



# Synthesis of trifluoromethyl group bearing indoline-based heterocyclic systems and their application for the detection of cyanide



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## ABSTRACT

New derivatives of 5a,6-dihydro-12*H*-indolo[2,1-*b*][1,3]benzoxazine and 1',3,3',4-tetrahydrospiro[chromene-2,2'-indole] that possess trifluoromethyl groups on the indoline part of the molecule were synthesised, and their potential application for the detection of cyanide was evaluated. It was demonstrated that the new fluorinated chemosensors exhibited significantly shorter response times to cyanide detection compared with corresponding analogues bearing nitro groups. Structures of the newly synthesised compounds were assigned using standard <sup>1</sup>H, <sup>13</sup>C, <sup>15</sup>N and <sup>19</sup>F NMR spectroscopy techniques.

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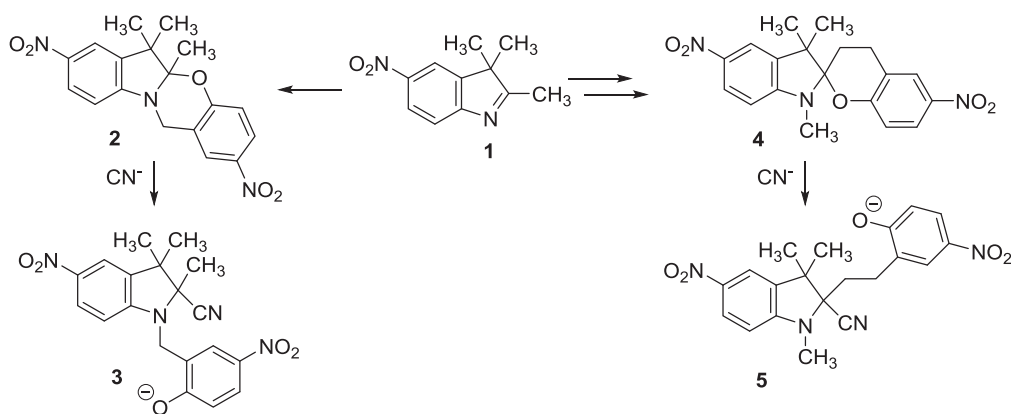
## 1. Introduction

The electron-withdrawing trifluoromethyl group (CF<sub>3</sub>) is considered to be an important structural motif in synthetic organic chemistry with applications in pharmaceuticals, agrochemicals and materials [1,2]. This group possesses unique steric and electronic properties, is resistant to metabolic oxidation and is often used as bioisosteres of methyl or chloride groups in the design of biologically active molecules [3,4]. Drugs such as the highly active antiretroviral therapy agent Sustiva, antidepressant Prozac, nonsteroidal anti-inflammatory agent Celebrex, pesticide Thiazopyr and the herbicide Fluzinam all possess trifluoromethyl moieties [5]. Recent examples on the beneficial effects of trifluoromethyl groups on target properties of functional materials include dyes for dye-sensitised solar cells [6,7], chelating agents [8], overcharge protection agents in lithium-ion batteries [9] and liquid crystals [10]. This work aims to synthesise trifluoromethyl group bearing indoline adducts with 2-chloromethyl-4-nitrophenol and to investigate their potential as molecular chemosensors for cyanide detection.

Large amounts of cyanide are applied in a number of industrial processes every year, including gold extraction [11], electroplating [12] and nitrile synthesis [13]. However, the wide use of this highly toxic chemical has created a number of serious problems for the environment and human health [14]. Numerous methods have been developed to determine the presence of cyanide in food, drinking water, and the environment [15], but optical chemosensing of cyanides has been one of the most convenient and actively studied methods over the past decade [16,17]. For example, Ren et al. demonstrated that 2,8-dinitroindolo[2,1-*b*][1,3]benzoxazine (**2**, Scheme 1) obtained by the one step reaction of 2,3,3-trimethyl-5-nitro-3*H*-indole (**1**) with 2-chloromethyl-4-nitrophenol and treatment with sodium cyanide yielded the stable adduct **3**, which included a 4-nitrophenolate chromophore as a side chain that absorbed at approximately 410 nm [18]. This compound was commercialised by Sigma-Aldrich as a selective and sensitive optical chemosensor for the detection of cyanides [19]. Recently, we developed a new type of molecular chemosensor, including compound **4**, that possesses a 1',3,3',4-tetrahydrospiro[chromene-2,2'-indole] ring system [20,21]. These switches demonstrate a distinct colour change when treated with cyanide in acetonitrile solution buffered with sodium phosphate, and this procedure (e.g., leading to the formation of the adduct **5**) is not significantly affected by other common anions. They exhibit high sensitivity to low concentrations of cyanide, meeting the water quality control

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**Scheme 1.** Cyanide receptors based on 2,3,3-trimethyl-5-nitro-3*H*-indole.

criterion of sensitivity below 0.05 mg/L, and show a very fast response. In this study, we developed methods to prepare compounds that possess analogous ring systems as **2** and **4** with trifluoromethyl groups at the indoline C-5 atom. In addition to the synthesis, we investigated the effects of these chemical modifications on their functional properties.

