

Cite this: *Chem. Sci.*, 2021, 12, 12993

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Selective functionalization of the 1*H*-imidazo[1,2-*b*]pyrazole scaffold. A new potential non-classical isostere of indole and a precursor of push–pull dyes†

Kuno Schwärzer,^a Saroj K. Rout,^a Derya Bessinger,^a Fabio Lima,^b Cara E. Brocklehurst,^b Konstantin Karaghiosoff,^a Thomas Bein^a and Paul Knochel^a

We report the selective functionalization of the 1*H*-imidazo[1,2-*b*]pyrazole scaffold using a Br/Mg-exchange, as well as regioselective magnesiations and zincations with TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl), followed by trapping reactions with various electrophiles. In addition, we report a fragmentation of the pyrazole ring, giving access to push–pull dyes with a proaromatic (1,3-dihydro-2*H*-imidazol-2-ylidene)malononitrile core. These functionalization methods were used in the synthesis of an isostere of the indolyl drug pruvanserin. Comparative assays between the original drug and the isostere showed that a substitution of the indole ring with a 1*H*-imidazo[1,2-*b*]pyrazole results in a significantly improved solubility in aqueous media.

Received 29th July 2021
Accepted 28th August 2021

DOI: 10.1039/d1sc04155j

rsc.li/chemical-science

Introduction

N-heterocyclic scaffolds are key structural units for pharmaceutical, agrochemical and material science applications.^{1,2} The study of less common heterocyclic ring systems is of special interest, since new physicochemical and medicinal properties may be expected from such classes of molecules.³ Condensed five membered N-heterocycles such as 1*H*-imidazo[1,2-*b*]pyrazoles of type 1 recently attracted much attention due to the diverse and very useful bioactivities (antimicrobial,^{4,5} anti-cancer,^{6,7} anti-inflammatory⁸) of such molecules (Fig. 1).

Furthermore, the scaffold 1 can also be considered as a potential non-classical isostere of indole (2). The search for new indole replacements is mainly motivated by their often low solubility and metabolic stability.⁹ The promising indolyl drug pruvanserin (3, selective 5-HT_{2A} serotonin receptor antagonist)^{10–12} has been discontinued in phase II clinical trials as a drug for the treatment of insomnia.¹³ The corresponding 1*H*-imidazo[1,2-*b*]pyrazole isostere 4 was predicted to display improved solubility in physiological media. We therefore have developed a toolbox allowing the selective functionalization of

the 1*H*-imidazo[1,2-*b*]pyrazole skeleton, which enabled the preparation of the pruvanserin isostere 4 in order to compare the physicochemical properties of the matched pair 3 and 4 (Fig. 2).

Previously reported protocols for the preparation of 1*H*-imidazo[1,2-*b*]pyrazoles require the synthesis of new starting materials for every functionalized derivative, as the ring fusion is only achieved in the final steps.^{14–17} To avoid this issue, we have chosen a synthetic approach involving a successive and selective functionalization of the readily available 1*H*-imidazo[1,2-*b*]pyrazole scaffold. Therefore, we envisioned to employ a Br/Mg-exchange as well as selective magnesiations and zincations using metal amides. Previously, we have reported

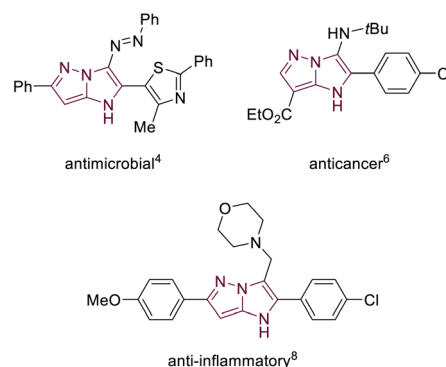


Fig. 1 Examples of 1*H*-imidazo[1,2-*b*]pyrazoles with biological activities.

^aDepartment Chemie, Ludwig-Maximilians-Universität München, Munich 81377, Germany. E-mail: Paul.Knochel@cup.uni-muenchen.de

^bGlobal Discovery Chemistry, Novartis Institutes of BioMedical Research, Basel 4057, Switzerland

† Electronic supplementary information (ESI) available: Deposition number 2097280 (7a) contains the supplementary crystallographic data for this paper. CCDC 2097280. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc04155j

