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ORIGINAL PAPER

# Synthesis of some di- and trifluoro quinoxaline and dioxine derivatives from pentafluoropyridine

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**Abstract** Novel [6,6,6] ring fused tricyclic systems can be readily synthesized in one-pot annulation reaction of pentafluoropyridine or 4-phenylsulfonyl tetrafluoropyridine with appropriate difunctional nitrogen and oxygen nucleophiles attached to aromatic rings. Reaction of 4-phenylsulfonyl tetrafluoropyridine with 2,6-diaminopyridine gave [6,5,6] ring fused systems arising from a tandem $S_NAr$ and cyclisation process. From this investigation, di- and trifluorinated quinoxaline and dioxine scaffolds were synthesized.

**Keywords** Quinoxaline · Pentafluoropyridine · Fused tricyclic system · Synthesis

## Introduction

Pentafluoropyridine has attracted considerable interest due to its synthetic utility. Several polyfunctional pyridine derivatives and preparation of new heterocyclic, aromatic heterocyclic and macrocyclic systems could be accessed from simple reaction conditions [1–7]. All five fluorine atoms in pentafluoropyridine may be substituted by an appropriate nucleophile due to its highly electron efficient aromatic ring system. It is well established that the order of nucleophilic attack on pentafluoropyridine is $4 > 2 > 3$, for monosubstitution reactions involving a range of nucleophiles [8–10]. However, this may be depended on the effect of each substituent once attached to the heterocyclic ring as well as the nature of the attacking nucleophile. On the other hand, this site-reactivity order may be altered by reaction of pentafluoropyridine with bidentate nucleophiles [11]. Sandford and his co-worker recently demonstrated the reactions of various 2,3,5,6-tetrafluoropyridine derivatives **1** (X = CN, $NO_2$, H, MeO, EtO, $Et_2N$, *i*-PrNH, $CF(CF_3)_2$ and Br) to assess the influence of the substituent at the 4-position upon reactions with difunctional N-nucleophile such as *N*,*N*-diethylamine, and *N*,*N*'-dimethylethylene diamine (Scheme 1) [12].

There are few papers concerning the reactions involving identical bidentate nucleophiles attached to the aromatic rings with pentafluoropyridine derivatives [2]. In this paper, we report our studies concerning synthesis of [6,6,6]- and [6,5,6]-ring fused tricyclic systems by carrying out the reactions of pentafluoropyridine and 4-phenylsulfonyl tetrafluoropyridine and appropriate difunctional nitrogen and oxygen nucleophiles attached to aromatic rings.

## Results and discussion

The reaction of pentafluoropyridine (**1a** X = F) with pyrocatechol **2a** in the presence of cesium carbonate in DMSO solvent gave 1,3,4-trifluorobenzo[5,6][1,4]dioxino[2,3-*c*]pyridine **3a**, arising from the substitution of the most activated fluorine atom at the 4-position of the pyridine ring followed by intermolecular ring closure at the geometrically accessible 3-position (Table 1, entry 1). A small amount of non-cyclised product **3b** was obtained reflecting the lower reactivity of 3 or 5-position which allows intermolecular substitution to compete effectively with the intramolecular cyclisation process. Purification of **3a** and **3b** was achieved by column chromatography. Identification of **3a** was done by $^{19}F$ NMR analysis, in

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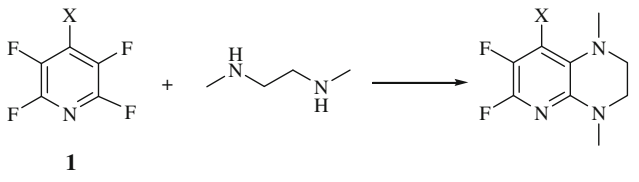



X= CN, $NO_2$, H, MeO, EtO, $Et_2N$, i-PrNH, $CF(CF_3)_2$ and Br

**Scheme 1** Reactions of various 2,3,5,6-tetrafluoropyridine derivatives with diamines

which the resonance attributed to fluorines located *ortho* to ring nitrogen have a chemical shift of –104.58 ppm and –93.41 ppm similar to the shift observed for the **3c**. The corresponding resonance for F-3 in **3a** occurs at –164.27 ppm similar to the analogous system **3c**. The reaction of **1a** with benzene-1,2,3-triol **2b** bearing three nucleophilic sites gave **3c** as only product, arising from initial attack at the 2-position of the two pyridine rings and subsequent cyclization, respectively (Table 1, entry 2). Identification of **3c** was done from $^{19}F$ NMR analysis in which the resonance attributed to four fluorine atoms located ortho positions of both nitrogen rings had a chemical shift in the range −88.8 to −89.9 ppm and the resonance attributed to three fluorine atoms located *meta* positions of both nitrogen rings had a chemical shift of −156.1 and −163.1 ppm.

By a similar procedure, **1a** reacted with benzene-1,2-diamin **2c** and 4-methylbenzene-1,2-diamine **2d** to give the corresponding tricyclic system **3d** and **3f**. But a trace amount of these compounds was obtained and in contrast, bis-pyridyl bridged products **3e** and **3g** were isolated as the major products reflecting the lower reactivity of the *meta* position which allows intermolecular substitution to compete effectively with the intramolecular cyclisation process.

In order to further develop routes to [6,6,6] tricyclic systems, we studied reactions of 4-phenylsulfonyl tetrafluoropyridine (**1b** X = $SO_2Ph$), bearing phenylsulfonyl functionality at the 4-positions, with appropriate difunctional nitrogen or oxygen nucleophiles (Table 1, entry 5–11).

