

Isatin, a Versatile Molecule: Studies in Brazil

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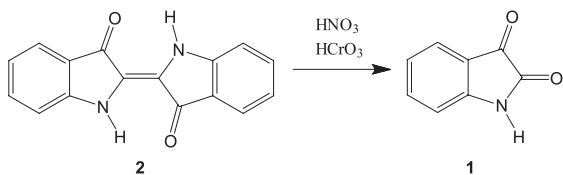
A isatina é uma molécula pequena, versátil e de ampla aplicação farmacológica. Estas características fazem da isatina e de seus derivados uma fonte de estudos químicos e farmacológicos atraente para diversos grupos de pesquisa. Embora possua estrutura relativamente simples, é rica em possibilidades de transformações químicas. Este artigo apresenta um painel dos diversos trabalhos desenvolvidos por grupos brasileiros que envolvem modificações estruturais, ensaios biológicos e investigações de novos métodos para a síntese de isatinas.

Isatin is a small, versatile and widely applicable pharmacological molecule. These characteristics make isatin and its derivatives attractive to many research groups as resources for chemical and pharmacological studies. Although it has a relatively simple structure, isatin is a useful chemical scaffold for a variety of chemical transformations. This article discusses several studies performed by Brazilian groups, including investigations of its structural changes, biological assay designs and new methods for the synthesis of isatin.

Keywords: isatin, medicinal chemistry, synthesis, Brazilian research groups

1. Introduction

Isatin (1*H*-indole-2,3-dione) (**1**) is a naturally occurring heterocycle that was first synthesised by Erdmann and Laurent in 1840, when these researchers reacted indigo (**2**) with nitric and chromic acids (Scheme 1).¹



Scheme 1. Preparation of isatin by Erdmann and Laurent.

Isatin is one of the few compounds to have been synthesised before it was discovered in nature. Isatin and its derivatives have been found in the parotid gland secretions of the *Bufo* frog,² the egg masses of the Australian mollusc *Dicathais orbita*,³ plants of the *Isatis* genus⁴ and the species *Couroupita guianensis*, Aubl, *Melochia tomentosa* and *Boronella koniamboensis*.⁵

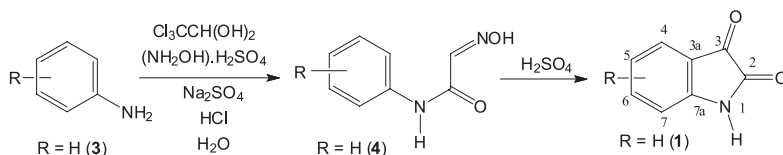
The synthetic versatility of isatin makes it an important raw material for the synthesis of a wide spectrum of

bioactive compounds. Isatin derivatives exhibit antiviral, anti-inflammatory, anticonvulsant and antitumor activities, among others. Some reviews of the pharmacological activities and synthesis of isatins, including oxindoles and indoles, have been published recently.⁶

Since the first synthesis of isatin from indigo, several isatin synthesis schemes have been reported, e.g., by Sandmeyer,⁷ Gassman *et al.*,⁸ Martinet⁹ and Stolle.¹⁰ Sandmeyer's method, the oldest, is still the most widely used, and it allows the synthesis of various substituted isatins, generally with high yields. The Sandmeyer's route, as modified by Marvel and Hiers,¹¹ involves the treatment of aniline or substituted anilines with chloral hydrate and sulfate, hydrochloride or other hydroxylamine salts in sodium sulfate solution and subsequent cyclisation with concentrated sulfuric acid (Scheme 2). This method is therefore simple and employs relatively inexpensive reagents.

The number of publications on the topic of isatins has grown over the years (Figure 1). In early 2012, 245 articles on this topic could be accessed.¹² This high number of articles is evidence that this molecule remains a current research interest, despite the fact that this compound was obtained for the first time in 1840.

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Scheme 2. The Sandmeyer's method, as modified by Marvel and Hiers.

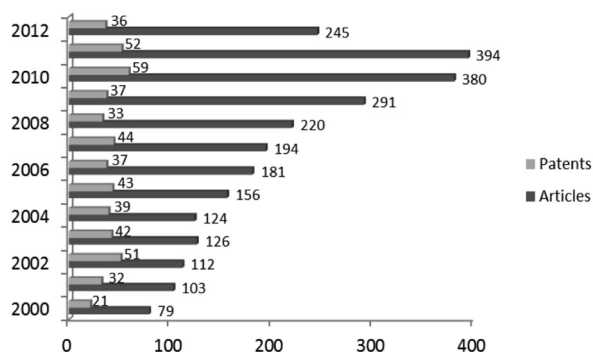


Figure 1. Numbers of articles and patents on isatins per year since 2000.

India, China and the United States of America lead the number of publications on isatin (Figure 2). Brazil occupies the ninth position with 55 publications, representing approximately 4% of all publications on chemical and pharmacological studies of isatins since its discovery.¹³

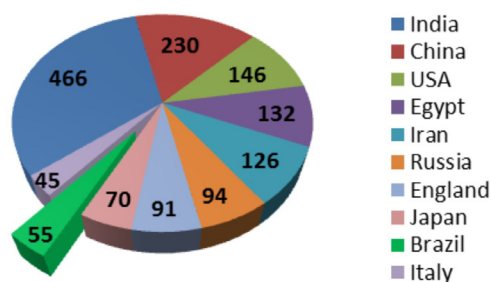


Figure 2. Number of articles on isatin by country since its discovery.

In this article, the studies on isatins that have been published by Brazilian groups are presented from a historical perspective. Selected reports from other countries are also described to provide an overview of the recent advances in this area.

2. Isatins as synthetic intermediates and pharmacological studies

2.1. Preparation of azepines

The two carbonyls in the isatin molecule are chemically distinct. While C-3 is extremely susceptible to nucleophilic attack, C-2 reacts with nucleophiles only under specific

conditions. Therefore, reactions of *N*-acylisatins with nucleophiles lead to heterocyclic ring opening.