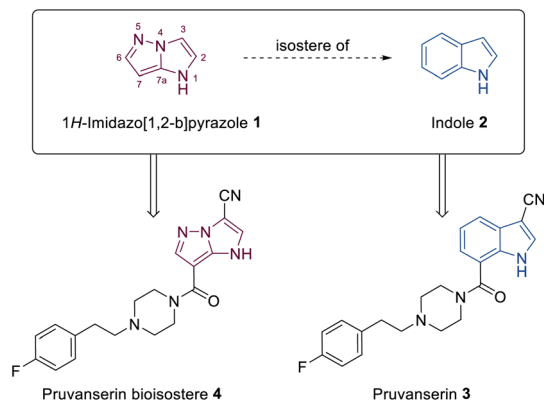
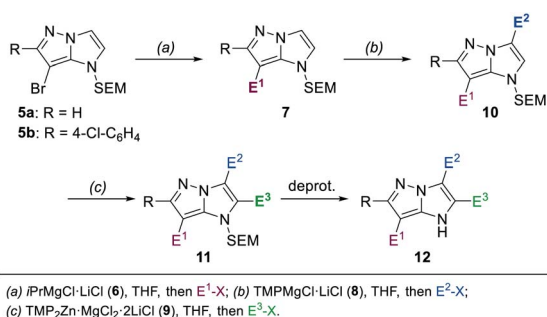
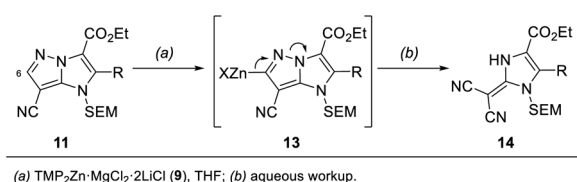


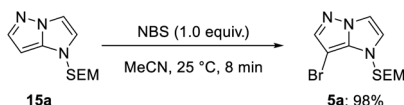
Fig. 2 1*H*-Imidazo[1,2-*b*]pyrazole (1) as a potential replacement of indole (2) as shown for the 5-HT_{2A} serotonin receptor antagonist pruvanserin (3).



Scheme 1 Functionalization of SEM-protected 1*H*-imidazo[1,2-*b*]pyrazoles of type 5 via a sequence consisting of a Br/Mg-exchange and two consecutive metalations, each followed by electrophile trapping.



Scheme 2 Fragmentation of functionalized 1*H*-imidazo[1,2-*b*]pyrazoles of type 11 leading to fluorescent push-pull dyes of type 14.



Scheme 3 Selective bromination of the SEM-protected 1*H*-imidazo[1,2-*b*]pyrazole 15a.

a range of powerful Br/Mg-exchange reagents^{18,19} as well as kinetically highly active, sterically hindered TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl).^{21,22} These organometallic reagents have been used successfully in the selective functionalization of various N-heterocycles, including 1,3,4-oxadiazoles and 1,2,4-triazoles,²³ and other unsaturated substrates.²³

Herein, we report such a selective functionalization sequence starting with the two readily available 7-brominated, SEM-protected 1*H*-imidazo[1,2-*b*]pyrazoles 5a and 5b¹⁵ (Scheme 1). First, a Br/Mg-exchange with *i*PrMgCl·LiCl (6),¹⁸ followed by trapping reactions with various electrophiles, yielded mono-substituted 1*H*-imidazo[1,2-*b*]pyrazoles of type 7. Two further functionalizations in the 3- and 2-positions were achieved through consecutive metalations with TMPMgCl·LiCl (8),²⁰ and TMP₂Zn·MgCl₂·2LiCl (9).²¹ Subsequent quenching reactions with various electrophiles then gave access to the increasingly functionalized 1*H*-imidazo[1,2-*b*]pyrazoles of type 10 and 11 respectively. After deprotection of the SEM-group, a N-heterocyclic compound of type 12 was obtained.

In addition, we report a mild fragmentation of the pyrazole ring^{24–27} in functionalized 1*H*-imidazo[1,2-*b*]pyrazoles of type 11 induced by metalation at the 6-position with TMP₂Zn·MgCl₂·2LiCl (9) (Scheme 2). This reaction proceeded *via* zincated intermediates of type 13 and led to a series of (1,3-dihydro-2*H*-imidazol-2-ylidene)malononitriles of type 14. While some (1,3-dihydro-2*H*-imidazol-2-ylidene)malononitriles were already reported,^{28,29} this fragmentation provided an entry to a variety of newly functionalized derivatives of type 14. This functional group diversity was essential for tuning the fluorescent properties of the push-pull dyes 14.³⁰

Finally, we report a concise synthesis of the 1*H*-imidazo[1,2-*b*]pyrazole isostere 4 of pruvanserin as well as an experimental evaluation of its physicochemical properties in comparison to the original drug (3).

Results and discussion

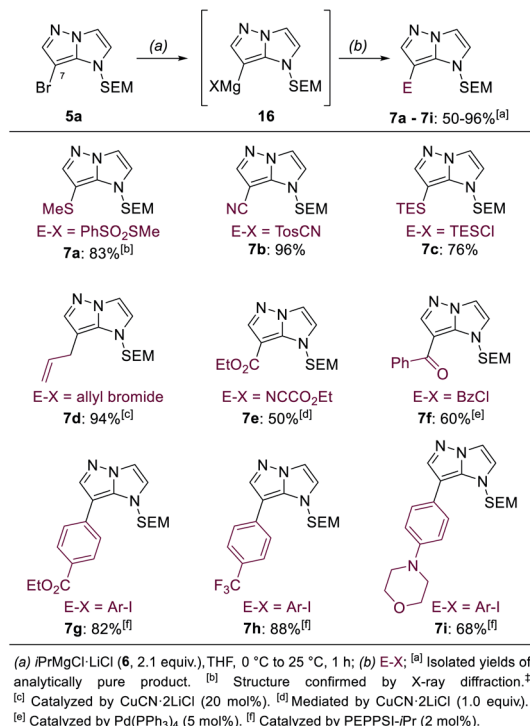
Functionalization of the heterocyclic scaffold

In order to differentiate all of the positions in the SEM-protected^{31–33} 1*H*-imidazo[1,2-*b*]pyrazole 15a, we performed a selective bromination with *N*-bromosuccinimide (NBS, 1.0 equiv.) in acetonitrile (25 °C, 8 min, Scheme 3), providing the 7-bromide 5a in 98% yield.

