A highly efficient method for the synthesis of novel 1'*H*-spiro[indene-2,2'-quinazoline]-1,3,4'(3'*H*)-trione derivatives

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A series of novel ninhydrin-derived spiro-quinazolinone derivatives in moderate to good yields have been synthesised through a ferric chloride catalysed reaction in 1,2-dichloroethane.

Keywords: spiro compounds, primary amines, ninhydrin, ferric chloride

Nitrogenous heterocycles are found in the core structure of numerous natural products and pharmaceutical agents. Therefore, much effort has been devoted to access new nitogen-containing cycles. The resultant compounds could be utilised as potential bioactive entities in drug discovery. The interesting biologically active molecules, quinazoline and quinazolinones exhibit diverse properties.[1,2] For instance, gefitinib[3] **1** and raltitrexed[4] **2** have been described as EGFR (epidermal growth factor receptor) inhibitors and antitumour agents respectively. Moreover, spiro-based heterocycles are of high interest to medicinal chemists for their prevalence in many bioactive molecules. The asymmetric spiro carbon atom often gives the molecule special stereochemical features required for interactions with biological systems. As such, spiro quinazolinone systems have versatile pharmacological properties such as the potential inhibitory activity against SIRT1 of **3** [5] and the antitumour character of **4**.[6]

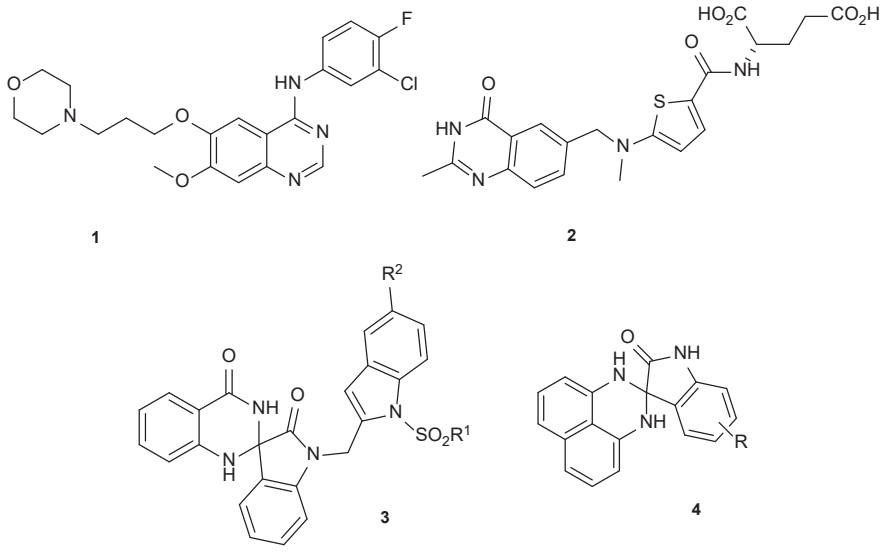
The most well-established strategy for the synthesis of 2,3-dihydro quinazolinones has been based on the condensation of 2-aminobenzamides with carbonyl functionality employing different catalysts like $CuCl_2$,[7] $TiCl_4$-Zn,[8] *p*-TsOH,[9] NH_4Cl,[10] β-cyclodextrin-SO_3H,[11] TCT,[12] I_2 [13] and acidic SiO_2.[14] Furthermore, utilising isatoic anhydride[15-19] and 2-nitrobenzamides[20] with the assistance of the appropriate reducing agent, provides a route for an alternative method of construction of quinazolines.

Focused on 2-aminobenzamide chemistry[21] and concerned with the synthesis of new heterocyclic compounds,[22-27] we now report the $FeCl_3$-catalysed synthesis of 1'*H*-spiro[indene-2,2'-quinazoline]-1,3,4'(3'*H*)-trione derivatives from isatoic anhydride **5** and amines **6**, and the reaction of various 2-amino-*N*-substituted benzamides **7a–h** and ninhydrin **8** in 1,2-dichloroethane.

Results and discussion

As mentioned above, the activity of iodine in similar reactions encouraged us to examine other Lewis acids. So, we carried out the model reaction by taking **8** (1 equiv.) and 2-amino-*N*-benzyl benzamide **7a** (1 equiv.). Benzamide derivatives were prepared by the simple reaction between isatoic anhydride **5** and amine derivatives **6a–h** in water at room temperature (Scheme 1).[28,29]

Screening of the model reaction was conducted using different solvents, Lewis acids and varying temperature as indicated in Table 1. The transformation catalysed by $FeCl_3$ in refluxing 1,2-dichloroethane (DCE) afforded the expected product in 64% yield, whereas by applying CuI, CuBr and $CuBr_2$ as the catalyst, the yields dropped to 59%, 36%, 27% respectively (entries 2–4). In contrast to other solvents such as CH_3CN, DMF, and 1,4-dioxane (entries 5–7), DCE was found to be the solvent of choice based on isolated yields. There was no noticeable improvement in the reaction yield when the reaction was attempted at lower temperatures (entry 8). Next, varied



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