, may lead to a novel class of pyrrolopyridazines (**4**) of potential biological interest (Fig. 2).

Over a period of more than a century, only few methods



1 2 3

Figure 1. Some nitrogen containing fused heterocycles.

☆ 5-Azaindolizine or pyrrolo[1,2-*b*]-pyridazine has been named as azolopyridazine according to IUPAC nomenclature; DRF Publication No. 173.

Keywords: pyridazines; aluminium chloride; regioselective heteroarylation; C–C bond formation.

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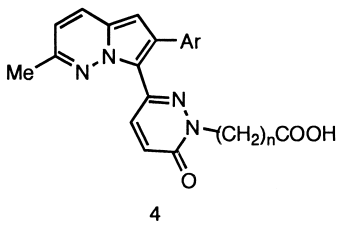

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Figure 2. Design of novel adenosine A1 receptor antagonists.

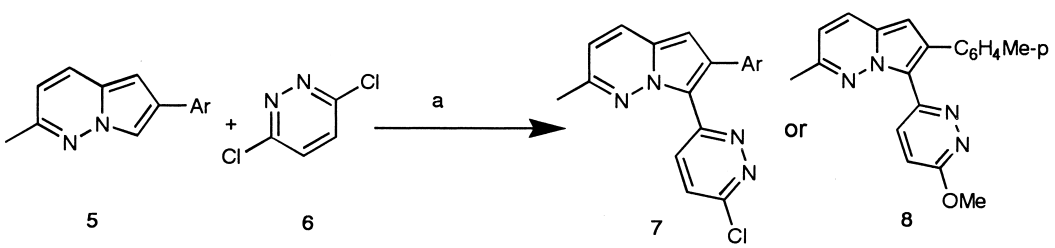
have been reported for the synthesis of pyrrolopyridazine and its derivatives. They are prepared by (i) the reaction of dimethylpyridazine with α-bromoketones followed by cyclization in the presence of alkali,[11] (ii) reaction of pyridazines with diphenylcyclopropenone[9a,12] or (iii) 1,3-dipolar cycloaddition reactions[13] of pyridazinium dicyanomethylides, obtained from pyridazine and tetracyanoethylene oxide, with dipolarophiles such as dimethyl acetylenedicarboxylate or cyanoacetylene.[13c] On the other hand the synthesis of 6-(hetero)aryl substituted pyridazin-3-one proceeds via three steps procedure involving condensation of hydrazine with appropriately substituted 1,4-dicarbonyl compounds.[1b,2e,4] However, these synthetic routes to obtain **4** are either inappropriate (due to the non-availability of the required starting material) or unattractive due to the lengthy synthetic procedure.

We focused on the methods available in the literature[14] that could be utilized for the straightforward preparation of **4** via C–C bond formation as the key synthetic step. Among the methods available for aryl–aryl bond formation Friedel–Crafts arylation and palladium-catalyzed cross-coupling reaction[14d,f] including Suzuki coupling are the most popular. In view of cost effectiveness and availability of starting materials, we chose the $AlCl_3$ induced arylation reaction[15] to generate a combinatorial library based on pyrrolopyridazines **4**. To the best of our knowledge no successful heteroarylation of the pyrrolopyridazine system using a similar methodology has hitherto been described in the literature.

2. Results and discussion

The regioselective heteroarylation reaction of pyrrolo[1,2-*b*]pyridazines was carried out successfully under the Friedel–Crafts reaction condition according to Scheme 1. When 5.6 equiv. of 6-aryl substituted pyrrolo[1,2-*b*]pyridazines **5** (Ar=aryl group) were reacted with 6.04 equiv. of 3,6-dichloropyridazine **6** in the presence of 6.06 equiv. of $AlCl_3$ using dichloroethane as solvent, 7-pyridazinylpyrrolo[1,2-*b*]pyridazines **7** were formed as the exclusive products in good yields. The results are summarized in Table 1.

As can be seen from Table 1, the heteroarylation reaction was well tolerated in the presence of various substituted aryl groups at position 6 of the pyrrolopyridazine moiety. An alkyl group at the *p*-position of the aryl ring was found to be effective in terms of yield (see entries 1, 11 and 12). A fluorine substituent at the *o*-position to the alkyl group enhanced the yield (entry 11), whereas branching of the



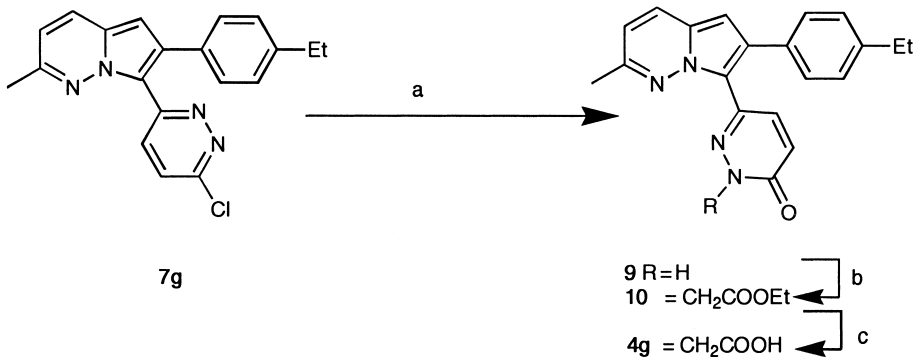
5 6 7 8

Scheme 1. *Reagents and conditions*: (a) $AlCl_3$, dichloroethane, 50–60°C, 48 h.

