An expedient synthesis of novel 2-substituted thiazolo[4,5-f]isoquinolines/quinolines and benzo[1,2-d:4,3-d’]bisthiazoles and their potential as inhibitors of COX-1 and COX-2

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Abstract

An efficient, general synthesis of 2-substituted thiazolo[4,5-f]isoquinolines, thiazolo[4,5-f]quinolines and benzo[1,2-d:4,3-d’]bisthiazoles has been accomplished from 5-nitroisoquinoline/quinoline and 6-nitrobenzothiazole, respectively, and all the products have been thoroughly identified spectroscopically (IR, 1H and 13C NMR, LR/HR EI/FAB/ESI-MS). The synthesis of thiazolo[4,5-f]isoquinolines constitutes the first synthesis of this class of heteroarenes. Eighteen compounds, covering all three types, were screened for inhibition of COX-1 and COX-2, and some of them showed moderate activities.

Keywords: Thiazoloisoquinolines, thiazoloquinolines, benzobisthiazoles, COX-inhibition

Introduction

The thiazole ring is an important pharmacophore,1 and many thiazolyl compounds2 and annulated thiazoles3 are used in human therapeutics, veterinary medicine and as lead molecules for drugs.4 Additionally, thiazoles find application in other fields like polymers, liquid crystals, photoinucleases, fluorescent dyes, insecticides, antioxidants, etc.1 The reported diverse biological activities and industrial usefulness of annulated thiazoles of both natural and synthetic origins drew our attention to condensed thiazoles. Although a variety of such compounds have been synthesised,3 we became particularly interested in thiazoloisoquinolines since, of the twelve
possible isomeric structures of this class, only three isomers, viz. thiazolo[4,5-f]-, [4,5-g]- and [5,4-g]-isoquinolines have not yet been synthesised.

Amongst these three, the thiazolo[4,5-f]-isoquinolines became our target molecules simply because Taurins et al. had earlier failed to synthesise this isomer by a unified approach,\(^5\)-\(^7\) which they successfully applied in synthesising five other isomeric thiazoloisoquinolines, viz. the [4,5-c]-, [5,4-c]-, [4,5-f]-, [4,5-h]- and [5,4-h]-isomers. This route comprised the acid (EtOH-HCl)-catalysed cyclisation of ortho-amino-thiocyanato-isoquinolines. Our motivation was to overcome this failure, and we achieved our goal by developing a brief, three/four-step synthesis of 2-substituted thiazolo[4,5-f]-isoquinolines starting from commercially available 5-nitroisoquinoline. Indeed, Taurins' group had used the same starting material, viz. the derived aminoisoquinoline and attempted to thiocyanate it at C-6 by treatment with potassium thiocyanate and bromine in acetic acid in cold, which resulted in the formation of, contrary to expectation, the 8-thiocyanato isomer, which was clearly not cyclisable.\(^7\) Taurins' work is shown in Scheme 1.

![Scheme 1](image)

We have developed a general synthesis of a number of 2-alkylamino/anilino-, 2-alkythio- and 2-alkyl/phenylthiazolo[4,5-f]-isoquinolines and later extended this methodology successfully to the synthesis of similarly substituted thiazolo[4,5-f]quinolines and benzo[1,2-d:4,3-d‘]bisthiazoles. A few products of each type were screened for their anti-inflammatory potential by measuring their ability to inhibit cyclooxygenase (both COX-1 and COX-2). The details of the syntheses and the results of screening for bioactivity are presented in this communication.

### Results and Discussion

#### Synthesis of 2-alkylaminothiazolo[4,5-f]isoquinolines

The targeted thiazoloisoquinoline nucleus was prepared by cyclisation of appropriate thioureidoisoquinolines which, in turn, were prepared by the condensation of 5-aminoisoquinoline 1 with alkyl isothiocyanates. Thus, 1,\(^8\) prepared by reduction (SnCl\(_2\)·H\(_2\)O);\(^9\)
83%/NH₂NH₂H₂O/Pd-C;¹⁰ 98%) of 5-nitroisoquinoline, was condensed separately with two equivalents of methyl, ethyl, n-propyl and benzyl isothiocyanates in methanol under reflux.¹¹ The products, one in each case, were identified as the corresponding 5-(N'-alkylthioureido)isoquinolines 2a-d by analysing their IR, ¹H and ¹³C NMR, LR and HR EI-MS spectra. In these thioureas, the Ar-NH-C=S protons expectedly appeared downfield at δ 8.2-9.8 (br s) than the R-NH-C=S protons which appeared at δ 5.8-7.7, and the C=S carbons were recorded at δ 182-183.

Each of 2a-d was cyclised efficiently (92-98%) by Hugershoff reaction (bromine in acetic acid)¹² to the corresponding 2-alkylaminothiazolo[4,5-f]isoquinolines 3a-d (Scheme 2; Table 1, see next page), identified spectroscopically. The disappearance of the signals for the aryl NH proton and the thiocarbonyl carbon and the appearance, instead, of a non-protonated carbon signal at δ 169-170 (C-2) in the products supported the occurrence of cyclisation. Since the starting material was 5-aminooisoquinoline, angular cyclisation at C-6 of the isoquinoline nucleus was the only possibility, leading to the [4,5-f]-isomers. Indeed, the appearance of two ortho-coupled (J=8.5 Hz), one-proton doublets at δ 7.8-8.0 (H-9) and 7.6-7.7 (H-8) lent support to the occurrence of angular cyclisation.

Scheme 2

To the best of our knowledge, this piece of work constitutes the first ever synthesis of the thiazolo[4,5-f]isoquinoline ring. Pertinently, in this and all subsequent classes of novel compounds, the individual ¹H and ¹³C NMR assignments of one member of each type were ascertained by analysing their HMQC and HMBC correlations.¹³ These assignments have been shown in the data of the relevant compounds in the Experimental.

This protocol was next extended to the synthesis of similarly fused thiazolo[4,5-f]quinolines and benzol[1,2-d:4,3-d'] / [1,2-d:4,5-d']bisthiazoles starting from 5-aminoquinoline and 6-aminobenzothiazole, respectively. The reason for choosing these thiazoloheteroaryl nuclei was threefold. Firstly, some members of particularly the thiazolo[4,5-f]quinolines and quinolones were reported to display significant bioactivities, e.g. mutagenic, cardiotonic and dopaminergic properties.¹⁴a-f Secondly, although a few members of these two classes of condensed thiazoles had earlier been synthesised using different routes,¹⁵ a general method was still lacking. Thirdly,
the starting amines could easily be prepared by reduction of the corresponding nitro compounds which are cheap and commercially available.

Table 1. Synthesis of 2-alkylaminothiazolo[4,5-f]quinolines and -benzo[1,2-d:4,3-d′]bisthiazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine$^a$ + RNCS</th>
<th>Time (h)</th>
<th>Thioureido Derivative$^b$</th>
<th>Yield$^c$ (%)</th>
<th>Time$^d$ (h)</th>
<th>Cyclised Product</th>
<th>Yield$^e$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 + MeNCS</td>
<td>7</td>
<td>2a</td>
<td>84</td>
<td>0.5</td>
<td>3a</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>1 + EtNCS</td>
<td>10</td>
<td>2b</td>
<td>92</td>
<td>0.5</td>
<td>3b</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>1 + n-PrNCS</td>
<td>10</td>
<td>2c</td>
<td>89</td>
<td>0.5</td>
<td>3c</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>1 + BnNCS</td>
<td>5</td>
<td>2d</td>
<td>94</td>
<td>0.5</td>
<td>3d</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>4 + MeNCS</td>
<td>5</td>
<td>7a</td>
<td>90</td>
<td>3.0$^e$</td>
<td>9a</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>4 + EtNCS</td>
<td>5</td>
<td>7b</td>
<td>86</td>
<td>5.0$^e$</td>
<td>9b</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>4 + n-PrNCS</td>
<td>6</td>
<td>7c</td>
<td>80</td>
<td>4.0$^e$</td>
<td>9c</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>4 + BnNCS</td>
<td>1</td>
<td>7d</td>
<td>100</td>
<td>2.0$^e$</td>
<td>9d</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>5 + MeNCS</td>
<td>6</td>
<td>8a</td>
<td>87</td>
<td>0.25</td>
<td>10a</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>5 + EtNCS</td>
<td>5</td>
<td>8b</td>
<td>85</td>
<td>0.25</td>
<td>10b</td>
<td>83</td>
</tr>
<tr>
<td>11</td>
<td>5 + n-PrNCS</td>
<td>5</td>
<td>8c</td>
<td>85</td>
<td>0.25</td>
<td>10c</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>5 + BnNCS</td>
<td>5</td>
<td>8d</td>
<td>88</td>
<td>0.25</td>
<td>10d</td>
<td>87</td>
</tr>
</tbody>
</table>

$^a$1 mmol and RNCS (2 mmol for 1; 1.5 mmol for 4,5) were used.

$^b$1 mmol and Br$_2$-AcOH, 10-15 °C to r.t. (for 2) or Br$_2$-CHCl$_3$, 5-10 °C to r.t., 30 min, then reflux (for 7) or Br$_2$-CHCl$_3$, r.t.(for 8) were used for cyclisation to 3,9,10.

$^c$Yields refer to isolated pure products.

$^d$At room temperature.

$^e$Time of reflux.

Synthesis of 2-alkylaminothiazolo[4,5-f]quinolines and -benzo[1,2-d:4,3-d′]bisthiazoles

5-Nitroquinoline and 6-nitrobenzothiazole, procured commercially, were reduced to the corresponding amines 4$^{16}$ (85%) and 5$^{17}$ (82%) using hydrazine hydrate and palladium-on-charcoal in the first case and stannous chloride and hydrochloric acid in the second case. When 5 was attempted to be prepared from 6-nitrobenzothiazole using the hydrazine reagent, 6-nitro-2,3-dihydrobenzothiazole 6 was isolated (88%) as the only product (Scheme 3). It had previously

![Scheme 3](image_url)
been prepared from 6-nitrobenzothiazole by reduction with tetrabutylammonium borohydride in dimethylsulfoxide. The methylene protons flanked between NH and S appeared unusually downfield at δ 6.83 (s).

Each of 4 and 5 was treated, as in the isoquinoline series, with methyl, ethyl, n-propyl and benzyl isothiocyanates separately in methanol under reflux to form the respective 5-(N'-alkylthiourea)quinolines 7a-d and 6-(N'-alkylthiourea)benzothiazoles 8a-d as the sole products. In these thioureas too, the Ar-NH-C=S protons appeared downfield (δ 9.6-9.8, br s) than the R-NH-C=S protons (δ 7.5-7.8, br s for 7a-c and 8a-c; δ 8.2, br s for 7d, 8d) whereas the C=S carbons appeared at the same range of ca. δ 181-183 as in the case of 2a-d.