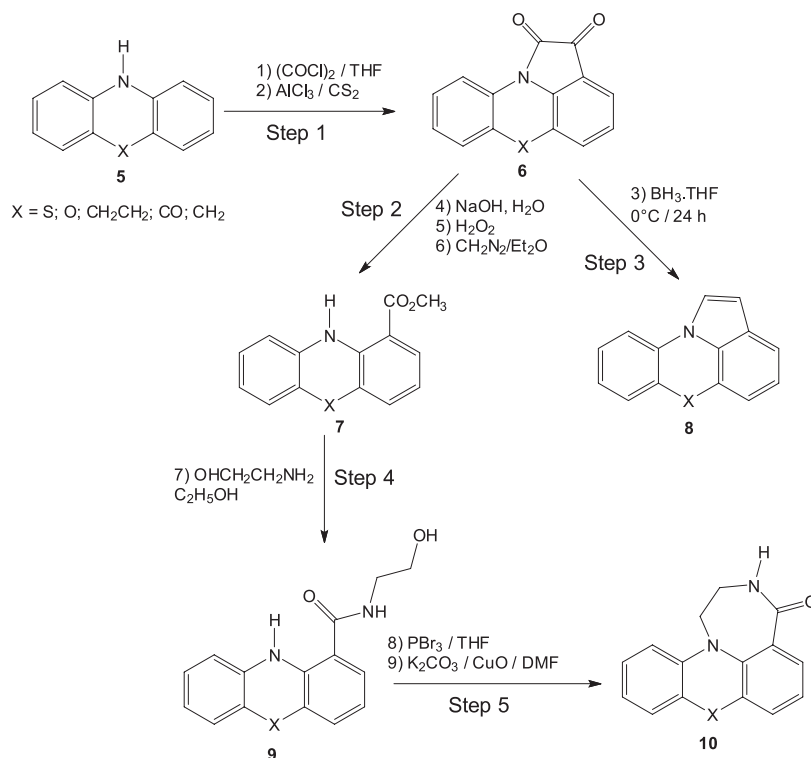
One of the first articles published on isatins in Brazil reported the synthesis of 10*H*-phenoxazine-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine tetracyclic derivatives (Scheme 3). The preparation of isatin **6** was carried out via the Stolle method (step 1). Hydrolytic cleavage of these isatins, followed by oxidative decarboxylation and diazomethane esterification, produced ester **7** (step 2). The reaction of **7** with ethanolamine in ethanol generated the acridine amide **9** (step 4), which was cyclised to produce an azepine amide **10** at high yields (step 5). Another explored reaction was the carbonyl reduction of compound **6**, employing borane in tetrahydrofuran (THF) to generate compound **8** at yields of more than 90% (step 3).¹⁴

2.2 Preparation of *N*-alkylisatins, *N*-alkylindoles and fluoroindolines

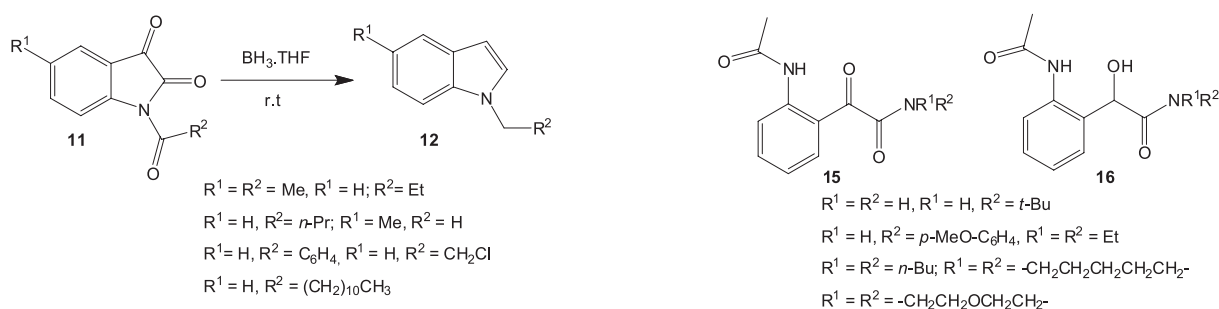
In 1994, Pinto *et al.*¹⁵ showed that *N*-acetylisatins (**11**)¹⁶ were suitable substrates for the synthesis of *N*-alkylindoles (**12**) under mild reaction conditions (Scheme 4). In general, the *N*-alkylation of an indole produces a mixture of products due to side substitution reactions at C-3, but the method described in the article provided pure products with good yields. This method uses BH_3 as the reducing agent and is performed at room temperature.

Indoles (**14**) have also been prepared from *N*-substituted-5-nitro-isatin (**13**) using the $ZrCl_4/NaBH_4$ system in DME (dimethyl ether) at room temperature, with a yield of 74% (Scheme 5). The direct reduction of 5-nitro-isatin produced the desired 5-nitroindole but with a yield of only 30%.¹⁷

N-Acetyl-isatin can be opened in the presence of amines to produce phenylglyoxamides (**15**) and mandelamides (**16**).^{18,19} The scaffolds of these compounds are found in molecules that exhibit a variety of biological activities due to their potential hydrogen bond interactions with the active sites of enzymes. Gonçalves *et al.*²⁰ investigated the direct and indirect effects of intra and intermolecular hydrogen bonds in phenylglyoxamides and mandelamides (Figure 3) based on experimental ¹H and ¹³C nuclear magnetic resonance (NMR) spectroscopy and theoretical ¹H and ¹³C NMR density functional theory with

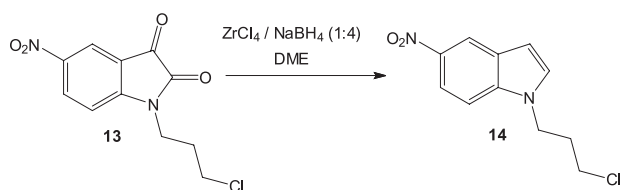


Scheme 3. The synthesis of azepine amide **10** (X = S, O, CH₂-CH₂, CH₂).



Scheme 4. Reaction conditions for the preparation of *N*-alkylindoles.

Figure 3. Structures of phenylglyoxamides (**15**) and mandelamides (**16**).



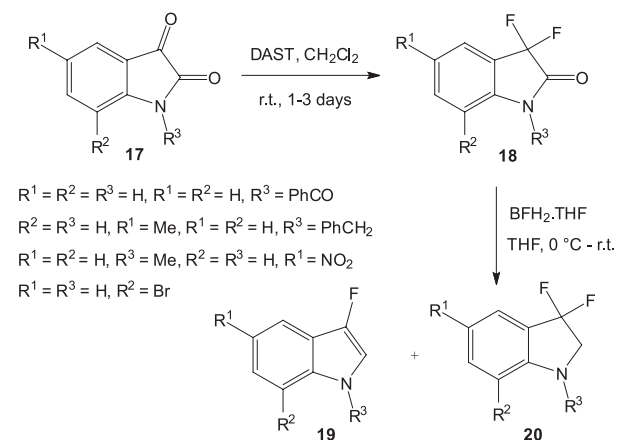
Scheme 5. Preparation of indoles from *N*-substituted-5-nitro-isatin.

gauge-including atomic orbital (DFT-GIAO) (B3LYP/6-311++G**//B3LYP/6-31G*) calculations. The authors investigated the effects of diamagnetic susceptibility anisotropy on both compounds.

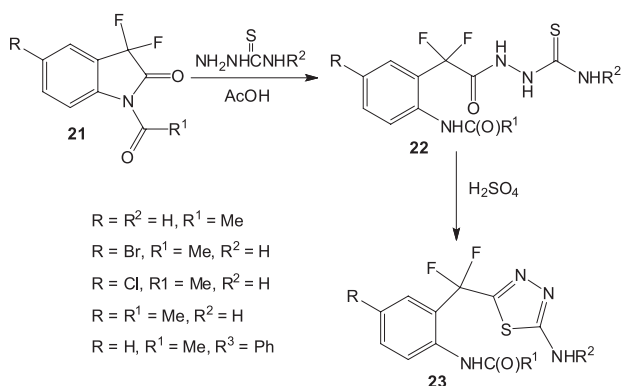
The introduction of fluorine atoms into an organic compound is a strategy that is frequently used to develop new drugs because this atom can modify the physical,²¹ chemical and biological properties of a molecule. Torres *et al.*²²

showed that the [BH₂.THF] complex could also be used to obtain 3-fluoroindoles (**19**) and 3,3-difluoroindolines (**20**) from the reduction of 3,3-difluoro-2-oxindoles (**18**) (Scheme 6). Isatin substrates were easily transformed into the corresponding difluoro compounds through a reaction with diethylaminosulfur trifluoride (DAST) followed by treatment with excess “borane” in THF.