The phenylsulfonyl group is strong electron withdrawing group that helps to maintain the reactivity of pyridine ring toward further nucleophilic substitution processes. This allows annulation and further functionalization to proceed. Annulation processes involving the reaction between 4-phenylsulfonyl tetrafluoropyridine and difunctional nitrogen or oxygen nucleophiles in the presence of sodium bicarbonate in diluted acetonitrile solution to minimize intermolecular reaction were studied. Nitrogen or oxygen binucleophiles reacted efficiently with 4-phenylsulfonyl tetrafluoropyridine to give tetrahydropyrido[2,3-b]oxazine, quinoxaline or pyrazine systems by substitution at the 2-position of the pyridine ring followed by intermolecular ring closure at the geometrically accessible 3-position.

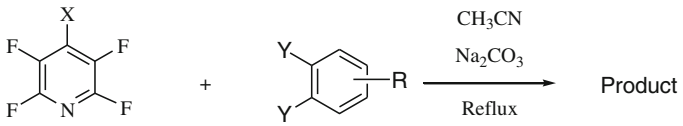
The reaction of 4-phenylsulfonyl tetrafluoropyridine with pyrocatechol **2a** bearing two nucleophilic sites, after refluxing in DMSO, gave **3h**, arising from the initial attack of oxygen nucleophile at the 2-position of the pyridine ring and subsequent cyclization, respectively. By similar procedures, the related 3,4-dihydroxy nitrobenzene **2e** gave the mixture of analogous products **3i** and **3j** in the ratio of 2:1 by $^{19}F$ NMR analysis of the reaction mixture and 4-methylbenzene-1,2-diol **2f**, gave the mixture of analogous products **3k** and **3l** in the ratio of 1:4 by $^{19}F$ NMR analysis of the reaction mixture (Table 1, entries 5–7). The reaction of **1b** with benzene-1,2,3-triol **2b** (Table 1, entry 8) bearing three nucleophilic sites gave **3m** as the only product, arising from initial attack at the 2-position of the two pyridine rings and subsequent cyclization, respectively. Identification of **3h–m** was done by $^{19}F$ NMR analysis, in which the resonance attributed to fluorine located *ortho* to ring nitrogen have a chemical shift in the range of –91.95 to –95.29 ppm similar to the shift observed for the **3a** and **3b**. The corresponding resonance for the fluorine located *meta* to ring nitrogen occurs at the range of –144.03 to –165.64 ppm similar to the analogous system.

Bifunctional nucleophiles **2c** and **2d**, where both nucleophilic sites are amino groups, reacted efficiently with **1b** to give high yields of azatricyclic fused systems **3n** and **3o**, respectively (Table 1, entries 9 and 10). Purification of **3n** was achieved by recrystallization of the crude product mixture from dichloromethane, while **3o** was purified by column chromatography on silica gel, resulting in a lower isolated yield.

Identification of **3n** and **3o** was done by $^{19}F$ NMR analysis in which the resonance attributed to fluorine located *ortho* to ring nitrogen had a chemical shift of −112.9 and −113.0 ppm, respectively, similar to the analogous system in which *ortho* fluorine was adjacent to the NH group (−105.7 ppm) [14]. The corresponding resonance for F-3 in **3n** and **3o** occurs at −165.7 and −166.0 ppm.

2-Aminophenol **2g**, have both nitrogen and oxygen nucleiphilic site, reacted efficiently with **1b** to give good yields of tricyclic fused systems **3p** (Table 1, entry 11). A small amount (3 %) of **3q** product was identified by $^{19}F$ NMR analysis but could not be isolated. Purification of **3p** was achieved by recrystallization of the crude product mixture from *n*-hexane/ethyl acetate. Identification of **3p** and **3q** was done by $^{19}F$ NMR analysis in which the resonance attributed to fluorine located at ortho to ring nitrogen had a chemical shift of −103.0 and −92.2 ppm for **3p** and **3q**, respectively, similar to the shifts observed