The thioureas 7a-d were then cyclised by bromine in chloroform to the 2-alkylamino derivatives of thiazolo[4,5-f]quinolines 9a-d which displayed similar spectroscopic behaviour as in the case of cyclisation of 2 to 3. The angular modes of cyclisation were similarly ascertained from the appearance of two ortho-coupled (J=8.5 / 9 Hz), one-proton doublets at ca. δ 7.65 (H-8) and 8.0 (H-9) in 9a-d.

The cyclisation of 8a-d by bromine in chloroform furnished 2-alkaminobenzo[1,2-d:4,3-d′]bisthiazoles 10a-d, the products of angular cyclisation, which was evident from their conspicuous ²H NMR data (δ 7.5-7.7 and 7.9-8.0, d, 1H each, J=8.5 / 9 Hz; H-4 and H-5, respectively). Linear cyclisations would have resulted in benzo[1,2-d:4,5-d′]bisthiazoles 11, in which H-4 and H-8, the corresponding benzenoid protons would have appeared as one-proton, singlet each. These syntheses and the reactions details are depicted in Scheme 4 and Table 1.
Synthesis of 2-alkylthiothiazolo[4,5-f]isoquinolines, -thiazolo[4,5-f]quinolines and -benzo-[1,2-d:4,3-d']bisthiazoles

We next adopted a related approach for achieving a general synthesis of 2-alkylthio derivatives of the three classes of heteroarenes. Each of 1, 4 and 5 was first converted to its methyl and ethyl dithiocarbamates 12-14a,b by successive treatments with carbon disulfide-pyridine and methyl/ethyl iodide.\(^{19}\) Some of their significant \(^1\)H and \(^{13}\)C NMR spectroscopic data are discussed later. These were then cyclised by bromine in acetonitrile or bromine in chloroform at room temperature to the respective 2-alkylthio derivatives of thiazolo[4,5-f]isoquinolines 15a,b, thiazolo[4,5-f]quinolines 16a,b and benzo[1,2-d:4,3-d']bisthiazoles 17a,b, i.e. the angularly cyclised products in all the cases (Scheme 5; Table 2, see next page).

Scheme 5

The mode of cyclisation in each case was discernible from a comparison of the NMR data of the dithiocarbamates and the products. Thus, in all the three series, (i) the ArNHCS signals observed at \(\delta\) 11.8-11.9 for 12-14a,b disappeared, (ii) two one-proton doublets with ortho-couplings appeared at around \(\delta\) 8.0 corresponding to H-8 and H-9 of the isoquinoline/quinoline series and H-4 and H-5 of the benzothiazole series, and (iii) the thiocarbonyl carbon signal at ca. \(\delta\) 199-202, observed for 12-14a,b disappeared and a non-protonated carbon (C-2) appeared at \(\delta\) 167-169.

Synthesis of 2-anilinothiazolo[4,5-f]isoquinolines, -thiazolo[4,5-f]quinolines and -benzo-[1,2-d:4,3-d']bisthiazoles

We further developed a general synthesis of the three types of 2-anilinothiazoloheteroarenes by cyclisation of the respective \(N^r\)-phenylthioureides 2e, 7e and 8e which were attempted to be prepared from 1, 4 and 5 by separate condensations with phenyl isothiocyanate in methanol under reflux. But, different results were obtained for 1 and 5 on one hand and for 4 on the other...
Table 2. Synthesis of 2-alkylthiothiazolo/heteroarenes 15, 16, 17 from 1, 4, 5 via the N-(heteroaryl)dithiocarbamates 12, 13, 14

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine&lt;sup&gt;a&lt;/sup&gt; + RI</th>
<th>Time (h)</th>
<th>Dithiocarbamate&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;c&lt;/sup&gt; (%)</th>
<th>Time (h)</th>
<th>Cyclised Product</th>
<th>Yield&lt;sup&gt;c&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 + MeI</td>
<td>overnight</td>
<td>12a</td>
<td>63</td>
<td>0.5</td>
<td>15a</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>1 + EtI</td>
<td>overnight</td>
<td>12b</td>
<td>62</td>
<td>1.0</td>
<td>15b</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>4 + MeI</td>
<td>7</td>
<td>13a</td>
<td>70</td>
<td>2.0</td>
<td>16a</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>4 + EtI</td>
<td>8</td>
<td>13b</td>
<td>75</td>
<td>2.0</td>
<td>16b</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>5 + MeI</td>
<td>7</td>
<td>14a</td>
<td>72</td>
<td>0.25</td>
<td>17a</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>5 + EtI</td>
<td>8</td>
<td>14b</td>
<td>75</td>
<td>0.25</td>
<td>17b</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup>1 mmol, CS<sub>2</sub> (3 mmol)/Py (for 1,5) or Py-Et<sub>3</sub>N (for 4), RI (3 mmol) were used.
<sup>b</sup>1 mmol and Br<sub>2</sub> (1.5/3 mmol)-CH<sub>3</sub>CN, 10-15 °C to r.t. (for 12 / 13) or Br<sub>2</sub> (1.5 mmol)-CHCl<sub>3</sub>, r.t. (for 14) were used for cyclisation.
<sup>c</sup>Yields refer to isolated pure products.

hand. For 1 and 5, a number of products were formed and the reactions never went to completion even after a prolonged period. We, therefore, resorted to a different protocol.<sup>20</sup> Thus, 2e (expected from 1) and 8e (expected from 5) were prepared in excellent yields by a reasonably fast (1/2 h) reaction of aniline with ethyl N-(5-isoquinolinyl/6-benzothiazolyl)dithiocarbamates 12b / 14b (Scheme 6).

![Scheme 6](image-url)
From 4 were obtained two different, somewhat unexpected products, viz. the known \(N, N'-\text{diphenylthiourea} \ 18^{21} \) (38%) and the novel methyl \(N-(5\text{-quinolinyl})\text{thiocarbamate} \ 19 \) (46%) were formed. The EI-MS of 19 expectedly recorded the base peak at \(m/z\ 186\), i.e. at \([M-\text{MeOH}]^+\). We believe, 18 and 19 were formed from 5-(\(N'-\text{phenylthioureido}\))quinoline 7e, the expected initial condensation product, by thermal cleavage to aniline and 5-isothiocyanatoquinoline 20. While the condensation of aniline with phenyl isothiocyanate led to the formation of 18, the condensation of 20 with methanol resulted in the formation of 19 (Scheme 7).

\[
\begin{align*}
\text{Scheme 7}
\end{align*}
\]

The desired intermediate 7e was, therefore, prepared in the same way as 8e was prepared from 2e. Thus, aniline was condensed efficiently with ethyl \(N-(5\text{-quinolinyl})\text{dithiocarbamate} \ 13b \) in methanol under reflux to furnish 7e as the only product. Each of the thioureides 2e, 7e and 8e was then cyclised by bromine in acetic acid (for 2e) or in chloroform (for 7e and 8e), which furnished the 2- anilino derivatives of thiazolo[4,5-f]isoquinoline 3e, thiazolo[4,5-f]quinoline 9e and benzo[1,2-d:4,3-d']bisthiazole 10e, respectively.

Angular cyclisation was observed in all the three compounds. Thus, H-8 and H-9 of the isoquinoline 3e and the quinoline 9e appeared downfield (\(\delta\ 7.8\) and 8.1) whereas C-2 appeared upfield (\(\delta\ 164\)) than those in the 2-alkylamino derivatives 3a-d and 9a-d. However, in the case of the benzobisthiazole 10e, no such distinctive feature was observed. The preparation of 3e, 9e and 10e from 12-14b via 2e, 7e and 8e are shown in Scheme 6 (see previous page) and the results in Table 3 below.

**Synthesis of 2-alkyl/phenylthiazolo[4,5-f]isoquinolines, -thiazolo[4,5-f]quinolines and -benzo [1,2-d:4,3-d']bisthiazoles**

Employing a slightly different approach, the 2-alkyl/phenyl derivatives of these thiazolo-heteroarenes were then prepared by the cyclisation of \(N-(5\text{-isoquinolinyl/quinolinyl})\) and \(N-(6-
benzothiazolyl)thioamides which, in turn, were prepared by thionation of the corresponding amides.

**Table 3.** Synthesis of 2-anilinothiazoloheteroarenes 3e, 9e, 10e from N-(heteroaryl) dithiocarbamates 12b,13b,14b via (N'-phenylthioureido)heteroarenes 2e, 7e, 8e

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ethyl dithiocarbamate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time&lt;sup&gt;b&lt;/sup&gt; (h)</th>
<th>(N'-Phenylthioureido)-heteroarenes&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;c&lt;/sup&gt; (%)</th>
<th>Time&lt;sup&gt;d&lt;/sup&gt; (h)</th>
<th>Cyclised product</th>
<th>Yield&lt;sup&gt;e&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12b</td>
<td>1</td>
<td>2e</td>
<td>95</td>
<td>0.5</td>
<td>3e</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>13b</td>
<td>1</td>
<td>7e</td>
<td>85</td>
<td>3.0&lt;sup&gt;e&lt;/sup&gt;</td>
<td>9e</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>14b</td>
<td>2</td>
<td>8e</td>
<td>92</td>
<td>0.25</td>
<td>10e</td>
<td>90</td>
</tr>
</tbody>
</table>

<sup>a</sup>1 mmol and PhNH<sub>2</sub> (1.5 mmol) were refluxed in CH<sub>2</sub>Cl<sub>2</sub> (for 12b) or in MeOH (for 13b, 14b).

<sup>b</sup>1 mmol and Br<sub>2</sub>-AcOH, 10-15 °C to r.t. (for 2e) or Br<sub>2</sub>-CHCl<sub>3</sub>, 5-10 °C to r.t., 30 min, then reflux (for 7e) or Br<sub>2</sub>-CHCl<sub>3</sub>, r.t. (for 8e) were used for cyclisation.

<sup>c</sup>Yields refer to isolated pure products.

<sup>d</sup>At room temperature.

<sup>e</sup>Time of reflux.

