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SYNTHESIS AND BIOACTIVITY OF PYRROLOINDAZOLES: AN OVERVIEW

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Abstract – In this review, the synthesis and bioactivity of pyrroloindazoles have been presented. The pyrroloindazoles were synthesised either by the heteroannulation of tetrahydro-indolones/isoindolones, aminoindazoles, Sonogashira/Cacchi indazolic substrates or acyl/aroylindole ketoxime dinitrophenyl ethers or by the cycloaddition of indolynes, indazolic betaines, styrylpyrazoles and nitroindazoles. Several pyrroloindazoles showed analgesic, antiinflammatory and antitumor properties, inhibition of Pim kinase and soluble guanylate cyclase, and antagonism of NMDA-receptor.

CONTENTS

1. INTRODUCTION

Heterocycles are integral parts of the majority of current drugs[1] because they modulate the druglikeness of such molecules.[2,3] Heterocyclic compounds, therefore, play a crucial role in drug development[4,5] and consequently in our daily life.[6] Amongst heterocycles, indolic substances are by far the most thoroughly studied class[7-9] displaying diverse bioactivities.[10-12] Two current reviews on the biomedical importance of indoles[13,14] are pertinent in this regard.

In contrast, indazoles, the bioisosters of indoles, have been studied to a lesser extent.[15-17] There are three indazolic natural products (*Nigella* alkaloids),[18-20] a few indazolic drugs, viz. bendazac lysine,[21] benzydamine,[22] granisetron,[23,24] lonidamine,[25-28] YC-1[29-31] and axitinib[32] and an illegal cannabinoid substitute (APINACA or AKB-48) reported from Japan[33] and detected in "herbal incense" or "spice" in Italy.[34] Two recent reviews[35,36] cover the bioactivities of indazoles. The medicinal aspects of both indoles and indazoles have also been reviewed recently.[37]

Since both indoles and indazoles are useful molecules, pyrroloindazoles (which may also be considered as pyrazoloindoles), henceforth abbreviated as PIZs, are a matter of curiosity since a PIZ embodies both an indole and an indazole nucleus. Although a large number of PIZs have been synthesised and quite a few of them display a variety of bioactivities, no review appears to exist on the synthesis and bioactivities of PIZs. The present review is expected to fill in this lacuna.

2. REVIEW

Eight isomeric classes of PIZs (**I**-**VIII**) (Figure 1) have been synthesised till date. Of them, P[2,3-*g*]IZs (**I**) were the first to have been synthesised and their synthesis has also been more extensively studied.

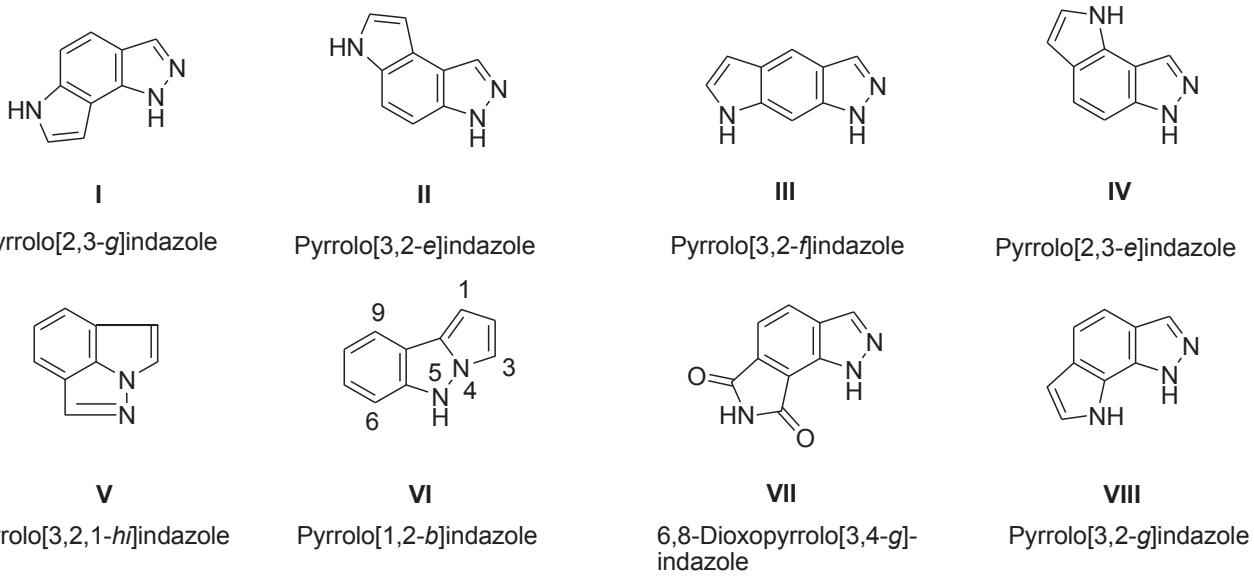
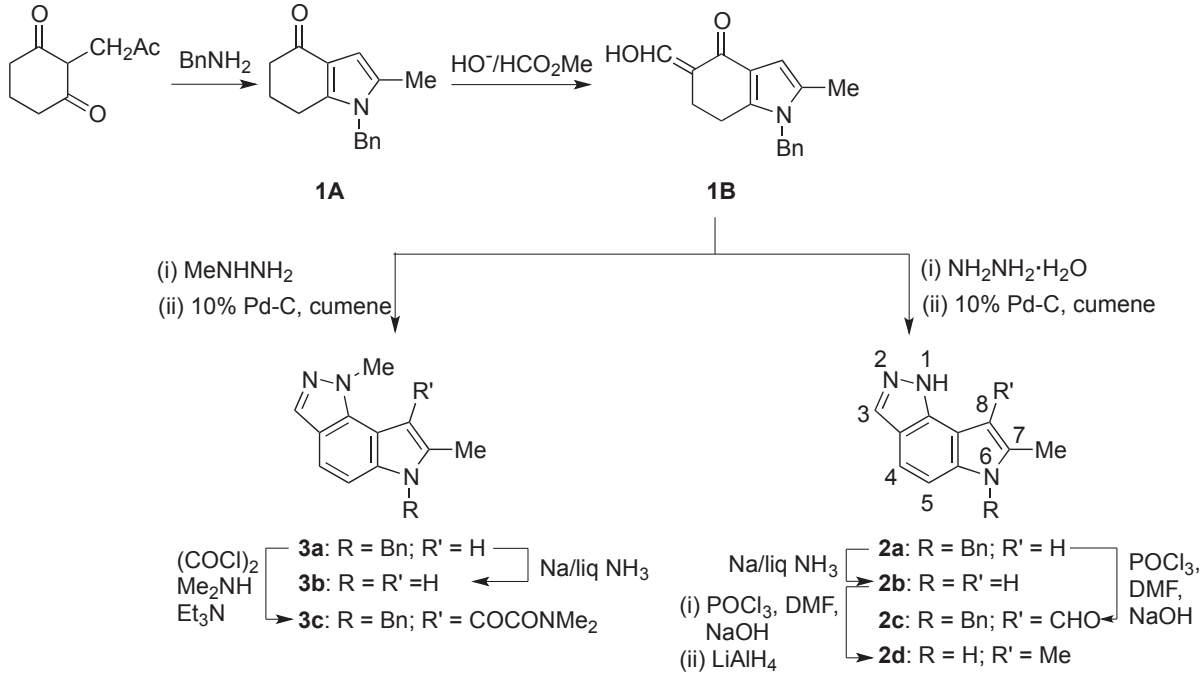


Figure 1. Isomeric pyrroloindazoles reported till date

Accordingly, the PIZs have been discussed here chronologically, beginning with the P[2,3-*g*]IZs. Since the PIZs are, as per the mancude system of IUPAC nomenclature, considered as dihydro-PIZs, the P[2,3-*g*]IZs, for example, are represented as 1,6-dihydro- or 1*H*,6*H*-P[2,3-*g*]IZs.