**Table 1** Nucleophilic substitution of **1** with **2**




**1** (**1a**; X = F, **1b**; X = $SO_2Ph$) **2** **3**

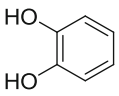
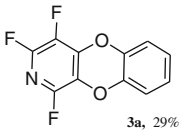
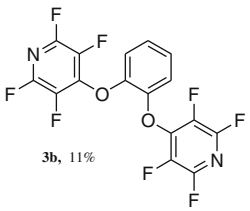
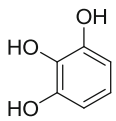
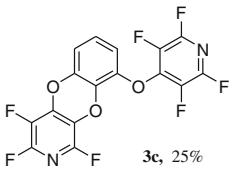
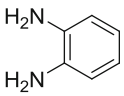
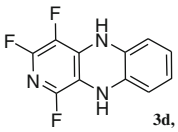
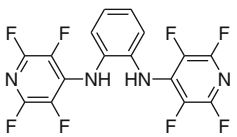
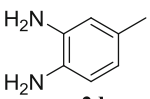
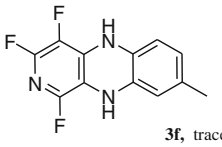
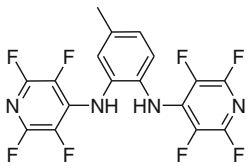
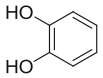
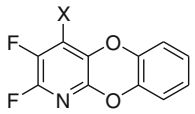
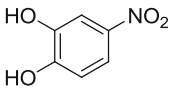
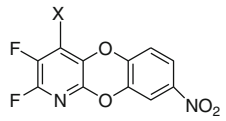
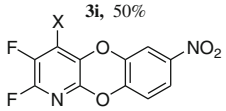
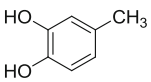
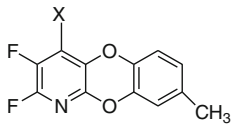
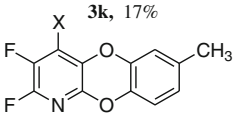
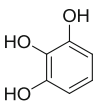
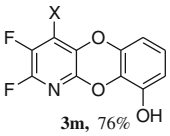
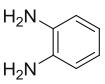
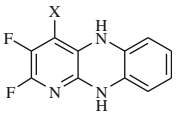
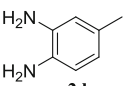
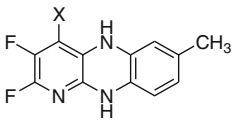
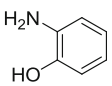
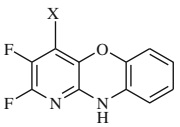
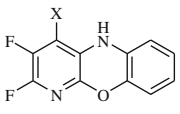
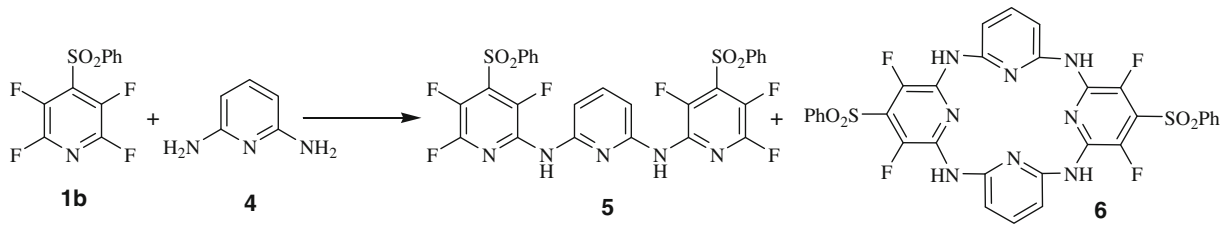
| Entry | X | Binucleophile | Product(s) |
|---|---|---|---|
| 1 | F |  **2a** |  **3a,** 29%  **3b,** 11% |
| 2 | F |  **2b** |  **3c,** 25% |
| 3 | F |  **2c** |  **3d,** trace  **3e,** 65% |
| 4 | F |  **2d** |  **3f,** trace  **3g,** 48% |

**Table 1** continued

| Entry | X | Binucleophile | Product(s) |
|---|---|---|---|
| 5 | $SO_2Ph$ |  **2a** |  **3h,** 80% |
| 6 | $SO_2Ph$ |  **2e** |  **3i,** 50%  **3j,** 25% |
| 7 | $SO_2Ph$ |  **2f** |  **3k,** 17%  **3l,** 78% |
| 8 | $SO_2Ph$ |  **2b** |  **3m,** 76% |
| 9 | $SO_2Ph$ |  **2c** |  **3n,** 35% |
| 10 | $SO_2Ph$ |  **2d** |  **3o,** 46% |
| 11 | $SO_2Ph$ |  **2g** |  **3p,** 70%  **3q,** trace |



