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ORIGINAL RESEARCH

Efficient entry to diversely functionalized spirooxindoles from isatin and their biological activity

Mazaahir Kidwai · Arti Jain · Vishal Nemaysh · Rakesh Kumar · Pratibha Mehta Luthra

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Abstract A collection of structurally complex and chemically diverse small molecules is a useful tool to explore cell circuitry. In this article, we have reported the two step synthesis of diverse spirooxindoles. The key reaction to assemble the spirooxindole core is a Lewis acid catalyzed three component coupling. The final library of compounds was then analyzed for their cytotoxic activity against U87 human glioma cells. It is noteworthy to mention that this is the first report on the pharmaceutical evaluation of such compounds. Although the activity is moderate, it opens the door for new chemical modifications of spirooxindoles.

Keywords Diversified series of spirooxindoles · Novel compounds · Green methodology · Two step multicomponent reaction · Pharmacological activity

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Present Address:
M. Kidwai (✉)
Jiwaji University, Gwalior, M.P., India
e-mail: kidwai.chemistry@gmail.com

M. Kidwai · A. Jain
Green Chemistry Research Laboratory, Department of Chemistry, University of Delhi, New Delhi 110007, India

V. Nemaysh · R. Kumar · P. M. Luthra
Neuropharmaceuticals Research Laboratory, Dr. B. R. Ambedkar Center for Biomedical Research, University of Delhi, New Delhi 110007, India

Introduction

In recent years, the trend in combinatorial library design has shifted to include target class focusing along with diversity and drug likeness criteria. A goal of chemical genetics is to find small molecules that modulate the individual functions of gene products with high potency and specificity (Schreiber, 2000).

Molecules bearing the spirooxindole moiety are widely found in nature (Williams and Cox, 2003; Galliford and Scheidt, 2007; Cui *et al.*, 1996a, b; Kang *et al.*, 2002; Rahman *et al.*, 1987). Among the oxygen-containing heterocycles fused with spirooxindole ring system, 4*H*-chromenes are of particular utility as they belong to "privileged medicinal scaffolds," (Evans *et al.*, 1988; Patchett and Nargund, 2000; DeSimone *et al.*, 2004; Skommer *et al.*, 2006; Bonsignore *et al.*, 1993; Konkoy *et al.*, 2000). But Spiro[indole-chromene] unit is an unprivileged heterocyclic motif because this unit is not involved in the core of a large family of alkaloid natural products. Recently, Nandakumar *et al.* (2010) have explored the antimicrobial activity of 2′-(indol-3-yl)-2-oxospiro(indoline-3,4′-pyran)derivatives. But no report is available for the pharmacological evaluation of Spiro[indole-pyranopyrimindines] and Spiro[indol-pyranopyrazoles]. This is very unfortunate as pyran nucleus has been found to be associated with a group of biological activities. (Kulkarni and Kaul, 1980).

Heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically active compounds (Elguero *et al.*, 2002; Penning *et al.*, 1997). Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiro-indoline derivatives highly enhances biological activity (Joshi *et al.*,

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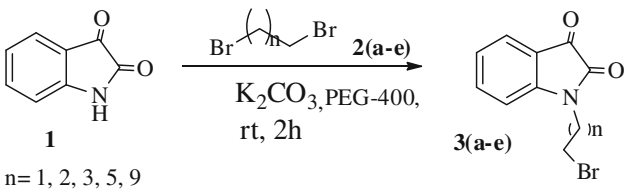
1988). Our laboratory has been interested in exploring diversity oriented synthesis (DOS), especially using MCR's as well as to find space for the new biological active motifs (Kidwai *et al.*, 2012a, b).