Table 1. $AlCl_3$ induced heteroarylation of pyrrolo[1,2-*b*]pyridazine

Entry	Starting material **5**; Ar=	Product	Temperature (°C)	Time (h)	Yield[a] (%)
1	4-Methylphenyl	**7a**	60	48	65
2	4-Methylphenyl	**7a**	rt	48	–
3	4-Methylphenyl	**7a**	60	12	28
4	4-Methylphenyl	**7a**	60	24	33
5	4-Methylphenyl	**7a**[b]	60	48	–
6	4-Isobutylphenyl	**7b**	60	48	42
7	4-Chlorophenyl	**7c**	55	48	50
8	2,4-Dimethoxyphenyl	**7d**	60	48	60
9	4-Fluorophenyl	**7e**	50	48	71
10	4-Fluorophenyl	**7e**	rt	48	12
11	3-Fluoro-4-methylphenyl	**7f**	55	48	89
12	4-Ethylphenyl	**7g**	60	48	76
13	4-(*N*-Methylsulfonyl) aminophenyl	**7h**	60	48	4
14	4-Methoxyphenyl	**7i**	55	48	93
15	4-Nitrophenyl	**7j**	60	48	72
16	4-Methylphenyl	**8**[c]	60	48	20

[a] Yield of isolated products.
[b] Reaction was carried out in the absence of $AlCl_3$.
[c] 3-Chloro-6-methoxypyridazine was used in place of **6**.



Scheme 2. *Reagents and conditions*: (a) CH_3COONa, CH_3COOH, reflux, 5 h; (b) ethylbromoacetate, DMF, K_2CO_3; (c) MeOH–H_2O, K_2CO_3.

alkyl group led to lowering of the yield (entry 6). A halogen at the *p*-position was well tolerated (entries 7 and 9). An excellent yield of product was observed when a strong electron donating group such as methoxy occupied the *p*-position (entry 14), while no significant effect was observed when a strong electron withdrawing group (entry 15) was present at the same position. The *N*-methylsulfonylamino group was found to be a poor substituent in our heteroarylation reaction (entry 13).

3,6-Dichloropyridazine **6** was used as heteroaryl halide in most of the arylation reactions. However, use of 3-chloro-6-methoxypyridazine was also found to be satisfactory albeit in lower yield (entry 16) and 3-chloro-1,6-dihydro-6-pyridazinone failed to react under the conditions employed in the reaction. The reaction was found to be moisture sensitive as **6** was hydrolyzed to the corresponding pyridazinedione (maleic hydrazide) in the presence of $AlCl_3$ upon exposure to the moisture.

The molar ratio of reagents, reaction time and temperature was optimized to achieve maximum yield and was found to be a 1:1.08:1.08 ratio of **5** and **6** with $AlCl_3$ as reagent. No reaction occurred without $AlCl_3$ (entry 5). The reactions were usually carried out at 50–60°C (entries 2 and 10) for 48 h. Either lower yields (10–15%) or the formation of no products were observed when the reaction was carried out at room temperature. Dicholoroethane was the solvent of choice. Use of other chlorinated solvents such as dichloromethane was also investigated and was found to be ineffective.

The heteroarylation reaction was found to be highly regioselective. The structures of the products isolated were established from analytical and spectroscopic data.[16–17] In the ^{1}H NMR spectra the pyridazinyl hydrogens were at δ 7.80±0.30 and δ 7.30±0.50 as two doublets. Regioselective substitution at the 7-position of **7** was confirmed by analysis of the ^{1}H NMR and ^{13}C NMR[17] spectra of starting material and product. A singlet at δ 7.90±0.30 in the ^{1}H NMR spectra of starting materials **5** was assigned as the proton at position 7. This disappears in the corresponding spectra of products **7**. Moreover the signal at δ 6.6 due to the hydrogen at the 5-position of **5** was found to remain unchanged in the ^{1}H NMR spectra of **7**. Similarly the unsubstituted C-5 could be seen at δ_C 95–105 ppm in ^{13}C NMR spectra[17] of **5** and **7** which would have appeared in a more down field region if the pyridazine moiety was attached with it. On the other hand C-7 of **5** appeared at δ_C 120–126 ppm, and was shifted to δ_C 140–155 ppm in the case of product **7**.

6-Arylpyrrolopyridazines **5**, key substrates for the heteroarylation reaction, were prepared by an established procedure.[11,18,19]

We have described an efficient and practical method for the synthesis of 6,7-disubstituted pyrrolopyridazines through an $AlCl_3$ induced coupling reaction. Interestingly, little is known about either Friedel–Crafts or $AlCl_3$ induced reactions on nitrogen containing heterocycles.[20] The nitrogen containing heterocycles, e.g. pyridine derivatives, due to the enhanced electron deficiency of the six membered ring as well as their complexation with $AlCl_3$,[21] have been identified as poor substrates for $AlCl_3$ mediated alkylation/acylation reactions. We did not encounter this problem, probably due to the poor availability of the lone pair of electrons on either of the nitrogen atoms of the pyrrolopyridazine ring. This was supported by the observation that like pyridine none of **5a–j** generated the corresponding salt when treated with hydrochloric acid under protic conditions.[20b] However, it is the same feature in the case of 3,6-dichloropyridazine, which actually promotes its reaction with nucleophilic pyrrolopyridazine derivatives.