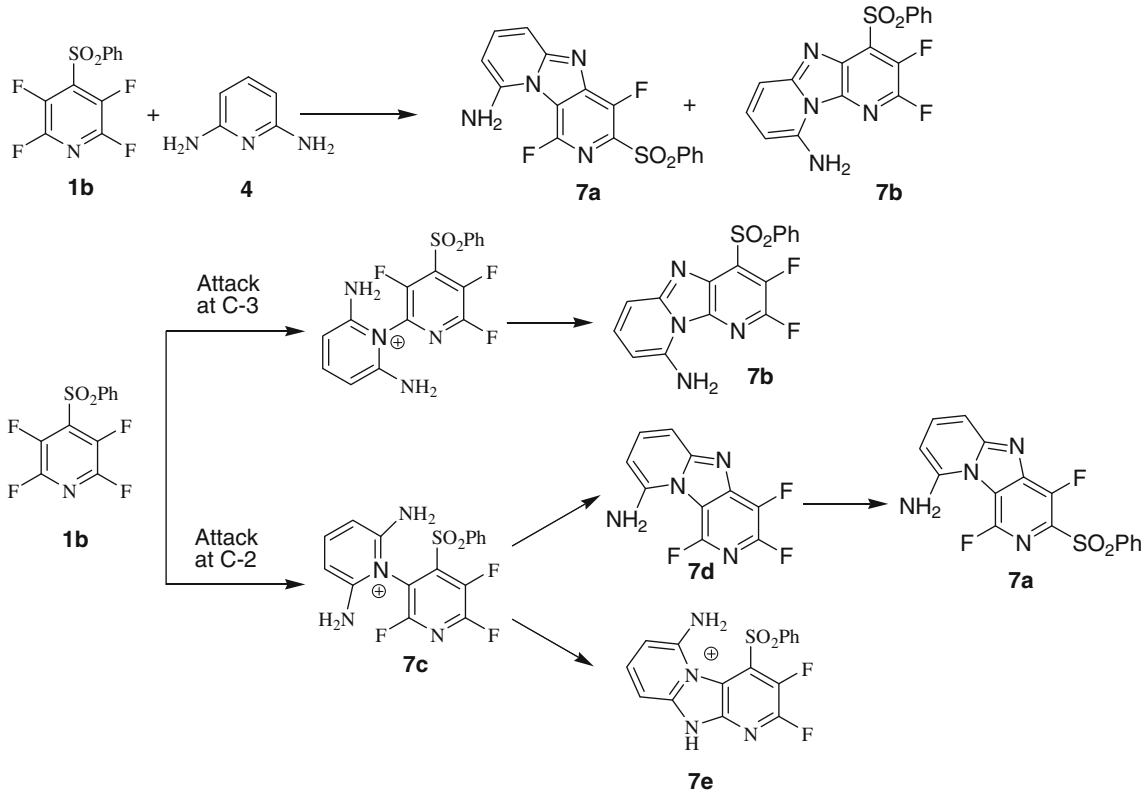

**Scheme 2** Synthesis of macrocycel from pentafluoropyridine

for the analogous systems. The regioselectivity of nucleophilic substitution of **1** with **2** may be explained by the activating influences of the pyridine ring's nitrogen that significantly activates the *ortho* and *para* sites to itself.

With this encouraging result in hand, we interested to obtain macrocycle **6** or bis-pyridyl product **5** by reaction of 4-phenylsulfonyl tetrafluoropyridine with pyridine-2,6-diamine **4**. However, the attempt to obtain **6** and **5** was failed (Scheme 2).

The reaction of **4** with **1b** was less selective than the reactions described above and two major products, 7a and 7b, were present in the reaction mixture as determined by $^{19}$F NMR spectroscopy. Purification allowed the isolation of small quantities of the two major products **7a** and **7b**. **7a** and **7b** were identified by $^{19}$F NMR spectroscopy.

A postulated mechanism for this process that leads to **7a** and **7b** is shown in Scheme 3, and provides an indication of how the products arise from initial nucleophilic attack by **4** at the 2- and 3- positions of the pyridine ring, adapting a mechanism postulated by Sandford [13] concerning reactions between 4-phenylsulfonyl tetrafluoropyridine and 2-amino-3-picoline. Displacement of fluorine at the 2-position leads directly to product **7b**, whilst displacement of fluorine at the 3-position gives intermediate **7c**, which gives rise to **7d** or **7e** by intramolecular cyclisation at the 4- or 2-position, displacing phenylsulfonyl or fluorine, respectively. Reaction of **7d** with the phenylsulfonyl anion, which is now present in the reaction mixture, gives **7a**. This process is, therefore, complicated by the fact that the phenylsulfonyl group, which is attached to the site para to




**Scheme 3** Synthesis of difluoro dipyridoimidazolylamine

ring nitrogen that remains most activated towards nucleophilic attack, is labile and may be readily displaced by nucleophiles.

## Conclusion

In conclusion, we showed that pentafluoropyridine **1a** can be used as a substrate for the synthesis of some trifluorobenzo[5,6][1,4]dioxino derivatives upon reaction with various aromatic dioles. In contrast, aromatic diamines give bis-pyridyl bridged compounds as the major products. Also, tricyclic difluoro-8-nitro-4-phenylsulfonylbenzo[5,6][1,4] dioxino[2,3-*b*]pyridine difluoro 4-benzenesulfonyl-5,10-di hydro-pyrido[2,3-b]quinoxaline scaffolds can be readily synthesized in one-pot processes from pentafluoropyridine and various aromatic diols and diamines, respectively. The regioselectivity of nucleophilic substitution in this process may be explained by the activating influence of pyridine ring nitrogen that significantly activates the *ortho* and *para* sites to itself.

## Experimental section

All solvents were dried using the literature procedures and distilled before use. The reactions were carried out under an atmosphere of air unless otherwise specified. The elemental analyses for C, H, and N were performed using Heraeus CHN-O-Rapid analyzer. The $^{1}$H NMR spectra were recorded at 500 MHz. The $^{13}$C NMR spectra were recorded at 125 MHz. The $^{19}$F NMR spectra were recorded at 470 MHz. In the $^{19}$F NMR spectra, upfield shifts were quoted as negative and referred to $CFCl_3$. Mass spectra were obtained by a Micromass Platform II: EI mode (70 eV). Column chromatography was performed using silica (Merck #60). Silica plates (Merck) were used for TLC analysis.

General procedure for preparation of 6,7-difluoro-2,3-dihydro-8-(phenylsulfonyl)pyrido[3,2-*b*][1,4]oxazin or pyrazine system

Sodium carbonate (3 mmol) was added to the mixture of **2** (1 mol) in acetonitrile (10 mL) under argon. Then **1** (1 mol) was added and the resulting solution was refluxed at 95 °C for 2 d. The reaction mixture was cooled to room temperature and the solvent was evaporated. The reaction mixture was poured onto 0.2 M hydrochloric acid (30 ml) and then extracted with dichloromethane. The solvent was evaporated to yield the crude product, which was then purified by recrystallization or column chromatography on silica gel.