2.1 Synthesis of pyrrolo[2,3-*g*]indazoles (I)

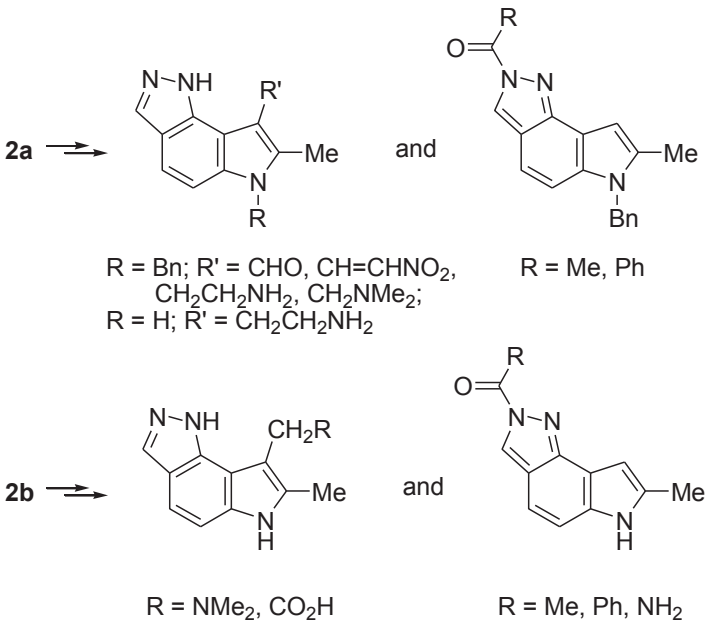
The first synthesis of PIZs was reported in a US Patent in 1968.[38] A large number of substituted 7-methyl-3*H*,6*H*-P[2,3-*g*]IZs were reportedly prepared by the heteroannulation of the known α-hydroxymethylenetetrahydroindol-4-one (**1B**) or its precursor (**1A**) with (substituted) hydrazines, followed by aromatisation (Pd-C) and indolic *N*-debenzylation (Na/liq NH_3) and, in some cases, substitution at indolic C-3. The crucial indolone **1B** was prepared from 2-acetonylcyclohexane-1,3-dione *via* **1A** (Scheme 1).



Scheme 1. Synthesis of 7-methyl-P[2,3-*g*]IZs

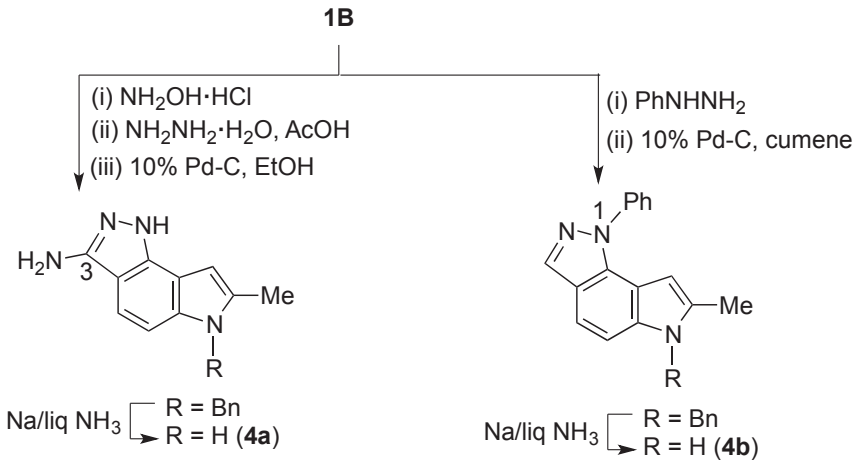
Some of the resulting novel PIZs proved to be bioactive, discussed later.

Several 1- and 2-substituted derivatives of **2a** and **2b** were also prepared by derivatisation (Scheme 2).



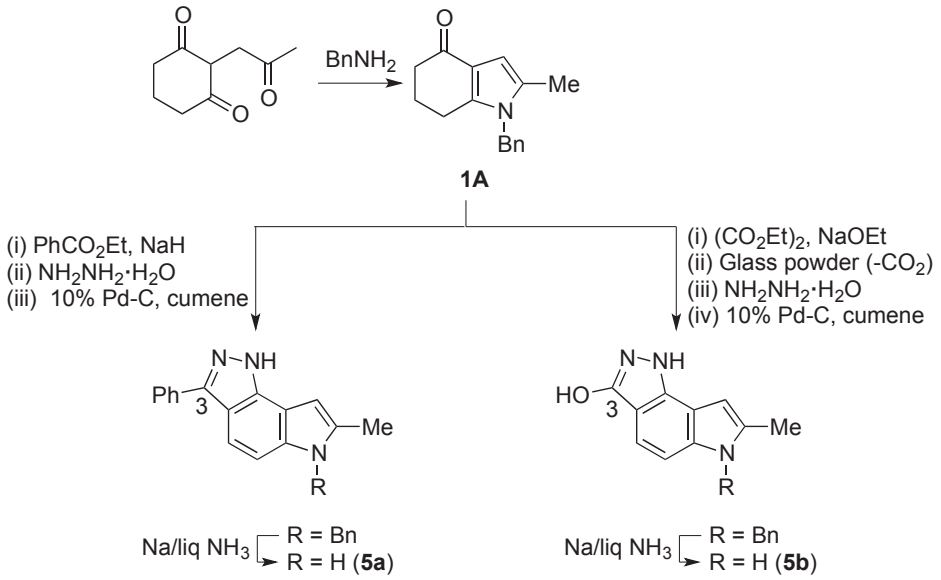
Scheme 2. Synthesis of 1- and 2-substituted analogues of **2a**,**b**

3-Amino (**4a**) and 1-phenyl (**4b**) derivatives of the parent 7-methyl-P[2,3-*g*]IZ (**2b**) were prepared from **1B** in a similar way (Scheme 3).



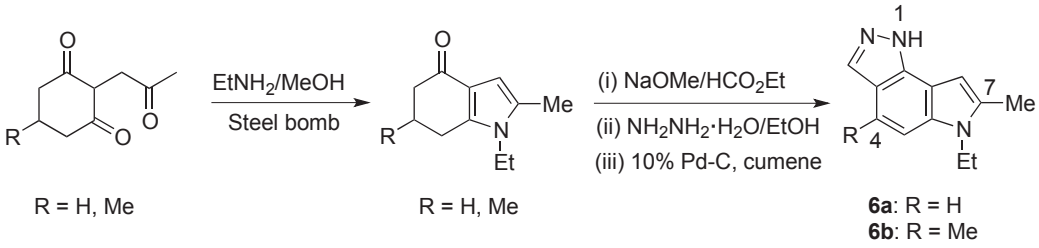
Scheme 3. Synthesis of 3-amino- and 1-phenyl-**2b**

The precursor **1A** was converted to 3-phenyl and 3-hydroxy derivatives of **2b** by initial acylation, followed by similar routes (Scheme 4).



Scheme 4. Synthesis of 3-phenyl- and 3-hydroxy-**2b**

6-Ethyl analogues of **2b**, viz. **6a**,**b** were similarly prepared from the corresponding tetrahydroindol-4-ones which, in turn, were prepared from appropriately substituted cyclohexane-1,3-diones (Scheme 5).



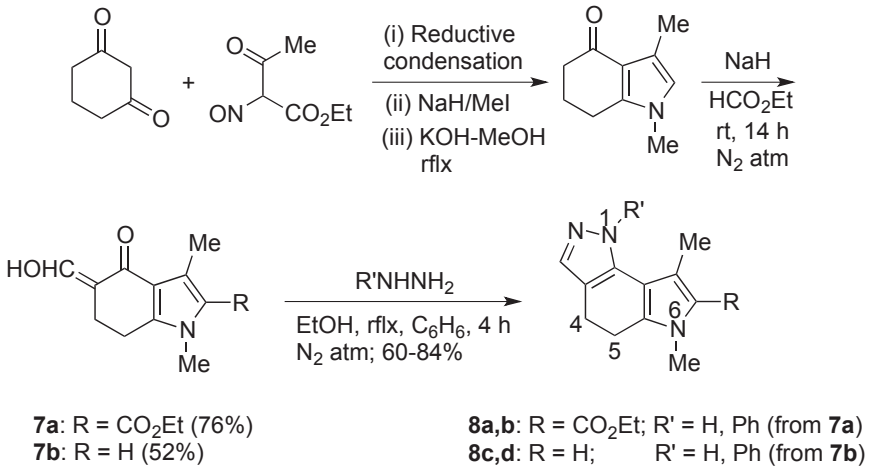
Scheme 5. Synthesis of 6(*N*)-ethyl analogues of **2b**

In a subsequent patented report,[39] several P[2,3-*g*]IZs were prepared by treating a substituted 6-hydrazinoindazole with a ketone and then cyclising the resulting hydrazone in an acidic or aq. alcoholic medium at room temperature to boiling point. The details of this work could not be retrieved.

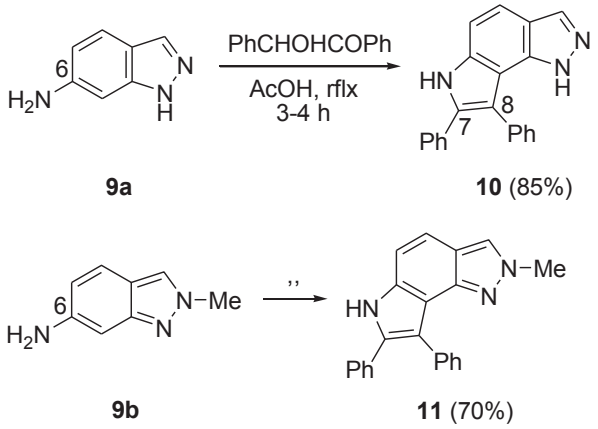
Subsequently, N. Anand *et al*. followed the same path to prepare four 4,5-dihydro-1*H*,6*H*-P[2,3-*g*]IZs (**8a-d**) starting from the tetrahydroindolones (Scheme 6).[40]

The 8-Me protons were stated to appear at δ 2.56 in **8a** but at δ 1.66 at **8b** due to the positioning of the methyl group in the shielding zone of the phenyl group of the latter.

