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Synthesis of pyrrolo[3,2,1-*hi*]indazoles from indole-7-ketoximes

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Abstract—Treatment of the 2,4-dinitrophenyl ethers of some indole-7-ketoximes with base results in a cyclisation reaction to yield pyrrolo[3,2,1-*hi*]indazoles.

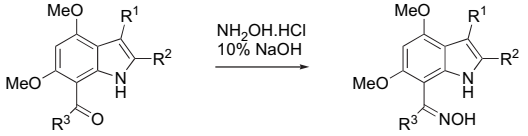
1. Introduction

We have previously reported that indole-7-carbaldehydes can be converted into the corresponding indole-7-carbonitriles by treatment of carbaldoxime 2,4-dinitrophenyl ether intermediates with base.[1] The related ketoximes can be derived from 7-acyl-, 7-aroyl- and 7-glyoxyloyl-indoles, and we wished to investigate the behaviour of their 2,4-dinitrophenyl ethers under similar conditions. One possible outcome could in principle be a Beckmann rearrangement leading to a 7-amidoindole, an extremely useful addition to the range of indole functionality. Two other possibilities might be cyclisation processes either directly onto an intermediate electron-deficient nitrogen atom arising from the loss of a 2,4-dinitrophenolate anion or radical, or alternatively onto an electron-deficient carbon atom generated by a Beckmann rearrangement process. In any cyclisation process, the most likely event would be bond formation with the indole nitrogen atom, leading to formation of either a pyrazole or an imidazole ring, respectively, in the above two scenarios.

2. Results and discussion

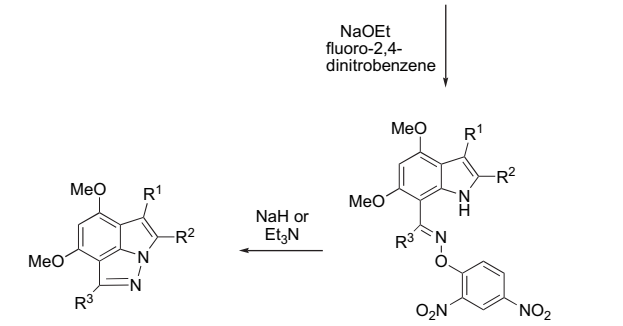
2.1. Formation of indole-7-ketoximes and ketoxime ethers

The various 7-acyl-, 7-aroyl- and 7-glyoxyloyl-indoles **1** and **3–6** have already been reported.[2,3] The 7-acetylindole **2** is detailed here for the first time, although closely related to several known compounds.[4,5] Treatment of these compounds with hydroxylamine hydrochloride and sodium hydroxide generally gave high yields (78–99%) of the indole-7-ketoximes **7–12**, except for the glyoxylic amide **6**, which gave only a 51% yield of the oxime **12** (Scheme 1). The reactions were considerably slower than those for the related aldehydes,[1] requiring approximately two days instead of 2 h for completion. In each case only one isomer was observed, and the structures were confirmed by their spectroscopic data as the respective *anti*-isomers. In particular the imine infrared stretching frequencies[5] were consistent with that



	R^1	R^2	R^3
1	4-BrC_6H_4	Me	Me
2	4-ClC_6H_4	H	Me
3	Ph	Me	4-ClC_6H_4
4	4-BrC_6H_4	Me	CF_3
5	4-BrC_6H_4	Me	CO_2Et
6	4-BrC_6H_4	Me	$CONMe_2$

	R^1	R^2	R^3	Yield %
7	4-BrC_6H_4	Me	Me	81
8	4-ClC_6H_4	H	Me	80
9	Ph	Me	4-ClC_6H_4	78
10	4-BrC_6H_4	Me	CF_3	85
11	4-BrC_6H_4	Me	CO_2Et	99
12	4-BrC_6H_4	Me	$CONMe_2$	51



	R^1	R^2	R^3	Yield %
19	4-BrC_6H_4	Me	Me	63
20	4-ClC_6H_4	H	Me	69
21	Ph	Me	4-ClC_6H_4	10
22	4-BrC_6H_4	Me	CF_3	29
23	4-BrC_6H_4	Me	CO_2Et	21
24	4-BrC_6H_4	Me	$CONMe_2$	30

	R^1	R^2	R^3	Yield %
13	4-BrC_6H_4	Me	Me	49
14	4-ClC_6H_4	H	Me	64
15	Ph	Me	4-ClC_6H_4	78
16	4-BrC_6H_4	Me	CF_3	100
17	4-BrC_6H_4	Me	CO_2Et	100
18	4-BrC_6H_4	Me	$CONMe_2$	100

Scheme 1.

Keywords: Indoles; Oxime ethers; Pyrazoles; Pyrroles; Pyrrolo-indazoles.
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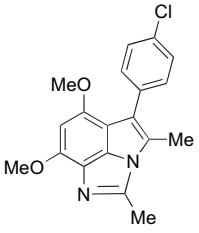
assignment, which was further supported by ^{1}H NMR spectroscopic data showing hydrogen bonding of the indole NH to the oxime N atom. For example, in oxime **7**, the two resonances at 10.49 and 10.89 ppm were unequivocally assigned to the indole NH and oxime OH protons, respectively, on the basis of NOE experiments. Irradiation of the C2-methyl protons affected the indole NH and C3-aryl proton resonances; irradiation of the ketoxime methyl protons affected the methoxy, H5, NH and OH resonances; irradiation of the 6-methoxy protons affected the methyl ketoxime and H5 resonances.