*1,3,4-trifluorobenzo[e]pyridino[3,2-b]1,4-dioxin (3a) and 1,2-bis[2,3,5,6-tetrafluoro]-pyrid-4-yloxy]benzene (**3b**)*

Sodium carbonate (0.25 g, 3 mmol), pyrocatechol **2a** (0.11 g, 1 mol), pentafluoropyridine (0.17 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 2:3) gave 1,3,4-trifluorobenzo[e]pyridino[3,2-b]1,4-dioxin **3a** and 1,2-bis[2,3,5,6-tetrafluoro]-pyrid-4-yloxy]benzene **3b, 3a:** 0.03 gr, (29 %), white solid; mp: 210–215 °C. $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta_F$ −164.3 (m,1F, F-4), −104.8 (m, 1F, F-1), −93.4 (m, 1F, F-3). MS (EI, 70 Ev): *m/z* (%) = 24.0 ($M^+$, 30.1), 223.9, 222.9 (100), 193.9, 148.9, 92.9, 52.0. **3b**: 0.02gr, (11 %), white solid; mp: 279–283 °C. $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta_F$ −165.3 (m,4F, F-3,5), −87.8 (m, 4F, F-2,6). MS (EI, 70 eV): *m/z* (%) = 408.9 ($M^+$, 3.1), 407.8, 239.9, 238.9, 209.9, 191.9, 162.9, 119.4 (100), 73.9, 62.9.

*1,2,3-trifluoro-9-(2,3,5,6-tetrafluoro-pyridin-4-yloxy)-benzo[5,6][1,4]dioxino[2,3-c]pyridine (**3c**)*

Sodium carbonate (0.25 g, 3 mmol), pyrogallol **2b** (0.13 g, 1 mol), pentafluoropyridine (0.17 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 2:3) gave 1,3,4-trifluoro-9-(2,3,5,6-tetrafluoro-pyridin-5-yloxy)-benzo[5,6][1,4]dioxino[3,2-c]pyridine **3c**, 0.05 g (25 %), white solid; mp: 93–95 °C. $^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 6.86–7.09 (m, 3H, Ar–H). $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 114.7 (Ar–C), 116.3 (Ar–C), 124.7 (Ar–C), 125.6 (Ar–C), 131.5 (ddd, $^{1}J_{CF} = 258.8$, $^{2}J_{CF} = 30.8$, $^{3}J_{CF} = 6.8$ Hz, C-3), 134.5 (Py–C), 134.3 (ddd, $^{1}J_{CF} = 260.4$, $^{2}J_{CF} = 28.5$, $^{3}J_{CF} = 14.0$ Hz, C-3), 142.1 (dd, $^{1}J_{CF} = 181.6$, $^{2}J_{CF} = 16.1$ Hz, C-3), 140.2 (Ar–C), 142.2 (m, Py-C), 142.5 (ddm, $^{1}J_{CF} = 233.5$, $^{2}J_{CF} = 12.3$ Hz, C-2), 143.2 (ddm, $^{1}J_{CF} = 200.5$, $^{2}J_{CF} = 14.6$ Hz, C-2), 143.3 (Ar–C). $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta_F$ −163.1 (1F, m,F-4), −156.1 (2F, m, F-3,5), −89.9 (1F, m, F-1), −89.1 (1F, m, F-3), -88.8 (2F, F-2,6). MS (EI), *m/z* (%) = 404 ($M^+$, 100), 403 (80). Anal. Calcd for $C_{16}H_3N_2F_7O_3$: C, 47.5; H, 0.7; N; 6.9. Found: C, 47.6; H, 0.7; N, 6.8.

*N,N$^{1}$-Bis-(2,3,5,6-tetrafluoro-pyridine-4-yl) benzene-1,2-diamine **3e***

Sodium carbonate (0.25 g, 3 mmol), benzene-1,2-diamine **2c** (0.11 g, 1 mol), pentafluoropyridine (0.17 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:4) gave 1,3,4-trifluorobenzo[e]pyridino[3,2-b]1,4-dioxin **3e:** 0.13 gr, (65 %), white solid; mp:

148–149 °C. $^{1}$H NMR (500 MHz, DMSO): $\delta_H$ 6.6 (Ar–H), 7.0 (m, Ar–H), 8.7 (s, 2H, NH). $^{13}$C NMR (125 MHz, DMSO): $\delta_C$ 115.3 (Ar–C), 123.7 (s, Ar–C), 126.9 (Ar–C), 131.0 (dd, $^{1}J_{CF} = 249.0$ Hz, $^{2}J_{CF} = 32.8$ Hz, 4C, C-3,5), 137.2 (m, $^{2}J_{CF} = 11.5$ Hz, 2C, C-4), 143.6 (dd,$^{1}J_{CF} = 240.6$ Hz, $^{2}J_{CF} = 21.1$ Hz, 4C, C-2,6). $^{19}$F NMR (470 MHz, DMSO): $\delta_F$ −160.5 (m, 4F, F-3,5), −97.3 (m, 4F, F-2,6).

*4-Methyl-N,N$^{1}$-Bis-(2,3,5,6-tetrafluoro-pyridine-4-yl)benzene-1,2-diamine* ***3g***

Sodium carbonate (0.25 g, 3 mmol), 4-methylbenzene-1,2-diamine **2d** (0.12 g, 1 mol), pentafluoropyridine (0.17 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:3) gave 4-Methyl-N,N$^{1}$-Bis-(2,3,5,6-tetrafluoro-pyridine-4-yl)benzene-1,2-diamine **3g**: 0.1 gr, (48 %), white solid; mp: 156–160 °C.