In search of fluorescent condensed indazoles, each of 6-aminoindazole (**9a**) and its 2-methyl derivative (**9b**) was separately condensed with benzoin in acetic acid under reflux to furnish the corresponding 7,8-diphenyl-1*H*,6*H*- (**10**) and -2*H*,6*H*-P[2,3-*g*]IZs (**11**) (Scheme 7).[41] The angular structures were claimed primarily on the basis of ^{1}H NMR spectroscopic data. None of the products showed strong fluorescence.



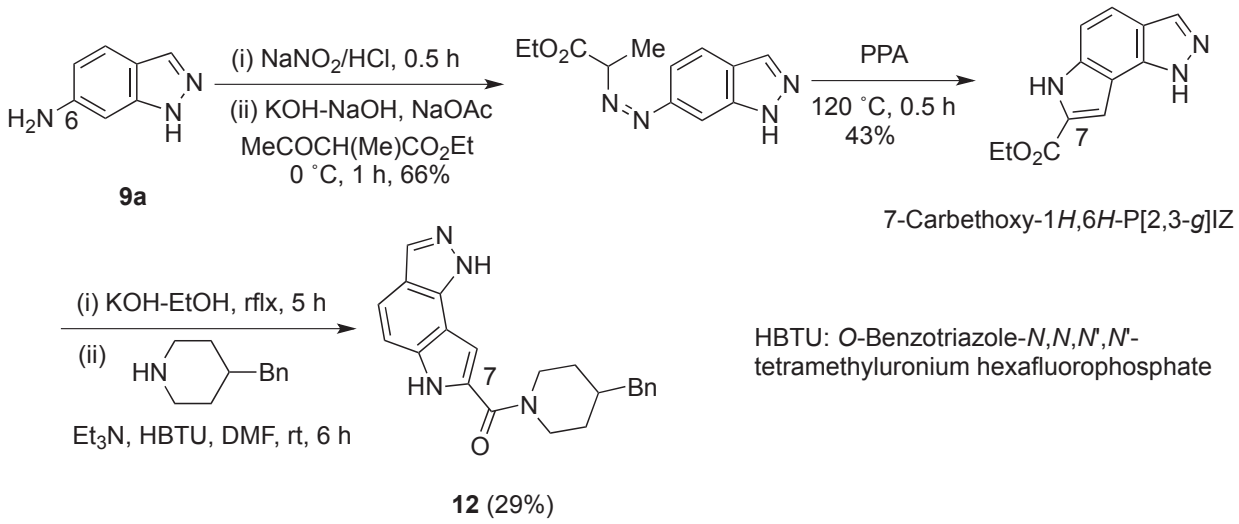
Scheme 6. Further syntheses of 4,5-dihydro-P[2,3-*g*]IZs from tetrahydroindolones



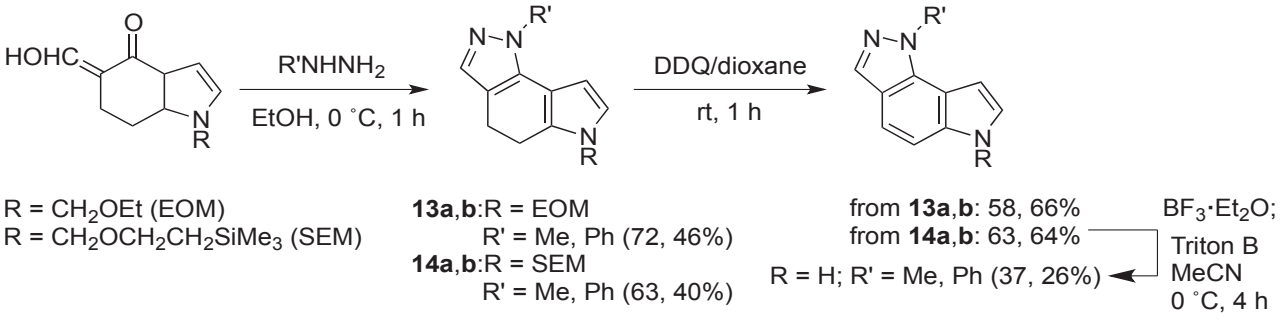
Scheme 7. Heteroannulation of 6-aminoindazoles

In search of novel potential NR2B subtype-selective *N*-methyl-D-aspartate (NMDA)- receptor antagonists for the treatment of neuropathic pain, 7-carbethoxy-1*H*,6*H*-P[2,3-*g*]IZ was prepared from **9a** by the Fischer/Japp-Klingemann procedure. The structures were fully supported by ^{1}H NMR and HRMS data. The derived carboxamide (**12**) (Scheme 8) proved to be bioactive,[42-44] discussed later.

In search of inhibitors of sGC (soluble guanylate cyclase), potential therapeutic agents in hypotension, 1-methyl/phenyl-1*H*,6*H*-P[2,3-*g*]IZs were prepared from 1-substituted 5-hydroxymethylene-4-oxo-4,5,6,7-tetrahydroindoles (Scheme 9), following the earliest reported method. The two 4,5-dihydro-6(*N*)-SEM-PIZs (**14a**,**b**) were oxidised (DDQ) and then deprotected by $BF_3 \cdot Et_2O$, followed by Triton B to the corresponding 1-substituted PIZs in 37/26% yields.[45] Some of the products displayed expected bioactivity, discussed later.

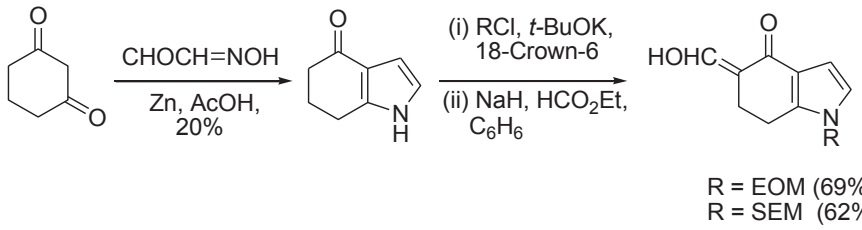


Scheme 8. Fischer/Japp-Klingemann route to a bioactive P[2,3-*g*]IZ



Scheme 9. Synthesis of sGC-inhibitory (dihydro)-P[2,3-*g*]IZs

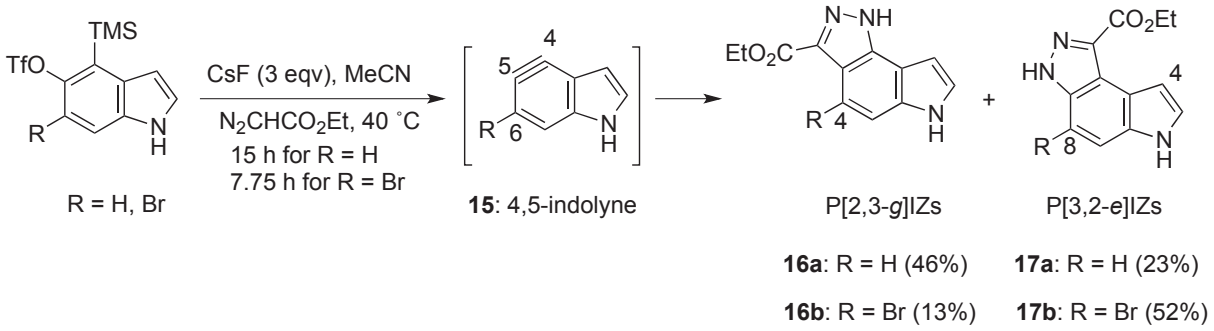
The starting 5-hydroxymethylenetetrahydroindolones were prepared from cyclohexnane-1,3-dione in a three-step procedure, shown below (Scheme 10).