Thus, each of the three amines 1, 4 and 5 was separately acylated with all or some of acetic, propionic and <i>i</i>-butyric/n-butyric anhydrides (and pyridine) and benzoylated using benzoyl chloride-triethylamine to efficiently furnish the N-(5-isquinolinyl/quinolinyl)amides 21a-d/22a-d and the N-(6-benzothiazolyl)amides 23a-c. These were then smoothly thionated to the corresponding thioamides 24a-d, 25a-d and 26a-c by refluxing with Lawesson’s reagent in benzene.<sup>22</sup>

Strangely, when 24a was attempted to be cyclised by bromine in acetic acid or in acetonitrile, dethionation, regenerating 21a, was the only outcome. The desired cyclisation of 24a to 2-methylthiazolo[4,5-]<i>f</i>isooquinoline 27a was, therefore, efficiently accomplished by Jacobson reaction<sup>23</sup> by treatment with aqueous alkaline potassium ferricyanide at room temperature.

Because of this success, each of 24b-d, 25a-d and 26a-c was similarly cyclised to the corresponding 2-alkyl/ phenyl derivatives of thiazolo[4,5-]<i>f</i>isooquinolines 27b-d, thiazolo[4,5-]<i>f</i>-quinolines 28a-d and benzo[1,2-d:4,3-d’]bisthiazoles 29a-c in excellent yields (Scheme 8 below; Table 4).

In this series too, the angular mode of cyclisation in each case was evident from a similar appearance of two ortho-coupled, one-proton doublets at around δ 8.0, corresponding to H-8 and H-9 for 27 and 28 and H-4 and H-5 for 29.
Scheme 8

Table 4. Synthesis of 2-alkyl/phenylthiazoloheteroarenes 27, 28, 29 from heteroaryl-amides 21, 22, 23 via heteroarylthioamides 24, 25, 26

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine a</th>
<th>Amide b</th>
<th>Yield c (%)</th>
<th>Time (h)</th>
<th>Thioamide d</th>
<th>Yield c (%)</th>
<th>Time (h)</th>
<th>Cyclised Product</th>
<th>Yield c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 + Ac₂O</td>
<td>21a</td>
<td>99</td>
<td>1.0</td>
<td>24a</td>
<td>98</td>
<td>0.25</td>
<td>27a</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>1 + (EtCO)₂O</td>
<td>21b</td>
<td>95</td>
<td>0.5</td>
<td>24b</td>
<td>91</td>
<td>0.5</td>
<td>27b</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>1 + (i-PrCO)₂O</td>
<td>21c</td>
<td>93</td>
<td>1.0</td>
<td>24c</td>
<td>98</td>
<td>0.5</td>
<td>27c</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>1 + PhCOCl</td>
<td>21d</td>
<td>90</td>
<td>1.0</td>
<td>24d</td>
<td>96</td>
<td>0.25</td>
<td>27d</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>4 + Ac₂O</td>
<td>22a</td>
<td>86</td>
<td>1.5</td>
<td>25a</td>
<td>80</td>
<td>1.0</td>
<td>28a</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>4 + (EtCO)₂O</td>
<td>22b</td>
<td>94</td>
<td>1.0</td>
<td>25b</td>
<td>83</td>
<td>1.0</td>
<td>28b</td>
<td>87</td>
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<tr>
<td>7</td>
<td>4 + (n-PrCO)₂O</td>
<td>22c</td>
<td>90</td>
<td>1.0</td>
<td>25c</td>
<td>88</td>
<td>1.5</td>
<td>28c</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>4 + PhCOCl</td>
<td>22d</td>
<td>100</td>
<td>1.5</td>
<td>25d</td>
<td>93</td>
<td>1.5</td>
<td>28d</td>
<td>89</td>
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<tr>
<td>9</td>
<td>5 + Ac₂O</td>
<td>23a</td>
<td>100</td>
<td>5.0</td>
<td>26a</td>
<td>70</td>
<td>5 min</td>
<td>29a</td>
<td>93</td>
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<tr>
<td>10</td>
<td>5 + (EtCO)₂O</td>
<td>23b</td>
<td>100</td>
<td>5.0</td>
<td>26b</td>
<td>71</td>
<td>5 min</td>
<td>29b</td>
<td>95</td>
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<td>11</td>
<td>5 + PhCOCl</td>
<td>23c</td>
<td>100</td>
<td>6.0</td>
<td>26c</td>
<td>74</td>
<td>5 min</td>
<td>29c</td>
<td>93</td>
</tr>
</tbody>
</table>

a 1 mmol and (RCO)₂O (1.5 mmol) (kept overnight) or PhCOCl (2 mmol for 1; 1.2 mmol for 4, 5) (kept for 2/2/1 h for 1/4/5) were used.
b 1 mmol and Lawesson’s reagent (1.2 mmol) were used.
c Yields refer to isolated pure products.
d 1 mmol, K₃[Fe(CN)₆] (6.5 mmol) and 4 M NaOH were used for cyclisation.
Synthesis of 2-aminobenzo[1,2-d:4,3-d′]bisthiazole

The 2-amino derivatives of all the three series were the next target molecules since the amino group can very well be converted to a number of other functionalities. These compounds had earlier been either prepared or attempted to be prepared from the corresponding heteroaryl amines. Thus, 2-aminothiazolo[4,5-j]quinoline 30 had previously been synthesised from 5-aminoquinoline 4 by treatment with potassium thiocyanate and bromine in glacial acetic acid.\textsuperscript{15b,d} But, as shown earlier (Scheme 1), when 5-aminoisoquinoline 1 was treated in a similar manner, thiocyanation took place at C-8 of 1, and 5-amino-8-thiocyanatoisoquinoline was the sole product.\textsuperscript{7}

2-Aminobenzo[1,2-d:4,3-d′]bisthiazole 31 had previously been prepared from 5 in two steps - treatment with ammonium thiocyanate, acetic acid and \textit{N},\textit{N}′-dichloroureia, followed by hydrochloric acid-catalysed cyclisation of the resulting 6-amino-7-thiocyanatobenzothiazole.\textsuperscript{15i} Clearly, there was room for improvement in the synthesis of 31 from 5, and we did it efficiently in one step by treatment with potassium thiocyanate and bromine in glacial acetic acid.

We have recorded for the first time the spectroscopic data of 31. Here too, angular cyclisation was indicated by two signals at \(\delta 7.52\) and 7.91 (d, \(J=8.5\) Hz, 1H each), corresponding to H-4 and H-5, respectively of the 31. Syntheses of 30 and 31 are depicted in Scheme 9.

\[\text{Scheme 9}\]

**Biological results. In vitro experiments. COX-1 inhibition**

In view of the reported anti-inflammatory activities of substituted isoquinolines,\textsuperscript{24a} quinolines,\textsuperscript{24b} condensed quinolines\textsuperscript{24c,d} and benzothiazoles,\textsuperscript{24e} we checked the anti-inflammatory potential of
the synthesised products by measuring their ability to inhibit cyclooxygenase (COX). Accordingly, eighteen assorted products, viz. the thiazoloisoquinolines 3a,d,e, 15a, 27a,d, the thiazoloquinolines 9a,d, 16a, 28a,d and the benzobisthiazoles 10a,d,e, 17a, 29a,d, 30 were screened for inhibition of both COX-1 and COX-2 using naproxen\textsuperscript{25} as the standard following a recent protocol.\textsuperscript{26} These compounds were added to the assay mixture at 200 µM using arachidonic acid at a concentration of 0.1 µM. The results are presented in Table 5.

Table 5. Results of screening of thiazoloisoquinolines, thiazoloquinolines and benzobisthiazoles for inhibition of COX–1 and COX–2

<table>
<thead>
<tr>
<th>Entry\textsuperscript{a}</th>
<th>Product: R=</th>
<th>Inhibition (%)\textsuperscript{b} of COX-1</th>
<th>Prediction (Pa)\textsuperscript{c} of biological activity</th>
<th>ClogP\textsuperscript{26}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a: MeNH</td>
<td>75</td>
<td>0.677</td>
<td>1.29</td>
</tr>
<tr>
<td>2</td>
<td>3d: PhCH2NH</td>
<td>8</td>
<td>0.098</td>
<td>3.06</td>
</tr>
<tr>
<td>3</td>
<td>3e: PhNH</td>
<td>71</td>
<td>0.456</td>
<td>4.43</td>
</tr>
<tr>
<td>4</td>
<td>15a: MeS</td>
<td>67</td>
<td>0.627</td>
<td>3.03</td>
</tr>
<tr>
<td>5</td>
<td>27a: Me</td>
<td>36</td>
<td>0.478</td>
<td>2.37</td>
</tr>
<tr>
<td>6</td>
<td>27d: Ph</td>
<td>37</td>
<td>0.588</td>
<td>3.97</td>
</tr>
<tr>
<td>7</td>
<td>9a: MeNH</td>
<td>66</td>
<td>0.652</td>
<td>2.66</td>
</tr>
<tr>
<td>8</td>
<td>9d: PhCH2NH</td>
<td>0</td>
<td>0.124</td>
<td>4.11</td>
</tr>
<tr>
<td>9</td>
<td>16a: MeS</td>
<td>45</td>
<td>0.613</td>
<td>3.24</td>
</tr>
<tr>
<td>10</td>
<td>28a: Me</td>
<td>49</td>
<td>0.452</td>
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<tr>
<td>11</td>
<td>28d: Ph</td>
<td>57</td>
<td>0.650</td>
<td>4.18</td>
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<tr>
<td>12</td>
<td>10a: MeNH</td>
<td>62</td>
<td>0.241</td>
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<tr>
<td>13</td>
<td>10d: PhCH2NH</td>
<td>23</td>
<td>0.344</td>
<td>4.14</td>
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<tr>
<td>14</td>
<td>10e: PhNH</td>
<td>40</td>
<td>0.213</td>
<td>4.67</td>
</tr>
<tr>
<td>15</td>
<td>17a: MeS</td>
<td>39</td>
<td>0.387</td>
<td>3.26</td>
</tr>
<tr>
<td>16</td>
<td>29a: Me</td>
<td>28</td>
<td>0.369</td>
<td>2.60</td>
</tr>
<tr>
<td>17</td>
<td>29d: Ph</td>
<td>29</td>
<td>0.355</td>
<td>4.20</td>
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<tr>
<td>18</td>
<td>30: NH2</td>
<td>14</td>
<td>0.196</td>
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<tr>
<td>19</td>
<td>Naproxen</td>
<td>86</td>
<td>–</td>
<td>–</td>
</tr>
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</table>

\textsuperscript{a}Entries 1-6, 7-11 and 12-18 correspond to 2-substituted thiazoloisoquinolines, thiazoloquinolines and benzobisthiazoles, respectively.

\textsuperscript{b}Compound concentration was 200 µM in each case.

\textsuperscript{c}Pa values were determined using PASS software.

