European Journal of Medicinal Chemistry 74 (2014) 50–64

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Novel spirooxindole–pyrrolidine compounds: Synthesis, anticancer and molecular docking studies

Y. Arun [a], K. Saranraj [a], C. Balachandran [b], P.T. Perumal [a,*]

[a] Organic Chemistry Division, CSIR-Central Leather Research Institute, Chennai 600020, India
[b] Division of Microbiology and Cancer Biology, Entomology Research Institute, Loyola College, Chennai 600034, India

ARTICLE INFO

Article history:
Received 7 November 2013
Received in revised form
17 December 2013
Accepted 22 December 2013
Available online 3 January 2014

Keywords:
Spirooxindole
Pyrrolidine
Multicomponent reaction
Azomethine ylide cycloaddition
Anticancer activity
Molecular docking

ABSTRACT

Novel spirooxindole–pyrrolidine compounds have been synthesised through 1,3-dipolar cycloaddition of azomethine ylides generated from isatin and sarcosine or thioproline with the dipolarophile 3-(1*H*-imidazol-2-yl)-2-(1*H*-indole-3-carbonyl)acrylonitrile under the optimised reaction condition. Synthesised compounds were evaluated for their anticancer activity against A549 human lung adenocarcinoma cancer cell line. Among the 29 tested compounds **4j**, **6b** and **6h** showed very high activity 66.3%, 64.8% and 66.3% at 25 μg/mL concentration against A549 lung adenocarcinoma cancer cell line. These spirooxindole–pyrrolidine compounds can be promising therapeutic agents for A549 lung adenocarcinoma cancer cell line.

1. Introduction

Spirooxindole represents essential substructures for the synthesis of biologically important synthetic and natural compounds in drug discovery. Specifically, spirooxindole–pyrrolidines are found in a number of biologically active natural (Fig. 1) and synthetic products [1–8]. Interestingly, synthesised spirooxindole–pyrrolidine compounds have been identified as antimicrobial [9], anticancer [10–12], anti-inflammatory [13], antimycobacterial [14] and acetylcholinesterase (AChE) inhibitor [15,16]. The prevalence of these structures has resulted in the production of diverse libraries of small molecules for biological evaluation.

Cancer is unregulated and uncontrolled cell growth and the reason for more deaths in worldwide. In particular, lung cancer is the leading cause of death from cancer and it occurs more commonly after the age of 60 years. But, some people are at a higher risk of developing lung cancer early because of their smoking habit and their life style changes. Generally, curing of cancer is difficult because of the side effect of drugs on the normal cells and makes some other abnormalities in our body and also cancer drugs have to be cheaper and more effective. Hence, developing the new therapeutic drugs for cancer treatment is more important to improve the efficiency and efficacy of the drugs on the cancer cells [17].

Chemists are facing a major challenge to synthesis biologically important compounds because of multistep processes, selectivity of the desire product over to side products and tedious separation and purification steps to attain highly pure drug molecules. Conventionally, the drugs have been synthesised by multistep reaction sequences which are associated with difficult isolation of the desire product, low yields and high cost. In modern approach, the multicomponent reactions (MCRs) are useful to synthesise biologically important novel compounds. In contrast with linear-type syntheses, the MCR strategy involves the rapid combination of three or more simple molecules and produce structurally complex and diverse molecules in a single step reaction [18–20].

2. Results and discussion

2.1. Chemistry

In continuation of our studies in the synthesis of novel biologically important heterocyclic compounds especially spirooxindoles [21] using multicomponent 1,3-dipolar azomethine ylide cycloaddition reaction [9,10,22], we herein report the one pot tandem reaction of 1,3-dipolar cycloaddition reaction to form the imidazole appended novel spirooxindole–pyrrolidine derivatives. In the

* Corresponding author. Tel./fax: +91 44 24913289.
E-mail address: ptperumal@gmail.com (P.T. Perumal).

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http://dx.doi.org/10.1016/j.ejmech.2013.12.027

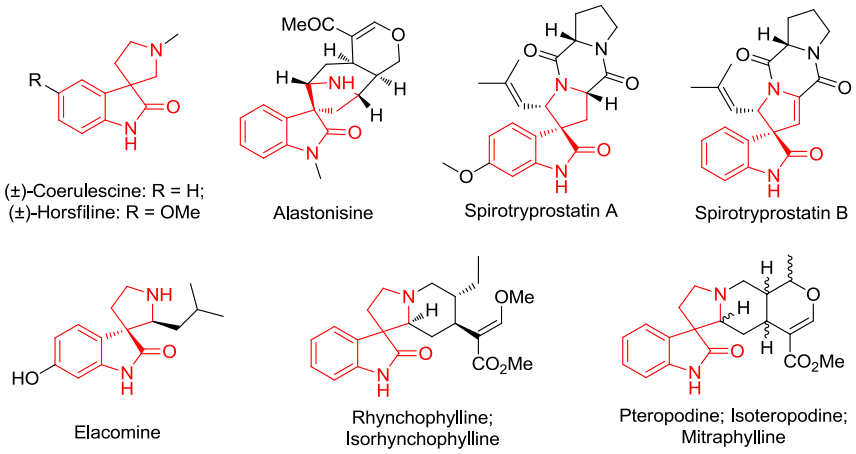
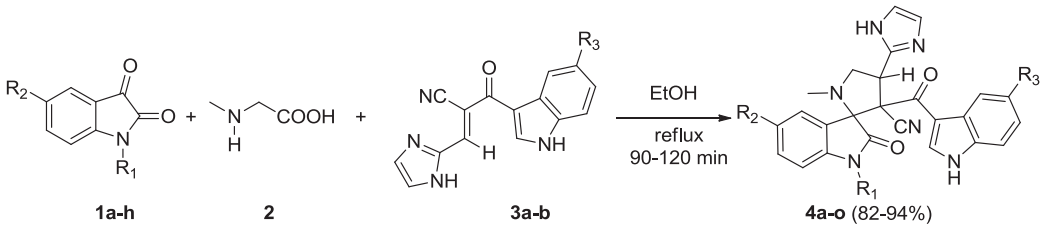


Fig. 1. Naturally occurring spirooxindole–pyrrolidine compounds.