The interaction of organic compounds with proteins is an extremely important biochemical problem with many interesting facets. One of these is the extent to which drugs or metabolically necessary compounds will be restricted in their movements in the cell or intercellular fluids such as blood. Such restriction of movement will depend on how firmly they are bound to the protein with which they come into contact (Hansch *et al.*, 1965). One of the most important forces holding proteins and small organic molecules together appears to be termed as hydrophobic bonding (Kauzmann, 1959). Nature has provided effective examples via natural products, which in turn have stimulated the development of target oriented synthesis (TOS). A number of biologically active compounds have been isolated from plants and marine sponges, which contained a lipophilic (hydrophobic) moiety in the form of alkyl/alkenyl chain attached to either benzene or heterocyclic skeleton (Jain *et al.*, 2005; Kubo *et al.*, 1993). Hence, our objective is to check the synthesized compounds bearing additional alkyl chain and then to check its viability as biologically active compounds.

The development of a facile procedure for the synthesis of heterocyclic compounds is a major challenge of modern heterocyclic chemistry in the view of the environmental, practical, and hence economic issues. Replacement of volatile organic solvents with environmental benign solvents has received considerable attention in organic synthesis (Sheldon, 2005). Several solvent systems, including water (Cornils and Herrmann, 1998), supercritical fluids (Leitner, 2002), ionic liquids (Sheldon, 2001), and soluble polymers (Haimov and Neumann, 2002; Chandrasekhar *et al.*, 2002) have been exploited over the several years as alternative reaction media.

Cancer is one of the most devastating disease causing more than 10 million new cases every year worldwide. The global burden of cancer is continuously increasing day by day. In the year 2000, 5.3 million men and 4.7 million women developed a malignant tumor and 6.2 million died from the disease. The number of new cases is expected to grow by 50 % over the next 20 years to reach 15 million by 2020. Due to the lack of tumor-specific anticancer agents, the discovery and development of new types of highly selective anticancer agents is still a very urgent topic. Herein, we present our contribution to concise construction of novel spirooxindoles and their evaluation for cytotoxic activity.



Scheme 1 Synthesis of bromoalkylisatin using K_2CO_3 in PEG-400 at room temperature

Results and discussion

Chemistry

It has been suggested that aliphatic chain reduces the polarity of the whole compound. This leads to an increase in lipophilicity of the molecule, which in turn, favors its permeation through the lipoid layer of the membrane; this enables the compound to cross the bacterial membrane/any other more effectively thereby increasing the biological activity of the compounds.

On the basis of the above hypothesis, our first task was to attach an aliphatic chain on the nitrogen of isatin.

A literature survey has revealed that the reaction of isatin with dibromoalkanes proceeds in hazardous organic solvent like acetonitrile/DMF in the presence of K_2CO_3 (Marina *et al.*, 2010). In order to maintain our goal to explore environmentally benign protocols, we used PEG-400 as solvent with K_2CO_3 for preparing the bromoalkyl isatin.

First of all, 1-(2-bromoethyl)-indole-2,3-dione was synthesized via isatin alkylation with excess of dibromoethane in PEG 400 at room temperature in the presence of potassium carbonate. Excellent yield of product (80 %) was obtained by stirring the reaction mixture for 2 h (Scheme 1).

The structure of products **3a–e** were confirmed by spectral studies as exemplified for compound **3a** as follows: the ^{1}H

Table 1 Effect of solvents on the synthesis of bromoalkylisatins

Solvents	Time (h)	Yield (%)[a]
Ethanol	3	70
Acetonitrile	2	80
DMF	2	80
Dioxane	4	55
THF	5	50
Toluene	5	48
PEG-200	2	80
PEG-400	2	80
PEG-600	3	65
PEG-800	3.5	50

Reaction condition: isatin (1 mmol), dibromoethane (excess); solvent; catalyst K_2CO_3; room temperature

[a] Isolated yields

Table 2 Optimization of concentration of K_2CO_3 for the synthesis bromoethylisatin

Entry	K_2CO_3 (mol%)	Time (h)	Yield (%)[a]
1	3	4	70
2	5	4	72
3	10	2	80
4	15	2	82

Reactions were performed with isatin (0.01 mmol), dibromoethane (excess), and K_2CO_3 (× mol%) in PEG-400 (3 ml) by stirring the mixture at room temperature