$^{1}$H NMR (500 MHz, DMSO): $\delta_H$ 2.2 (s, 3H, $CH_3$), 6.5 (s, Ar–H), 6.6 (s, Ar–H), 6.7 (s, Ar–H), 8.7 (s, 2H, NH). $^{13}$C NMR (125 MHz, DMSO): $\delta_C$ 20.9 (s, $CH_3$), 115.2 (s, Ar–C), 116.5 (s, Ar–C), 121.3 (s, Ar–C), 126.6 (s,Ar–C), 127.8 (s, Ar–C), 131.3 (dd, $^{1}J_{CF} = 250.1$ Hz, $^{2}J_{CF} = 34.9$ Hz, 4C, C-3,5), 137.5 (m, $^{2}J_{CF} = 14.1$ Hz, 2C, C-4), 143.5 (dd, $^{1}J_{CF} = 199.9$ Hz, $^{2}J_{CF} = 16.1$ Hz, 4C, C-2,6). $^{19}$F NMR (470 MHz, DMSO): $\delta_F$ −161.0 (m, 2F, F-3′,5′), −160.5 (m, 2F, F-3,5), −97.4 (m, 2F, F-2′,6′), −97.3(m, 2F, F-2,6).

*2,3-difluoro-4-phenylsulfonylbenzo[5,6][1,4] dioxino[2,3-b]pyridine* ***3h***

Sodium carbonate (0.25 g, 3 mmol), pyrocatechol **2a** (0.11 g, 1 mol), 4-phenylsulfonyl tetrafluoropyridine (0.29 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:3) gave 2,3-difluoro-4-phenylsulfonylbenzo[5,6][1,4]dioxino[2,3-*b*]pyridine **3h**, 0.28 g (80 %), yellow solid; mp: 206–208 °C. $^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 6.86–8.14 (m, 9H, Ar–H) $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 116.39 (Ar–C), 125.03 (Ar–C), 125.28 (m, C-4), 125.58 (Ar–C), 125.72 (Ar–C), 128.26 (Ar–C), 128.41 (Ar–C), 129.24 (Ar–C), 129.40 (Ar–C), 129.27 (d, $^{3}J_{CF} = 9.3$ Hz, C-3*b*), 134.71 (d, $^{3}J_{CF} = 8.6$ Hz, C-2*b*), 137.74 (dd, $^{1}J_{CF} = 265.9$ Hz, $^{2}J_{CF} = 30.1$ Hz), 140.79 (Ar–C), 142.23 (Ar–C), 144.82 (dd, J = 234.6, J = 19.2 Hz) $^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) −144.03 (d, $^{3}J_{FF} = 23.6$ Hz, 1F, F-3), –91.95 (d, $^{3}J_{FF} = 23.6$ Hz, 1F, F-2). MS (EI), *m/z* (%) = 361 ($M^+$, 100), 220 (80). Anal. Calcd for $C_{17}H_9NF_2O_4S$: C, 56.5; H, 2.5; N; 3.9. Found: C, 56.4; H, 2.3; N, 3.8.

*2,3-difluoro-8-nitro-4-phenylsulfonylbenzo[5,6][1,4] dioxino[2,3-b]pyridine* ***3i*** *and 2,3-difluoro-7-nitro-4-phenylsulfonylbenzo[5,6][1,4]dioxino[2,3-b]pyridine* ***3j***

Sodium carbonate (0.25 g, 3 mmol), 3,4 dihydroxy nitrobenzene **2e** (0.15 g, 1 mol), 4-phenylsulfonyl tetrafluoropyridine (0.29 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:1) gave 2,3-difluoro-8-nitro-4-phenyl sulfonylbenzo[5,6][1,4]dioxino[2,3-*b*]pyridine **3i** and 2,3-difluoro-7-nitro-4-phenylsulfonylbenzo[5,6][1,4]dioxino[2,3-*b*]pyridine **3j**, **3i:** 0.20 g (50 %), brown solid; mp: 135–137 °C. $^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 7.21–8.52 (m, 8H, Ar–H) $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 112.90 (Ar–C), 115.32 (Ar–C), 118.11 (Ar–C), 125.94 (Ar–C), 126.23 (m, C-4), 127.93 (Ar–C), 128.20(Ar–C), 133.26 (m, C-5a), 133.85 (Ar–C), 137.00 (dd, $^{1}J_{CF} = 264.6$ Hz, $^{2}J_{CF} = 28.1$ Hz, C-3), 141.12 (Ar–C), 142.10 (dd, $^{1}J_{CF} = 230.9$, $^{2}J_{CF} = 18.0$ Hz, C-2), 144.33 (Ar–C), 146.47 (Ar–C), 154.71 (d, $^{3}J_{CF} = 9.0$ Hz, C-10a), $^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) –165.93 (d, $^{3}J_{FF} = 22.3$ Hz, 1F, F-3), –94.89 (d, $^{3}J_{FF} = 22.3$ Hz, 1F, F-2). MS (EI), *m/z* (%) = 406 ($M^+$, 100), 266 (80). Anal. Calcd for $C_{17}H_8N_2F_2O_6S$: C, 50.3; H, 2.0; N; 6.9. Found: C, 50.2; H, 2.1; N, 6.7.