We have extended the scope of our $AlCl_3$ induced methodology to the synthesis of a compound having potential biological interest (Scheme 2). Compound **7g** was hydrolyzed to pyridazinone derivative **9** using sodium acetate in acetic acid under reflux. The resulting compound was treated with ethylbromoacetate in the presence of potassium carbonate in DMF at room temperature to afford the ester **10** that was finally hydrolyzed to give the expected product **4g** (Ar=$C_6H_4C_2H_5$-*p*) in good yield.

3. Conclusion

In conclusion, we have applied the $AlCl_3$ mediated reaction to develop a general and convenient method for the synthesis of diaryl nitrogen containing heterocycles. Our method involves use of readily available starting materials, inexpensive reagents and mild reaction conditions. The method offers an adaptable and single step procedure to introduce the pyridazinyl group at position 7 of the pyrrolo[1,2-*b*]pyridazine nucleus having a wide range of

aryl residues at position 6. Thus the protocol could be a useful alternative to the Suzuki coupling and other transition metal catalyzed reactions when applied to similar type of nitrogen containing heterocyclic systems. The method has been utilized for synthesis of compounds of possible biological importance. Application of this methodology to other heterocyclic systems in order to open new avenues towards the synthesis of biologically active compounds is under active investigation.

4. Experimental

4.1. General methods

Unless stated otherwise, reactions were performed in dried glassware under nitrogen atmosphere. All the solvents used were commercially available and distilled before use. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254; Merck), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (SRL 230–400 mesh) using distilled petroleum ether, ethyl acetate, dichloromethane, chloroform and methanol. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$, DMSO-d_6 or MeOH-d_4 solution on Varian Gemini 200 MHz spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a Perkin–Elmer 1650 FT-IR spectrometer. UV spectra were recorded on Shimadzu UV 2100S UV–Vis recording spectrophotometer. Melting points were determined using Buchi melting point B-540 apparatus and are uncorrected. Thermal analysis data was generated with the help of Shimadzu DSC-50 detector. MS spectra were obtained on a HP-5989A mass spectrometer. Purity was determined by HPLC (AGIL-AUTO) using the condition specified in each case: column, mobile phase (range used), flow rate (ranges used), detection wavelength, retention times. Microanalyses were performed using Perkin–Elmer 2400 CHNS/O analyzer. Acetophenones and their bromo derivatives were either purchased or prepared according to the procedure described in the literature.[19] 4-isobutylacetophenone[19f] was brominated according to the procedure described in the literature.[19e] 3,6-dichloropyridazine is commercially available and 3-chloro-6-methoxypyridazine was prepared according to the procedure described in the literature.[22]

4.2. General procedure for preparation of 5

Step 1. A mixture of 2-bromo-1-aryl-1-ethanone (13.21 mmol) and dimethylpyridazine[18] (26.38 mmol) in ethyl acetate (10 mL) was stirred at 70°C for 12 h. The reaction mixture was cooled to room temperature and the solvent was decanted out from the separated mass. The residue was dried and used for the next step without further purification.

Step 2. A mixture of salt (5.97 mmol) as obtained above and sodium bicarbonate (17.85 mmol) in ethanol (10 mL) was heated to reflux with vigorous stirring for 12 h. After diluting with water (100 mL) the mixture was extracted with chloroform (3×50 mL). Organic layers collected, combined, washed with water (2×75 mL), dried (Na_2SO_4) and concentrated under vacuum to give the desired product.

4.2.1. 6-(4-Methylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (5a). Yield=0.81 g (61%); mp 138–139°C; δ_H (200 MHz, $CDCl_3$) 7.92 (s, 1H), 7.66–7.53 (m, 3H), 7.21 (d, J=7.8 Hz, 2H), 6.67 (s, 1H), 6.40 (d, J=8.8 Hz, 1H), 2.45 (s, 3H, *Me*), 2.37 (s, 3H, *Me*); ν_{max} (KBr) 1595 cm^{-1}; *m/z* (CI, *i*-butane) 223 (100, MH$^+$); found C, 81.15; H, 6.34; N, 12.58; $C_{15}H_{14}N_2$ requires C, 81.05; H, 6.35; N, 12.60%.

4.2.2. 6-(4-Isobutylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (5b). The title compound was prepared from 2-bromo-1-(4-isobutylphenyl)-1-ethanone (prepared by brominating[19e] 4-isobutylacetophenone[19f]) according to the procedure described earlier. Yield=0.49 g (31%); low melting; δ_H (200 MHz, $CDCl_3$) 7.93 (s, 1H), 7.61–7.54 (m, 3H), 7.17 (d, J=8.3 Hz, 2H), 6.68 (s, 1H), 6.40 (d, J=9.3 Hz, 1H), 2.53 (d, J=8.3 Hz, 2H, *CH*$_2$CHMe$_2$), 2.45 (s, 3H, *Me*), 1.92–1.85 (m, 1H, CH$_2$*CH*Me$_2$), 0.93 (d, J=6.8 Hz, 6H, 2*Me*); ν_{max} (KBr) 1590 cm^{-1}; *m/z* (CI, *i*-butane) 265 (100, MH$^+$); found C, 81.75; H, 7.64; N, 10.57; $C_{18}H_{20}N_2$ requires C, 81.78; H, 7.62; N, 10.60%.