Scheme 10. Synthesis of 5-hydroxymethylenetetrahydroindol-4-ones

Indolynes, generated *in situ*, function as electrophilic indole surrogates and can react with synthetically useful nucleophiles regioselectively. During studies on understanding and modulating the regioselectivities of indolynes, generated *in situ*, it was hypothesised that a bromine at C-6 of the

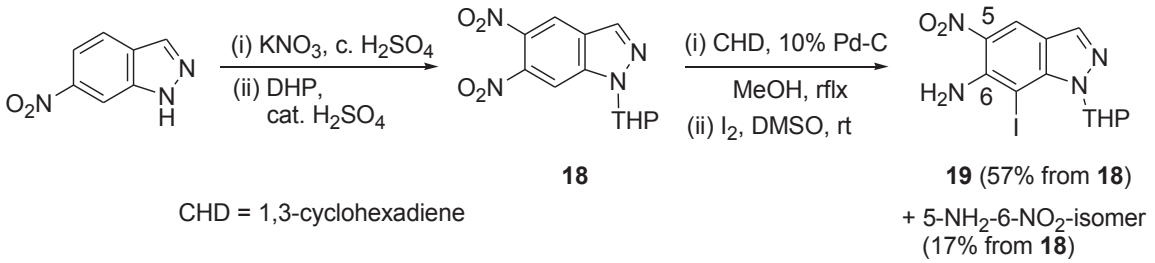
4,5-indolyne **15** would reverse its regioselectivity at C-4. This hypothesis was validated by the energy minimised structure of 6-bromo-4,5-indolyne and proven by actual chemical reactions. Thus, **15**, generated *in situ*, reacted with ethyl diazoacetate to furnish a mixture of the 1*H*,6*H*-P[2,3-*g*]IZs (**16a**/**b**) and the 1*H*,6*H*-P[3,2-*e*]IZs (**17a**/**b**) (Scheme 11).[46,47]



Scheme 11. Synthesis of isomeric PIZs *via* indolynes

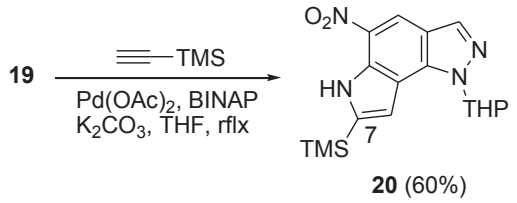
The PIZs **16a**,**b** resulted from nucleophilic attack at C-5 whereas the PIZs **17a**,**b** resulted from attack at C-4 of the respective indolynes (**15**), generated *in situ*. The observed reversal of regioselectivity was stated to have arisen from a combination of indolyne distortion and steric effects caused by the bromide substituent.

A number of 7- and 8-substituted and 7,8-disubstituted 1*H*,6*H*-P[2,3-*g*]IZs were synthesised using palladium-catalysed annulations of the *ortho*-amino-iodoindazole (**19**) with activated acetylenes.[48] The starting material was prepared from commercially available 6-nitroindazole (Scheme 12).



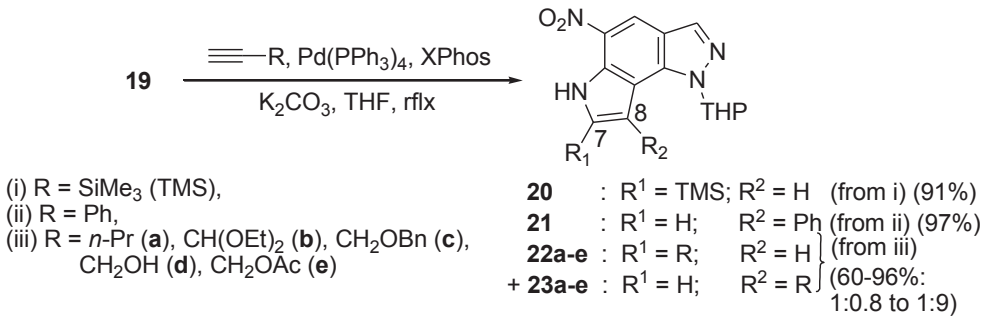
Scheme 12. Synthesis of intermediate for the PIZ **20**

The reaction of **19** with TMS-acetylene using $Pd(OAc)_2$/BINAP as the catalyst furnished a 1*H*,6*H*-P[2,3-*g*]IZ (**20**) efficiently (Scheme 13).



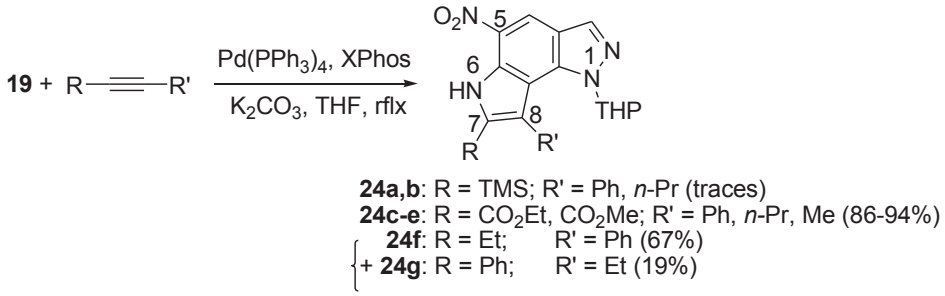
Scheme 13. Pd-catalysed annulation of **19**

Changing the catalyst to $Pd(PPh_3)_4$/XPhos led to an enhanced yield of **20** (from **19**) and, when applied to phenylacetylene, efficiently provided a PIZ (**21**) with reverse regioselectivity. But for other terminal acetylenes used, the reagent led to a mixture of the corresponding 7/8-isomers (**22a-e** + **23a-e**) in each case (Scheme 14). The observed unusual reactivity and regioselectivity were thought to be due, in part, to an effect of the bulky electron-rich ligand XPhos. Larock annulation was assumed to be most likely involved in the formation of **20**.



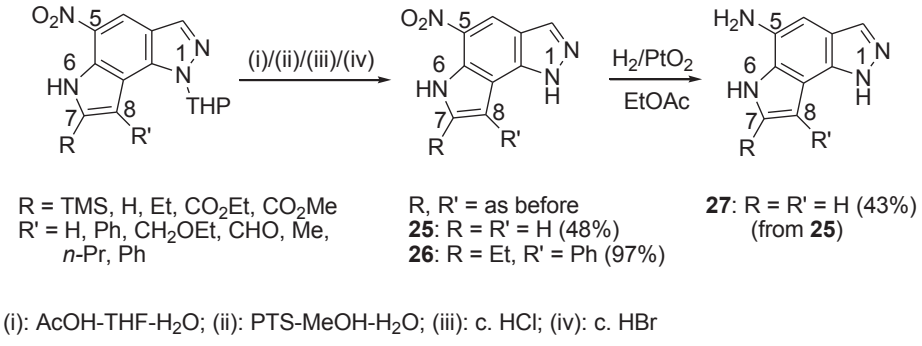
Scheme 14. Modified route to P[2,3-*g*]IZs using terminal alkynes

Internal alkynes furnished mixed results (Scheme 15).



Scheme 15. Synthesis of P[2,3-*g*]IZs using internal alkynes

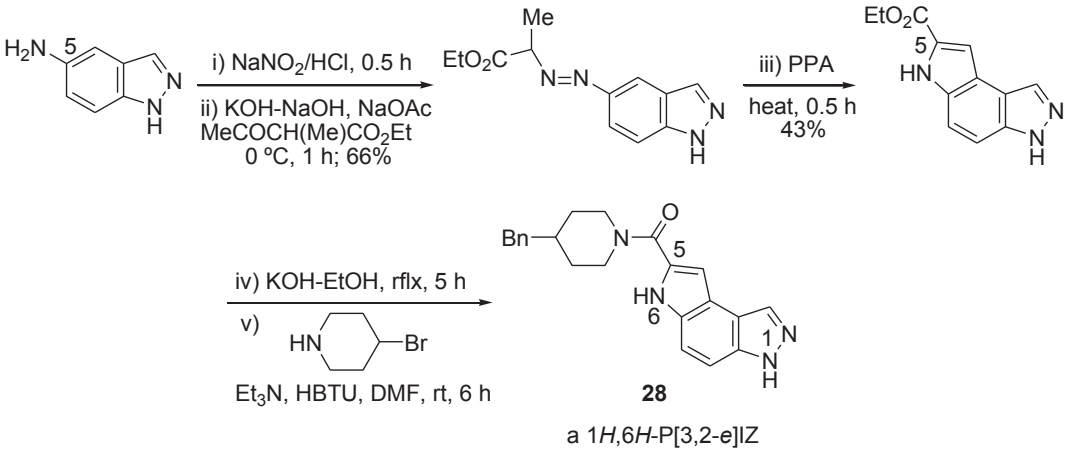
Subsequently, a number of deprotected 5-nitro-1*H*,6*H*-P[2,3-*g*]IZs and the corresponding 5-amino-PIZs were prepared (Scheme 16).[49] Some of the PIZs (**25**-**27**) inhibited Pim kinases (see later).