N-Acyl-3,3-difluoro-2-oxindoles (**21**) have been shown by Boechat *et al.*²³ to be extremely versatile starting materials for the synthesis of a variety of compounds because they undergo heterocyclic ring opening in the presence of nucleophiles, such as water, alcohols, amine and thiosemicarbazides (**22**). In reactions with thiosemicarbazides, acid-catalysed cyclisations yield *N*-(2-((5-aminoaryl-1,3,4-thiadiazol-2-yl)difluoromethyl)-4-(*R*)-phenyl)acetamide (**23**) (Scheme 7).



Scheme 6. Reaction conditions for the preparation of fluoroindoles.



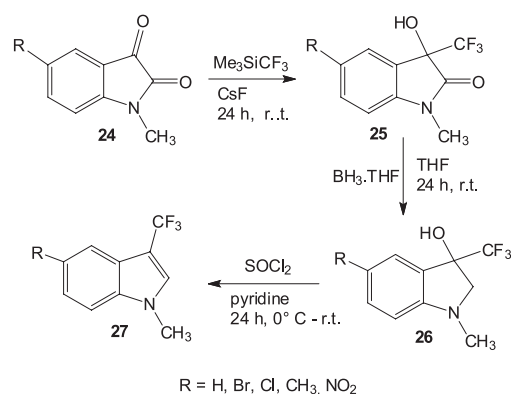
Scheme 7. Preparation of thiadiazoles (**23**) from *N*-acyl-3,3-difluoro-2-oxindoles (**21**).

Bastos *et al.*²⁴ have described the synthesis of novel 3-trifluoromethylindoles (**27**) from isatins (**24**) using (trifluoromethyl)trimethylsilane (Me_3SiCF_3) as a nucleophilic agent, producing 3-hydroxy-3-(trifluoromethyl)indolin-2-one (**25**). Subsequently, compounds **25** were reduced using $[BH_3 \cdot THF]$ complex yielding 3-(trifluoromethyl)indolin-3-ol (**26**) that, in turn, suffered dehydration generating **27** in 82-98% yields (Scheme 8).

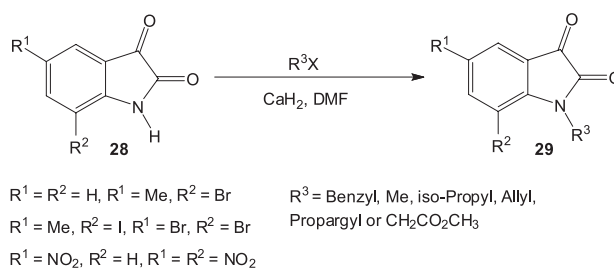
Garden *et al.*²⁵ have described the synthesis of *N*-alkylated isatins (**29**) from the respective isatins (**28**) using calcium hydride and alkyl halide in DMF (Scheme 9). This method has proven to be useful for *N*-alkylating a large number of isatins with electron-donating and electron-withdrawing substituents on the aromatic ring.

2.3 Convolutamydines

Convolutamydines A-E (**30-34**) (Figure 4) are alkaloids that share the 4,6-dibromo-3-hydroxyoxindole moiety. These compounds have been isolated from the Floridian marine bryozoan *Amathia convoluta* by Kamano *et al.*²⁶



Scheme 8. Reaction conditions for the preparation of 3-(trifluoromethyl)indoles (**27**).



Scheme 9. Preparation of *N*-alkylated isatins.

4,6-Dibromo-3-(2-oxopropyl)-3-hydroxy-2-oxindole (convolutamydine A) (**30**) strongly promotes inhibition of the differentiation of HL-60 human promyelocytic leukaemia cells. The fact that convolutamydine A was isolated from this bryozoan in only $8.6 \times 10^{-6}\%$ yield has motivated the development of a synthetic route to this compound.

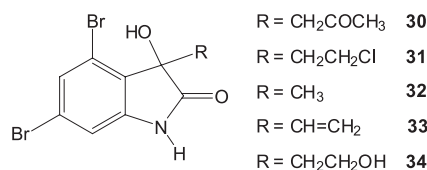


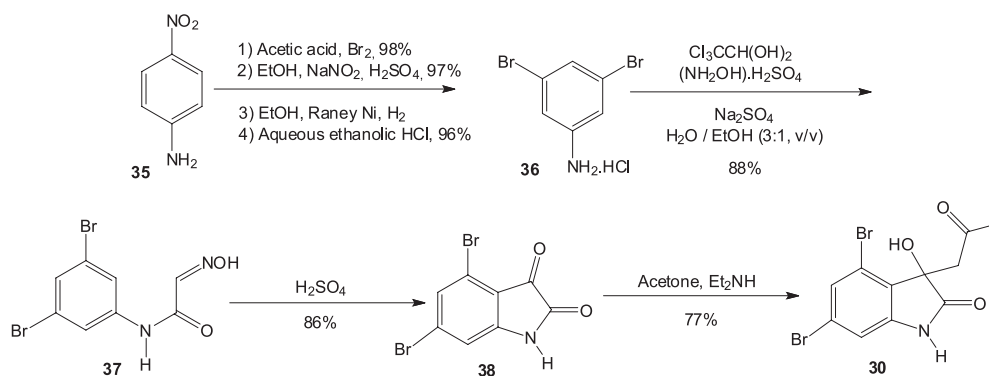
Figure 4. The structures of convolutamydines A-E.

4,6-Dibromoisatin (**38**, Scheme 10) seemed to be an obvious precursor for the synthesis of **30**, however, it was necessary to develop an efficient synthesis scheme for 3,5-dibromoisitrosoacetanilide (**37**) to improve upon the 10% yield described in the literature. Therefore, Garden *et al.*²⁷ proposed a modification of the Sandmeyer's method for the synthesis of this compound (88% yield) and a new route to convolutamydine A, as summarised in Scheme 10.

In recent years, enantiomerically enriched convolutamydine A-E and their derivatives have been synthesised using asymmetric catalysts, especially proline

derivatives. The catalysts that have been employed for the synthesis of the *R* or *S* convolutamydine A enantiomers are presented in Table 1.

Tryptophols are found in natural sources, and a number of derivatives are known to be pharmaceutically important starting materials. For instance, 7-ethyltryptophol (**45**)³⁴ has



Scheme 10. Reaction conditions for the preparation of **30**.

Table 1. Structures of asymmetric catalysts used in the convolutamydine A synthesis

Catalyst	Convolutamydine A enantiomer	Enantiomeric excess / %	Reference
<p>39 R = 2,6-diisopropylphenyl</p>	R	97	28
<p>40 2SbF₆⁻</p>	R	99	29
<p>41</p>	R	97	30
<p>42</p>	R	94	31
<p>43</p>	S	60	32
<p>44</p>	R	97	33

been used for the synthesis of Etodolac, a non-steroidal anti-inflammatory drug, and β -(phenylmethyl)indole-3-ethanol (**46**)³⁵ has been used for the preparation of Pemedolac, a potent analgesic (Figure 5).