4.2.3. 2-Bromo-1-(4-isobutylphenyl)-1-ethanone. Low melting solid, yield 68%; ^{1}H NMR ($CDCl_3$): δ 7.89 (dd, J=5.8, 5.8 Hz, 2H), 7.25 (dd, J=6.3, 6.3 Hz, 2H), 4.44 (s, 2H, *CH*$_2$CO), 2.56–2.51 (m, 2H, *CH*$_2$CHMe$_2$), 1.94–1.84 (m, 1H, CH$_2$*CH*Me$_2$), 0.91 (d, J=6.35 Hz, 6H, 2*Me*); MS (CI, *i*-butane): 256 (100, MH$^+$), 255 (100). Elemental analysis found C, 56.39; H, 5.90; $C_{12}H_{15}BrO$ requires C, 56.49; H, 5.93%.

4.2.4. 6-(4-Chlorophenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (5c). Yield=0.68 g (47%); mp 146–148°C; δ_H (200 MHz, $CDCl_3$) 7.91 (s, 1H), 7.62–7.51 (m, 3H), 7.36 (d, J=8.3 Hz, 2H), 6.66 (s, 1H), 6.43 (d, J=9.3 Hz, 1H), 2.45 (s, 3H, *Me*); ν_{max} (KBr) 1594 cm^{-1}; *m/z* (CI, *i*-butane) 243 (100, MH$^+$); found C, 69.25; H, 4.56; N, 11.59; $C_{14}H_{11}ClN_2$ requires C, 69.28; H, 4.57; N, 11.54%.

4.2.5. 6-(2,4-Dimethoxyphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (5d). Yield=1.10 g (69%) (gum); δ_H (200 MHz, $CDCl_3$) 7.90 (s, 1H), 7.59 (d, J=9.3 Hz, 1H), 7.27–7.17 (m, 2H), 6.92 (d, J=8.3 Hz, 1H), 6.65 (d, J=1.5 Hz, 1H), 6.42 (d, J=9.3 Hz, 1H), 3.96 (s, 3H, O*Me*), 3.92 (s, 3H, O*Me*), 2.46 (s, 3H, *Me*); ν_{max} (KBr) 1598 cm^{-1}; *m/z* (CI, *i*-butane) 269 (100, MH$^+$); found C, 71.64; H, 6.00; N, 10.41; $C_{16}H_{16}N_2O_2$ requires C, 71.62; H, 6.01; N, 10.44%.

4.2.6. 6-(4-Fluorophenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (5e). Yield=0.79 g (59%); mp 147–148°C; δ_H (200 MHz, $CDCl_3$) 7.89 (s, 1H), 7.62–7.56 (m, 3H), 7.13–7.04 (m, 2H), 6.64 (s, 1H), 6.43 (d, J=9.3 Hz, 1H), 2.46 (s, 3H, *Me*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.35, 159.48, 150.40, 131.09, 127.52, 127.36, 126.81, 126.48, 115.84, 115.41, 113.55, 112.09, 96.47, 21.69; ν_{max} (KBr) 1590 cm^{-1}; *m/z* (CI, *i*-butane) 227 (100, MH$^+$); found C, 74.43; H, 4.91; N, 12.30; $C_{14}H_{11}FN_2$ requires C, 74.32; H, 4.90; N, 12.38%.

4.2.7. 6-(3-Fluoro-4-methylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (5f). Yield=0.76 g (53%); mp 153–155°C; δ_H (200 MHz, $CDCl_3$) 7.85 (s, 1H), 7.57 (d, *J*=8.8 Hz, 1H), 7.44–7.39 (m, 2H), 7.04–7.00 (m, 1H), 6.61 (d, *J*=1.5 Hz, 1H), 6.39 (d, *J*=9.3 Hz, 1H), 2.43 (s, 3H, *Me*), 2.31 (d, *J*=1.5 Hz, 3H, *Me*); ν_{max} (KBr,) 1592 cm^{-1}; *m/z* (CI, *i*-butane) 241 (100, MH^+); found C, 74.95; H, 5.44; N, 11.68; $C_{15}H_{13}FN_2$ requires C, 74.98; H, 5.45; N, 11.66%.

4.2.8. 6-(4-Ethylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (5g). Yield=1.20 g (85%); mp 143–144°C; δ_H (200 MHz, $CDCl_3$) 7.92 (s, 1H), 7.61–7.56 (m, 3H), 7.24 (d, *J*=8.3 Hz, 2H), 6.68 (s, 1H), 6.40 (d, *J*=9.3 Hz, 1H), 2.73–2.61 (m, 2H, CH_2CH_3), 2.45 (s, 3H, *Me*), 1.26 (t, *J*=7.5 Hz, 3H, CH_2CH_3); ν_{max} (KBr) 1593 cm^{-1}; *m/z* (CI, *i*-butane) 237 (100, MH^+); found C, 81.36; H, 6.80; N, 11.80; $C_{16}H_{16}N_2$ requires C, 81.32; H, 6.82; N, 11.85%.

4.2.9. *N*-[4-(2-Methylpyrrolo[1,2-*b*]pyridazin-6-yl)-phenyl]methanesulphonamide (5h). The title compound was prepared from *N*-(4-acetylphenyl)methanesulfonamide[19e] according to the procedure described earlier. Yield=0.90 g (50%); mp 178–179°C; δ_H (200 MHz, $CDCl_3$) 7.90 (s, 1H), 7.64–7.55 (m, 3H), 7.21 (d, *J*=7.8 Hz, 2H), 6.64 (s, 1H), 6.43–6.33 (m, 2H), 3.01 (s, 3H, $NHSO_2Me$), 2.44 (s, 3H, *Me*); ν_{max} (KBr) 1590 cm^{-1}; *m/z* (CI, *i*-butane) 302 (100, MH^+); found C, 59.75; H, 5.00; N, 14.00; $C_{15}H_{15}N_3O_2S$ requires C, 59.78; H, 5.02; N, 13.94%.