Scheme 16. Transformations to Pim kinase-inhibitory P[2,3-*g*]IZs

2.2 Synthesis of pyrrolo[3,2-*e*]indazoles (II)

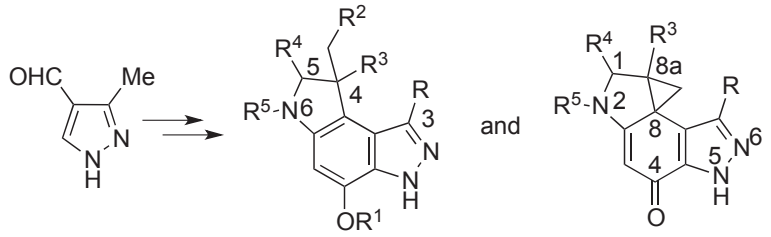
In the same work where P[2,3-*g*]IZs were prepared from 6-aminoindazoles by Fischer/Japp-Klingemann procedure,[42] a P[3,2-*e*]IZ was prepared from 5-aminoindazole using the same route. It was converted to the corresponding carboxamide (**28**) (Scheme 17) which proved to be bioactive (see later).



Scheme 17. Fischer/Japp-Klingemann route to a bioactive P[3,2-*e*]IZ

The indolyne route to [3,2-*e*]-type PIZs has already been discussed.[46,47]

In search of novel antineoplastic agents, 4-formyl-3-methylpyrazole was converted in several steps to a number of 4,5-dihydro-1*H*,6*H*-P[3,2-*e*]IZs (**29A**, **29B**) (Scheme 18).[50] Since patented, the details of the work could not be retrieved.

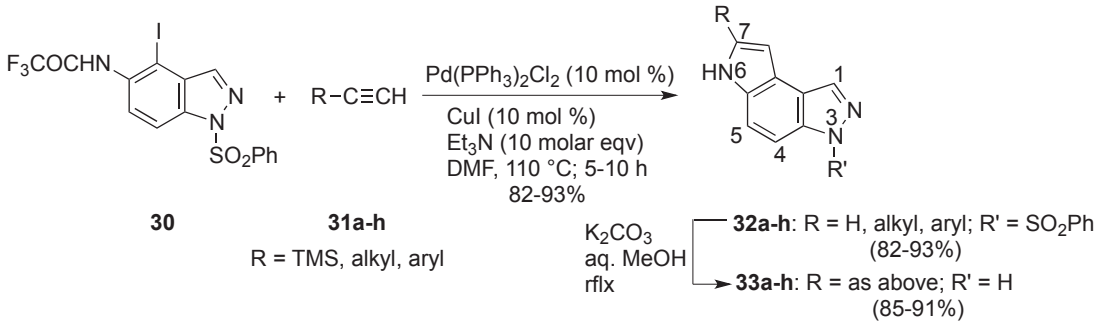


29A **29B**

R = H, C_1-C_4 alkyl; R^1 = H, C_1-C_4 alkyl, COR^6, alkylcarbamoyl, etc.;
R^2 = halo; R^3, R^4 = H or alkyl; R^5 = H, COR^7 where R^7 = (aryl)hydrocarbyl, alkoxy, etc.

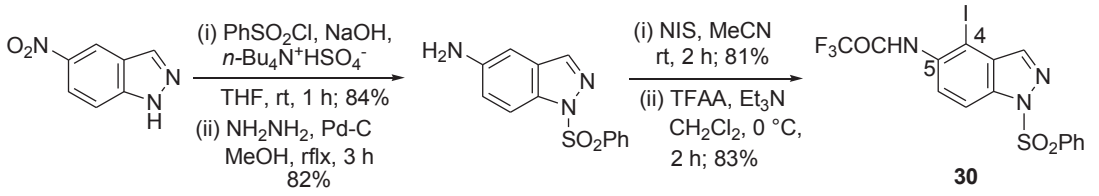
Scheme 18. Synthesis of novel antitumor P[3,2-*e*]IZs

The authors of the present review developed the first general synthesis of 7-substituted 1*H*,6*H*-P[3,2-*e*]IZs (**33a-h**) by tandem Sonogashira/Cacchi coupling-heteroannulation of 4-iodo-1-phenylsulfonyl-5-trifluoroacetamidoindazole (**30**) with a number of terminal acetylenes (**31a-h**) using $Pd(PPh_3)_2Cl_2$ (10 mol%) as the catalyst, CuI (10 mol%) as the co-catalyst and Et_3N (10 eqv) as the base in DMF under argon atmosphere at 110 °C, followed by *N*(3)-deprotection of the resulting PIZs (**32a-h**) by aq. methanolic K_2CO_3 under reflux (Scheme 19).[51]



Scheme 19. First general synthesis of 7-substituted P[3,2-*e*]IZs

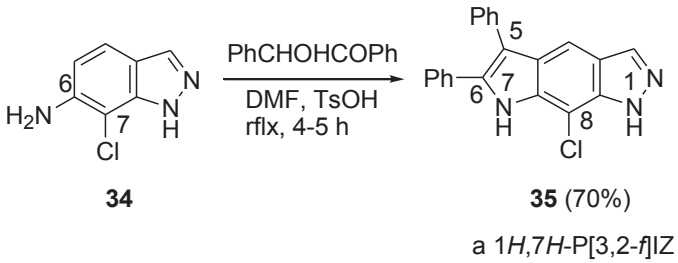
The starting indazole was efficiently prepared from commercially procured 5-nitroindazole by successive *N*(3)-protection (-SO_2Ph), reduction of the nitro to the amine, iodination (*ortho*- to the amine) and *N*-trifluoroacetylation (Scheme 20).



Scheme 20. Synthesis of Sonogashira/Cacchi substrate **30**

2.3 Synthesis of pyrrolo[3,2-*f*]indazoles (III)

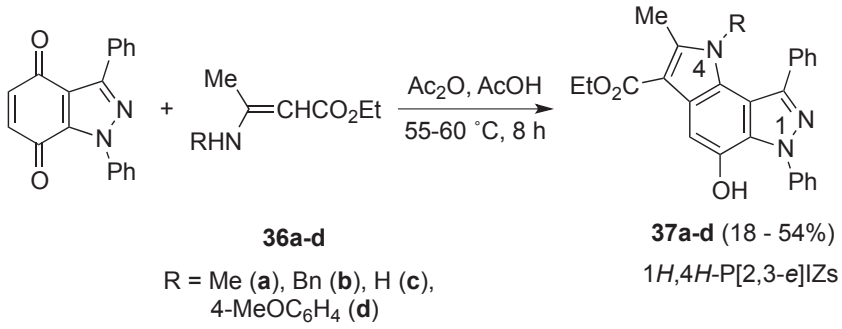
Following their previously reported route to P[2,3-*g*]IZs,[41] Seshadri *et al.* blocked the 7-position of 6-aminoindazole and carried out its acid-catalysed condensation with benzoin, which efficiently furnished 1*H*,7*H*-P[3,2-*f*]IZ (**35**) (Scheme 21). Pertinently, this compound was erroneously named as a pyrrolo[2,3-*f*]indazole. Although this work was undertaken in search of fluorescent PIZs, **35** did not show strong fluorescence.



Scheme 21. Only reported synthesis of a P[3,2-*f*]IZ

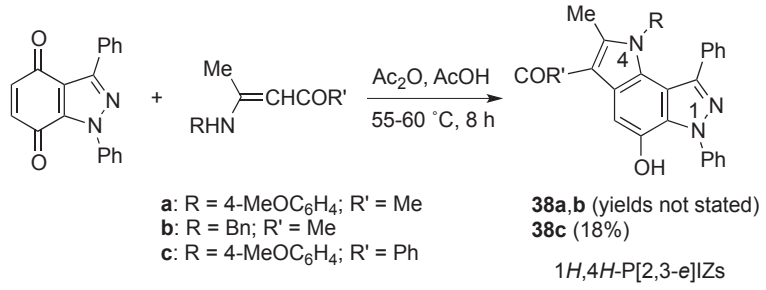
2.4 Synthesis of pyrrolo[2,3-*e*]indazoles (IV)

In this first report on the use of heterocyclic quinones in Nenitzescu reaction, 1,3-diphenyl-4,7-dioxo-4,5,6,7-tetrahydroindazole was condensed with four ethyl β-(alkyl/aryl)aminocrotonates (**36a-d**), which furnished the four P[2,3-*e*]IZs (**37a-d**) (Scheme 22).[52] Varying amounts of the corresponding furoindazoles were also formed (not shown here).