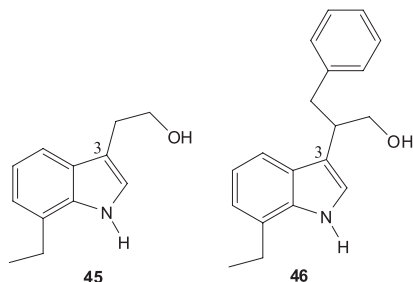
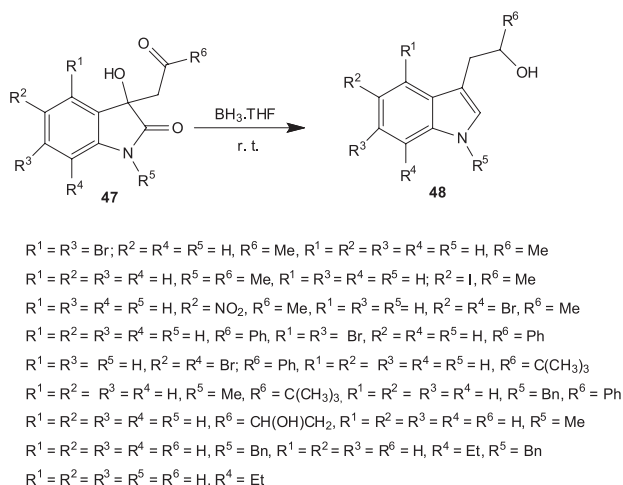


Figure 5. Structures of 7-ethyltryptophol (**45**) and β -(phenylmethyl)indole-3-ethanol (**46**).

Garden *et al.*³⁶ have prepared tryptophols and indoles bearing a C-3 hydroxyethyl side chain from convolutamydine A derivatives (Scheme 11). Convolutamydine A derivatives (**47**) subjected to reduction with BH_3 in THF produce the corresponding tryptophols (**48**) in good yields.



Scheme 11. Reaction conditions for the preparation of tryptophols (**48**) from convolutamydine A derivatives (**47**).

Figueiredo *et al.*³⁷ have studied the antinociceptive effects of convolutamydine A (**30**) and two of its synthetic analogues (**49**, **50** Figure 6). The systemic administration of these compounds has been shown to have strong antinociceptive effects in acute pain models, comparable to those of morphine.

2.4 Hydroxyacetophenone derivatives

The reduction of ethyl spiro-3,3-(ethylenedioxy)-2-oxindole carboxylates (**53**) under different conditions yields α -hydroxyacetophenone derivatives (**56**) (Scheme 12),

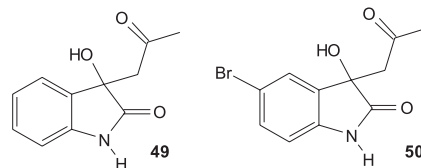


Figure 6. Structures of the synthetic analogues of convolutamydine A.

which are potential synthetic intermediates for the preparation of 1,2-diols, 1,2-aminoalcohols, phenethylalcohols or phenethylamines.³⁸

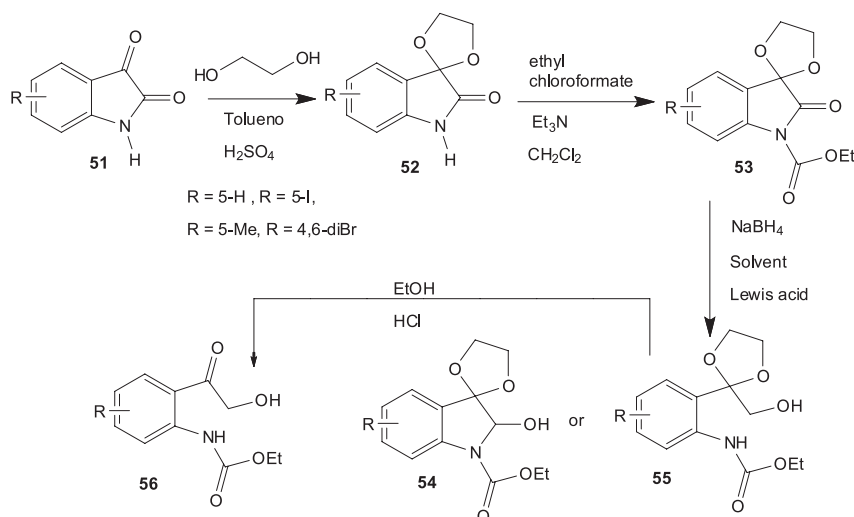
Compounds **52** were obtained using the traditional method of isatin ketalisation, i.e., by mixing ethylene glycol, toluene and a catalytic amount of H_2SO_4 . The reaction with ethyl chloroformate and Et_3N in CH_2Cl_2 furnished the respective compounds **53**. Compounds **53** were reduced with sodium borohydride in solvents with different polarities in the presence and absence of Lewis acids (LiBr , CaCl_2 , ZnCl_2 or Li_2CO_3). The **54:55** ratio was found to be both solvent and metal ion dependent. The interaction of the metal cation with the spiro-1,3-dioxolane ring oxygen has been proposed to facilitate the further coordination of the metal with the endocyclic amide carbonyl, which is then activated for regioselective reduction.

Isatin carbamate derivatives (**53**, Scheme 12 and **57**, Figure 7) exhibit intense vasodilatory activity, especially **53** ($\text{R} = \text{H}$), which is the most potent derivative. These compounds have been shown to increase the endothelial levels of NO, which activates the production of enzymes responsible for vascular relaxation, i.e., guanosine 3',5'-cyclic monophosphate (cGMP) and guanylate cyclase (GC). Therefore, carbamate derivatives may represent an alternative treatment for hypertension.³⁹

In a continuing effort to identify potential drugs for the treatment of vascular disorders, Gabriel *et al.*⁴⁰ evaluated the effects of the 2-hydroxyacetophenone derivatives of isatins **56** ($\text{R} = \text{H}$ e $\text{R} = \text{I}$) on the contractility of the rat aorta and papillary muscles. Both compounds had concentration-dependent (5-100 mM) relaxation effects, promoting vasodilation and negative cardiac inotropism by stimulating bradykinin, muscarinic and opioid receptors in smooth and cardiac muscles.

2.5 The reduction of isatylidenemalonyl, cyanocinnamate and benzylidene-malononitrile derivatives

The natural enzyme cofactors NAD(P) and NAD(P)H have inspired many researchers to use the Hantzsch's ester (**57**) and 1,4-dihydropyridine analogues as biomimetic reducing agents for ketones, aldehydes and α,β -unsaturated compounds.⁴¹ Encouraged by the results reported in the



Scheme 12. Synthesis scheme for the preparation of α -hydroxyacetophenone derivatives (56) from isatins (51).