Treatment of the indole-7-ketoximes **7–12** with sodium in absolute ethanol, followed by addition of fluoro-2,4-dinitrobenzene at room temperature, yielded the oxime ethers **13–18** in 49–100% yield (Scheme 1). Except for the amido-substituted compound **18**, all of these oxime ethers showed only one isomer with an *anti*-configuration, based on infrared[6] and ^{1}H NMR spectroscopic data. This assignment is also logical for steric reasons as the bulky ether group would probably tend to be away from the NH of the indole ring.



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2.2. Formation of pyrrolo-indazoles

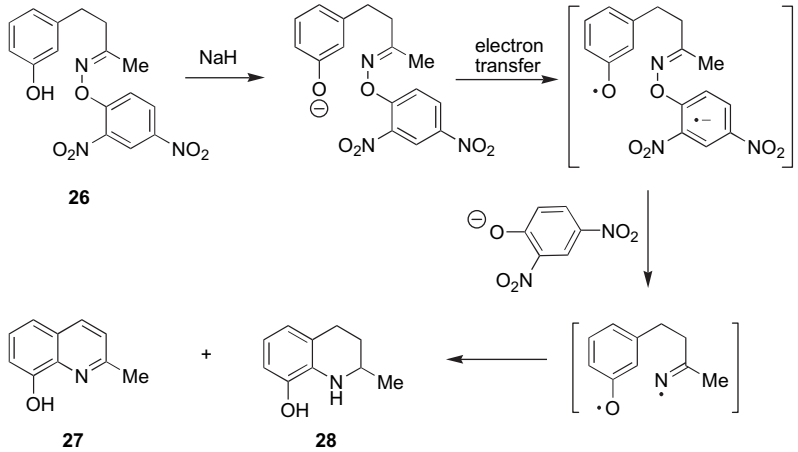
Treatment of the indole ketoxime ether **13** with triethylamine in tetrahydrofuran under reflux for 6 h gave a white solid as the major product after chromatography. The mass spectrum of the product showed a molecular ion at m/e 384 (^{79}Br, 23%), while its infrared spectrum showed that there was no NH stretching frequency present. The ^{1}H NMR spectrum displayed two singlet resonances at 2.67 and 2.75 ppm for protons of the two methyl groups and a singlet at 6.29 ppm corresponding to H5 of the starting indole. It was clear that the elimination of the dinitrophenoxy group had occurred and some kind of cyclisation had taken place onto the indole N atom. Two options were considered. Direct cyclisation would result in bond formation between the oxime and indole nitrogen atoms to give the pyrrolo-indazole **19**. On the other hand, if a Beckmann rearrangement preceded cyclisation, the pyrrolo-benzimidazole **25** could be formed.

The pyrrolo-indazole structure **19** was confirmed by NMR spectroscopy. Initial analysis with NOESY ^{1}H NMR spectroscopy failed to give any useful information, and HMBC ^{1}H–^{13}C NMR spectra could only differentiate between the resonances of the two methyl groups. However, analysis with ^{1}H–^{15}N correlations (HSQC-HMBC NMR spectra) gave clear evidence that the methyl group of the ketoxime ether has a correlation with its nitrogen atom at 216 ppm, while the C2-methyl group protons correlate with the nitrogen atom of the indole. These data are consistent with the structure **19**, but not with structure **25**, in which the ketoxime ether methyl group would be expected to correlate with each of the nitrogen atoms. The yield of compound **19** was 63%.

The other oxime ethers **14–18** were also treated with base and converted into the pyrrolo-indazoles **20–24** in somewhat variable yields ranging from 10–69%. It was observed that different bases could be utilised for the cyclisation reaction. If an electron-donating R^3 substituent was present on the oxime ether, cyclisation occurred readily with the use of a weak base such as triethylamine. If an electron-withdrawing group was present, cyclisation required a stronger base such as sodium hydride. It was found that the indole oxime ether **15** could only be converted into its geometrical *syn*-isomer when heated under reflux with triethylamine for two days, while treatment with sodium hydride gave a low yield of the pyrrolo-indazole **21** together with the *syn*-isomer.

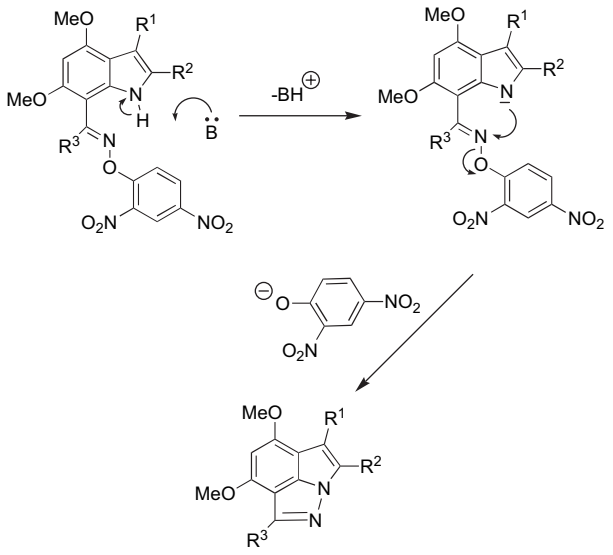
The pyrrolo-indazoles **19–24** all exhibited a bright yellow fluorescence under long-wavelength ultraviolet light.

Narasaka and co-workers have investigated various cyclisation reactions of oxime ethers.[7,8] The cyclisation of either the *syn*- or *anti*-isomer of the 2-(3-hydroxyphenyl)ethyl ketone *O*-2,4-dinitrophenyloxime **26** on treatment with sodium hydride gave a mixture of the quinoline **27** and the tetrahydroquinoline **28**, proceeded via a radical mechanism involving an alkylideneaminyl radical (Scheme 2). While



Scheme 2.

such a radical mechanism is possible for the conversion of indole oxime ethers **13**–**18** into the pyrrolo-indazoles **19**–**24**, the presence of the *anti*-configuration supports a displacement mechanism, with attack of the indole anion on the nitrogen atom of the oxime ether with simultaneous release of the dinitrophenoxide anion (Scheme 3).