From the data presented in Table 5, the following observations could be made. With the exception of compound 27d (entry 6), all compounds inhibit COX-1 in the range of 8% 3d to 75% 3a. COX-1 inhibitory activity was found to be strongly dependent on the nature of the rings and on the substituents at C-2. As regards the first point, thiazoloisoquinolines are more active
than the thiazoloquinolines and the benzobisthiazoles. As regards the second point, a high level of activity (62-75%) was observed for the 2-methylamino compounds in all the three series.

In the case of thiazoloisoquinolines in particular, the presence of methylamino, anilino and methylthio groups were found to be favourable for COX-1 inhibitory activity, whereas methyl and phenyl groups led to decrease in activity. The lowest inhibitory activity was observed for the benzylamino derivative 3d. In the case of the thiazoloquinolines, the most active compounds are the 2-methylamino 9a and the 2-phenyl 28d derivatives while the benzylamino derivative 9d was completely void of COX-1 inhibition. In the benzobisthiazole series, the methylamino derivative 10a was most active, the anilino 10e and the methylthio 17a derivatives were less active and the rest displayed poor activity.

COX-2 Inhibition
All the compounds showed no or low (0-36%) inhibition of COX-2 when they were added to the reaction mixture at 200 µM using an arachidonic acid (substrate) concentration of 0.1 µM.

2-Methylthiobenzobisthiazole 17a exhibited the best COX-2 inhibition (36%), followed by the 2-amino derivative 30. Although the 2-substituted benzobisthiazoles possessed the lowest COX-1 inhibitory activity, they displayed better COX-2 inhibition than shown by the two other groups. All our synthesised compounds are less potent COX-1 and COX-2 inhibitors than naproxen.

No correlation could be found between the activity of the compounds and their lipophilicity, which is reflected in their ClogP values. The computer predictions of biological activity spectra of the compounds were ascertained using PASS software.

Conclusions
We have accomplished the first general synthesis of 2-alkylamino/anilino-, 2-alkylthio- and 2-alkyl/phenylthiazolo[4,5-f]isoquinolines in three/four steps from a commercially available starting material and extended the protocols to the synthesis of novel, similarly substituted thiazolo[4,5-f]quinolines and benzo[1,2-d:4,3-d′]bisthiazoles. All compounds, mostly new, were unambiguously identified by thorough spectroscopic analyses. In all the cases, angular cyclisation did take place, which was concluded from ¹H NMR data. Moreover, this study also contains the definitive ¹H and ¹³C NMR assignments of at least one member of each class. Some of the final products, viz. 3a,e, 9a, 10a and 15a showed cognizable inhibition of COX-1 while only 17a and 30 displayed noticeable inhibition of COX-2.

Since the steps throughout are brief and simple, the starting materials and the reagents are cheap and the yields of the products are very good to excellent, the present piece of work is significant and holds the promise of being useful in designing the synthesis of similarly substituted other classes of thiazoloheteroarenes.
Experimental Section

General. The nitro compounds and all reagents were procured commercially. All solvents were dried and purified as per literature. Melting points were determined in open capillaries on a Toshniwal apparatus and are uncorrected. FT-IR spectra were recorded on KBr pellets (unless stated otherwise) in a Perkin-Elmer RX 1 FT-IR spectrophotometer or in nujol mull in a Nicolet Impact 410 spectrophotometer. NMR (1H, 500 MHz; 13C, 125 MHz; DEPT 135, HMQC and HMBC) spectra were recorded in a Bruker DRX-500 spectrometer. The LR EI/FAB-MS spectra were recorded on a JEOL JMS-AX505HA mass spectrometer and the HR EI/FAB-MS and ESI-MS spectra on a JEOL JMS-700 Mstation and a Q-TOF MICRO YA263 mass spectrometer, respectively. GC EI-MS were recorded in a Thermo Scientific Trace GC Ultra - POLARIS Q 230LT mass spectrometer. Elemental analyses were carried out in a Perkin Elmer 2400 Series II C, H, N Analyser. TLCs were carried out on silica gel G (Merck, India) plates and column chromatographies (CCs) on silica gel (60–120 mesh, Qualigens, India). Organic layers were dried using anhydrous Na2SO4. PE, DCM and EA stand for petroleum ether, bp. 60–80 °C, dichloromethane and ethyl acetate, respectively.

Typical procedures for the preparation of amines (1, 4, 5)

Reduction by stannous chloride. A solution of 5-nitroisoquinoline (0.35 g, 2 mmol) in EtOH (20 mL) containing SnCl2.2H2O (2.26 g, 10 mmol) was refluxed on steam-bath for 30 min. A usual work-up,9 followed by crystallisation of the product from PE/DCM furnished pure 1. Yield 0.24 g (83%); orange-yellow needles; mp 127–128 °C (lit.8a mp 128–129 °C). Its 1H and 13C NMR data agreed with literature values8b,c with one exception - δC=4a and δC=8a should be (HMQC, HMBC) 125.6 and 130.1, respectively as against δ 129.49 and 125.09, assigned earlier.8c A solution of 6-nitrobenzothiazole (0.18 g, 1 mmol) in MeOH-HCl (1:1, 10 mL) containing SnCl2.2H2O (0.9 g, 5 mmol) was refluxed for 15 min. It was worked up usually17 and the product was crystallised from PE/DCM to furnish pure 5. Yield 0.123 g (82%); straw yellow needles; mp 82–84 °C (lit.17 mp 84–85 °C); IR (nujol) 3363, 3317, 1653, 1600, 1553, 1295, 1129, 1049, 917, 837, 718 cm⁻¹. 1H NMR (CDCl3) δ 3.87 (s, 2H), 6.85 (dd, J1=9 Hz, J2=2 Hz, 1H), 7.14 (d, J=2 Hz, 1H), 7.88 (d, J=9 Hz, 1H), 8.68 (s, 1H). 13C NMR δ 106.0, 116.1, 124.3, 150.1 (all Ar-CH), 135.9, 145.2, 147.2 (all Ar-C).

Reduction by hydrazine hydrate and palladium-on-charcoal. A solution of 5-nitroisoquinoline/quinoline (0.35 g, 2 mmol) in EtOH (30 mL) containing NH2NH2H2O (0.6 mL, 2 mmol) and 10% Pd/C (0.035 g, 10% w/w) was refluxed on steam-bath for 30 min. The solution was filtered hot through a bed of Celite®, washed with hot EtOH (2×10 mL), the solvent distilled off from the pooled filtrates and the resulting residue crystallised from PE/DCM to furnish pure 1 and 4.

5-Aminoisoquinoline (1). Yield 0.282 g (98%).

5-Aminoquinoline (4). Yield 0.245 g (85%); straw-yellow needles; mp 108–110 °C (lit.16 mp 110 °C). IR, 1H and 13C NMR data agreed to those reported in the literature.8b,c,16
Attempted preparation of (5) using hydrazine hydrate. A solution of 6-nitrobenzothiazole (1 mmol) in EtOH (15 mL) containing NH₂NH₂.H₂O (1 mmol) and 10% Pd/C (0.018 g) was refluxed on steam-bath for 1 h. A similar work-up as before led to a residue which was crystallised from PE/EA to furnish 6-nitro-2,3-dihydrobenzothiazole 6. Yield 0.16 g (88%); deep yellow needles; mp 162–164°C (lit. 18 mp 163–164°C); IR (nujol) 3376, 1626, 1586, 1566, 1314, 1261, 1129, 923, 824, 751 cm⁻¹. ¹H NMR (DMSO-d₆) δ 4.30 (s, 1H), 6.71 (d, J = 9 Hz, 1H), 6.83 (s, 2H), 7.89 (dd, J₁ = 9 Hz, J₂ = 2.5 Hz, 1H), 8.03 (d, J = 2.5 Hz, 1H). ¹³C NMR δ 38.3 (CH₂), 113.9, 127.0, 132.6 (all Ar-CH), 114.2, 136.6, 156.3 (all Ar-C).

General procedure for the synthesis of 5-(N’-alkylthioureido)isoquinolines (2a-d), -quinolines (7a-d), and 6-(N’-alkylthioureido)benzothiazoles (8a-d)

A solution of 1/ 4/ 5 (1 mmol) in MeOH (10–15 mL) containing Me/Ethn-Pr/Bn-NCS (2 mmol each for 1 and 1.5 mmol each for 4 and 5) was refluxed until (see Table 1) the amine was fully consumed (TLC). The solution was concentrated on steam-bath, allowed to cool down to r.t. and the resulting crystals filtered under suction and recrystallised to furnish the pure thioureido derivative 2, 7, 8a-d.

5-(N’-Methylthioureido)isoquinoline (2a). Yield 0.182 g (84%); light brown granules (from PE/DCM); mp 176–177 °C; IR 3244, 3164, 1587, 1544, 1523, 1384, 1372, 1322, 1267, 1227, 1061, 816, 764 cm⁻¹. ¹H NMR (DMSO-d₆) δ 2.91 (s, 3H, NHCH₃), 7.63 (br, 1H, R-NH), 7.68 (t, J = 7.5 Hz, 1H, H-7), 7.70 (d, J = 5.5 Hz, 1H, H-4), 7.75 (d, J = 8 Hz, 1H, H-6), 8.03 (d, J = 8.5 Hz, 1H, H-8), 8.52 (d, J = 6 Hz, 1H, H-3), 9.34 (s, 1H, H-1), 9.72 (br s, 1H, Ar-NH). ¹³C NMR δ 32.3 (NHCH₃), 116.7 (CH-4), 126.9 (CH-8), 128.2 (CH-7), 129.8 (CH-6), 129.9 (C-8a), 133.2 (C-4a), 134.7 (C-5), 143.7 (CH-3), 153.3 (CH-1), 183.5 (C=S). LR EI-MS m/z (%) 217 (M⁺), 186, 184, 183, 161, 144 (100), 128, 117, 101, 74; HR EI-MS m/z calcd for C₁₁H₁₁N₃S (M⁺): 217.0674; found: 217.0675.