Scheme 1. Synthesis of spirooxindole–pyrrolidines (**4a**–**o**) from substituted isatin **1a**–**h**, sarcosine **2** and dipolarophile **3a** or **3b**.

present investigation, the 1,3-dipolar cycloaddition of azomethine ylides, generated *insitu via* decarboxylative condensation of substituted isatins **1a**–**h** and sarcosine **2** to 3-(1*H*-imidazol-2-yl)-2-(1*H*-indole-3-carbonyl)acrylonitrile **3a** or 3-(1*H*-imidazol-2-yl)-2-(5-methoxy-1*H*-indole-3-carbonyl)acrylonitrile **3b** in ethanol afforded novel spirooxindole–pyrrolidine **4a**–**o** in high yields (Scheme 1).

Different solvents such as methanol, ethanol, dimethyl sulfoxide and acetonitrile were used to optimise the reaction condition. Among these, ethanol is the suitable solvent to give high yields at minimum time and also purification of the product by precipitation is much easier when compared to dimethyl sulfoxide and acetonitrile. Finally, this reaction was performed by heating an equimolar mixture of substituted isatins **1a**–**h,** sarcosine **2** and 3-(1*H*-imidazol-2-yl)-2-(1*H*-indole-3-carbonyl)acrylonitrile **3a** or 3-(1*H*-imidazol-2-yl)-2-(5-methoxy-1*H*-indole-3-carbonyl)acrylonitrile **3b** in ethanol under reflux for 1–2 h. After completion of the reaction (TLC), the reaction mixture was poured into ice-water, the resulting solid was filtered off and washed with ethanol to obtain pure spirooxindole–pyrrolidine derivatives **4a**–**o** in 82–94% yields (Table 1).

To further explore the potential of this protocol for novel spirooxindole–pyrrolidine synthesis, this reaction was further explored by heating an equimolar mixture of substituted isatin **1a**–**h**, thioproline **5** and 3-(1*H*-imidazol-2-yl)-2-(1*H*-indole-3-carbonyl)acrylonitrile **3a** or 3-(1*H*-imidazol-2-yl)-2-(5-methoxy-1*H*-indole-3-carbonyl)acrylonitrile **3b** in ethanol under reflux for 1.5 h and obtained pure spirooxindole–pyrrolidine derivatives **6a**–**n** in 82–95% yields (Scheme 2). The results are summarised in Table 2.

The two possible regio approaches of 1,3-dipole and dipolarophile were shown in path A and B in Scheme 3. In the dipolarophile, electron density of the β-position is decreased by the carbonyl and nitrile groups. This leads to regioselective product which cyclises only *via* path B rather than path A. But, two diastereomers are possible for this regioselective product which were shown in path X and Y in Scheme 3. The transition state formed by path Y stabilised by secondary orbital interaction between carbonyl groups of 1,3-dipole and dipolarophile, whereas no such secondary orbital interaction is possible in path X, hence the reaction proceeds *via* path Y and only leading to regio- and diastereoselective spirooxindole–pyrrolidine products.

The structure of novel spirooxindole–pyrrolidine derivatives by 1,3-dipolar cycloaddition of azomethine ylide was elucidated with the help of IR, ^{1}H NMR, ^{13}C NMR and Mass data as illustrated for **4a**. In the IR spectrum, the sharp absorption bands at 1720 and 1631 cm^{-1} correspond to C=O stretching frequency of ketone and amide groups and the absorption band at 2243 cm^{-1} corresponds to C≡N stretching frequency. Also the absorption bands at 3394 and 3290 cm^{-1} correspond to the N–H groups present in the product **4a**. In the ^{1}H NMR spectrum, a singlet in the region δ: 10.48 ppm confirmed the presence of –NH proton of spirooxindole–pyrrolidine and the two singlets in the region δ: 11.95 & 11.86 ppm confirmed the presence of two –NH proton of imidazole and indole. The peaks in the range of δ: 6.65–8.15 ppm shows the 11 aromatic protons. The dd peak at δ: 5.37 ppm with the *J* value 10.3 and 7.4 Hz for a proton shows the presence of hydrogen attached with imidazole ring. The two triplets at δ: 3.91 and 3.53 ppm with the *J* value 7.9 and 9.5 Hz for two protons showed the presence of pyrrolidine ring –CH_2 group. The signal at δ: 2.10 ppm for three protons confirmed the presence of –NCH_3 group. The ^{13}C NMR, the peak at δ: 76.0 ppm corresponds to the spiro carbon of spirooxindole–pyrrolidine and the peak at δ: 64.9 ppm corresponds to the another spiro carbon of the compound **4a**. The peaks at δ: 181.0 and 174.9 ppm confirmed the presence of two carbonyl groups. In DEPT 135 and 90, the peaks at δ: 54.6 & 35.0 ppm confirms the presence of –CH_2 and –NCH_3 groups respectively. A distinguishing peak observed at *m*/*z*: 437.17050 in