[a] Isolated yield

Table 3 PEG 400 recycling studies

Catalyst recycle	Fresh	2	3	4
Yield (%)[a]	80	80	78	77

Reactions were performed with isatin (0.01 mmol), dibromoethane (excess), and K_2CO_3 (10 mol%) in PEG-400 (3 ml) by stirring the mixture at room temperature

[a] Isolated yield

NMR spectrum peaks at δ 3.59 and 4.75 reveals the presence of two methylene groups. Absence of peak at δ 8.56 shows the removal of N–H by CH_2CH_2Br. The nature of reaction media has an important role in the alkylation process in the presence of K_2CO_3 (10 mol%). The yields of products were excellent in polar solvents, such as PEG, CH_3OH, DMF, and CH_3CN, whereas the yields were much lower in less-polar solvents such as toluene, THF, and dioxane. We have also tried various PEGs with different molecular weights. As the molecular weight of PEGs increases, viscosity also increases, which led to the highly viscous reaction mixture thus giving low yields of products (Table 1).

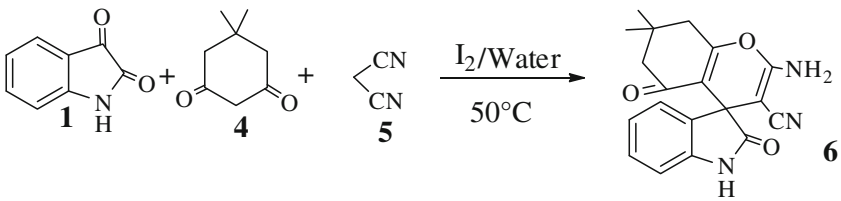
Catalyst concentration plays a major role in the optimization of the product yield. By increasing the molar concentration of potassium carbonate from 5 to 15 mol%, it was observed that increased loading of the catalyst from 10 to 15 mol% gave almost the same yield of the product. But when we used 2–8 mol% of the catalyst, low yield was obtained. 10 mol% of potassium carbonate (K_2CO_3) was the suitable choice for an optimum yield of the products (Table 2).

In order to test the solubility and reusability of PEG-400 as a solvent, the reaction mixture was extracted with solvent ether, since PEG is immiscible with solvent ether. To the recovered crude PEG (≈3 ml), distilled ethanol (10 ml) was added and passed through a very short pad of silica gel and activated charcoal. The colorless organic layer was evaporated under reduced pressure. PEG-400 was further dried under high vacuum overnight and used for the next run. The recovered PEG-400 was reused up to three cycles with a little loss of reactivity (Table 3).