Scheme 3.

3. Conclusions

The treatment of 2,4-dinitrophenyl ethers to a range of indole-7-ketoximes with base provides an effective method for the synthesis of the novel pyrrolo[3,2,1-*hi*]indazoles.

4. Experimental

4.1. General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX300 spectrometer. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI) at UNSW, or a Shimadzu LCMS QP 8000 (ESI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Ultraviolet–visible spectra were recorded using a Varian Cary 100 Scan Spectrometer. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 60GF$_{254}$.

4.1.1. 1-[3-(4-Chlorophenyl)-4,6-dimethoxyindol-7-yl]-ethanone (2). To a solution of 3-(4-chlorophenyl)-4,6-dimethoxyindole[9] (0.50 g, 1.74 mmol) at 0 °C in *N*,*N*-dimethylacetamide (1 mL) was slowly added phosphoryl chloride (1.1 mL, 11.8 mmol). The mixture was heated to 50–60 °C, stirred at this temperature overnight and quenched with ice/water. Aqueous sodium hydroxide (2 M) was added until a pH of 14 was reached, followed by 3 h of stirring at room temperature. The precipitate was filtered off and purified by chromatography (dichloromethane) yielding compound **2** (0.30 g, 52%) as a white solid, mp 202–204 °C. (Found: C, 65.5; H, 4.9; N, 4.3. $C_{18}H_{16}ClNO_3$ requires C, 65.6; H, 4.9; N, 4.3%). ν_{max}: 3328, 2942, 2844, 1624, 1585, 1561, 1343, 1272, 1216, 1093, 965, 796 cm^{-1}. λ_{max}: 232 nm (ε 22,300 cm^{-1} M^{-1}), 250 (24,500), 323 (13,200). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.69 (3H, s, Me), 3.90 (3H, s, OMe), 4.01 (3H, s, OMe), 6.23 (1H, s, H5), 7.08 (1H, d, *J* 1.9 Hz, H2), 7.32, 7.49 (4H, AA′BB′, Ar), 11.06 (1H, br s, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 33.1 (Me), 55.1 (OMe), 56.2 (OMe), 87.3 (C5), 121.7 (C2), 127.6, 130.6 (ArCH), 104.8, 110.2, 117.1, 131.6, 134.2, 139.0, 159.3, 161.0 (ArC), 198.6 (CO).

4.1.2. 1-[3-(4-Bromophenyl)-4,6-dimethoxy-2-methyl-indol-7-yl]ethanone oxime (7). The 7-acetylindole **1**[2] (0.88 g, 2.28 mmol), hydroxylamine hydrochloride (0.25 g, 3.60 mmol) and potassium hydroxide (0.5 g, 8.93 mmol) in 95% ethanol (50 mL) were heated under reflux for 45 h. After cooling, cold water was added and the mixture was acidified with 1 M HCl. The solution was cooled and the resulting white precipitate was filtered off and dried. Column chromatography (dichloromethane/ethyl acetate, 95:5) yielded the oxime **7** (0.74 g, 81%) as a white solid, mp 221–222 °C. (Found: C, 56.9; H, 4.8; N, 6.9. $C_{19}H_{19}BrN_2O_3$ requires C, 56.6; H, 4.7; N, 6.9%). ν_{max}: 3380, 1596, 1289, 1140, 1001, 912, 824, 782 cm^{-1}. λ_{max}: 231 nm (ε 27,100 cm^{-1} M^{-1}), 313 (9250), 398 (4150). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 2.12 (3H, s, Me), 2.23 (3H, s, MeC=N), 3.69, 3.79 (6H, 2s, 2×OMe), 6.36 (1H, s, H5), 7.24, 7.48 (4H, AA′BB′, ArH), 10.49 (1H, s, NH), 10.88 (1H, s, OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 12.1 (Me), 16.1 (*Me*C=N), 55.5, 57.3 (OMe), 89.8 (C5), 130.2, 132.9 (ArCH), 103.7, 111.4, 111.5, 118.6, 131.4, 135.1, 135.8, 152.3, 153.5 (ArC), 153.9 (C=N). Mass spectrum (EI): *m*/*z* 405 (M+1, ^{81}Br, 17%), 404 (99), 403 (M+1, ^{79}Br, 15), 402 (100), 371 (23), 276 (25), 275 (28).

4.1.3. 1-[3-(4-Chlorophenyl)-4,6-dimethoxyindol-7-yl]-ethanone oxime (8). This was prepared as described for the oxime **7** from the 7-acetylindole **2** (0.50 g, 1.52 mmol), hydroxylamine hydrochloride (0.17 g, 2.45 mmol) and potassium hydroxide (0.33 g, 5.88 mmol) in 95% ethanol (30 mL) under reflux for 45 h. After filtration the product was chromatographed (dichloromethane/ethyl acetate, 95:5) to yield oxime **8** (0.52 g, 80%) as a white solid, mp 171 °C. (Found: C, 62.1; H, 4.8; N, 8.1. $C_{18}H_{17}ClN_2O_3 \cdot 0.2H_2O$ requires C, 62.1; H, 5.0; N, 8.0%). ν_{max}: 3418, 3353, 1585, 1349, 1285, 1213, 1089, 994 cm^{-1}. λ_{max}: 230 nm (ε 24,700 cm^{-1} M^{-1}). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 2.15 (3H, s, Me), 3.80, 3.84 (6H, 2s, 2×OMe), 6.44 (1H, s, H5), 7.16 (1H, d, *J* 2.6 Hz, H2), 7.34, 7.51 (4H, AA′BB′, ArH), 10.67 (1H, br, NH), 10.88 (1H, s, OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 15.9 (Me), 55.5, 57.3 (OMe), 89.9 (C5), 123.4 (C2), 127.8, 130.9 (ArCH), 103.9, 110.2, 115.8, 130.1, 135.4, 136.6, 152.5, 154.4 (ArC), 154.7 (C=N). Mass spectrum (EI): *m*/*z* 346 (M, ^{37}Cl, 35%), 344 (M, ^{35}Cl, 100), 313 (23), 311 (34).