**3j**: 0.10 g (25 %), orange solid; mp: 120–125 °C. $^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 6.88–9.21 (m, 8H, Ar–H) $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 111.95 (Ar–C), 116.44 (Ar–C), 118.38 (Ar–C), 126.81 (Ar–C), 126.87 (m, C-4), 128.00 (Ar–C), 128.29 (Ar–C), 133.52 (m, C-5a), 134.26 (Ar–C), 136.23 (dd, $^{1}J_{CF} = 261.0$ Hz, $^{2}J_{CF} = 27.8$ Hz, C-3), 140.77 (Ar–C), 142.13 (dd, $^{1}J_{CF} = 231.1$, $^{2}J_{CF} = 18.8$ Hz, C-2), 146.21 (Ar–C), 147.81 (Ar–C), 155.21 (d, $^{3}J_{CF} = 7.1$ Hz, C-10a). $^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) −165.64 (d, $^{3}J_{FF} = 22.4$ Hz, 1F, F-3), –95.29 (d, $^{3}J_{FF} = 22.4$ Hz, 1F, F-2). MS (EI), *m/z* (%) = 406 ($M^+$, 100), 266 (75). Anal. Calcd for $C_{17}H_8N_2F_2O_6S$: C, 50.3; H, 2.0; N; 6.9. Found: C, 50.2; H, 1.8; N, 6.8.

*4-Benzenesulfonyl-2,3-difluoro-5,10-dihydro-pyrido[2,3-b]quinoxaline* ***3n***

Sodium carbonate (0.25 g, 3 mmol), benzene-1,2-diamine **2c** (0.11 g, 1 mol), 4-phenylsulfonyl tetrafluoropyridine (0.29 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 2:3) gave 4-benzenesulfonyl-2,3-difluoro-5,10-dihydro-pyrido[2,3-b]quinoxaline **3n**, 0.13 g (35 %), orange solid; mp: 240–245 °C. $^{19}$F NMR(470 MHz, $CDCl_3$): $\delta_F$ −165.7 (1F, d, $^{3}J_{FF} = 28.2$ Hz, F-3), −112.9 (1F, d, $^{3}J_{FF} = 28.2$ Hz, F-2). MS (EI, 70 Ev): *m/z* (%) = 359.7 ($M^+$, 2.41), 238.1, 157.0, 132.0, 77.03 (100).

*4-Benzenesulfonyl-2,3-difluoro-7-methyl-5,10-dihydro-pyrido[2,3-b]quinoxaline **3o***

Sodium carbonate (0.25 g, 3 mmol), 4-methylbenzene-1,2-diamine **2d** (0.10 g, 1 mol), 4-phenylsulfonyl tetrafluoro-pyridine (0.29 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:1) gave 4-benzenesulfonyl -2,3-difluoro-7-methyl-5,10-dihydro-pyrido[2,3-b]quinoxaline **3o**, 0.17 g (46 %), orange oily. $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta_H$ 1.2 (s, 3H, $CH_3$), 7.5–8.4 (m, Ar–H). $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta_F$ −166.0 (1F, d, $^{3}J_{FF}$ = 28.2 Hz, F-3), −113.0 (1F, d, $^{3}J_{FF}$ = 28.2 Hz, F-2). MS (EI, 70 Ev): *m/z* (%) = 373.8 ($M^+$, 2.4), 263.0, 148.9 (100), 103.9, 77, 57.0.

*4-Benzenesulfonyl-2,3-difluoro- 8-methyl-benzo[5,6][1,4]dioxino[2,3-b]pyridine **3k** and 4-benzenesulfonyl-2,3-difluoro-7-methyl-benzo[5,6][1,4]dioxino[2,3-b]pyridine **3l***

Sodium carbonate (0.25 g, 3 mmol), 4-methylbenzene-1,2-diol **2f** (0.12 g, 1 mol), 4-phenylsulfonyl tetrafluoropyridine (0.29 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 2:1) gave 2,3-difluoro-8-methyl-4-phenylsulfonylbenzo[5,6][1,4]dioxino[2,3-*b*]pyridine **3k** and 2,3-difluoro-7-methyl-4-phenylsulfonylbenzo[5,6][1,4] dioxino[2,3-*b*]pyridine **3l**, **3k:** 0.09 (17 %), brown solid; mp: 264–268 °C. $^{19}$F NMR ($CDCl_3$): δ (ppm) –147.2 (d, $^{3}J_{FF}$ = 21.6 Hz, 1F, F-3), −95.2 (d, $^{3}J_{FF}$ = 21.6 Hz, 1F, F-2). **3l:** 0.32 gr (78 %), yellow solid; mp 245–249 °C. $^{1}$H NMR (500 MHz, DMSO): $\delta_H$ 2.2 (s, 3H, $CH_3$), 6.8 (m, 1H, Ar–H), 6.9 (Ar–H), 7.7 (m, 2H, Ar–H), 7.8 (m, 1H, Ar–H), 8.1 (m, 2H, Ar–H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta_C$ 20.1 (s, $CH_3$), 113.0 (s, Ar–C), 114.3 (d, Ar–C), 115.8 (s, Ar–C), 116.3 (s, Ar–C), 116.5 (s, Ar–C), 116.9 (s, Ar–C), 125.3 (m, C-3b), 127.9 (s, Ar–C), 129.4 (s, Ar–C), 131.6 (m, C-4), 132.2 (s, Ar–C) 137.7 (dd, C-3), 140.1 (m, C-2b), 141.3 (s, Ar–C),141.6 (m, Ar–C), 144.8 (m, C-2). $^{19}$F NMR (470 MHz, DMSO): $\delta_F$ −147.3 (m, 1F, F-3), −95.0 (m, 1F, F-2). MS (EI, 70 Ev): *m/z* (%) = 375.0 ($M^+$, 3.11), 318.0, 233.8, 149.0, 77.0 (100).