## 2. Results and discussion

### 2.1. Synthesis

The synthetic strategy used to prepare the desired trifluoromethyl group possessing compounds is outlined in [Scheme 2](#). The initial compound 5-trifluoromethyl-2,3,3-trimethyl-3*H*-indole (**6**) was obtained from 4-trifluoromethylphenylhydrazine and 2-methylbutanone via a Fischer indole synthesis as described previously [22,23]. When compound **6** was treated with 2-chloromethyl-4-nitrophenol (**7**) in acetonitrile, the reaction afforded 8-(trifluoromethyl)-5a,6-dihydro-12*H*-indolo[2,1-*b*][1,3]benzoxazine (**8**) as a white crystalline solid ([Scheme 2](#)).

The synthesis of 5'-trifluoromethyl-1',3,3',4'-tetrahydrospiro[chromene-2,2'-indoles] **11a–c** first required the preparation of 1-substituted 5-trifluoromethyl-3*H*-indolium salts **9a–c** by alkylating compound **6** with methyl iodide, ethyl iodide and allyl bromide, respectively. Treatment of the salts **9a–c** with a base afforded 5-trifluoromethyl-2-methylidene indolines **10a–c**, which were used in subsequent reactions without further purification. The reaction of the heterocyclic enamines **10a–c** with 2-chloromethyl-4-nitrophenol (**7**) in acetonitrile resulted in alkylation at the  $\beta$ -carbon atom of the enamine moieties followed by

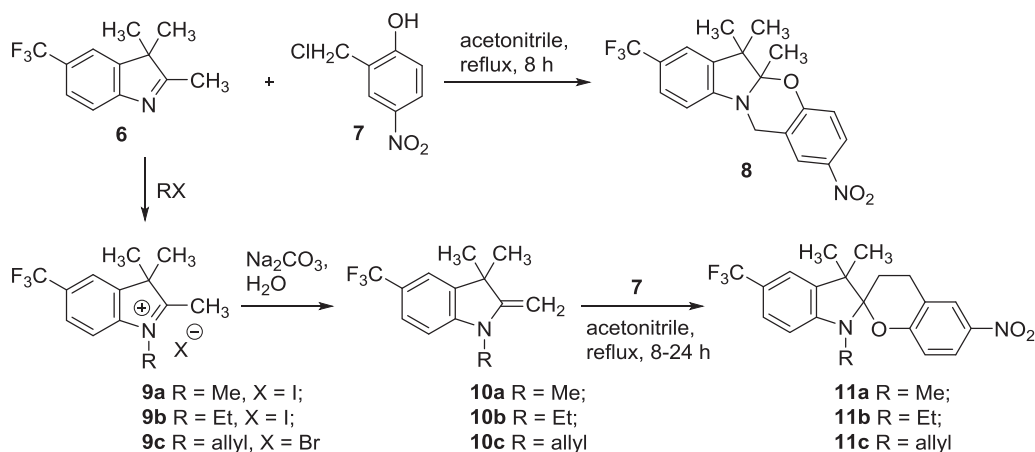
nucleophilic addition of the phenolic oxygen atom to the  $\alpha$ -carbon atoms. This afforded the spiro compounds **11a–c**, which were isolated from the reaction mixture by column chromatography.

### 2.2. NMR structural investigations

The structures of the newly synthesised heterocyclic derivatives were investigated and confirmed by NMR spectroscopy using the combined application of standard NMR techniques such as COSY, DEPT, HSQC and HMBC, and  $^{19}\text{F}$  spectra.

Characteristic signals in the  $^1\text{H}$  NMR spectrum of the chiral 8-(trifluoromethyl)-5a,6-dihydro-12*H*-indolo[2,1-*b*][1,3]benzoxazine (**8**), which possesses an asymmetric C-5a atom, were the slightly broadened singlets of the diastereotopic geminal methyl groups at C-6 at 1.21 and 1.56 ppm. The broadening of the aforementioned signals demonstrates that the equilibrated inversion of the chiral centre at C-5a and fast conversion between the corresponding *R*- and *S*-enantiomers takes part in solution, as previously shown with similar types of compounds [24,25]. The  $^{13}\text{C}$  NMR spectrum of **8** contained a signal for C-5a at 102.7 ppm, which is covalently bonded with N- and O-atoms, while the corresponding carbon resonance of  $\text{CF}_3$  was located at 124.8 ppm with a relevant  $^1\text{J}(\text{C},\text{F})$  coupling constant of 270 Hz. In the  $^{19}\text{F}$  NMR spectrum, the  $\text{CF}_3$  group had a chemical shift at  $-64.14$  ppm [26,27]. The full assignment of  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$  and  $^{19}\text{F}$  chemical shifts for compound **8** is presented in [Fig. 1A](#).

The  $^1\text{H}$  NMR spectra of the chiral spiro compounds **11a–c** contained the peaks of the geminal 3',3'- $\text{CH}_3$  groups between 1.26 and 1.32 ppm, while the corresponding  $^{13}\text{C}$  NMR signal of the spiro-C-3' atom was present at ca. 104 ppm [28]. In the  $^{19}\text{F}$  NMR



**Scheme 2.** General synthesis of chemosensors (**8**, **11a–c**) bearing trifluoromethyl substituents in the indoline part of the heterocyclic system.

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