4.1.4. 1-[4,6-Dimethoxy-2-methyl-3-phenylindol-7-yl]-1-[4-chlorophenyl]methanone oxime (9). Indole **3**[2] (0.31 g, 0.76 mmol), hydroxylamine hydrochloride (0.11 g, 1.58 mmol), pyridine (3 mL) and absolute ethanol (3 mL) were heated under reflux for 24 h. After cooling, the solvent was evaporated off under reduced pressure. The residue was dissolved in dichloromethane, acidified with 1 N HCl, washed with water and dried. The solvent was evaporated off and the residue was chromatographed (dichloromethane/ethyl acetate, 95:5) to give the oxime **9** (0.25 g, 78%) as a light brown solid, mp 128 °C. (Found: C, 68.1; H, 5.1; N, 6.8. $C_{24}H_{21}ClN_2O_3 \cdot 0.1H_2O$ requires C, 68.2; H, 5.1; N, 6.6%). ν_{max}: 3422, 1599, 1574, 1289, 1213, 1148, 1091, 991 cm^{-1}. λ_{max}: 247 nm (ε 38,650 $cm^{-1}\,M^{-1}$), 314 (10,700). ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 2.18, 2.22 (3H, 2s, *syn* and *anti* Me), 3.55, 3.63, 3.67, 3.70 (6H, 4s, *syn* and *anti* OMe), 6.33, 6.39 (1H, 2s, *syn* and *anti* H5), 7.18–7.58 (9H, m, *syn* and *anti* ArH), 10.43, 10.64 (1H, 2s, *syn* and *anti* NH), 11.27, 11.40 (1H, 2s, *syn* and *anti* OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 12.2 (Me), 55.5, 57.1 (OMe), 89.4 (C5), 125.3, 127.4, 128.2, 128.5, 130.9 (ArCH), 98.5, 111.7, 112.7, 131.3, 133.3, 134.6, 136.0, 136.5, 150.4, 152.4 (ArC), 154.1 (C=N). Mass spectrum (EI): *m/z* 422 (M, ^{37}Cl, 32%), 420 (M, ^{35}Cl, 100), 404 (24), 389 (28), 387 (65), 291 (21), 267 (44).

4.1.5. 1-[3-(4-Bromophenyl)-4,6-dimethoxy-2-methylindol-7-yl]-2,2,2-trifluoroethanone oxime (10). This was prepared as described for oxime **7** from 7-trifluoroacetylindole **4**[2] (0.50 g, 1.13 mmol), hydroxylamine hydrochloride (0.10 g, 1.44 mmol) and pyridine (5 mL) in absolute ethanol (2.5 mL) under reflux for 24 h. After extraction and concentration, the residue was chromatographed (dichloromethane/ethyl acetate, 95:5) to give the oxime **10** (0.44 g, 85%) as a white solid, mp 212–214 °C. (Found: C, 50.2; H, 3.6; N, 6.1. $C_{19}H_{16}BrF_3N_2O_3$ requires C, 49.9; H, 3.5; N, 6.1%). ν_{max}: 3516, 3361, 1594, 1370, 1347, 1194, 1139, 988 cm^{-1}. λ_{max}: 231 nm (ε 24,200 $cm^{-1}\,M^{-1}$), 319 (10,300). ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 2.22 (3H, 2s, Me), 3.72, 3.78 (6H, 2s, 2×OMe), 6.40 (1H, s, H5), 7.26, 7.49 (4H, AA′BB′, ArH), 10.75 (1H, s, NH), 12.37 (1H, s, OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 12.1 (Me), 55.5, 57.1 (OMe), 88.8 (C5), 92.3 (CF_3), 130.3, 132.9 (ArCH), 111.2, 111.5, 131.8, 134.6, 135.6, 142.3, 142.8, 153.8 (ArC), 155.1 (C=N). Mass spectrum (EI): *m/z* 459 (M+1, ^{81}Br, 16%), 458 (100), 457 (M+1, ^{79}Br, 13), 456 (96), 372 (24), 370 (23), 362 (21), 345 (24), 276 (49), 261 (41).