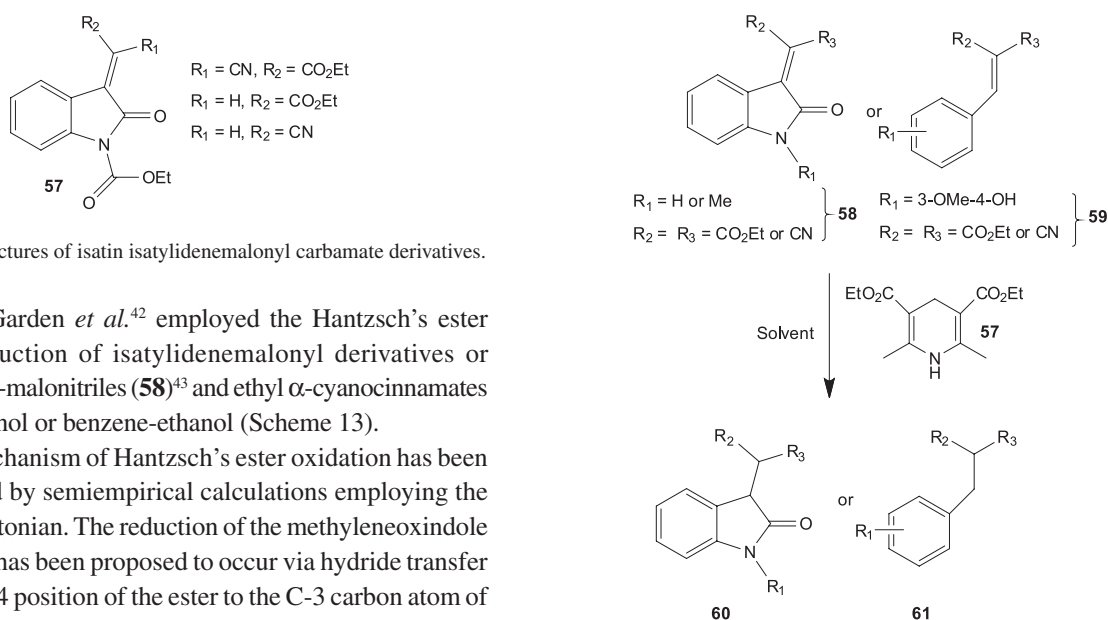


Figure 7. Structures of isatin isatylidenemalonyl carbamate derivatives.

literature, Garden *et al.*⁴² employed the Hantzsch's ester for the reduction of isatylidenemalonyl derivatives or benzylidene-malonitriles (58)⁴³ and ethyl α -cyanocinnamates (59) in ethanol or benzene-ethanol (Scheme 13).

The mechanism of Hantzsch's ester oxidation has been investigated by semiempirical calculations employing the PM3 Hamiltonian. The reduction of the methyleneoxindole derivatives has been proposed to occur via hydride transfer from the C-4 position of the ester to the C-3 carbon atom of the exocyclic double bond and via proton transfer from the protonated dihydropyridine intermediate to C-4 (Figure 8).

Scheme 13. Reduction of isatin and cyanocinnamate derivatives using the Hantzsch's ester.

2.6 Amaryllidaceae alkaloids

Torres *et al.*⁴⁴ have described the synthesis of Amaryllidaceae alkaloids from *N*-benzylisatin ketal

precursors, such as 62, via palladium-catalysed cyclisation in a Heck-type reaction (step 1). Scheme 14 shows the reaction conditions for the synthesis of anhydrolycorinone (66) and hippadine (67) alkaloids.

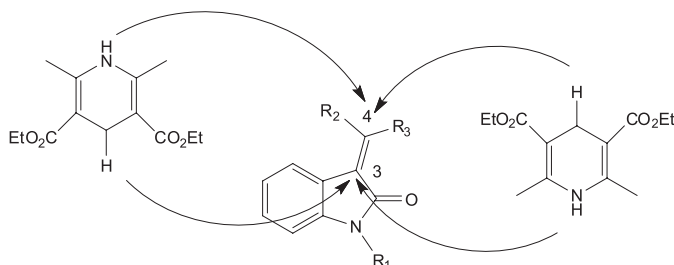
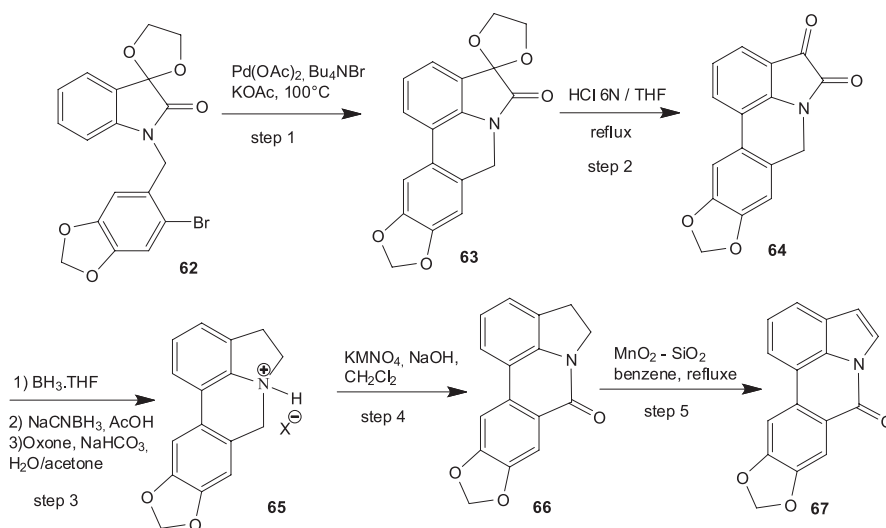


Figure 8. Representation of the hydride and proton transfers upon the reduction of methyleneoxindole derivatives.



Scheme 14. Synthesis of anhydrolycorinone (**66**) and hippadine (**67**) alkaloids.

This synthetic route also produces dehydroanhydrolycorinone (**68**), pratosine (**69**), assoanine (**70**), anhydrolycorin-7-one (**71**) and oxoassoanine (**72**) alkaloids (Figure 9).

2.7 N-Ribonucleoside isatins

Isatin derivatives (**73**) have been coupled to the 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose ribonucleoside (**74**) using Lewis acid catalysis (Scheme 15), and the resulting novel isatin ribonucleosides (**75**) have been screened for *in vitro* antiviral activity in cells infected with HSV-1 (herpes simplex type 1 virus). These compounds exhibited HSV-1 inhibition percentages ranging from 15 to 66%.⁴⁵

2.8 Isatin and inflammation

Several studies have shown that nitric oxide synthase (NOS) and cyclooxygenase (COX-2) play key roles in