Scheme 22. First synthesis of P[2,3-*e*]IZs using Nenitzescu reaction

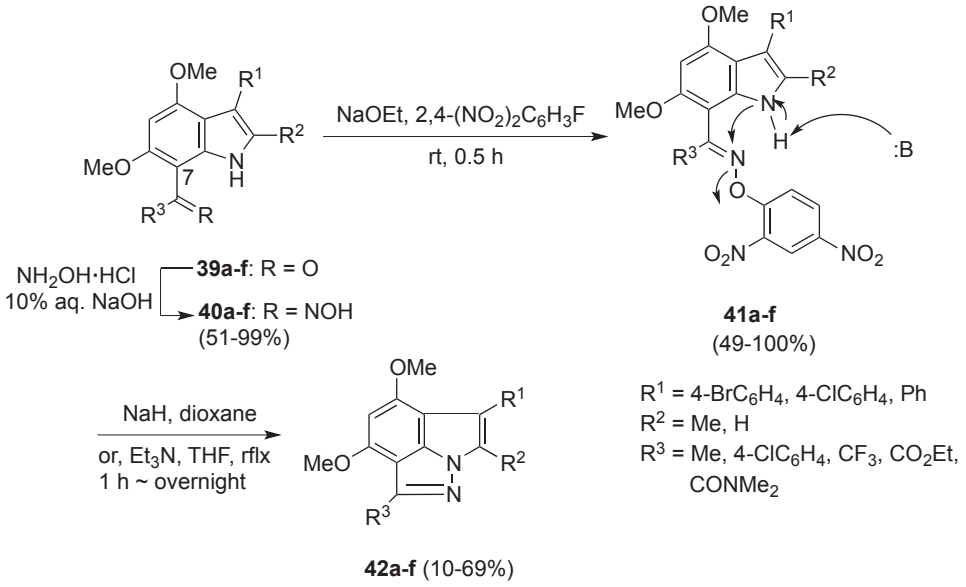
In continuation, the reaction of the same dioxoindazole with 3-enaminoketones was carried out, which similarly furnished the P[2,3-*e*]IZs (**38a-c**) (Scheme 23).



Scheme 23. Further synthesis of P[2,3-*e*]IZs using enaminoketones

2.5 Synthesis of pyrrolo[3,2,1-*hi*]indazoles (V)

The *anti*-2,4-dinitrophenyl ethers (**41a-f**) of the ketoximes of 7-acyl/aroyl-indoles (**39a-f**) underwent base-catalysed cyclisation to lead to a novel series of P[3,2,1-*hi*]IZs (**42a-f**) in poor to good yields (Scheme 24).[53] The alternative possible structures of the products resulting from initial Beckmann rearrangement, followed by cyclisation, were ruled out mainly from observed ^{1}H-^{15}N correlations (HSQC-HMBC NMR spectra) of the products. The *anti*-configuration of compounds **41** supports a displacement mechanism.



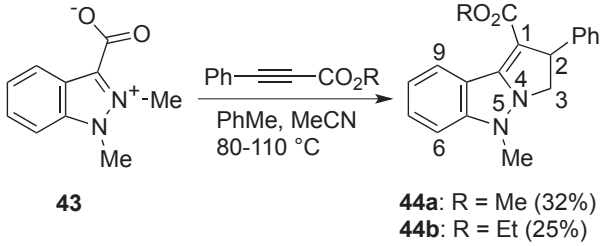
Scheme 24. Only reported synthesis of P[3,2,1-*hi*]IZs

The PIZs **42a-f** exhibited bright yellow fluorescence under long-wavelength UV light.

2.6 Synthesis of pyrrolo[1,2-*b*]indazoles (VI)

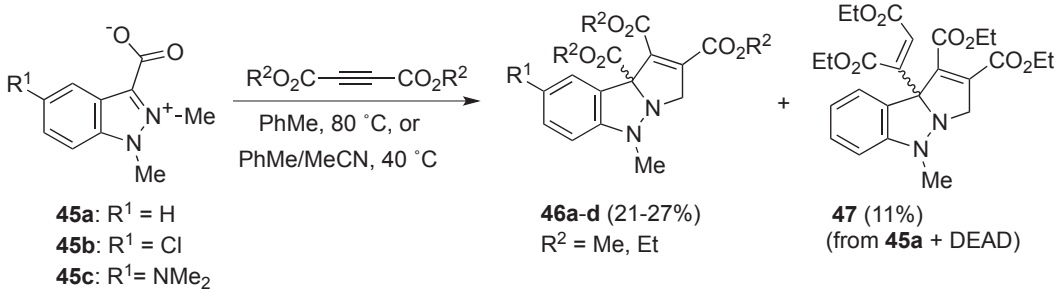
N-Heterocyclic carbene-induced cycloaddition reaction of indazoles with activated acetylenes furnished novel P[1,2-*b*]IZs. Thus, the treatment of the mesomeric betaine 1,2-dimethylindazolium-3-carboxylate

(**43**) with methyl/ethyl 3-phenylpropiolates under thermal condition furnished 3,5-dihydro-2*H*-P[1,2-*b*]IZs (**44a**,**b**) in low yields (Scheme 25).[54]



Scheme 25. Synthesis of P[1,2-*b*]IZs *via* cycloaddition of an indazolic betaine

Analogously, the betaines **45a-c** reacted with dimethyl and diethyl acetylenedicarboxylates (DMAD and DEAD, respectively) separately to furnish the 5,9b-dihydro-3*H*-P[1,2-*b*]IZ triesters (**46a-d)** as yellow oils. The reaction of **45a** with DEAD furnished two by-products, one of which was a 9b-(substituted but-2-en-2-yl)-3*H*-P[1,2-*b*]IZ derivative (**47**) (Scheme 26).



Scheme 26. Analogous synthesis of further P[1,2-*b*]IZs

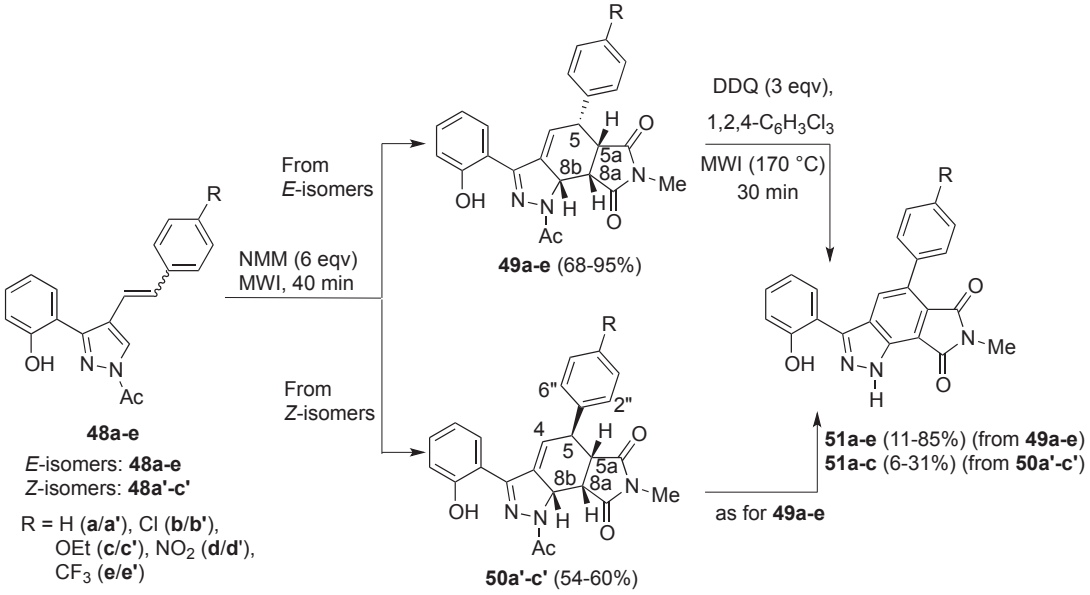
2.7 Synthesis of pyrrolo[3,4-*g*]indazoles (VII)

It had earlier been shown that *E*-1-acetyl-3-(2-hydroxyphenyl)-5-styrylpyrazole (**48a**) reacts with *N*-methylmaleimide (NMM) to give the expected cycloadduct (**49a**) in poor yield along with by-products.[55]

In continuation, they treated the *E*/*Z*-styrylpyrazoles (**48a-e**) with NMM under microwave irradiation (MWI; 800 Watt) in a solvent-free manner to furnish an epimeric mixture (at C-5) of the adducts (**49a-e** from *E*-isomers and **50a'-c'** from *Z*-isomers). Treatment of both classes of products by DDQ led to aromatisation and *N*-deacetylation, furnishing the 6,8-dioxo-1*H*-P[3,4-*g*]IZs (**51**) (Scheme 27).[56] When the reactions were carried out thermally (anhydrous 1,2,4-trichlorobenzene, DDQ, 170 ºC), it furnished the products (**51**) in better yields.