4.1.6. Ethyl 2-[3-(4-bromophenyl)-4,6-dimethoxy-2-methylindol-7-yl]-2-(hydroxyimino)acetate (11). This was prepared as described for oxime **7** from indole **5**[2] (0.40 g, 0.90 mmol), hydroxylamine hydrochloride (0.13 g, 1.87 mmol) and pyridine (4 mL) in absolute ethanol (2.5 mL) under reflux for 16 h. After extraction and concentration, the residue was chromatographed (dichloromethane/ethyl acetate, 95:5) to give the oxime **11** (0.41 g, 99%) as a yellow solid, mp 182–184 °C (dec). (Found: C, 54.6; H, 4.6; N, 6.1. $C_{21}H_{21}BrN_2O_5$ requires C, 54.7; H, 4.6; N, 6.1%). ν_{max}: 3400, 3330, 1732, 1595, 1357, 1210, 998, 911, 787 cm^{-1}. λ_{max}: 231 nm (ε 26,350 $cm^{-1}\,M^{-1}$), 252 (24,800), 329 (14,100). ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 1.24 (3H, m, *syn* and *anti* CH_2–*Me*), 2.21, 2.28 (3H, 2s, *syn* and *anti* Me), 3.73 (6H, m, *syn* and *anti* OMe), 4.23 (2H, m, *syn* and *anti* OCH_2), 6.35, 6.39 (1H, 2s, *syn* and *anti* H5), 7.27–7.51 (4H, 2d, *J* 8.7 Hz, *syn* and *anti* ArH), 10.29, 10.39 (1H, 2s, *syn* and *anti* NH), 11.35, 12.17 (1H, 2s, *syn* and *anti* OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 12.1, 12.2 (Me), 14.4, 14.5 (CH_2–*Me*), 55.5, 55.6, 57.0, 57.9 (OMe), 60.8, 60.9 (OCH_2), 88.9, 90.0 (C5), 130.3, 130.4, 132.9, 133.0 (ArCH), 96.7, 96.9, 111.2, 111.3, 111.9, 112.3, 118.6, 119.0, 131.2, 131.4, 133.7, 134.5, 135.3, 135.8, 145.7, 149.4, 153.6, 154.6 (ArC), 155.3, 155.7 (C=N), 164.1, 164.4 (C=O). Mass spectrum (EI): *m/z* 463 (M+1, ^{81}Br, 17%), 462 (100), 461 (M+1, ^{79}Br, 13), 460 (95), 444 (29), 430 (41), 371 (52), 357 (89), 276 (91), 261 (85).

4.1.7. *N,N*-Dimethyl-2-[3-(4-bromophenyl)-4,6-dimethoxy-2-methylindol-7-yl]-2-(hydroxyimino)acetamide (12). This was prepared as described for the oxime **7** from indole **6**[2] (0.50 g, 1.1 mmol), hydroxylamine hydrochloride (0.14 g, 2.01 mmol) and pyridine (5 mL) in absolute ethanol (5 mL) under reflux for 48 h. After extraction and concentration, the residue was chromatographed (dichloromethane/methanol, 95:5) to give the oxime **12** (0.26 g, 51%) as a white solid, mp 256–257 °C. (Found: C, 54.5; H, 4.8; N, 9.2. $C_{21}H_{22}BrN_3O_4$ requires C, 54.8; H, 4.8; N, 9.1%). ν_{max}: 3386, 3153, 1636, 1585, 1213, 1127, 1002 cm^{-1}. λ_{max}: 231 nm (ε 29,000 $cm^{-1}\,M^{-1}$), 326 (13,250). ^1H NMR spectrum (300 MHz, DMSO-d_6): δ 2.27 (3H, s, Me), 2.88, 2.93 (6H, 2s, NMe_2), 3.71, 3.73 (6H, 2s, 2×OMe), 6.36 (1H, s, H5), 7.26, 7.50 (4H, 2d, *J* 8.7 Hz, ArH), 10.34 (1H, br, NH), 11.17 (1H, s, OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 12.2 (Me), 33.6, 36.7 (NMe_2), 55.6, 58.1 (OMe), 90.2 (C5), 130.3, 133.1 (ArCH), 98.4, 111.8, 112.1, 118.9, 131.0, 134.3, 135.4, 151.9, 155.2 (ArC), 155.4 (C=N), 165.5 (C=O). Mass spectrum (EI): *m/z* 462 (M+1, ^{81}Br, 18%), 461 (100), 460 (M+1, ^{79}Br, 16), 459 (97), 443 (26), 372 (62), 371 (45), 370 (58), 276 (45), 261 (59).

4.1.8. 1-[3-(4-Bromophenyl)-4,6-dimethoxy-2-methylindol-7-yl]ethanone *O*-2,4-dinitrophenyloxime (13). Indole oxime **7** (0.20 g, 0.49 mmol) was dissolved in absolute ethanol (20 mL) and sodium (18 mg, 0.78 mmol) was added. The solution became clear and was stirred at room temperature for 30 min. The mixture was cooled in an ice-bath, and fluoro-2,4-dinitrobenzene (0.1 mL, 0.83 mmol) was added dropwise. The mixture was stirred for another 2 h and the resulting precipitate was filtered off, washed with absolute ethanol and dried to yield the oxime ether **13** (0.14 g, 49%) as an orange solid, which could not be fully purified. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.67, 2.74 (6H, 2s, 2×Me), 3.92, 4.03 (6H, 2s, 2×OMe), 6.29 (1H, s, H5), 7.32 (1H, d, *J* 9.4 Hz, ArH), 7.46–7.56 (4H, m, ArH), 8.44 (1H, dd, *J* 9.4, 2.6 Hz, ArH), 9.06 (1H, d, *J* 2.6 Hz, ArH), 11.0 (1H, br, NH). The sample was not soluble enough for ^{13}C NMR measurement.

4.1.9. 1-[3-(4-Chlorophenyl)-4,6-dimethoxyindol-7-yl]-ethanone *O*-2,4-dinitrophenyloxime (14). This was prepared as described for indole **13** from indole oxime **8** (0.18 g, 0.54 mmol), absolute ethanol (20 mL), sodium (18 mg, 0.78 mmol) and fluoro-2,4-dinitrobenzene (0.1 mL, 0.83 mmol). After filtration, washing and chromatography (dichloromethane) it was dried to yield the oxime ether **14** (0.17 g, 64%) as an orange solid, mp 102 °C (dec).