5-(N’-Methylthioureido)quinoline (7a). Yield 0.195 g (90%); pale cream coloured shining globules (from MeOH); mp 228–230 °C (dec.); IR (nujol) 3147, 1613, 1593, 1553, 1516, 1496, 1313, 1266, 1241, 1082, 1056, 890, 799, 731 cm⁻¹. ¹H NMR (DMSO-d₆) δ 2.88 (s, 3H, NHCH₃), 7.51 (d, J = 7 Hz, 1H, H-6), 7.53-7.59 (m, 1H, R-NH), 7.56 (dd, J₁ = 8.5 Hz, J₂ = 4 Hz, 1H, H-3), 7.75 (t, J = 8 Hz, 1H, H-7), 7.94 (d, J = 8.5 Hz, 1H, H-8), 8.23 (d, J = 8.5 Hz, 1H, H-4), 8.90 (ill-splited, 1H, H-2), 9.72 (br s, 1H, Ar-NH). ¹³C NMR δ 32.4 (NHCH₃), 122.2 (CH-3), 126.13 (CH-6), 126.15 (C-4a), 128.5 (CH-8), 130.0 (CH-7), 132.4 (CH-4), 135.6 (C-5), 149.3 (C-8a), 151.4 (CH-2), 183.5 (C=S). LR EI-MS m/z (%) 217 (M⁺), 184, 183, 182, 161, 155, 144 (100), 142, 128, 117, 116, 101, 74; HR EI-MS m/z Calcd for C₁₁H₁₁N₃S: 217.0674; found: 217.0677.

6-(N’-Methylthioureido)benzothiazole (8a). Yield 0.194 g (87%); yellow needles (from MeOH); mp 164–166 °C; IR (nujol) 3238, 3182, 1558, 1518, 1262, 1049, 830, 724 cm⁻¹. ¹H NMR (DMSO-d₆) δ 2.92 (d, J = 4 Hz, 3H, NHCH₃), 7.44 (d, J = 8 Hz, 1H), 7.76 (br s, 1H), 8.0 (d, J = 8.5 Hz, 1H), 8.20 (d, J = 2 Hz, 1H), 9.29 (s, 1H), 9.73 (br s, 1H). ¹³C NMR δ 32.1 (NHCH₃), 117.4, 123.6, 123.7, 156.2 (all Ar-CH), 134.8, 137.6, 150.9, 182.2 (all Ar-C); LR EI-
General procedure for the synthesis of 2-alkylaminothiazolo[4,5-f]isoquinolines (3a-d), -thiazolo [4,5-f]quinolines (9a-d), and -benzo[1,2-d:4,3-d']bisthiazoles (10a-d)

A solution of Br₂ (1.5 mmol, ca. 0.2 mL) in AcOH (0.8 mL) for 2a-d or in CHCl₃ (2 mL) for 7a-d/8a-d was separately added dropwise with stirring to a solution (precooled to 10–15 °C for 2, 5–10 °C for 7 and at r.t. for 8) of 2 (1 mmol in CH₂CN, 20–30 mL)/7/8 (1 mmol each in CHCl₃, 15–20 mL). The solution was then allowed to come up to r.t., and the stirring was continued at r.t. for 2, 8 or the solution was refluxed for 7 until (see Table 1) it was fully consumed.

In each case, excess bromine was destroyed by 10% aq. Na₂S₂O₃. For 2, the acidic solution was made alkaline with saturated aq. NaHCO₃ and the precipitated product was crystallised to furnish pure 3a-d.

For 7 and 8, the biphasic solution was extracted with CHCl₃ (3×20 mL) and the residue obtained from the CHCl₃ extract was purified either by CC, followed by crystallisation (for 7), or directly by crystallisation (for 8) to furnish 9a-d and 10a-d, respectively.

2-Methylaminothiazolo[4,5-f]isoquinoline (3a). Yield 0.212 g (98%); light brown flakes (from EA/MeOH); mp 240 °C (dec.); IR 3213, 1619, 1592, 1542, 1489, 1403, 1374, 1252, 1206, 1032, 904, 831, 801 cm⁻¹. ¹H NMR (DMSO-d₆) δ 3.03 (d, J = 4.5 Hz, 3H, NHCH₃), 7.71 and 7.98 (d, J = 8.5 Hz, 1H each, H-8 and H-9, respectively), 8.14 (d, J = 5.5 Hz, 1H, H-4), 8.24 (q, J = 4.5 Hz, 1H, Ar-NH), 8.50 (d, J = 5.5 Hz, 1H, H-5), 9.26 (s, 1H, H-7). ¹³C NMR δ 31.6 (NHCH₃), 117.1 (CH-4), 120.5 (CH-8), 121.7 (CH-9), 127.8 (C-7a), 128.6 (C-3b), 129.9 (C-9a), 143.6 (CH-5), 147.5 (C-3a), 152.8 (CH-7), 169.6 (C-2). LR EI-MS m/z (%) 215 (M⁺, 100), 214, 187, 186, 173; HR ESI-MS m/z calcd for C₁₁H₁₀N₃S (M+H)⁺: 216.0590; found: 216.0595.

2-Methylaminothiazolo[4,5-f]quinoline (9a). Eluted with PE/EA (3:1); yield 0.189 g (88%); cream coloured leaflets (from PE/EA/MeOH); mp 227–230 °C (dec.); IR (nujol) 3213, 1593, 1540, 1240, 1222, 1202, 1075, 897, 807 cm⁻¹. ¹H NMR (DMSO-d₆) δ 3.02 (d, J = 4.5 Hz, 3H, NHCH₃), 7.51 (dd, J₁ = 8.5 Hz, J₂ = 4 Hz, 1H, H-3), 7.65 and 8.04 (d, J = 9 Hz, 1H each, H-8 and H-9, respectively), 8.19 (q, J = 4.5 Hz, 1H, Ar-NH), 8.72 (d, J = 8.5 Hz, 1H, H-4), 8.84 (ill-split d, 1H, H-2). ¹³C NMR δ 31.6 (NHCH₃), 121.64 (C-3b), 121.69 (CH-5), 122.2 (CH-8), 123.4 (CH-9), 125.6 (C-9a), 132.5 (CH-4), 147.7 (C-7a), 148.9 (C-3a), 150.2 (CH-6), 170.1 (C-2). LR EI-MS m/z (%) 215 (M⁺, 100), 214, 187, 186; HR EI-MS m/z calcd for C₁₁H₉NₛS: 215.0517; found: 215.0517.

2-Methylaminobenzol[1,2-d:4,3-d']bisthiazole (10a). Yield 0.187 g (85%); off-white needles (from PE/DCM); mp 118–119 °C; IR (nujol) 3230, 1629, 1540, 1281, 1162, 1062, 930, 830, 797 cm⁻¹. ¹H NMR (DMSO-d₆) δ 2.97 (d, J = 4.5 Hz, 3H, NHCH₃), 7.58 and 7.92 (d, J = 8.5 Hz, 1H each), 8.16 (q, J = 4.5 Hz, 1H), 9.20 (s, 1H). ¹³C NMR δ 31.6 (NHCH₃), 118.1, 121.3, 153.1 (all Ar-CH), 122.3, 126.9, 149.6, 151.7, 167.5 (all Ar-C). LR EI-MS m/z (%) 221 (M⁺, 100), 220, 193, 192; HR EI-MS m/z calcd for C₉H₇NₛS₂: 221.0081; found: 221.0083.
General procedure for the synthesis of alkyl N-(5-isooquinoliny/quinolinyldithiocarbamates (12, 13a, b) and N-(6-benzothiazolyl)dithiocarbamates (14a, b)

A solution of 1/5 (0.144 g, 1 mmol) in Py (1.5/1 mL) or 4 in Py-Et2N (10:1; 1 mL) was cooled (ice-salt mixture) to −5 °C. CS2 (0.2 mL, 3 mmol) was added to it, and the solution was stirred for 1 h maintaining the temperature at −5 to 0 °C. MeI or EtI (3 mmol) was added to the reaction mixture and stirred at r.t. until (see Table 2) the starting materials were fully consumed. Usual work-ups, followed by either purification by CC and subsequent crystallisation (for 1 and 5) or directly by crystallisation (for 4) furnished pure 12-14 a,b.

**Methyl N-(5-isooquinolinyldithiocarbamate** (12a). Eluted with PE/EA (4:1); yield 0.147 g (63%); off-white crystals (from PE/EA); mp 153-154 °C; IR 3102, 1625, 1590, 1536, 1489, 1371, 1330, 1274, 1036, 986, 826, 750 cm⁻¹. 1H NMR (DMSO-d₆) δ 2.58 (br s, 3H, SCH₃), 7.61 (d, J = 6 Hz, 1H, H-4), 7.72 (t, J = 7.5 Hz, 1H, H-7), 7.77 (dd, J₁ = 7.5 Hz, J₂ = 1 Hz, 1H, H-6), 8.14 (d, J = 8 Hz, 1H, H-8), 8.54 (d, J = 6 Hz, 1H, H-3), 9.38 (s, 1H, H-1), 11.88 (br s, 1H, Ar-NH). 13C NMR δ 19.1 (SCH₃), 116.5 (CH-4), 128.1 (CH-7, 8), 128.5 (C-8a), 129.7 (C-4a), 130.6 (CH-6), 132.7 (C-5), 144.2 (CH-3), 153.5 (CH-1), 202.1 (C=5). LR EI-MS m/z (%) 234 (M⁺), 218, 187, 186 (100), 161, 159, 144, 128, 101, 81, 69; LR FAB-MS m/z 235 (M+H)⁺; HR EI-MS m/z calcd for C₁₁H₁₀N₂S₂ (M⁺): 234.0286; found: 234.0282.

**Methyl N-(5-quinolinyldithiocarbamate** (13a). Yield 0.164 g (70%); light brown globules (from EA/MeOH); mp 145–147 °C; IR 3442, 3110, 1613, 1591, 1572, 1548, 1498, 1466, 1394, 1327, 1309, 1204, 1085, 1034, 1018, 980, 957, 917, 878, 813, 794, 742 cm⁻¹; 1H NMR (DMSO-d₆) δ 2.58 (s, 3H), 7.59 (ill-split d, J = 5.5 Hz, 2H), 7.80 (t, J = 7.5 Hz, 1H), 8.04 and 8.16 (d, J = 7.5 Hz, 1H each), 8.94 and 11.89 (br s, 1H each). 13C NMR δ 19.1 (CH₃), 122.7, 129.9, 132.3, 151.8 (all Ar-CH), 125.4, 126.6, 149.0, 202.1 (all Ar-C). LR EI-MS m/z (%) 234 (M⁺), 187, 186 (100), 161, 128, 101, 91; HR EI-MS m/z calcd for C₁₁H₁₀N₂S₂ (M⁺): 234.0286; found: 234.0287.