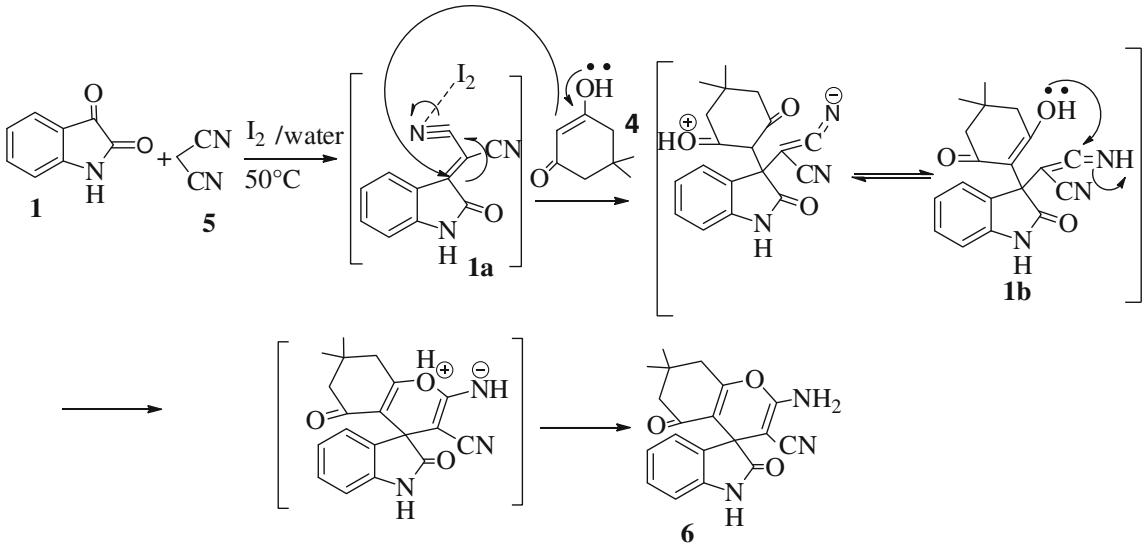
PEGs could be regarded as open-chain crown ethers as they are able to form complexes with alkaline and alkaline-earth cations in protic and aprotic solvents (Yanagida *et al.*, 1978). We postulated that in the PEG/K_2CO_3 system, the CO_3^{2-} anion could be brought into solution through the coordination of the cationic center of K_2CO_3 with the oxygen atom of PEG (Wang *et al.*, 2007). Thus, the reaction of the CO_3^{2-} anion with isatin was elevated by enhancing the nucleophilicity of nitrogen for addition to dibromoalkanes.

The reaction of isatin with an equimolar amount of dimedone and malononitrile as a model reaction was examined to establish the feasibility of the strategy and optimization of the reaction conditions. It is well known that the choice of an appropriate reaction medium is of crucial importance for successful synthesis. So to begin with, the model reaction was done in water without any catalyst at 100 °C. Even after 6 h only 40 % product was formed. In recent times, the usage of molecular iodine has received considerable attention as an inexpensive, nontoxic, water soluble, readily available catalyst with high tolerance to air and moisture for various organic synthesis (Togo and Lida, 2006). The key reaction to assemble the spirooxindole core is a Lewis acid variant of three component coupling. Hence we tried the same reaction with I_2 in water at 50 °C. To our delight, deep red violet color of the 3-cyanomethylene oxindole formed immediately after the addition of the catalyst. A colorless product separated out only after 1 h of stirring, which suggested that conjugated oxindolidine system was converted to unconjugated oxindoles (Scheme 2).

We proposed the following possible mechanism to account for the formation of **6**. The process represents a typical cascade reaction in which the isatin **1** first condenses with malononitrile **5** to afford isatylidene malononitrile derivative (**1a**). This step can be regarded as a fast knoevenagel addition. Then (**1a**) undergoes Michael addition with dimedone **4** to give the intermediate (**1b**)



Scheme 2 Synthesis of spirooxindole using equimolar each of isatin, dimedone, and malononitrile at 50 °C