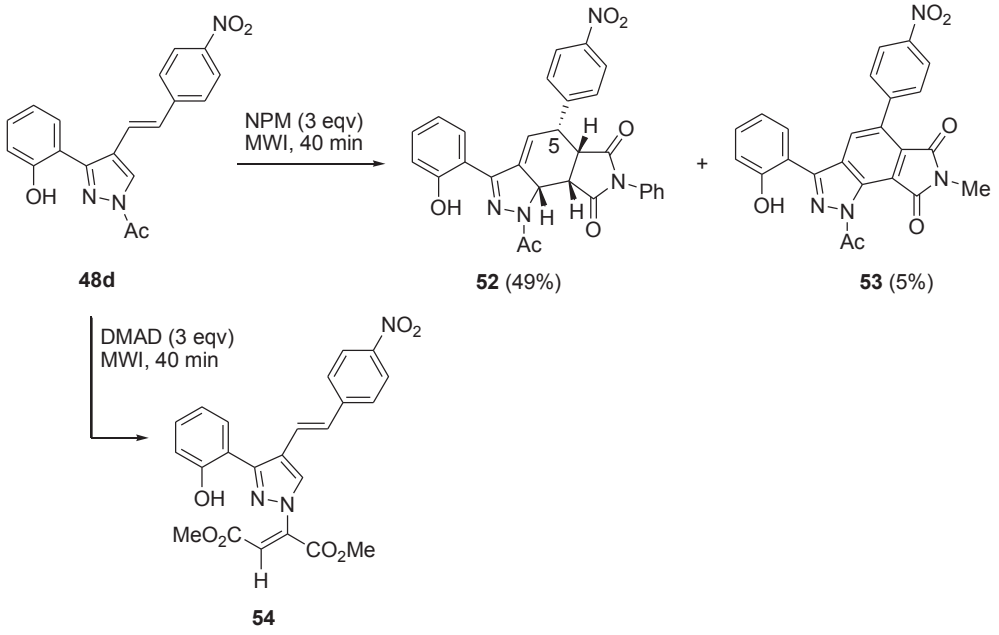
The *cis*-configurations of (i) H-5 and H-5a, H-5a and H-8a, and H-8a and H-8b in **49a-e** and (ii) H-5a and

H-8a, and H-8a and H-8b in **50a'-c'** were ascertained from the observed ^{1}H-^{1}H COSY correlations for **49** (H-4 to H-5a to H-8a to H-8b) and **50** (H-8a to H-5a to H-2'',6'').



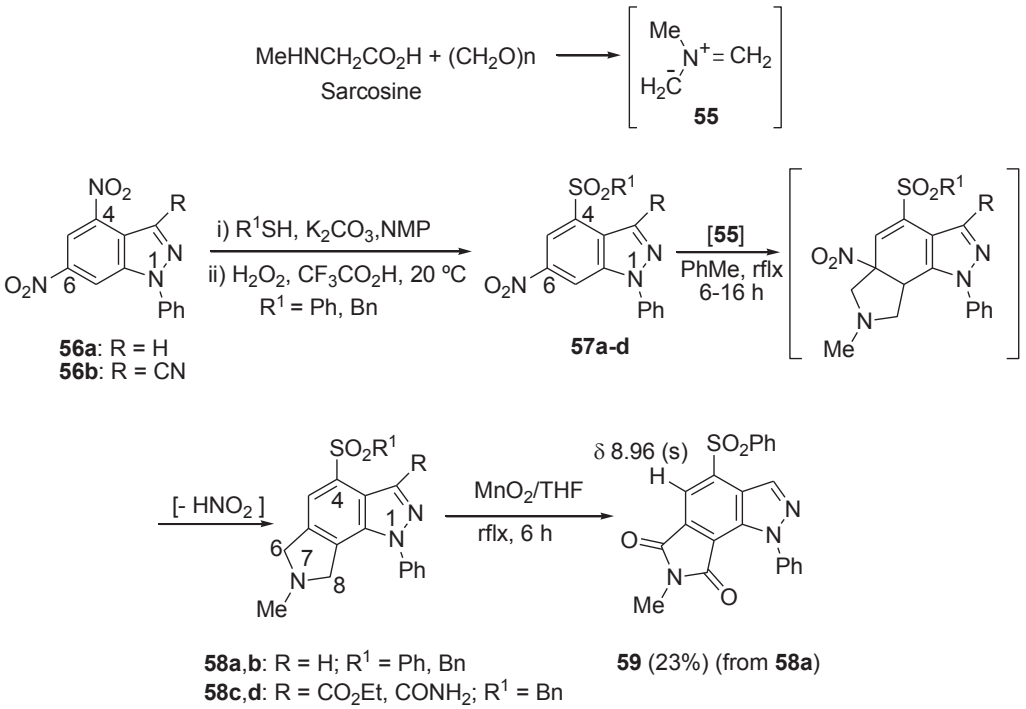
Scheme 27. Cycloaddition of styrylpyrazoles to P[3,4-g]IZs

The reaction of **48d** (*E*-isomer) with *N*-phenylmaleimide (NPM) and DMAD separately under similar conditions as above provided the cycloadduct (**52)** as the major product and the oxidised PIZ **53** as the minor product from NPM and a trace amount of the corresponding conjugate addition product (**54**) from DMAD (Scheme 28). Throughout these studies, the products were characterised by ^{1}H NMR, HSQC, HMBC and EI-MS data.



Scheme 28. Similar synthesis of P[3,4-*g*]IZs

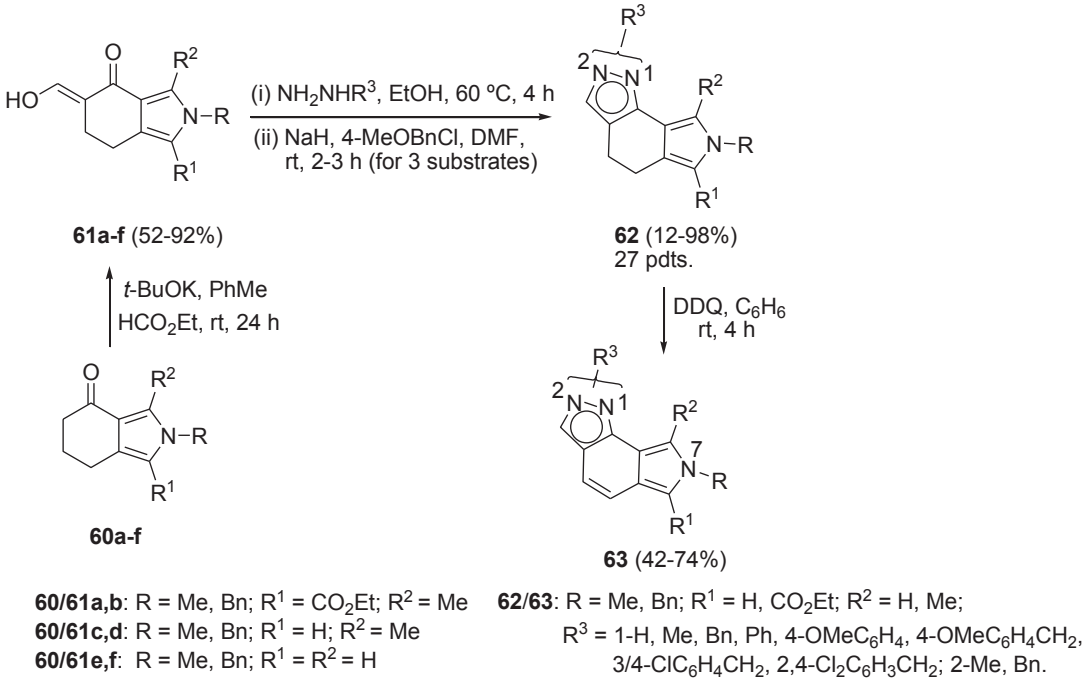
In continuation of their first report on the 1,3-dipolar cycloaddition (DCA) reactions of azomethine ylides with nitroarenes,[57] Bastrakov *et al.* studied the DCA reactions of the known indazoles **57a-d** with the unstabilised azomethine ylide **55**. While **55** was generated *in situ* from sarcosine and paraformaldehyde in refluxing toluene,[58] **57a-d** were prepared from the corresponding 4,6-dinitrophenylindazoles (**56a**,**b**). A single DCA reaction, followed by loss of nitrous acid, led to the formation of 6,8-dihydro-1*H*,7*H*-P[3,4-*g*]IZs (**58a-d**). An attempt to aromatise one of these PIZs (**58a**) by manganese dioxide led to the exclusive formation of the corresponding 6,8-dihydro-6,8 dioxo-1*H*,7*H*-P[3,4-*g*]IZ (**59**), albeit in low yield (Scheme 29).[59,60]



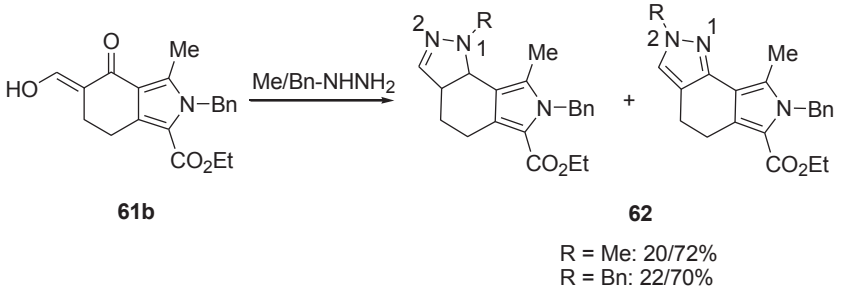
Scheme 29. Azomethine ylide route to P[3,4-*g*]IZs