**Methyl N-(6-benzothiazolyl)dithiocarbamate** (14a). Eluted with PE/EA (4:1); yield 0.172 g (72%); yellow leaflets (from EA/MeOH); mp 192–194 °C (dec.); IR 3154, 1568, 1519, 1473, 1338, 1219, 1030, 959, 835, 791, 741 cm⁻¹. 1H NMR (DMSO-d₆) δ 2.58 (s, 3H), 7.65 (br s, 1H), 8.07 (d, J = 8.5 Hz, 1H), 8.49 (br s, 1H), 9.37 and 11.85 (s, 1H each). 13C NMR δ 18.8 (CH₃), 118.3, 123.7, 124.2, 157.5 (all Ar-CH), 134.6, 137.9, 151.8, 199.3 (all Ar-C). LR ESI-MS m/z 241 (M+H)⁺, 263 (M+Na)⁺; GC-ESI MS m/z (%) 192 (100), 134. Anal. Calcd for C₉H₈N₂S₃: C, 45.00; H, 3.33; N, 11.66. Found: C, 45.11; H, 3.36; N, 11.70.

General procedure for the synthesis of 2-alkylthiothiazolo[4,5-f]isooquinolines (15a, b), -thiazolo[4,5-f]quinolines (16a, b) and -benzo[1,2-d:4,3-d']bisthiazoles (17a, b)

To a precooled (10 °C) solution of 12/13 (1 mmol in CH₂CN, 25–30 mL) or 14 (1 mmol in CHCl₃, 15 mL) was added a solution of Br₂ (1.5 mmol, for 12, 14; 3 mmol for 13) in CH₂CN (1 mL for 12; 3 mL for 13) or CHCl₃ (2 mL for 14), and the resulting solution was stirred at r.t. When the dithiocarbamate was consumed (see Table 2), the reaction mixture was worked up in the usual manner (10% aq. Na₂S₂O₃, stirred; aq. NaHCO₃). In the case of 12, the precipitated crude products were purified by CC and crystallised to furnish pure 15a, b.
In the cases of 13 and 14, since the products did not precipitate, the reaction mixtures were separately extracted with EA (3×20 mL) and CHCl₃ (3×20 mL), respectively. The residues resulting from the pooled extracts were crystallised to furnish pure 16, 17a,b.

2-Methylthiothiazolo[4,5-f]isoquinoline (15a). Eluted with PE/EA (17:3); yield 0.223 g (96%); white crystals (from PE/EA); mp 123–124 °C (dec.); IR 1614, 1549, 1487, 1437, 1368, 1307, 1288, 1194, 1032, 965, 900, 833, 815 cm⁻¹. ¹H NMR (CDCl₃) δ 2.87 (s, 3H, SCH₃), 7.79 and 7.88 (d, J = 8.5 Hz, 1H each, H-8 and H-9, respectively), 8.43 and 8.69 (d, J = 5.5 Hz, 1H each, H-4 and H-5, respectively), 9.29 (s, 1H, H-7). ¹³C NMR δ 16.6 (SCH₃), 117.0 (CH-4), 120.3 (CH-9), 123.8 (CH-8), 127.3 (C-7a), 130.6 (C-3b), 136.1 (C-9a), 144.7 (CH-5), 148.4 (C-3a), 152.3 (CH-7), 168.8 (C-2); LR EI-MS m/z (%) 232 (M⁺, 100), 200, 199, 173, 159, 137, 81, 69; HR EI-MS m/z calcld for C₁₁H₉N₂S (M⁺): 232.0129; found: 232.0132.

2-Methylthiothiazolo[4,5-f]quinoline (16a). Yield 0.22 g (95%); pale cream-coloured needles (from EtOH/H₂O); mp 124–125 °C; IR 1561, 1493, 1451, 1435, 1389, 1363, 1186, 1158, 1073, 1032, 1017, 902, 878, 808 cm⁻¹. ¹H NMR (CDCl₃) δ 2.86 (s, 3H), 7.53 (dd, J₁ = 8.5 Hz, J₂ = 4 Hz, 1H), 7.98 and 8.0 (d, J = 9.5 Hz, 1H each), 8.95 (dd, J₁ = 4 Hz, J₂ = 1.5 Hz, 1H), 9.0 (dd, J₁ = 8.5 Hz, J₂ = 1.5 Hz, 1H). ¹³C NMR δ 16.7 (CH₃), 122.0, 122.09, 126.2, 132.6, 150.4 (all Ar-CH), 123.2, 132.1, 147.6, 149.5, 169.0 (all Ar-C); LR EI-MS m/z (%) 232 (M⁺, 100), 217, 200, 199, 173, 159. HR EI-MS m/z calcld for C₁₁H₉N₂S: 232.0128; found: 232.0132.

2-Methylthiobenz[1,2-d:4,3-d′]bi(thiazole (17a). Yield 0.197 g (83%); off-white prisms (from PE/DCM); mp 135–136 °C; IR 1598, 1462, 1438, 1401, 1260, 1097, 1018, 968, 861, 806, 741 cm⁻¹. ¹H NMR (CDCl₃) δ 2.84 (s, 3H), 7.99 and 8.14 (d, J = 8.5 Hz, 1H each), 8.98 (s, 1H). ¹³C NMR δ 16.6 (CH₃), 120.4, 122.0, 152.7 (all Ar-CH), 126.6, 129.5, 151.2, 152.2, 167.9 (all Ar-C). GC-MS m/z (%) 238 (M⁺, 100), 205. Anal. Calcld for C₁₀H₉N₂S₃: C, 45.37; H, 2.52; N, 11.76. Found: C, 45.45; H, 2.57; N, 11.77.

**Reaction of (1, 4) and (5) with phenyl isothiocyanate**

When a solution of 1/ 5 (1 mmol each) and PhNCS (2/1.5 mmol) in MeOH (15 mL) was refluxed, the amine remained un consumed in each case even after 12 h and also produced a number of products (TLC). The reactions were, therefore, abandoned.

When a solution of 4 (1 mmol) and PhNCS (1.5 mmol) in MeOH (15 mL) was refluxed, the amine was fully consumed after 5 h. The removal of the solvent furnished a residue, which consisted of two products (TLC: Rf = 0.62 and 0.41, respectively in PE:EA=7:3). These were isolated by CC by elution with 15% and 30% EA in PE, respectively to furnish pure 18 and 19.

N,N'-Diphenylthiourea (18). Yield 0.086 g (38%); white shining needles (from PE/EA); mp 150–152 °C (lit.²¹ mp 153–154 °C). IR, ¹H and ¹³C NMR data agreed to those reported in the literature.²¹ GC-MS m/z (%) 194 (100), 77, 51.

Methyl N-(5-quinolinyl)thiocarbamate (19). Yield 0.1 g (46%); white needles (from PE/EA/MeOH); mp 174–175 °C (dec.); IR 3105, 1596, 1573, 1526, 1502, 1362, 1206, 1130, 1068, 803 cm⁻¹. ¹H NMR (DMSO-d₆) δ 3.98 (s, 3H), 7.46–7.62 (m, 1H), 7.56 (dd, ill-split, J₁ = 8 Hz, J₂ = 4 Hz, 1H), 7.76 (t, J = 8 Hz, 1H), 7.98 (d, J = 8 Hz, 1H), 8.22 (d, J = 7.5 Hz, 1H), 8.92
(dd, \( J_1 = 4 \text{ Hz}, J_2 = 1.5 \text{ Hz}, 1H \)), 11.21 (br s, 1H). GC-EI MS \( m/z \) 218 (M\(^+\)), 186 (100), 161, 128. Anal. Calcd for C\(_{11}\)H\(_{10}\)N\(_2\)SO: C, 60.55; H, 4.58; N, 12.84. Found: C, 60.50; H, 4.57; N, 12.87.

**General procedure for the synthesis of 5-(N'-phenylthioureido)-isoquinoline (2e), -quinoline (7e) and 6-(N'-phenylthioureido)benzothiazole (8e)**

A solution of ethyl \( N \)-(5-isoquinolinylinyquinolinyl)/\( N \)-(6-benzothiazolyldithiocarbamate 12b/13b/14b (1 mmol) and PhNH\(_2\) (0.14 mL, 1.5 mmol) in dry CH\(_2\)Cl\(_2\) (5–6 mL, for 12b) or MeOH (15 mL, for 13b, 14b) was refluxed until (see Table 3) the reaction was complete (TLC). The solvent was removed by distillation and the residue purified by crystallisation from MeOH, which furnished pure 2e, 7e and 8e.

### 5-(N'-Phenylthioureido)isoquinoline (2e).

Yield 0.215 g (77%); white needles; mp 168–170 °C (lit.\(^{29}\) mp 166–168 °C); IR 3263, 3194, 1591, 1535, 1494, 1379, 1257, 1227, 1031, 924, 827, 757 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\)) 7.13 (t, \( J = 7.5 \text{ Hz}, 1H \)), 7.33 (t, \( J = 8 \text{ Hz}, 2H \)), 7.52 (d, \( J = 7.5 \text{ Hz}, 2H \)), 7.68 (t, \( J = 7.5 \text{ Hz}, 1H \)), 7.79 (d, \( J = 7 \text{ Hz}, 1H \)), 8.03 (d, \( J = 8 \text{ Hz}, 1H \)), 8.54 (d, \( J = 6 \text{ Hz}, 1H \)), 9.33, 9.90 and 9.91 (s, 1H each). \(^{13}\)C NMR δ 117.0, 124.9 (2\( \times \)), 125.5, 126.9, 128.0, 129.3 (2\( \times \)), 130.0, 143.8, 153.4 (all Ar-CH), 129.8, 133.3, 135.4, 140.2, 182.2 (all Ar-C). LR EI-MS \( m/z \) (%) 279 (M\(^+\)), 245, 228, 194, 187, 186, 159, 144, 136, 135, 128, 93 (100), 77.

### 5-(N'-Phenylthioureido)quinoline (7e).

Yield 0.237 g (85%); off-white globules; mp 186–188 °C (dec.) (lit.\(^{30}\) mp 188–190 °C); IR 3148, 1594, 1538, 1510, 1497, 1371, 1267, 1204, 796, 745 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\)) δ 7.13 (t, \( J = 7.5 \text{ Hz}, 1H \)), 7.33 (t, \( J = 8 \text{ Hz}, 2H \)), 7.51 (d, \( J = 8 \text{ Hz}, 2H \)), 7.57 (dd, \( J_1 = 8.5 \text{ Hz}, J_2 = 4 \text{ Hz}, 1H \)), 7.58 (d, \( J = 7.5 \text{ Hz}, 1H \)), 7.75 (t, \( J = 8 \text{ Hz}, 1H \)), 7.94 and 8.35 (d, \( J = 8 \text{ Hz}, 1H \) each), 8.90 (dd, \( J_1 = 4 \text{ Hz}, J_2 = 1.5 \text{ Hz}, 1H \)), 9.88 and 9.91 (br s, 1H each). \(^{13}\)C NMR δ 122.1, 124.9 (2\( \times \)), 125.5, 126.3, 128.5, 129.3 (2\( \times \)), 129.9, 132.8, 151.3 (all Ar-CH), 126.2, 136.4, 140.3, 149.2, 182.4 (all Ar-C). GC-EI MS \( m/z \) (%) 186 (100), 142, 128.