4.2.10. 6-(4-Methoxyphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (5i). Yield=0.79 (56%); mp 133–134°C; δ_H (200 MHz, $CDCl_3$) 7.96–7.88 (m, 2H), 7.58 (d, *J*=8.8 Hz, 2H), 6.95–6.92 (m, 2H), 6.63 (s, 1H), 6.39 (d, *J*=9.3 Hz, 1H), 3.83 (s, 3H, O*Me*), 2.44 (s, 3H, *Me*); ν_{max} (KBr) 1601 cm^{-1}; *m/z* (CI, *i*-butane) 239 (100, MH^+); found C, 75.64; H, 5.90; N, 11.78; $C_{15}H_{14}N_2O$ requires C, 75.61; H, 5.92; N, 11.76%.

4.2.11. 6-(4-Nitrophenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (5j). Yield=0.78 g (52%); mp 197.5–198°C; δ_H (200 MHz, $CDCl_3$) 8.25 (d, *J*=8.8 Hz, 2H), 8.01 (s, 1H), 7.76 (d, *J*=7.8 Hz, 2H), 7.64 (d, *J*=9.3 Hz, 1H), 6.75 (s, 1H), 6.48 (d, *J*=9.3 Hz, 1H), 2.47 (s, 3H, *Me*); ν_{max} (KBr) 1595 cm^{-1}; *m/z* (CI, *i*-butane) 254 (100, MH^+); found C, 66.45; H, 4.35; N, 16.50; $C_{14}H_{11}N_3O_2$ requires C, 66.40; H, 4.38; N, 16.59%.

4.3. General procedure for preparation of 7

A mixture of 6-(4-aryl)-2-methylpyrrolo[1,2-*b*]pyridazine **5** (5.6 mmol), 3,6-dichloropyridazine (6.04 mmol) and $AlCl_3$ (0.81 g, 6.06 mmol) in dichloroethane (10 mL) was stirred under nitrogen atmosphere at 50–60°C for 48 h. The reaction mixture was poured into ice (10 g) and extracted with chloroform (3×20 mL). Organic layers combined, washed with water (2×30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the required product.

4.3.1. 7-(6-Chloro-3-pyridazinyl)-6-(4-methylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (7a). Yield=1.22 g (65%); light yellow powder, mp 248–249°C; δ_H (200 MHz, $CDCl_3$) 7.87 (d, *J*=9.3 Hz, 1H), 7.70 (d, *J*=8.8 Hz, 1H), 7.48 (d, *J*=8.8 Hz, 1H), 7.28 (d, *J*=8.8 Hz, 2H), 7.12 (d, *J*=7.8 Hz, 2H), 6.66 (s, 1H), 6.58 (d, *J*=9.3 Hz, 1H), 2.44 (s, 3H, *Me*), 2.34 (s, 3H, *Me*); ν_{max} (KBr) 1591 cm^{-1}; *m/z* (CI, *i*-butane) 335 (100, M^+); found C, 68.50; H, 4.57; N, 16.45; $C_{19}H_{15}ClN_4$ requires C, 68.16; H, 4.52; N, 16.73%; UV (EtOH, nm) 284.60, 246.00; HPLC: 97.46%. INERTSIL ODS 3V, H_2O/acetonitrile (30:70), 1.0 mL/min, 210 nm, retention time: 7.888 min.

4.3.2. 7-(6-Chloro-3-pyridazinyl)-6-(4-isobutylphenyl)-2-methyl pyrrolo[1,2-*b*]pyridazine (7b). Yield=0.88 g (42%); light yellow powder, mp >250°C; δ_H (200 MHz, $CDCl_3$) 8.02 (d, *J*=9.3 Hz, 1H), 7.79 (d, *J*=8.8 Hz, 1H), 7.67 (d, *J*=9.3 Hz, 1H), 7.25 (d, *J*=7.8 Hz, 2H), 7.07 (d, *J*=7.8 Hz, 2H), 6.70 (s, 1H), 6.67 (d, *J*=8.8 Hz, 1H), 2.58 (m, 2H, CH_2CHMe_2), 2.44 (s, 3H, *Me*), 1.92–1.85 (m, 1H, CH_2CHMe_2), 0.91 (d, *J*=6.8 Hz, 6H, 2*Me*); ν_{max} (KBr) 1590 cm^{-1}; *m/z* (CI, *i*-butane) 377 (100, M^+); found C, 70.41; H, 5.61; N, 14.77; $C_{22}H_{21}ClN_4$ requires C, 70.11; H, 5.62; N, 14.87%; UV (EtOH, nm) 246.60; HPLC: 97.76%. INERTSIL ODS 3V, H_2O/acetonitrile (20:80), 1.0 mL/min, 245 nm, retention time: 14.970 min.