(Found: C, 49.0; H, 3.1; N, 9.3. $C_{24}H_{19}ClN_4O_7 \cdot 1.3CH_2Cl_2$ requires C, 48.9; H, 3.5; N, 9.0%). ν_{max}: 3396, 1607, 1530, 1462, 1340, 1214 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.74 (3H, s, Me), 4.04, 4.06 (6H, 2s, 2×OMe), 6.35 (1H, s, H5), 7.36, 7.47 (4H, AA′BB′, ArH), 7.67 (1H, s, H2), 7.80 (2H, d, *J* 8.7 Hz, ArH and NH), 8.44 (1H, dd, *J* 9.4, 2.6 Hz, ArH), 9.06 (1H, d, *J* 2.6 Hz, ArH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 345 (100%), 327 (37).

4.1.10. 1-(4-Chlorophenyl)-1-[4,6-dimethoxy-2-methyl-3-phenylindole]methanone *O*-2,4-dinitrophenyloxime (15). This was prepared as described for indole **13** from indole oxime **9** (0.24 g, 0.57 mmol), absolute ethanol (25 mL), sodium (24 mg, 1.04 mmol) and fluoro-2,4-dinitrobenzene (0.1 mL, 0.83 mmol). After filtration, washing and chromatography (dichloromethane) it was dried to yield the oxime ether **15** (0.25 g, 78%) as an orange solid, mp 158–160 °C. (Found: C, 51.3; H, 3.3; N, 7.9. $C_{30}H_{23}ClN_4O_7 \cdot 1.8CH_2Cl_2$ requires C, 51.6; H, 3.6; N, 7.6%). ν_{max}: 3419, 1600, 1541, 1526, 1469, 1341, 1264, 1215, 1149, 924 cm^{-1}. λ_{max}: 228 nm (ε 32,250 $cm^{-1}\,M^{-1}$), 242 (32,100), 311 (24,650). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.27 (3H, s, Me), 3.66, 3.79 (6H, 2s, 2×OMe), 6.31 (1H, s, H5), 7.28–7.68 (10H, m, ArH and NH), 8.01 (1H, d, *J* 9.4 Hz, ArH), 8.44 (1H, dd, *J* 9.4, 2.6 Hz, ArH), 8.76 (1H, d, *J* 2.6 Hz, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 12.0 (Me), 55.2, 56.3 (OMe), 88.3 (C5), 118.3, 121.6, 125.6, 127.1, 128.7, 128.9, 129.4, 130.9 (ArCH), 95.5, 112.2, 114.3, 130.6, 132.5, 134.4, 135.5, 137.1, 137.2, 141.2, 154.3, 156.3, 157.0, 160.3 (ArC). Mass spectrum (EI): *m/z* 589 (M+1, ^{37}Cl, 2%), 588 (6), 587 (M+1, ^{35}Cl, 6), 586 (17), 513 (26), 294 (100), 293 (45).

4.1.11. 1-[3-(4-Bromophenyl)-4,6-dimethoxy-2-methylindol-7-yl]-2,2,2-trifluoroethanone *O*-2,4-dinitrophenyloxime (16). This was prepared as described for indole **13** from indole oxime **10** (0.15 g, 0.33 mmol), absolute ethanol (15 mL), sodium (0.02 g, 1.07 mmol) and fluoro-2,4-dinitrobenzene (0.06 mL, 0.33 mmol). After filtration and washing, it was dried to yield the oxime ether **16** (0.20 g, 100%) as an orange solid, mp 189 °C (dec). (Found: C, 48.3; H, 2.8; N, 8.7. $C_{25}H_{18}BrF_3N_4O_7$ requires C, 48.2; H, 2.9; N, 9.0%). ν_{max}: 3420, 1603, 1541, 1469, 1345, 1221, 1153, 1123, 933 cm^{-1}. λ_{max}: 233 nm (ε 35,750 $cm^{-1}\,M^{-1}$). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.33 (3H, s, Me), 3.79, 3.88 (6H, 2s, OMe), 6.28 (1H, s, H5), 7.28, 7.49 (4H, AA′BB′, ArH), 7.92 (1H, d, *J* 9.0 Hz, ArH), 7.94 (1H, br, NH), 8.48 (1H, dd, *J* 9.0, 2.6 Hz, ArH), 8.78 (1H, d, *J* 2.6 Hz, ArH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 624 (M, ^{81}Br, 1%), 622 (M, ^{79}Br, 1), 440 (95), 371 (100).

4.1.12. Ethyl 2-[3-(4-bromophenyl)-4,6-dimethoxy-2-methylindol-7-yl]-2-(*O*-2,4-dinitrophenyloxyimino)-acetate (17). This was prepared as described for indole **13** from indole oxime **11** (0.20 g, 0.43 mmol), absolute ethanol (20 mL), sodium (27 mg, 1.17 mmol) and 2,4-dinitrofluorobenzene (0.08 mL, 0.66 mmol). After filtration and washing, it was dried to yield the oxime ether **17** (0.27 g, 100%) as an orange solid, mp 179–180 °C. (Found: C, 51.4; H, 3.6; N, 8.7. $C_{27}H_{23}BrN_4O_9$ requires C, 51.7; H, 3.7; N, 8.9%). ν_{max}: 3434, 1743, 1591, 1542, 1342, 1208, 1159 cm^{-1}. λ_{max}: 230 nm (ε 39,900 $cm^{-1}\,M^{-1}$), 257 (38,400). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.39 (3H, t, *J* 7.2 Hz, CH_2*Me*), 2.37 (3H, s, Me), 3.78, 3.86 (6H, 2s, OMe), 4.41 (2H, q, *J* 7.2 Hz, OCH_2), 6.23 (1H, s, H5), 7.28, 7.49 (4H, 2d, *J* 8.6 Hz, ArH), 8.00 (1H, d, *J* 9.4 Hz, ArH), 8.42 (1H, s, NH), 8.47 (1H, dd, *J* 9.4, 2.6 Hz, ArH), 8.79 (1H, d, *J* 2.6 Hz, ArH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 629 (M+1, ^{81}Br, 26%), 627 (M+1, ^{79}Br, 26) 583 (12), 446 (100), 371 (55).