### 6-(N'-Phenylthioureido)benzothiazole (8e).

Yield 0.262 g (92%); brown prisms; mp 185–187 °C; IR 3182, 3035, 1592, 1528, 1318, 1250, 1197, 959, 836, 746 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\)) δ 7.12 (t, \( J = 7.5 \text{ Hz}, 1H \)), 7.33 (t, \( J = 7.5 \text{ Hz}, 2H \)), 7.48 (d, \( J = 7.5 \text{ Hz}, 2H \)), 7.55 (dd, \( J_1 = 8.5 \text{ Hz}, J_2 = 2 \text{ Hz}, 1H \)), 8.02 (d, \( J = 8.5 \text{ Hz}, 1H \)), 8.30 (d, \( J = 2 \text{ Hz}, 1H \)), 9.30, 9.88 and 9.99 (s, 1H each). \(^{13}\)C NMR δ 117.9, 123.4, 124.3, 124.7 (2\( \times \)), 125.4, 129.3 (2\( \times \)), 156.3 (all Ar-CH), 134.5, 137.9, 140.2, 151.0, 180.8 (all Ar-C); LR ESI-MS \( m/z \) 286 (M+H\(^+\)), 308 (M+Na\(^+\)). GC-EI MS \( m/z \) (%) 251, 192 (100), 150, 134, 93. Anal. Calcd for C\(_{14}\)H\(_{11}\)N\(_3\)S\(_2\): C, 58.94; H, 3.85; N, 14.73. Found: C, 58.86; H, 3.88; N, 14.77.

**General procedure for the synthesis of 2-anilinothiazolo[4,5-f]isoquinoline (3e), -thiazolo [4,5-f]quinoline (9e) and -benzo[1,2-d:4,3-d']bisthiazole (10e)**

A solution of 2e/7e/8e was cyclised by Br\(_2\) (1.5 mmol, ca. 0.2 mL) in AcOH (1.8 mL for 2e) or in CH\(_2\)Cl\(_2\) (2 mL for 7e/8e) in exactly the same manner as was done for 2a-d, 7a-d and 8a-d, and the products were purified by crystallisation.
2-Anilinothiazolo[4,5-f]isoquinoline (3e). Yield 0.27 g (97%); white crystals (from MeOH); mp 198–200 °C (dec.); IR 3206, 1617, 1577, 1540, 1488, 1371, 1286, 1219, 1198, 1028, 905, 830, 740 cm⁻¹. ¹H NMR (DMSO-d₆) δ 7.06 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.87 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8 Hz, 2H), 8.12 (d, J = 8.5 Hz, 1H), 8.30 (d, J = 5.5 Hz, 1H), 8.61 (br d, J = 3.5 Hz, 1H), 9.34 and 10.75 (s, 1H each). ¹³C NMR δ 117.2, 118.6 (2x), 121.7, 122.2, 123.1, 130.0 (2x), 144.0, 152.8 (all Ar-CH), 127.7, 129.1, 130.3, 141.4, 146.8, 164.0 (all Ar-C); LR EI-MS m/z (%) 277 (M⁺, 100). HR EI-MS m/z calcd for C₁₀H₁₁N₃S (M⁺): 277.0674; found 277.0674.

2-Anilinothiazolo[4,5-f]quinoline (9e). Yield 0.249 mg (90%); brownish yellow tiny rods (from PE/EA); mp 202–205 °C (dec.); IR 3258, 1604, 1573, 1534, 1493, 1443, 1396, 1360, 1312, 1247, 1198, 1073, 744 cm⁻¹. ¹H NMR (DMSO-d₆) δ 7.04 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 7.60 (dd, J₁ = 8 Hz, J₂ = 4 Hz, 1H), 7.78 and 8.16 (d, J = 9 Hz, 1H each), 7.89 (d, J = 8 Hz, 2H), 8.86 (d, J = 8 Hz, 1H), 8.89 and 10.74 (br s, 1H each). ¹³C NMR δ 118.6 (2x), 122.2, 123.0, 123.3, 123.8, 129.9 (2x), 132.6, 150.5 (all Ar-CH), 122.1, 125.9, 141.5, 147.7, 148.2, 164.4 (all Ar-C). GC-EI MS m/z (%) 277 (M⁺; 100), 276, 51. Anal. Calcd for C₁₆H₁₁N₃S: C, 69.31; H, 3.97; N, 15.16. Found: C, 69.38; H, 3.96; N, 15.19.

2-Anilinobenzo[1,2-d:4,3-d']bithiazole (10e). Yield 0.254 g (90%); off-white needles (from PE/DCM); mp 198–200 °C; IR 3223, 1565, 1529, 1465, 1314, 1266, 1100, 1072, 982, 928, 819, 739 cm⁻¹. ¹H NMR (CDCl₃ + DMSO-d₆) δ 7.05 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 2H), 7.44 (d, J = 7.5 Hz, 2H), 7.74 and 8.02 (d, J = 9 Hz, 1H each), 8.94 and 10.62 (s, 1H each). ¹³C NMR δ 118.6 (2x), 118.7, 118.9, 121.1, 129.2 (2x), 151.3 (all Ar-CH), 121.2, 126.3, 140.8, 149.9, 151.0, 168.5 (all Ar-C). GC-EI MS m/z (%) 283 (M⁺, 100), 282, 51. Anal. Calcd for C₁₄H₉N₃S₂: C, 59.36; H, 3.18; N, 14.84. Found: C, 59.44; H, 3.19; N, 14.80.

General procedure for N-Acylation of (1, 4, 5)
A solution of 1/ 4/ 5 (1 mmol) in dry Py (1.0 mL) containing Ac₂O/(EtCO)₂O/(i-PrCO)₂O/(n-PrCO)₂O (1.5 mmol) was kept overnight at r.t. In the case of 1, the solution was diluted with dry C₆H₆ (ca. 20 ml) and allowed to stand in cold when the product precipitated. For 4 and 5, the products appeared as crystals. These were filtered, washed free of Py with chilled C₆H₆ (for 1, 5) or PE–C₆H₆ (for 4), dried and purified by CC or crystallisation to furnish 21a-c (from 1), 22a-c (from 4) and 23a,b (from 5).

5-Acetamidoisoquinoline (21a). Eluted with PE/EA (2:3); yield 0.184 g (99%); white fluffy needles (from PE/EA); mp 160–162 °C (lit.¹¹ mp 162–164 °C); IR 3273, 1660, 1541, 1385, 1367, 1326, 1278, 1037, 823, 761, 749, 702 cm⁻¹. ¹H NMR (CDCl₃) δ 2.27 (s, 3H), 7.52 (t, J = 8 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.77 (d, J = 6 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H), 8.44 (d, J = 6 Hz, 1H), 9.17 (s, 1H), 9.28 (br s, 1H). ¹³C NMR δ 24.2 (CH₃), 115.5, 125.1, 125.6, 127.4, 143.0, 153.0 (all Ar-CH), 129.3, 130.6, 132.8, 170.2 (all Ar-C). LR EI-MS m/z (%) 186 (M⁺), 145, 144 (100), 117, 116, 43.

5-Acetamidoquinoline (22a). Yield 0.16 g (86%); white shining needles (from PE/C₆H₆); mp 172 °C (lit.¹² mp: not reported). The IR, ¹H NMR and GC-EI MS data agreed with those reported
in the literature. $^{13}$C NMR (CDCl$_3$ + DMSO-$d_6$) $\delta$ 24.0 (CH$_3$), 120.9, 122.5, 127.1, 129.3, 131.7, 150.5 (all Ar-CH), 123.7, 133.8, 148.8, 170.3 (all Ar-C).

6-Acetamidobenzothiazole (23a). Yield 0.192 g (100%); white needles (from PE/EA); mp 170–171 °C; IR (nujol) 3293, 1684, 1609, 1539, 1464, 1372, 1329, 1288, 1253, 1130, 906, 851, 771 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.09 (s, 3H), 7.55 (dd, $J_1 = 9$ Hz, $J_2 = 2$ Hz, 1H), 7.98 (d, $J = 8.5$ Hz, 1H), 8.52 (d, $J = 2$ Hz, 1H), 9.22 and 10.18 (s, 1H each). $^{13}$C NMR $\delta$ 24.9 (CH$_3$), 112.2, 119.4, 123.7, 155.3 (all Ar-CH), 135.0, 137.9, 149.8, 169.4 (all Ar-C). GC-EL MS $m/z$ (%) 192 (M$^+$), 150 (100). Anal. Calcd for C$_9$H$_8$N$_2$OS: C, 56.25; H, 4.16; N, 14.58. Found: C, 56.30; H, 4.14; N, 14.61.

**General procedure for N-benzyolisation of (1, 4, 5)**

To a solution of 1/4/5 (1 mmol) in DCM (20 mL) was added freshly distilled PhCOCl (2 mmol, 0.23 mL for 1, 1.2 mmol, 0.14 mL for 4/5), followed by dry Et$_3$N (2 mmol, 0.28 mL for 1; 1.2 mmol, 0.18 mL for 4/5). The resulting solution was stirred at r.t. until (see Table 4) the reaction was complete. The solution was diluted with water (25 mL) and extracted with DCM (3×15 mL). The pooled extracts furnished, after usual work-ups, residues which were purified by CC (for 1) or directly by crystallisation (for 4 and 5) to furnish 21d, 22d and 23c, respectively.

**General procedure for thionation of the amides (21a-d, 22a-d, 23a-c)**

A solution of the amide (1 mmol) in dry C$_6$H$_6$ (25–30 mL) containing Lawesson’s reagent (0.484 g, 1.2 mmol) was refluxed until (see Table 4) the starting material was consumed. The solvent was distilled off from the reaction mixture, the residue was worked up in the usual way and the resulting crude product was purified either by CC, followed by crystallisation (for 24b-d, 26a-c), or directly by crystallisation (for 24a, 25a-d).