Scheme 3 Plausible mechanism for the I_2 catalyzed synthesis of spirooxindoles

Scheme 4 Diversity-generating synthesis scheme using multicomponent reaction

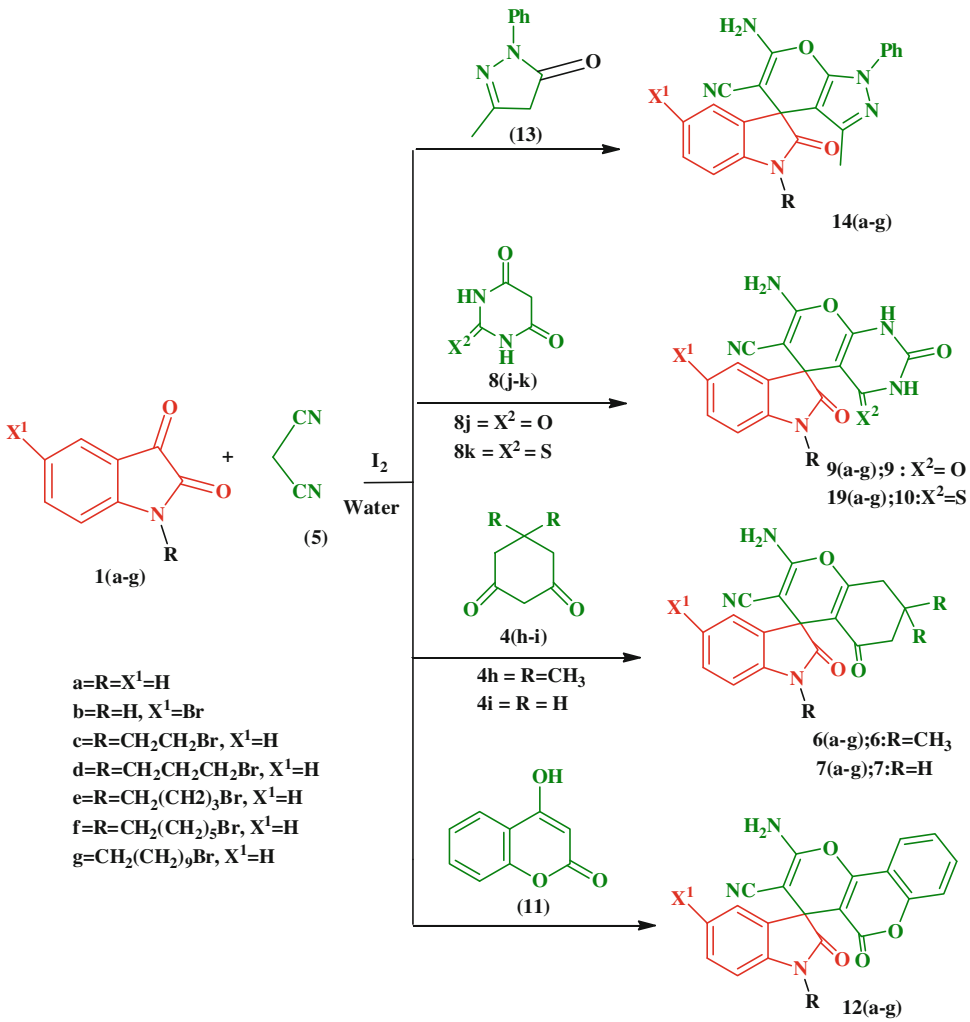


Table 4 Screening of compounds for cytotoxic activity on U87 human glioma cells

Compounds	MTT IC_{50} (μg/ml)	Compounds	MTT IC_{50} (μg/ml)	Compounds	MTT IC_{50} (μg/ml)
6a	78	**14c**	78	**12f**	156
7a	156	**6d**	312	**14f**	78
9a	312	**7d**	624	**6g**	2.5
10a	39	**9d**	312	**7g**	39
12a	78	**10d**	624	**9g**	39
14a	156	**12d**	156	**10g**	39
6b	156	**14d**	78	**12g**	39
7b	312	**6e**	156	**14g**	19
9b	78	**7e**	78	**3a**	4.9
10b	156	**9e**	312	**3b**	2.5
12b	78	**10e**	78	**3c**	19
14b	156	**12e**	78	**3d**	19
6c	78	**14e**	39	**3e**	19
7c	78	**6f**	78	**3f**	19
9c	78	**7f**	78	**3g**	4.9
10c	78	**9f**	78		
12c	78	**10f**	78		

Standard used is Carmustine (BCNU) with IC50 value is 3.9 μg/ml for MTT

followed by cycloaddition and dehydration to form the desired product (**6**) (Scheme 3).

In order to further explore the potential of present protocol for heterocyclic compound synthesis, and to form a huge library of diversified compounds for their biological evaluation, we investigated one pot reactions involving 1,3-cyclohexanedione, 4-hydroxy coumarin, barbituric acid, thiobarbituric acid, and 1-phenyl-3-methyl-2-pyrazolin-5-one as active methylene compounds in place of dimedone. Moreover, 5-bromoisatin and different bromoalkyl isatins were also tried with the above-listed active methylene compounds (Scheme 4).