4.1.13. *N*,*N*-Dimethyl-2-[3-(4-bromophenyl)-4,6-dimethoxy-2-methylindol-7-yl]-2-(*O*-2,4-dinitrophenyloxyimino)acetamide (18). This was prepared as described for indole **13** from indole oxime **12** (0.15 g, 0.33 mmol), absolute ethanol (15 mL), sodium (0.02 g, 0.87 mmol) and fluoro-2,4-dinitrobenzene (0.06 mL, 0.50 mmol). After filtration and washing, it was dried to yield the oxime ether **18** (0.20 g, 100%) as an orange solid, mp 162 °C (dec). (Found: C, 50.5; H, 3.8; N, 10.3. $C_{27}H_{24}BrN_5O_8 \cdot 1H_2O$ requires C, 50.3; H, 4.0; N, 10.8%). ν_{max}: 3428, 1646, 1585, 1515, 1343, 1296, 1215 cm^{-1}. λ_{max}: 230 nm (ε 45,650 $cm^{-1}\,M^{-1}$), 255 (42,800), 364 (18,850). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.32, 2.37 (3H, s, *syn* and *anti* Me), 2.99–3.18 (6H, m, *syn* and *anti* NMe_2), 3.75–3.88 (6H, m, *syn* and *anti* OMe), 6.20, 6.23 (1H, s, *syn* and *anti* H5), 7.46–7.52 (4H, m, *syn* and *anti* ArH), 7.83, 7.86 (1H, d, *J* 9.4 Hz, *syn* and *anti* ArH), 8.39–8.50 (1H, m, *syn* and *anti* ArH), 8.72, 8.90 (1H, d, *J* 2.6 Hz, ArH), 9.66 (1H, s, *syn* and *anti* NH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 509 (12%), 463 (46), 461 (41), 445 (100), 443 (98), 289 (47).

4.1.14. 5-(4-Bromophenyl)-6,8-dimethoxy-1,4-dimethylpyrrolo[3,2,1-*hi*]indazole (19). A mixture of indole oxime ether **13** (0.14 g, 0.24 mmol) and triethylamine (0.75 mL) in dry tetrahydrofuran (15 mL) was heated under reflux for 6 h with stirring. The solvent was evaporated off and the residue was dissolved in dichloromethane. The organic layer was washed with 2 M NaOH and water, dried and concentrated. Column chromatography (dichloromethane) yielded compound **19** (0.06 g, 63%) as a white solid, mp 180–181 °C. (Found: C, 59.1; H, 4.5; N, 7.4. $C_{19}H_{17}BrN_2O_2$ requires C, 59.2; H, 4.5; N, 7.3%). ν_{max}: 1682, 1603, 1511, 1234, 1122, 1000 cm^{-1}. λ_{max}: 229 nm (ε 25,500 $cm^{-1}\,M^{-1}$), 270 (13,450), 329 (15,900). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.67 (3H, s, Me), 2.75 (3H, s, MeC=N), 3.91, 4.03 (6H, 2s, 2×OMe), 6.29 (1H, s, H7), 7.48, 7.55 (4H, AA′BB′, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 10.7 (Me), 15.2 (*Me*C=N), 56.2, 56.7 (OMe), 92.1 (C7), 131.0, 131.2 (ArCH), 101.4, 103.5, 118.4, 119.9, 129.8, 134.1, 142.9, 151.1, 156.3, 158.4 (ArC). Mass spectrum (EI): *m/z* 387 (M+1, ^{81}Br, 20%), 386 (99), 385 (M+1, ^{79}Br, 23), 384 (100), 369 (55), 275 (90).

4.1.15. 5-(4-Chlorophenyl)-6,8-dimethoxy-1-methylpyrrolo[3,2,1-*hi*]indazole (20). This was prepared as described for indole **19** from indole oxime ether **14** (0.15 g, 0.29 mmol) and triethylamine (0.75 mL) in dry tetrahydrofuran (15 mL) under reflux for 6 h. After extraction and concentration, the residue was chromatographed (dichloromethane) to give the pyrrolo-indazole **20** (0.07 g, 69%) as a white solid, mp 198–200 °C. (Found: C, 66.0; H,

4.6; N, 8.7. $C_{18}H_{15}ClN_2O_2$ requires C, 66.2; H, 4.6; N, 8.6%). ν_{max}: 3102, 1675, 1604, 1505, 1333, 1220, 1176, 1117, 1067 cm^{-1}. λ_{max}: 230 nm (ε 20,200 $cm^{-1}\,M^{-1}$), 274 (12,400). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.74 (3H, s, Me), 4.03, 4.05 (6H, 2s, 2×OMe), 6.34 (1H, s, H7), 7.67 (1H, s, H2), 7.36, 7.80 (4H, AA′BB′, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 15.2 (Me), 56.3, 56.5 (OMe), 91.7 (C7), 118.6 (C2), 128.4, 128.6 (ArCH), 100.5, 103.4, 123.9, 132.0, 133.2, 144.4, 151.7, 157.2, 159.2 (ArC). Mass spectrum (EI): *m/z* 328 (M, ^{37}Cl, 31%), 326 (M, ^{35}Cl, 100), 311 (57), 261 (32).