*4-Benzenesulfonyl-2,3-difluoro-benzo[5,6][1,4]dioxino[2,3-b]pyridine-9-ol **3m***

Sodium carbonate (0.25 g, 3 mmol), Pyrogallol **2b** (0.13 g, 1 mol), 4-phenylsulfonyl tetrafluoropyridine (0.29 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:4) gave 4-Benzenesulfonyl-2,3-difluoro-benzo[5,6][1,4]dioxino[2,3-b]pyridine-9-ol **3m**, 0.29 g (76 %), brown solid; mp: 195–201 °C. $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta_H$ 6.9–8.1 (m, 9H, Ar–H). $^{19}$F NMR (470 MHz, $CDCl_3$): $\delta_F$ −163.4 (1F, d, $^{3}J_{FF}$ = 21.0 Hz, F-3), −93.6 (1F, d, $^{3}J_{FF}$ = 21.0 Hz, F-2).

*2,3-difluoro-4-phenylsulfonyl-10H-benzo[b]pyrido[2,3-e][1,4]oxazine **3p***

Sodium carbonate (0.25 g, 3 mmol), 2-aminophenol **2 g** (0.10 g, 1 mol), 4-phenylsulfonyl tetrafluoropyridine (0.29 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:3) gave 2,3-difluoro-4-phenylsulfonyl-10*H*-benzo[*b*]pyrido[2,3-*e*][1,4]oxazine **3p**, 0.25 g (70 %), yellow solid; mp: 230–231 °C. $^{1}$H NMR ($CDCl_3$): δ (ppm) 5.82 (bs, 1H, NH), 6.82–8.36 (m, 9H, Ar–H) $^{13}$C NMR ($CDCl_3$): δ (ppm) 114.8 (Ar–C), 116.6 (Ar–C), 119.9 (m, C-4a), 123.8 (Ar–C), 125.6 (Ar–C), 126.7 (d, $^{2}J_{CF}$ = 4.5 Hz, C-4), 127.0 (Ar–C), 127.8 (Ar–C), 128.7 (Ar–C), 135.3 (Ar–C), 137.2 (dd, $^{1}J_{CF}$ = 256.2 Hz, $^{2}J_{CF}$ = 28.3 Hz, C-3), 140.2 (Ar–C), 142.4 (Ar–C), 142.21 (dd, $^{1}J_{CF}$ = 234.2, $^{2}J_{CF}$ = 17.2 Hz, C-2), 144.27 (m, C-10a), $^{19}$F NMR ($CDCl_3$): δ (ppm) −145.81 (d, $^{3}J_{FF}$ = 22.7 Hz, 1F, F-3), –103.00 (d, $^{3}J_{FF}$ = 22.7 Hz, 1F, F-2). MS (EI), *m/z* (%) = 360 ($M^+$, 100), 2219 (70). Anal. Calcd for $C_{17}H_{10}N_2F_2O_3S$: C, 56.7; H, 2.8; N; 7.8. Found: C, 56.8; H, 2.9; N, 7.8.

*3-Benzenesulfonyl-1,4-difluoro-dipyrido[1,2-a;3′,4′-d]imidazol-6-ylamine (**7a**) and 4-Benzenesulfonyl-2,3-difluoro-dipyrido[1,2-a;3′,2′-d]imidazol-9-ylamine (**7b**) and 4-Benzensulfonyl-2,3-difluoro-dipyrido[2,1-a;2′,3′-d]imidazol-6-ylamine (**7e**)*

Sodium carbonate (0.25 g, 3 mmol), 2,6-diaminopyridine **4** (0.11 g, 1 mol), 4-phenylsulfonyl tetrafluoropyridine (0.29 g, 1 mol) and acetonitrile (10 mL) gave an oily product that was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:1) gave 3-benzenesulfonyl-1,4-difluoro-dipyrido[1,2-a;3′,4′-d]imidazol-6-ylamine **7a** and 4-benzenesulfonyl-2,3-difluoro-dipyrido[1,2-a;3′,2′-d]imidazol-9-ylamine **7b** and 4-benzensulfonyl-2,3-difluoro-dipyrido[2,1-a;2′,3′-d]imidazol-6-ylamine **7e**, **7a**: 0.09 g (23 %), orange solid; mp: 274–276 °C .$^{19}$F NMR (470 MHz, DMSO): $\delta_F$ −117.4 (d, $^{5}J_{FF}$ = 28.9 Hz, 1F, F-4), −82.9 (d, $^{5}J_{FF}$ = 28.9 Hz, 1F, F-1). **7b**: 0.18 g (52 %), orange solid; mp: 238–243 °C $^{19}$ F NMR (470 MHz, $CDCl_3$): $\delta_f$ −140.3 (d, $^{3}J_{FF}$ = 23.5 Hz, 1F, F-4), −96.7 (d, $^{3}J_{FF}$ = 23.5 Hz, 1F, F-5). $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta_H$ 6.1 (m, 1H, Ar–H), 6.5 (s, 1H, Ar–H), 7.6 (m, 2H, Ar–H), 7.6 (m, 1H, Ar–H), 8.3 (m, 2H, Ar–H). MS (EI, 70 Ev): *m/z* (%) = 360.9 ($M^+$, 2.7), 359.9, 295.0, 76.9, 69.0, 57.1, 55.0 (100). **7e**: 0.05 g (14 %), brown solid; mp: 263–267 °C, $^{19}$F NMR (470 MHz, DMSO): $\delta_F$ −171.0 (d, $^{3}J_{FF}$ = 11.0 Hz, 1F, F-3), −101.7 (d, $^{3}J_{FF}$ = 11.0 Hz, 1F, F-2).

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