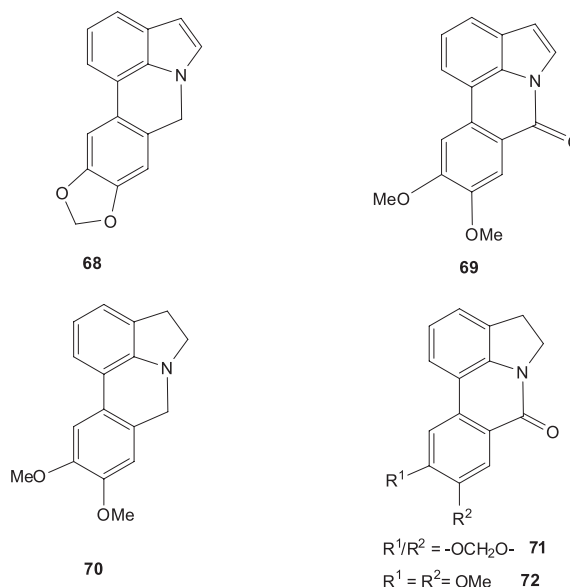
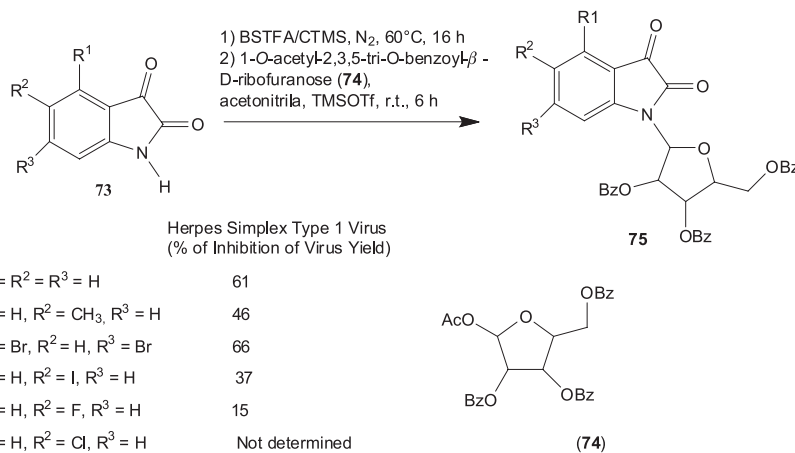


Figure 9. Structures of alkaloids.



Scheme 15. Synthetic route for the preparation of isatin nucleosides (**75**) and the corresponding HSV-1 inhibition percentages.

the development of inflammatory diseases, including carcinogenesis.⁴⁶ For this reason, Matheus *et al.*⁴⁷ have investigated the effects of isatin and its aromatic ring-substituted derivatives **76** (Figure 10) on the expression and activity of these two enzymes in RAW 264.7 cells stimulated with LPS/IFN- γ . Isatin derivatives inhibited both the expression and activity of NOS and COX-2 in macrophage cells, demonstrating their anti-inflammatory activities. Therefore, these compounds may be useful in the design of new lead compounds for the discovery of drugs with anti-inflammatory and anticancer activities

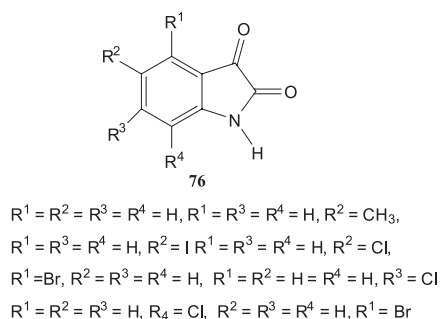
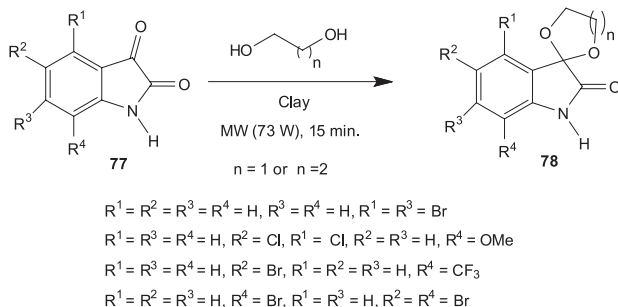


Figure 10. Structures of isatin and aromatic ring substituted derivatives.

2.9 Isatin ketals

Isatin ketals have anticonvulsant, psychotropic and anxiolytic properties.⁴⁸ The protection of the isatin ketonic carbonyl is often necessary to allow the chemical transformation of this molecule. Ribeiro *et al.*⁴⁹ developed a method to prepare the spiro[1,3-dioxolane-2,3'-indolin]-2'-one (**78**, $n = 1$) and spiro[1,3-dioxane-2,30-indolin]-2'-one (**78**, $n = 2$) isatin ketals using montmorillonite K10,⁵⁰ illite and smectite clays and microwave radiation under solvent-free conditions (Scheme 16). The K10 clay showed the best catalytic potential, providing almost all of the ketals in yields above 80%.



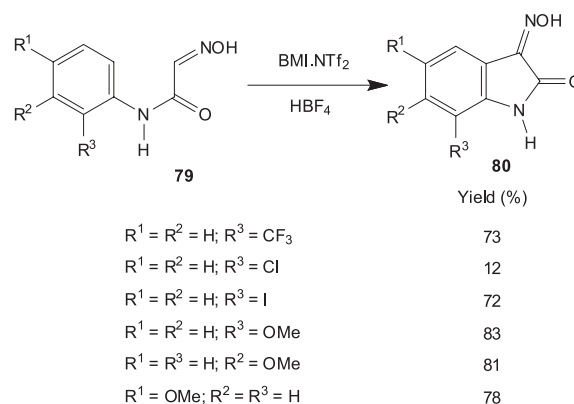
Scheme 16. Reaction conditions for the synthesis of isatin ketals.

Because endogenous isatin acts on the central nervous system (CNS),⁵¹ the hypnotic and sedative activities of

the isatin ketals shown in Scheme 16 have been evaluated by Zapata-Sudo *et al.*⁵² Their results suggested that these compounds may have beneficial effects on sleep disorders and could also be used for pre-anaesthesia or to maintain the effects of anaesthesia.

2.10 Problems encountered with the Sandmeyer's method

The Sandmeyer's method does not allow the preparation of isatins from isonitrosoacetanilides bearing electron-donating groups on the aromatic ring. To overcome this difficulty, Pinto *et al.*⁵³ have used ionic liquids in place of sulfuric acid. The cyclisation of isonitrosoacetanilides (**79**) using BMI.NTf₂ and HBF₄ (5 mol%) produced isatin-3-oximes (**80**) containing electron-withdrawing groups in high yields (Scheme 17)

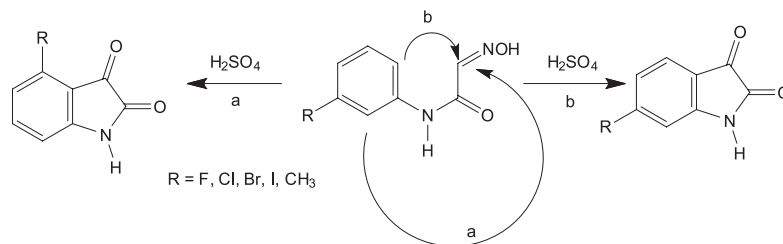


Scheme 17. Cyclisation reactions using BMI.NTf₂ and HBF₄.

In the case of 3-substituted isonitrosoacetanilides, the cyclisation step in the Sandmeyer's procedure can generate a mixture of two regioisomers (Scheme 18). Almeida *et al.*⁵⁴ prepared five pairs of such isatin isomers from 3-substituted-anilines, 4- and 6-fluoro-, chloro-, bromo-, iodo- and methylisatins and studied the separation of these isomers by high-speed counter-current chromatography (HSCCC). This technique was effective in all cases with the same solvent system (hexane:ethyl acetate:ethanol:water, 1:0.5:0.5:1 (v/v/v/v)), providing good results in a short time using lower solvent volumes than those used in conventional liquid chromatography.