A novel class of 4,5-dihydro-1*H*,7*H*-P[3,4-*g*]IZs were synthesised regioselectively by the annulation of the pyrazole ring on the isoindole moiety using the 5-hydroxymethylenetetrahydroisoindol-4-ones (**61a-f**) as the key intermediates. Thus, when **61a-f**, prepared from the corresponding tetrahydroisoindolones (**60a-f**),[61,62] were separately treated with hydrazine hydrate or methyl/benzyl/4-methoxyphenylhydrazine, the 4,5-dihydro-P[3,4-*g*]IZs (**62**) were formed. Some of these dihydro-PIZs were oxidized by DDQ to the corresponding 1*H*,7*H*- or 2*H*,7*H*-P[2,3-*g*]IZs (**63**) (Scheme 30).[63]

When treated with methylhydrazine and benzylhydrazine separately, **61b** furnished a mixture of the *N*(1)- and regioisomeric *N*(2)-substituted 4,5-dihydro-P[3,4-g]IZs (**62**) (Scheme 31).

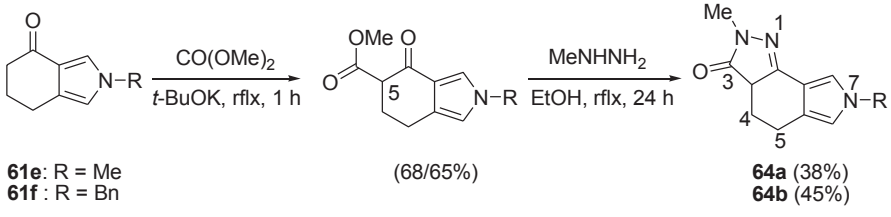


Scheme 30. Synthesis of P[3,4-*g*]IZs from tetrahydroisoindolones



Scheme 31. Similar synthesis of other P[3,4-*g*]IZs

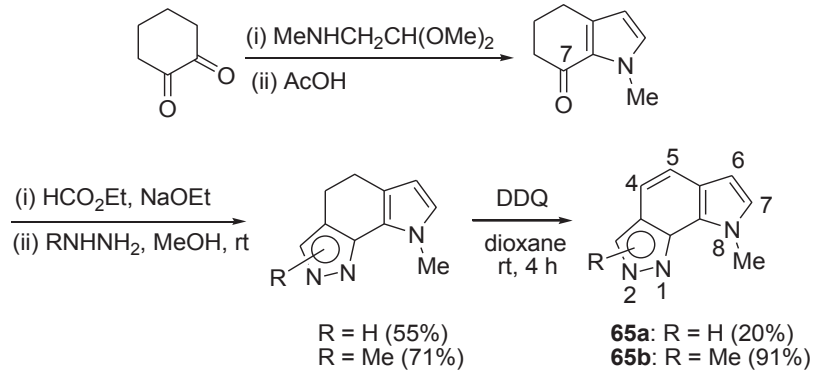
In a similar manner, *N*-methyl/benzylisoindol-4-ones (**60e,f**) furnished, *via* the derived 5-methoxycarbonyl derivatives, 7-methyl/benzyl derivatives of 2-methyl-4,5-dihydro-2*H*,7*H*-P[3,4-*g*]IZ-3-ones (**64a,b**) (Scheme 32).



Scheme 32. Similar synthesis of P[3,4-*g*]IZ-3-ones

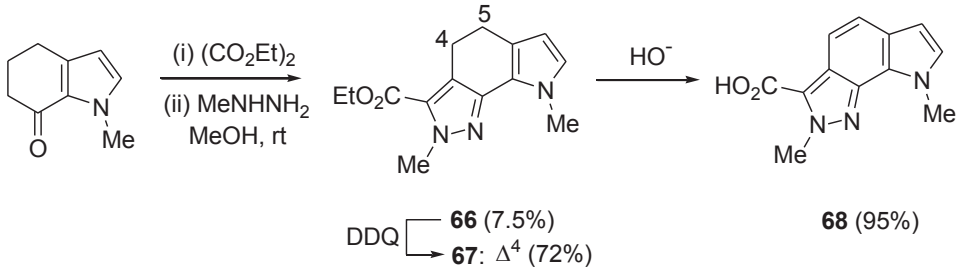
2.8 Synthesis of pyrrolo[3,2-*g*]indazoles (VIII)

8-Methyl derivatives of the then unknown 1(2)*H*,8*H*-P[3,2-*g*]IZs (**65a,b**) were synthesised by the heteroannulation of the 6-hydroxymethylene derivative of 1-methyl-4,5,6,7-tetrahydroindol-7-one, followed by aromatisation (Scheme 33).[64] The new PIZs resemble the structures of the B and C subunits of the antitumor, pyrroloindole antibiotic CC-1065.[65-67]



Scheme 33. Synthesis of P[3,2-*g*]IZs from *N*-methyltetrahydroindol-7-one

In the same report, 3-carboxy-2,8-dimethyl-2*H*,8*H*-P[3,2-*g*]IZ (**68**), a product more closely related to two other naturally occurring pyrroloindoles PDE-I and PDE-II,[68,69] was also synthesised from the same tetrahydroindolone (Scheme 34).



Scheme 34. Similar synthesis of a P[3,2-*g*]IZ

3. BIOACTIVITY OF PIZs

Amongst the eight classes of PIZs reported till date, only three classes, viz. the [2,3-*g*]-, [3,2-*e*]- and [3,4-*g*]-types displayed bioactivities of some kind. The rest were not reportedly tested for any biological activity.

Thus, some of the novel P[2,3-*g*]IZs, presented in Schemes 1-5, were claimed to be useful as non-addicting analgesics and anti-inflammatory agents in warm-blooded animals. They were active in antagonising the phenyl-*p*-quinone (PPQ) "writhing" syndrome.

When tested at oral doses of 100 or 200 mg/kg in mice, six PIZs (**2b-d**, **3a-c**) proved to be active.[38]

None of the 4,5-dihydro-1*H*,6*H*-P[2,3-*g*]IZs **8a-d** showed antibacterial (*Candida albicans*), antifungal (*T. mentagraphite*, *M. cannis*) or antiamoebic activity.[40]

The P[2,3-*g*]IZ carboxamide **12** showed acceptable NMDA-receptor antagonist activity in an assay using [3H-Ro-25-6981] as radioligand.[42-44]

Both the *N*-EOM-4,5-dihydro-P[2,3-*g*]IZs **13a** and **13b** showed significant inhibition of sGC. Indeed, the 6,7-dihydroindole ring present in **13a** and **13b** was considered to be a promising core structure for the inhibition of sGC, although **13b** (R' = Ph) transpired to be a superior inhibitor in the in vitro experiments.[45]

The three P[2,3-*g*]IZs **25-27** were tested for inhibition of Pim kinases. Of them, **26** was found to be the most active inhibitor of Pim kinase-1 (IC_{50} = 0.23 μM), while **27** transpired to be the most potent inhibitor of Pim-3 (IC_{50} = 33 nM), both at 10 μM concentrations. Based on molecular modeling experiments, the authors pointed out that the PIZ **27** can be used as a tool to study the biological role of Pim-3 compared to that of Pim-1 and Pim-2 and that the P[2,3-*g*]IZ scaffold could be used for the development of new potent inhibitors of Pim kinases.[49]

The P[3,2-*e*]IZ caboxamide **28** exhibited good NMDA-receptor antagonist activity.[42]

At 10 μM concentrations, the novel 4,5-dihydro-P[3,4-*g*]IZ-3-ones **62a** (R = R^2 = Me; R^1 = CO_2Et; R^3 = 1-H), **62b** (R = R^2 = Me; R^1 = CO_2Et; R^3 = 1-(4-MeOBn)) and **62c** (R = Bn; R^1 = H; R^2 = Me; R^3 = 1-H) exhibited modest in vitro antitumor properties against a panel of about 60 human tumour cell lines.[63]

4. CONCLUSION

This is the first review on the synthesis and bioactivity of all eight isomeric classes of PIZs, reported till date, which also includes a Sonogashira/Cacchi coupling-heteroannulation route to the general synthesis of 5-substituted P[3,2-*e*]IZs developed by the present authors. Although various isomeric PIZs have shown diverse bioactivities, the analgesic, anti-inflammatory and Pim kinase-inhibitory properties of P[2,3-*g*]IZs proved to be promising.

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