4.1.16. 1-(4-Chlorophenyl)-6,8-dimethoxy-4-methyl-5-phenylpyrrolo[3,2,1-*hi*]indazole (21). This was prepared as described for indole **19** from indole oxime ether **15** (0.30 g, 0.51 mmol) and sodium hydride (0.12 g, 80% dispersion in oil, 4.0 mmol) in dioxane (7.5 mL) under reflux for 1 h. After extraction and concentration, the residue was chromatographed (dichloromethane) to give the pyrrolo-indazole **21** (20 mg, 10%) as a yellow solid, mp 190–192 °C. (Found: C, 70.5; H, 4.9; N, 6.7. $C_{24}H_{19}ClN_2O_2\cdot 0.3H_2O$ requires C, 70.6; H, 4.8; N, 6.9%). ν_{max}: 1675, 1600, 1518, 1325, 1299, 1234, 1216, 1134, 1013 cm^{-1}. λ_{max}: 231 nm (ε 31,350 $cm^{-1}\,M^{-1}$), 246 (31,200), 318 (12,100). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.75 (3H, s, Me), 3.92, 4.06 (6H, 2s, 2×OMe), 6.37 (1H, s, H7), 7.30–7.66 (7H, m, ArH), 8.35 (1H, part of AA′BB′, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 10.6 (Me), 56.2, 56.8 (OMe), 92.8 (C7), 126.3, 127.9, 128.6, 129.4, 129.7 (ArCH), 101.6, 120.5, 129.6, 131.7, 134.4, 134.8, 142.7, 151.7, 155.4, 158.4 (ArC). Mass spectrum (EI): *m/z* 404 (M, ^{37}Cl, 35%), 402 (M, ^{35}Cl, 100), 387 (43), 291 (20), 220 (22).

4.1.17. 5-(4-Bromophenyl)-6,8-dimethoxy-4-methyl-1-trifluoromethylpyrrolo[3,2,1-*hi*]indazole (22). This was described as prepared for indole **19** from indole oxime ether **16** (0.20 g, 0.32 mmol) and sodium hydride (97 mg, 80% dispersion in oil, 3.23 mmol) in dioxane (5 mL) under reflux for 1 h. After extraction and concentration, the residue was chromatographed (dichloromethane) to give the pyrrolo-indazole **22** (41 mg, 29%) as a pale yellow solid, which could not be fully purified. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.68 (3H, s, Me), 3.95, 4.05 (6H, 2s, 2×OMe), 6.37 (1H, s, H7), 7.47, 7.58 (4H, AA′BB′, ArH).

4.1.18. Ethyl 5-(4-bromophenyl)-6,8-dimethoxy-4-methylpyrrolo[3,2,1-*hi*]indazole-1-carboxylate (23). This was prepared as described for indole **19** from indole oxime ether **17** (0.27 g, 0.43 mmol) and triethylamine (1 mL) in dry tetrahydrofuran (20 mL) under reflux overnight. After extraction and concentration, the residue was chromatographed (dichloromethane) to give the pyrrolo-indazole **23** (40 mg, 21%) as a yellow solid, which could not be fully purified. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.49 (3H, t, *J* 7.1 Hz, OCH_2Me), 2.70 (3H, s, Me), 3.94, 4.08 (6H, 2s, 2×OMe), 4.54 (2H, q, *J* 7.1 Hz, OCH_2), 6.38 (1H, s, H5), 7.48, 7.57 (4H, AA′BB′, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 10.5 (Me), 14.3 (OCH_2*Me*), 56.6, 56.7 (OMe), 61.6 (OCH_2), 93.9 (C5), 131.1, 131.2 (ArCH), 100.5, 102.7, 120.8, 122.5, 129.9, 133.1, 142.1, 142.6, 156.6, 158.8 (ArC), 162.0 (C═O). Mass spectrum (EI): *m/z* 444 (M, ^{81}Br, 35%), 442 (M, ^{79}Br, 28), 372 (23), 371 (100), 369 (96).

4.1.19. *N*,*N*-Dimethyl-5-(4-bromophenyl)-6,8-dimethoxy-4-methylpyrrolo[3,2,1-*hi*]indazole-1-carboxamide (24). This was prepared as described for indole **19** from indole oxime ether **18** (0.20 g, 0.32 mmol) and sodium hydride (0.12 g, 80% dispersion in oil, 4.0 mmol) in dioxane (4 mL) under reflux for 1 h. After extraction and concentration, the residue was chromatographed (dichloromethane) to give the pyrrolo-indazole **24** (42 mg, 30 %) as a pale yellow solid, mp 230–232 °C. (Found: C, 55.3; H, 4.4; N, 9.2. $C_{21}H_{20}BrN_3O_3\cdot 0.7H_2O$ requires C, 55.4; H, 4.7; N, 9.2%). ν_{max}: 1677, 1627, 1596, 1515, 1327, 1225, 1132, 1077, 1005 cm^{-1}. λ_{max}: 231 nm (ε 27,900 $cm^{-1}\,M^{-1}$), 329 (8250). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.67 (3H, s, Me), 3.21 (6H, s, NMe_2), 3.92, 4.04 (6H, 2s, OMe), 6.36 (1H, s, H5), 7.48, 7.56 (4H, 2d, *J* 8.3 Hz, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 10.5 (Me), 35.4, 38.7 (NMe_2), 56.7, 56.9 (OMe), 94.0 (C5), 131.1, 131.2 (ArCH), 100.7, 101.8, 120.5, 120.7, 129.6, 133.5, 141.6, 145.8, 156.3, 158.8 (ArC), 164.1 (C═O). Mass spectrum (EI): *m/z* 444 (M+1, ^{81}Br, 27%), 443 (100), 442 (M+1, ^{79}Br, 20), 441 (90), 372 (38), 371 (68), 370 (22), 369 (71), 275 (32).

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