5-Thioacetamidoisoquinoline (24a). Yield 0.199 g (98%); golden yellow prisms (from PE/EA); mp 208–210 °C (dec.); IR 3129, 1626, 1594, 1553, 1377, 1276, 1194, 1158, 1051, 1034, 825, 759, 713 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.75 (s, 3H), 7.69 (d, $J = 6$ Hz, 1H), 7.72 (t, $J = 8$ Hz, 1H), 7.78 (d, $J = 7.5$ Hz, 1H), 8.10 (d, $J = 8$ Hz, 1H), 8.52 (d, $J = 6$ Hz, 1H), 9.36 (s, 1H), 11.76 (br s, 1H). $^{13}$C NMR $\delta$ 34.4 (CH$_3$), 116.8, 128.0 (2x), 130.0, 143.9, 153.5 (all Ar-CH), 129.6, 132.2, 135.9, 203.8 (all Ar-C). LR EI-MS $m/z$ (%) 202 (M$^+$), 201, 169, 168, 161 (100), 144, 128, 117, 101, 59; HR EI-MS $m/z$ caled for C$_{11}$H$_8$N$_2$S (M$^+$), 202.0565; found 202.0569.

5-Thioacetamidoquinoline (25a). Yield 0.162 g (80%); brown tiny rods (from PE/EA/MeOH); mp 209–210 °C (dec.); IR 3126, 1614, 1595, 1575, 1556, 1502, 1471, 1371, 1315, 1173, 1158, 1142, 1083, 887, 804, 720 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.75 (s, 3H), 7.55 (dd, $J_1 = 8.5$ Hz, $J_2 = 4$ Hz, 1H), 7.58 (d, $J = 7.5$ Hz, 1H), 7.70 (dd, $J_1 = 8.5$ Hz, $J_2 = 7.5$ Hz, 1H), 8.01 (d, $J = 8.5$ Hz, 1H), 8.24 (ddd, $J_1 = 8.5$ Hz, $J_2 = 1.5$ Hz, $J_3 = 1$ Hz, 1H), 8.92 (dd, $J_1 = 4$ Hz, $J_2 = 1.5$ Hz, 1H), 11.77 (s, 1H). $^{13}$C NMR $\delta$ 34.4 (CH$_3$), 122.3, 126.1, 129.3, 129.9, 132.7, 151.6 (all Ar-CH), 125.0, 137.1, 148.9, 203.9 (all Ar-C). GC-EL MS $m/z$ (%) 202 (M$^+$), 169, 161 (100), 144, 128, 117. Anal. Calcd for C$_{11}$H$_8$N$_2$S: C, 65.34; H, 4.95; N, 13.86. Found: C, 65.29; H, 4.94; N, 13.89.
6-Thioacetamidobenzothiazole (26a). Eluted with PE/EA (4:1); yield 0.145 g (70%); yellow leaflets (from EA/MeOH); mp 223–224 °C; IR 3238, 1581, 1521, 1476, 1368, 1324, 1293, 1156, 1146, 1003, 919, 852, 814, 794, 743, 707 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\)) δ 2.64 (s, 3H), 7.74 (dd, \(J_1 = 8.5 \text{ Hz}, J_2 = 2 \text{ Hz}, 1\H)), 8.08 (d, \(J = 8.5 \text{ Hz}, 1\H)), 8.76 (d, \(J = 2 \text{ Hz}, 1\H)), 9.36 and 11.79 (s, 1H each). \(^13\)C NMR δ 35.9 (CH\(_3\)), 112.2, 117.4, 123.5, 157.3 (all Ar-CH), 134.4, 137.9, 151.7, 200.6 (all Ar-C). GC-ESI MS \(m/z\) (%) 208 (M\(^+\)), 207, 175, 167 (100), 150, 59. Anal. Calcd for C\(_9\)H\(_8\)N\(_2\)S\(_2\): C, 51.92; H, 3.84; N, 13.46. Found: C, 51.88; H, 3.83; N, 13.43.

**Attempted cyclisation of 5-thioacetamidoisoquinoline (24a) by Br\(_2\)/AcOH and Br\(_2\)/CH\(_3\)CN**

In two separate experiments, a solution of Br\(_2\) (1.5 mmol, 0.2 ml) in AcOH and in CH\(_3\)CN (0.8 mL each) was added dropwise with stirring to a solution of 24a (1 mmol) in CH\(_3\)CN (30 ml) at 10-15 °C. The reaction mixture was stirred at r.t. for 30 min, when 24a was found to be consumed. The product from both the experiments showed same R\(_f\) (0.40) on TLC (C\(_6\)H\(_6\):EA:MeOH=9:9:2) as that of 21a.

**General procedure for the synthesis of 2-alkyl/phenylthiazolo[4,5-f]isoquinolines (27a-d), -thiazolo[4,5-f]quinolines (28a-d) and -benzo[1,2-d:4,3-d’]bisthiazoles (29a-c)**

An aq. solution (12 ml) of K\(_2\)Fe(CN)\(_6\) (2.14 g, 6.5 mmol) was added to a solution of the thioamide 24a-d// 25a-d// 26a-c (1 mmol) in 4 M aq. NaOH (20 mL) at r.t. and the solution stirred until (Table 4) the reaction was complete (TLC). The reaction mixture was then extracted with EA (3×20 mL). The residue from the duly treated pooled extract was purified by CC (for 27c) or by crystallisation (for the rest).

2-Methylthiazolo[4,5-f]isoquinoline (27a). Yield 0.188 g (94%); cream coloured crystals (from PE/DCM); mp 133–135 °C; IR 1618, 1551, 1511, 1487, 1430, 1371, 1195, 1169, 1156, 986, 884, 842, 806, 774 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) δ 2.96 (s, 3H, Ar-CH\(_3\)), 7.86 and 7.96 (d, \(J = 8.5 \text{ Hz}, 1\H) each), 8.48 and 8.71 (d, \(J = 5.5 \text{ Hz}, 1\H) each), 9.32 (d, \(J = 0.5 \text{ Hz}, 1\H)). \(^13\)C NMR δ 20.5 (Ar-CH\(_3\)), 116.9, 120.7, 124.5, 144.7, 152.3 (all Ar-CH), 127.3, 131.4, 136.6, 148.3, 167.6 (all Ar-C). LR EI-MS \(m/z\) (%) 200 (M\(^+\), 100); 199; HR EI-MS \(m/z\) calcd for C\(_{11}\)H\(_8\)N\(_2\)S (M\(^+\)), 200.0399; found 200.0398.

2-Methylthiazolo[4,5-f]quinoline (28a). Yield 0.17 g (85%); pale yellow needles (from PE/EA); mp 109–111 °C (lit.\(^{15a}\) mp 108°C); IR (nujol) 1559, 1509, 1364, 1185, 1175, 1155, 1075, 901, 839, 810, 769 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) δ 2.94 (s, 3H) 7.55 (dd, \(J_1 = 8 \text{ Hz}, J_2 = 4.5 \text{ Hz}, 1\H)), 8.03 and 8.06 (d, \(J = 9 \text{ Hz}, 1\H) each), 8.97 (dd, \(J_1 = 4.5 \text{ Hz}, J_2 = 1.5 \text{ Hz}, 1\H)), 9.03 (dd, \(J_1 = 8 \text{ Hz}, J_2 = 1.5 \text{ Hz}, 1\H)); \(^13\)C NMR δ 20.5 (CH\(_3\)), 122.0, 122.5, 126.9, 132.4, 150.2 (all Ar-CH), 123.9, 132.7, 147.7, 149.4, 167.8 (all Ar-C). LR EI-MS \(m/z\) (%) 200 (M\(^+\), 100), 199, 159.

2-Methylbenzo[1,2-d:4,3-d’]bisthiazole (29a). Yield 0.19 g (93%); white prisms (from PE/DCM); mp 179–180 °C; IR 1538, 1475, 1459, 1389, 1329, 1252, 1169, 1098, 927, 849, 837, 817 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) δ 2.77 (s, 3H), 8.05 and 8.16 (d, \(J = 9 \text{ Hz}, 1\H) each), 9.04 (s, 1H). \(^13\)C NMR δ 20.4 (CH\(_3\)), 121.1, 121.8, 153.1 (all Ar-CH), 126.8, 128.6, 151.5, 151.9, 166.8 (all Ar-C). GC-ESI MS \(m/z\) (%) 206 (M\(^+\), 100), 205. Anal. Calcd for C\(_9\)H\(_8\)N\(_2\)S\(_2\): C, 52.42; H, 2.91; N, 13.59. Found: C, 52.49; H, 2.89; N, 13.62.
Synthesis of 2-aminobenzo[1,2-d:4,3-d′]bisthiazole (31)
KSCN (0.145 g, 1.5 mmol) was added to a solution of 5 (0.15 g, 1 mmol) in gl. AcOH (10 mL) at r.t. and a solution of Br$_2$ (1.5 mmol) in AcOH (2 mL) was added slowly to it with stirring. The stirring was continued for 15 min when the reaction was complete. The solution was poured into 10% aq. Na$_2$S$_2$O$_3$ solution (50 mL), stirred until the colour of bromine disappeared and extracted with DCM (3×20 mL). The resulting residue was crystallised from PE/EA to furnish pure 31. Yield 0.155 g (75%); yellow prisms; mp 300–302 °C (lit.\cite{15i} mp 301–302 °C); IR (nujol) 3327, 3224, 1659, 1564, 1530, 1418, 1289, 1122, 976, 930, 844, 811 cm$^{-1}$. $^1$H NMR (DMSO-d$_6$) $\delta$ 7.52 (d, $J = 8.5$ Hz, 1H), 7.70 (s, 2H), 7.91 (d, $J = 8.5$ Hz, 1H), 9.20 (s, 1H). $^{13}$C NMR $\delta$ 117.8, 121.2, 153.1 (all Ar-CH), 122.8, 126.8, 149.6, 151.8, 167.1 (all Ar-C). LR EI-MS m/z (%) 207 (M$^+$, 100), 180, 179.

Biological assay. In vitro experiments
In the in vitro assays, each experiment was performed in triplicate and the standard deviation of absorbance was less than 10% of the average values.

Screening of assorted products for inhibition of COX-1 and COX-2
The inhibitory activities of the compounds were measured using bovine COX-1 and human recombinant COX-2 enzymes included in the “COX Inhibitor Screening Assay” kit provided by Cayman (Cayman Chemical Co., Ann Arbor, MI). The assay directly measures PGF$_2\alpha$ produced by SnCl$_2$ reduction of COX-derived PGH$_2$. The prostanoid productions were quantified via enzyme immunoassay using a broadly specific antibody that binds to all the major prostaglandins. The final estimation of % inhibition (Table 5) was performed at a substrate concentration of 0.1 µM.

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Supplementary Data
The data for selected compounds from each series are presented in this paper. The data of rest of the compounds have been presented in the supplementary file.
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