4.3.3. 7-(6-Chloro-3-pyridazinyl)-6-(4-chlorophenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (7c). Yield=0.99 g (50%); light yellow powder, mp 239–240°C; δ_H (200 MHz, $CDCl_3$) 8.02 (d, *J*=8.8 Hz, 1H), 7.72 (d, *J*=9.3 Hz, 1H), 7.53 (d, *J*=8.8 Hz, 1H), 7.37–7.30 (m, 4H), 6.66 (s, 1H), 6.62 (d, *J*=8.8 Hz, 1H), 2.45 (s, 3H, *Me*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 164.38, 159.8, 155.50, 153.0, 150.87, 150.00, 133.74, 133.02, 130.70, 130.61, 129.23, 128.49, 127.29, 126.79, 126.70, 114.19, 101.28, 21.95; ν_{max} (KBr) 1592 cm^{-1}; *m/z* (CI, *i*-butane) 355 (100, M^+); found C, 60.96; H, 3.40; N, 15.39; $C_{18}H_{12}Cl_2N_4$ requires C, 60.86; H, 3.40; N, 15.77%; UV (EtOH, nm) 280.00, 146.80; HPLC: 94.87%. INERTSIL ODS 3V, H_2O/acetonitrile (30:70), 1.0 mL/min, 210 nm, retention time: 9.218 min.

4.3.4. 7-(6-Chloro-3-pyridazinyl)-6-(2,4-dimethoxyphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (7d). Yield=1.26 g (60%); light brown solid, δ_H (200 MHz, $CDCl_3$) 7.57 (d, *J*=9.3 Hz, 1H), 7.54–7.47 (m, 2H), 7.27–7.17 (m, 2H), 6.92 (d, *J*=8.3 Hz, 1H), 6.65 (s, 1H), 6.43 (d, *J*=9.3 Hz, 1H), 3.97 (s, 3H, O*Me*), 3.93 (s, 3H, O*Me*), 2.47 (s, 3H, *Me*); ν_{max} (KBr) 1590 cm^{-1}; *m/z* (CI, *i*-butane) 377 (100, M^+); found C, 63.19; H, 4.54; N, 14.52; $C_{20}H_{17}ClN_4O_2$ requires C, 63.08; H, 4.50; N, 14.71%.

4.3.5. 7-(6-Chloro-3-pyridazinyl)-6-(4-fluorophenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (7e). Yield=1.36 g (72%); light yellow powder, mp 237–238°C; δ_H (200 MHz, $CDCl_3$) 7.99 (d, *J*=9.3 Hz, 1H), 7.72 (d, *J*=9.3 Hz, 1H), 7.52 (d, *J*=9.3 Hz, 1H), 7.42–7.35 (m, 2H), 7.01 (t, *J*=8.8 Hz, 2H), 6.65 (s, 1H), 6.61 (d, *J*=9.3 Hz, 1H), 2.45 (s, 3H, *Me*); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 164.54, 159.65, 154.35, 152.94, 150.93, 150.74, 132.2, 131.02, 130.86, 130.72, 129.44, 127.25, 126.72, 115.41, 114.98, 114.12, 101.30, 21.92; ν_{max} (KBr) 1588 cm^{-1}; *m/z* (CI, *i*-butane) 339 (100, M^+); found C, 63.44; H, 3.49; N, 16.63; $C_{18}H_{12}ClFN_4$ requires C, 63.82; H, 3.57; N, 16.54%; UV (EtOH, nm) 282.00, 244.20; HPLC: 99.05%.

INERTSIL ODS 3V, H_2O/acetonitrile (30:70), 1.0 mL/min, 245 nm, retention time: 10.876 min.

4.3.6. 7-(6-Chloro-3-pyridazinyl)-6-(3-fluoro-4-methylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (7f). Yield=1.76 g (89%); white powder, mp 228–229°C; δ_H (200 MHz, $CDCl_3$) 7.96 (d, *J*=8.8 Hz, 1H), 7.71 (d, *J*=9.3 Hz, 1H), 7.51 (d, *J*=8.8 Hz, 1H), 7.23–7.11 (m, 2H), 6.97–6.88 (m, 1H), 6.63 (s, 1H), 6.60 (d, *J*=9.3 Hz, 1H), 2.45 (s, 3H, *Me*), 2.25 (s, 3H, *Me*); ν_{max} (KBr) 1590 cm^{-1}; *m/z* (CI, *i*-butane) 353 (100, M^+); found C, 64.78; H, 4.12; N, 15.58; $C_{19}H_{14}ClFN_4$ requires C, 64.69; H, 4.00; N, 15.88%; UV (EtOH, nm) 244.60; HPLC: 95.75%. INERTSIL ODS 3V, H_2O/acetonitrile (30:70), 1.0 mL/min, 210 nm, retention time: 8.076 min.

4.3.7. 7-(6-Chloro-3-pyridazinyl)-6-(4-ethylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine, (7g). Yield=1.48 g (76%); pale yellow powder, mp 227–228°C; δ_H (200 MHz, $CDCl_3$) 7.87 (d, *J*=8.8 Hz, 1H), 7.70 (d, *J*=8.8 Hz, 1H), 7.49 (d, *J*=8.8 Hz, 1H), 7.31 (d, *J*=8.3 Hz, 2H), 7.14 (d, *J*=8.3 Hz, 2H), 6.66 (s, 1H), 6.58 (d, *J*=8.8 Hz, 1H), 2.70–2.58 (m, 2H, CH_2CH_3), 2.44 (s, 3H, *Me*), 1.24 (t, *J*=7.6 Hz, 3H, CH_2CH_3); ν_{max} (KBr) 1593 cm^{-1}; *m/z* (CI, *i*-butane) 349 (100, M^+); found C, 68.56; H, 4.94; N, 16.27; $C_{20}H_{17}ClN_4$ requires C, 68.86; H, 4.91; N, 16.06%; UV (EtOH, nm) 245.80; HPLC: 98.52%. HICHROM RPB, H_2O/acetonitrile (30:70), 1.0 mL/min, 210 nm, retention time: 10.347 min.