The common spectral features in all these compounds are the presence of cyano group and amino group; in the IR spectrum, the stretching frequency appeared in the range of 2,100–2,300 cm^{-1}. Stretching frequency in the range of 3,100–3,400 cm^{-1} corresponds to $–NH_2$ functional group. In the ^1H NMR, a broad singlet for NH_2 appears in the range of 10–12 ppm. A characterization peak in the range of 90–100 ppm corresponding to cyano group attached carbon comes in ^{13}C NMR.

All the synthesized compounds were screened for their in vitro MTT cell line activity.

Hence we have investigated the cytotoxic effects of all the synthesized compounds on U87 human glioma cells.

Inspection of data in Table 4 revealed that the relative anticancer activity of compounds having alkyl chain with 10 carbon atoms was quite high as compared to others. These results indicated that the presence of lipophilic moiety often enhanced the biological activity of the compounds. Compounds **6g** and **3b** showed even far better activity than the standard used and hence could be used for the industrial purpose.

Conclusion

In conclusion, we have developed a simple and an efficient two step procedure for the synthesis of library of new series of spirooxindole derivatives. A privileged medicinal scaffold has been synthesized through three component reactions of structurally diverse isatins with malononitrile and barbituric acid/thiobarbituric acid/dimedone/1,3-cyclohexanedione, 4-hydroxycoumarin/1-phenyl-3-methyl-pyrazolin-5-one. It is a good attempt for the biological activity evaluation of spirooxindoles. Further studies to delineate the scope and limitations of the present methodology and skeleton modification for activity enhancement are under process.

Experimental

General

Some chemicals were purchased from Sigma-Aldrich and Lancaster and were used as such. All reactions and purity of products were monitored by thin layer chromatography (TLC) using aluminum plates coated with silica gel (Merck) employing ethylacetate and hexane (3:7). IR spectra were recorded on Perkin-Elmer FTIR-1710 spectrophotometer using Nujol film and KBr pellet. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JNMECX 400P FT NMR system using TMS as an internal standard. The chemical shift values are recorded on δ scale. Elemental analysis was performed on a Hereaus CHN rapid analyzer. ESI-MS mass spectra were recorded on a Waters LCT Micromass. The melting point of the compounds was measured through a Thomas-Hoover melting point apparatus and are uncorrected.

*Synthesis of products (**3a–e**)*

Potassium carbonate (10 mol%) was added to a stirred solution of 1*H*-indole-2,3-dione (1 mmol) in 3 ml PEG-400, then dibromo-alkane (2 mmol) was added. The mixture was then stirred at room temperature until the reaction was complete. The completion of the reaction was monitored through TLC. Later, distilled water (50 ml) was added to the reaction mixture and the product was extracted with diethyl ether (3 × 5 ml). The combined organic layer

was dried with anhydrous sodium sulfate and evaporated under *vaccuo*. The crude product, thus obtained was subjected to purification through column chromatography on silica gel (100–200 mesh size) using 25 % ethyl acetate in petroleum ether as eluent to yield product. The structures of all products were established on the basis of spectral analysis (IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis) and melting point determination.

Synthesis of spirooxaindoles

In a 50 ml round bottom flask, appropriate active methylene compound (0.01 mol), isatin/bromo isatin/*N*-alkyl isatin (0.01 mol), and malononitrile (0.01 mol) in 3 ml water. To this, iodine (10 mol%) was added, mixed, and stirred at 40 °C. The progress of reaction was monitored by TLC. The reaction mixture was treated with aqueous $Na_2S_2O_3$ solution. The solid product separated out was filtered, then washed with water and dried. The crude product thus obtained was subjected to purification by column chromatography on silica gel (60–120 mesh size) using ethylacetate in petroleum ether (10:90) as eluent to yield pure product. The structures of all products were established on the basis of spectral analysis (IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis) and melting point determination.

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