2.11 Iodination and chlorination of isatins

Because it is not possible to introduce an iodine substituent onto the aromatic ring using molecular iodine, it is necessary to find reagents that generate electrophilic iodine species. Garden *et al.*⁵⁵ have investigated the use of KICl₂ as an iodinating agent for different heterocyclic



Scheme 18. Pathway of (a) formation of 4-substituted-isatins, (b) formation of 6-substituted-isatins.

compounds, such as isatin, imidazole and pyrazole. All products were obtained with excellent yields.

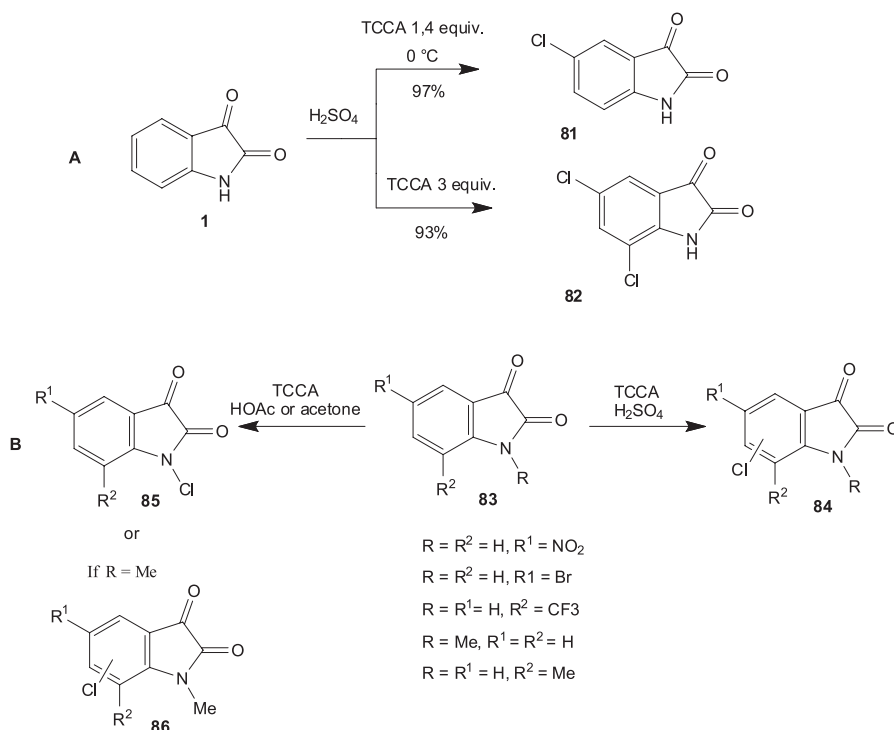
The chlorination of aromatic isatin with trichloro-isocyanuric acid (TCCA) using sulfuric acid as a catalyst was studied by Ribeiro *et al.*,⁵⁶ who obtained 5-chloroisatin (**81**) and 5,7-dichloroisatin (**82**) with excellent yields (Scheme 19A). A continued interest in the preparation of chlorinated isatins led Silva *et al.*⁵⁷ to investigate the chlorination of isatin and *N*-substituted isatin derivatives using TCCA under different conditions. In the presence of sulfuric acid, the isatin aromatic ring was always chlorinated at one or two positions, depending on the amount of TCCA used (Scheme 19B). In the presence of acetic acid or acetone, *N*-chlorinated products were formed because the isatin nitrogen was not replaced by a methyl group or a substituent at position 7. The reactions of isatins containing electron-withdrawing groups produce only monochlorinated products, except when there is competition from the *ipso* substitution.

2.12 Synthesis of ferrocenyl oxindoles and porphyrin indolin-2-one

Oxindoles are naturally occurring alkaloids that can be isolated from plants and are found in mammalian tissues. The C-3 isatin carbonyl can be removed selectively to yield the corresponding oxindoles because it is more electrophilic than the amide carbonyl (C₂). This difference in electrophilicity allows the synthesis of oxindoles from isatins using different methodologies to reduce the C-3 carbonyl, e.g., the Wolff-Kishner method.

Oxindole-based compounds **87**, **88** and **89** (Figure 11) have been shown to inhibit protein kinases via competition with ATP. For example, these compounds bind to residues in the ATP pocket of the tyrosine kinase (intracellular) domain of the VEGF receptor, which regulates angiogenesis.⁵⁸

As part of on-going research on the synthesis of new bioactive substances, Silva *et al.*⁵⁹ have reported the preparation of a series of ferrocenyl oxindoles (**92**, **93**) from



Scheme 19. Isatin chlorination with TCCA.

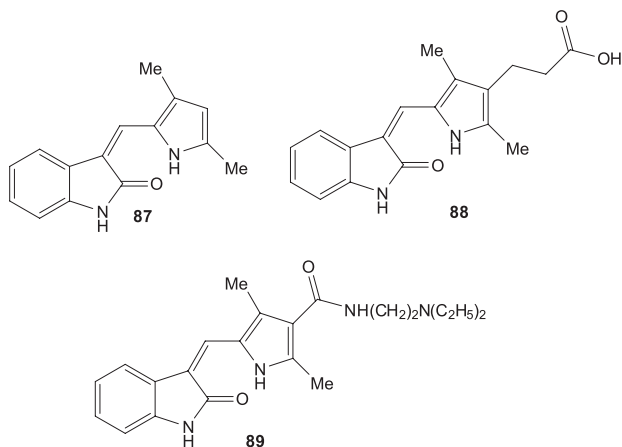


Figure 11. Structures of semaxanib **87**, SU6668 **88** and sunitinib **89**.

the reactions of oxindoles with ferrocenecarboxaldehyde (**91**) in the presence of morpholine or KOH as a catalyst (Scheme 20). *E*-products were obtained in the presence of either KOH or morpholine, however, substantially higher yields of the *Z*-products were noted when morpholine was used as the catalyst. Selectivity reversal was observed in the reactions of the di-substituted 5,7-dichloro (**90d**) and 5,7-dibromo (**90f**) oxindoles in the presence of this catalyst, with the predominant formation of the *Z*-products. The position rather than the nature of the substituent determined the outcome of the reaction: 4-7-dichloro (**90e**) and 4-6-dibromo (**90g**) derivatives reacted to yield only the *Z*-products, most likely due to steric effects.

The effects of the ferrocenyl oxindoles shown in Scheme 20 on the migration of tumour cells (MDA-MB-231 breast cancer cells) have been investigated using wound healing and Boyden chamber cell migration assays. The results of the latter assay revealed significant inhibition by the *E*

and *Z* isomers **92c/93c**, **92d/93d**, **93g** and **92g/93i**, which exhibited IC_{50} values between 0.49 and 1.85 μ M.

Additionally, the redox behaviour of all compounds was evaluated by cyclic voltammetry. The ferrocenyl (Fc) group was found to be more easily oxidised in the *Z* isomers than in the *E* isomers of the oxindoles **93a-93c** and **93g-93i**. Interestingly, the more easily oxidised substances had the lowest IC_{50} values in the biological assays, suggesting that (*E/Z*) isomerism could play an important role in the redox potential and thus the biological properties of these oxindole derivatives.