4.3.8. *N*-{4-[7-(6-Chloro-3-pyridazinyl)-2-methylpyrrolo[1,2-*b*]pyridazin-6-yl]phenyl}methanesulfonamide (7h). Yield=0.09 g (4%); Off white powder, mp 242–244°C; δ_H (200 MHz, $CDCl_3$) 9.79 (s, 1H), 8.22 (d, *J*=9.3 Hz, 1H), 8.05–8.01 (m, 2H), 7.29 (d, *J*=8.3 Hz, 2H), 7.14 (d, *J*=8.8 Hz, 2H), 6.84–6.80 (m, 2H), 3.33 (s, 3H, $NHSO_2Me$), 2.50 (s, 3H, *Me*); ν_{max} (KBr) 1589 cm^{-1}; *m/z* (CI, *i*-butane) 414 (100, M^+); found C, 55.04; H, 3.87; N, 17.19; $C_{19}H_{16}ClN_5O_2S$ requires C, 55.14; H, 3.90; N, 16.92%; UV (EtOH, nm) 254.40; HPLC: 97.84%. INERTSIL ODS 3V, H_2O/acetonitrile (30:70), 1.0 mL/min, 245 nm, retention time: 5.288 min.

4.3.9. 7-(6-Chloro-3-pyridazinyl)-6-(4-methoxyphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (7i). Yield=1.83 g (93%); white powder, mp 242–243°C; δ_H (200 MHz, $CDCl_3$) 7.86 (d, *J*=9.3 Hz, 1H), 7.67 (d, *J*=9.3 Hz, 1H), 7.46 (d, *J*=8.8 Hz, 1H), 7.33–7.23 (m, 2H), 6.83 (d, *J*=8.3 Hz, 2H), 6.61 (s, 1H), 6.56 (d, *J*=9.3 Hz, 1H), 3.78 (s, 3H, O*Me*), 2.42 (s, 3H, *Me*); ν_{max} (KBr) 1590 cm^{-1}; *m/z* (CI, *i*-butane) 351 (100, M^+); found C, 65.35; H, 4.34; N, 15.61; $C_{19}H_{15}ClN_4O$ requires C, 65.05; H, 4.31; N, 15.97%.

4.3.10. 7-(6-Chloro-3-pyridazinyl)-6-(4-nitrophenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (7j). Yield=1.47 g (72%); light brown powder, mp 288–289°C; δ_H (200 MHz, $CDCl_3$) 8.25–8.16 (m, 3H), 7.77 (d, *J*=8.8 Hz, 1H), 7.62–7.54 (m, 3H), 6.74 (s, 1H), 6.67 (d, *J*=9.3 Hz, 1H), 2.49 (s, 3H, *Me*); ν_{max} (KBr) 1591 cm^{-1}; *m/z* (CI, *i*-butane) 366 (100, M^+); found C, 59.47; H, 3.39; N, 19.01; $C_{18}H_{12}ClN_5O_2$ requires C, 59.11; H, 3.31; N, 19.15%; UV (EtOH, nm) 288.50, 242.50; HPLC: 98.74%. HICHROM RPB, H_2O/acetonitrile (40:60), 1.0 mL/min, 240 nm, retention time: 11.176 min.

4.3.11. 7-(6-Methoxy-3-pyridazinyl)-2-methyl-6-(4-methylphenyl)pyrrolo[1,2-*b*]pyridazine (8). The title compound was prepared from 6-(4-methylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazine (**5a**) and 3-chloro-6-methoxypyridazine[22] according to the procedure described earlier. Yield=0.37 g (20%); pale yellow solid, mp 288–289°C; δ_H (200 MHz, $CDCl_3$) 7.81 (d, *J*=9.2 Hz, 1H), 7.65 (d, *J*=9.3 Hz, 1H), 7.37–7.17 (m, 4H), 7.00 (d, *J*=7.8 Hz, 1H), 6.66 (s, 1H), 6.53 (d, *J*=9.3 Hz, 1H), 4.18 (s, 3H, O*Me*), 2.44 (s, 3H, *Me*), 2.34 (s, 3H, *Me*); ν_{max} (KBr) 1589 cm^{-1}; *m/z* (CI, *i*-butane) 330 (100, M^+); found C, 72.32; H, 5.37; N, 17.16; $C_{20}H_{18}N_4O$ requires C, 72.71; H, 5.49; N, 16.96%.