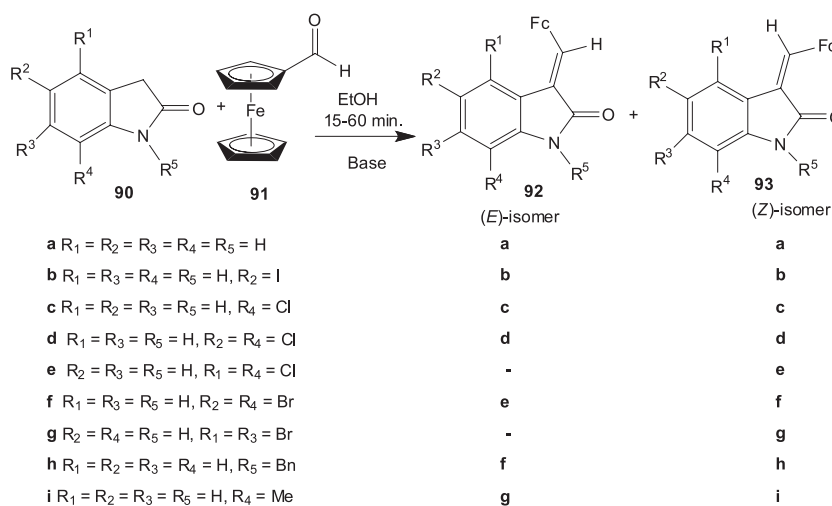
Porphyrin indolin-2-one conjugates (**97**) have been prepared by Menezes *et al.*⁶⁰ via the Buchwald-Hartwig palladium-catalysed amination of indolin-2-one derivatives (**94**) with 2-amino-5,10,15,20-tetraphenylporphyrinato nickel(II) (**96**), with good yields under mild conditions (Scheme 21).

2.13 The mechanism of the Sandmeyer cyclisation reaction

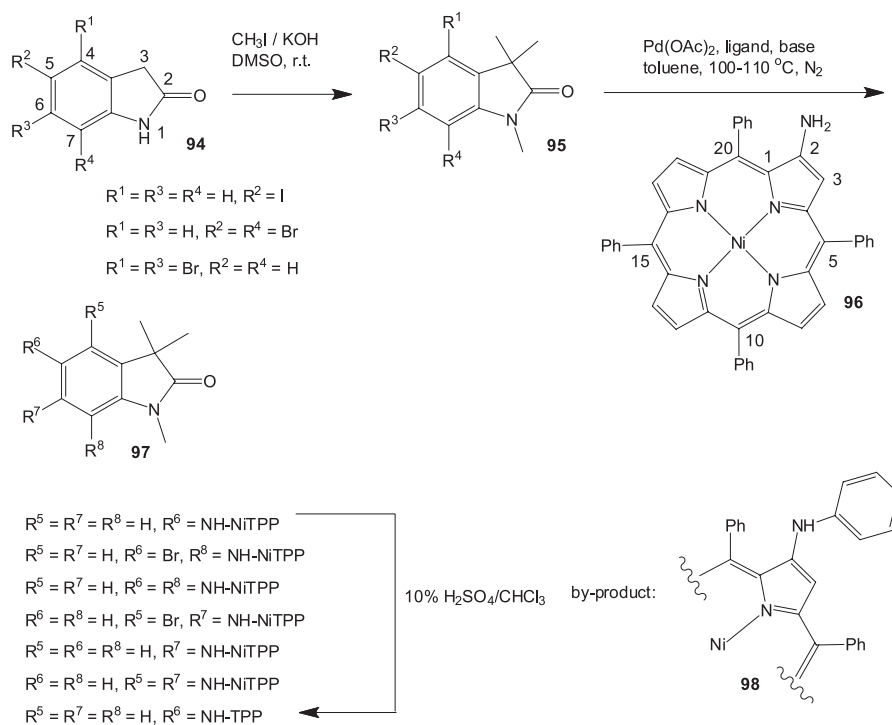
Because the mechanism of the Sandmeyer cyclisation reaction initially described in the literature⁶¹ was unclear, and the intermediates and possible pathways were not well characterised, Silva *et al.*⁶² monitored the cyclisation of isonitrosoacetanilide to isatin by electrospray ionisation tandem mass spectrometry (ESI-MS/MS) (Scheme 22). This technique allows the detection of transient ionic species with short lifetimes under mild conditions.

2.14 Isatin and chemistry education

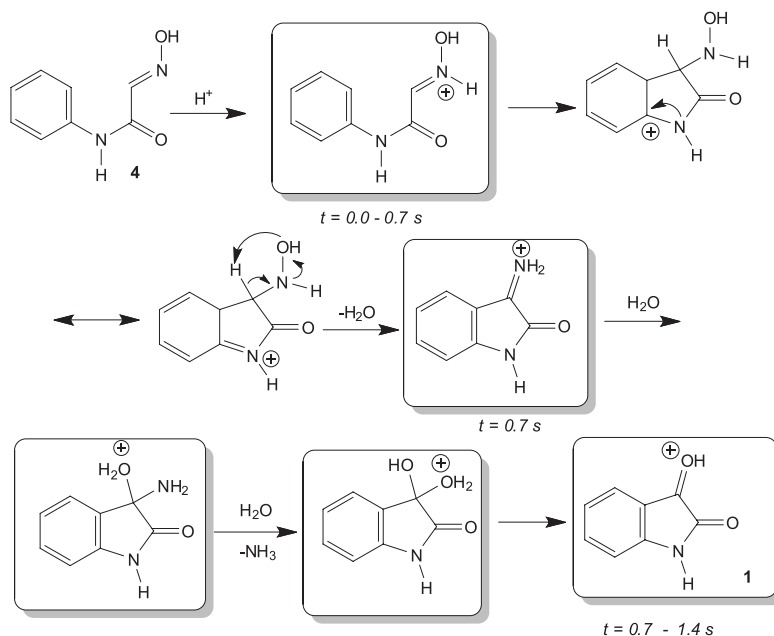
As previously discussed, the synthesis of isatin and its derivatives is generally simple and employs relatively inexpensive reagents. The Sandmeyer's method is easily



Scheme 20. Synthesis of ferrocenyl oxindoles.



Scheme 21. Synthesis of porphyrin indolin-2-one conjugates (**97**).



Scheme 22. Mechanism of the Sandmeyer cyclisation of isonitrosoacetanilide (**4**) to isatin (**1**), corroborated by on-line ESI-MS/MS monitoring.

reproduced and can be used in undergraduate experimental classes. In an effort to help chemistry teachers diversify and improve their experimental classes, Silva *et al.*⁶³ have proposed experiments involving the synthesis of isonitrosoacetanilides, isatins and convolutamydines, providing experimental procedures, methods for the characterisation of the resulting substances using

spectroscopic techniques and suggested topics for discussion in articles focused on chemistry education.

Conclusion

Isatin is a molecule with great synthetic versatility and enormous pharmacological potential that has been

intensively investigated by Brazilian research groups. Several structural modifications of the basic core of this molecule have been made, such as ring and alkyl group addition. These modifications often take advantage of the distinct reactivities of the two carbonyls and the N-H group. In addition to the synthesis of novel compounds, new methods of obtaining isatins have been explored by Brazilian groups.

The high number of citations of the work carried out in Brazil is indicative of the Brazilian contribution to the chemistry of isatins.

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