4.3.12. 3-[6-(4-Ethylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazin-7-yl]-1,6-dihydro-6-pyridazinone (9). A mixture of 350 mg (1.004 mmol) of 7-(6-chloro-3-pyridazinyl)-6-(4-ethylphenyl)-2-methlypyrrolo[1,2-*b*]pyridazine **7g** and 164 mg (2 mmol) of sodium acetate in 15 mL of acetic acid was heated to reflux under nitrogen atmosphere for 5 h with stirring. The mixture was then poured into 150 mL of cold water with stirring. Solid separated was filtered, washed with water (2×10 mL) and dried under vacuum to give the required product as a white powder, yield=0.28 g (85%); mp 214–215°C; DSC 214.47°C; ^1H NMR (DMSO-d_6): 13.15 (s, 1H, NH, exchangeable with D_2O), 7.96 (d, *J*=8.8 Hz, 1H), 7.70 (d, *J*=9.8 Hz, 1H), 7.31–7.17 (m, 4H), 6.98 (d, *J*=7.8 Hz, 1H), 6.75 (d, *J*=8.8 Hz, 1H), 2.65–2.57 (m, 2H, CH_2CH_3), 2.39 (s, 3H, *Me*), 1.19 (t, *J*=7.6 Hz, 3H, CH_2CH_3); ν_{max} (KBr): 3419, 1648 cm^{-1}; UV (MeOH, nm) 366.00, 249.50; *m/z* (CI, *i*-butane) 331 (100, MH^+); HPLC: 98.58%. HICHROM RPB, H_2O/acetonitrile (30:70), 1.0 mL/min, 250 nm, retention time: 7.554 min. Elemental analysis found C, 72.75; H, 5.47; $C_{20}H_{18}N_4O$ requires C, 72.71; H, 5.49%.

4.3.13. Ethyl 2-(3-[6-(4-ethylphenyl)-2-methylpyrrolo-[1,2-*b*]pyridazin-7-yl]-6-oxo-1,6-dihydro-1-pyridazinyl)-acetate (10). A mixture of 500 mg (1.51 mmol) of 3-[6-(4-Ethylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazin-7-yl]-1,6-dihydro-6-pyridazinone **9**, 300 mg (1.79 mmol) of ethyl bromoacetate and 540 mg (3.91 mmol) of potassium cabonate in 10 mL DMF was stirred at room temperature for 48 h. The mixture was poured into 50 mL of cold water with stirring. The separated solid was filtered washed with water (2×10 mL) and dried under vacuum to give the required product as a pale yellow powder, yield=0.27 g (43%); mp 149–150°C; DSC 150.26°C; ^1H NMR ($CDCl_3$): δ 7.70–7.63 (m, 2H), 7.35 (d, *J*=7.8 Hz, 2H), 7.15 (d, *J*=8.3 Hz, 2H), 6.97 (d, *J*=9.8 Hz, 1H), 6.63 (s, 1H), 6.53 (d, *J*=8.8 Hz, 1H), 4.80 (s, 2H, $CH_2COOCH_2CH_3$), 4.21–4.17 (m, 2H, OCH_2CH_3), 2.66–2.62 (m, 2H, CH_2CH_3), 2.45 (s, 3H, *Me*), 1.24 (t, *J*=7.3 Hz, 6H, 2*Me*); ν_{max} (KBr): 1730, 1670, 1590 cm^{-1}; UV (MeOH, nm) 369.50, 251.50; *m/z* (CI, *i*-butane): 417 (100, MH^+); HPLC: 96.59%. HICHROM RPB, H_2O/acetonitrile (30:70), 1.0 mL/min, 250 nm, retention time: 8.779 min. Elemental analysis found C, 69.27; H, 5.80; $C_{24}H_{24}N_4O_3$ requires C, 69.21; H, 5.81%.

4.3.14. 2-{3-[6-(4-Ethylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazin-7-yl]-6-oxo-1,6-dihydro-1-pyridazinyl}acetic acid (4g). A mixture of 200 mg (0.48 mmol) of ethyl 2-(3-(6-(4-ethylphenyl)-2-methylpyrrolo[1,2-*b*]pyridazin-7-yl)-6-oxo-1,6-dihydro-1-pyridazinyl)acetate **10** and 330 mg (2.39 mmol) of potassium carbonate was stirred in 15 mL of methanol and 3 mL of water for 24 h at room temperature. After removal of methanol under low vacuum the reaction mixture was poured into the 50 mL of cold water and then acidified by 33% HCl solution. Solid separated was filtered and washed with water (2×10 mL) to give the title compound as a light brown powder, yield=0.16 g (86%); DSC 208.55°C; ^{1}H NMR ($CDCl_3$): δ 7.67 (dd, J=9.3 Hz, 1.46 Hz, 2H), 7.34 (d, J=7.8 Hz, 2H), 7.16 (d, J=7.8 Hz, 2H), 7.02 (d, J=9.7 Hz, 1H), 6.63 (s, 1H), 6.57 (d, J=9.3 Hz, 1H), 4.88 (s, 2H, CH_2COOH), 3.86 (bs, 1H, COO*H*, exchangeable with D_2O), 2.70–2.59 (m, 2H, CH_2CH_3), 2.46 (s, 3H, *Me*), 1.23 (t, J=7.3 Hz, 3H, CH_2CH_3); ν_{max} (KBr): 3407 (b, s), 2899, 1723, 1639, 1576 cm^{-1}; UV (MeOH, nm) 369.00, 251.50; *m/z* (CI, *i*-butane): 389 (100, MH$^+$); HPLC: 98.91%. HICHROM RPB, 0.01 M KH_2PO_4/acetonitrile (55:45), pH=3.5, 1.2 mL/min, 250 nm, retention time: 16.943 min. Elemental analysis found C, 68.33; H, 5.20; $C_{22}H_{20}N_4O_3$ requires C, 68.03; H, 5.19%.

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