The prefunctionalization of the position 7 considerably facilitated further selective metalations of the 1*H*-imidazo[1,2-*b*]pyrazole scaffold. Furthermore, when the brominated 1*H*-imidazo[1,2-*b*]pyrazole 5a was treated with *i*PrMgCl·LiCl (6, 2.1 equiv., 0 °C to 25 °C, 1 h) in THF, the magnesiated 1*H*-imidazo[1,2-*b*]pyrazole 16 was obtained and after quenching with various electrophiles a range of products of type 7 was obtained (Scheme 4). This included the reactions with *S*-methyl sulfonothioate,³⁴ tosyl cyanide and TESCl leading to the products 7a–7c in 50–96% yield. The addition of CuCN·2LiCl³⁵ allowed an allylation in 94% yield (7d) and the formation of the ethyl ester 7e with ethyl cyanofomate in 50% yield. Additional reactions included an acylation with benzoyl chloride catalyzed by Pd(PPh₃)₄ (7f) in 60% yield and a range of Kumada-type cross-couplings with electron-deficient (7g, 7h) and electron-rich (7i) iodides catalyzed by PEPPSI-*i*Pr³⁶ in 68–88% yield.

The mono-functionalized products of type 7 were then submitted to a selective magnesiation at the 3-position using TMPMgCl·LiCl (8, 1.5 equiv., –20 °C, 2 h) in THF (Scheme 5).





Scheme 4 Selective functionalization of the brominated 1*H*-imidazo[1,2-*b*]pyrazole **5a** via Br/Mg-exchange leading to 7-functionalized 1*H*-imidazo[1,2-*b*]pyrazoles of type **7**.

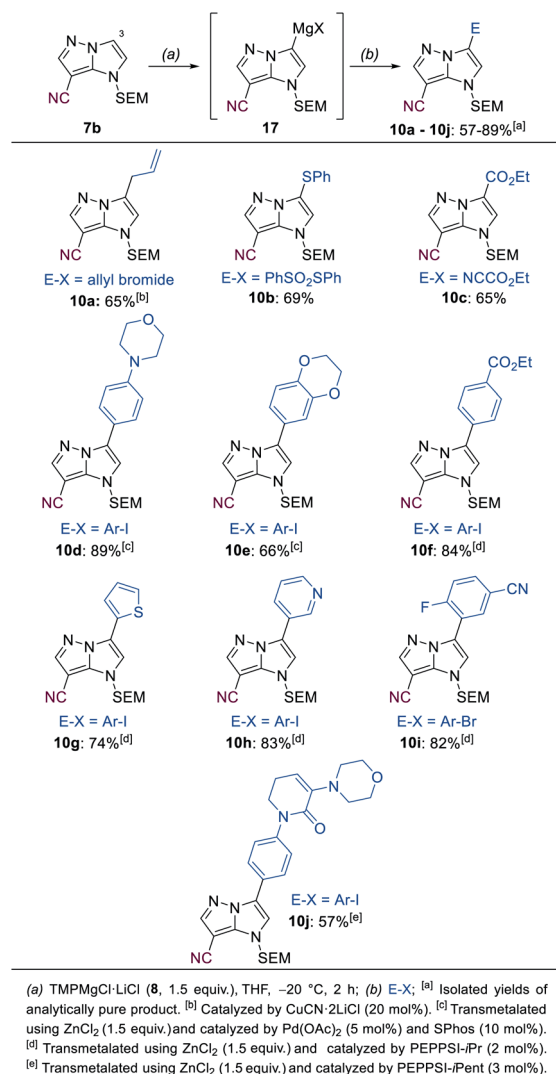
Thus, the cyano-substituted 1*H*-imidazo[1,2-*b*]pyrazole **7b** was magnesiated to generate the metalated intermediate **17**, which was then successfully reacted with a variety of electrophiles in 57–89% yield (**10a–10j**). This included a copper-catalyzed allylation in 65% yield (**10a**), a thiolation with *S*-phenyl sulfonothioate in 69% yield (**10b**) and the reaction with ethyl cyanoformate in 65% yield (**10c**). A transmetalation with ZnCl_2 allowed a series of Negishi-type cross-couplings affording the arylated products **10d–10j** in 57–89% yield. When electron-rich iodides were used (**10d**, **10e**), a mixture of 5 mol% $\text{Pd}(\text{OAc})_2$ and 10 mol% SPhos^{37} gave the best results. However, for electron-deficient and heteroaryl halides (**10f–10i**) the NHC catalyst $\text{PEPPSI-}i\text{Pr}^{36}$ (2 mol%) performed best. By increasing the reaction temperature from 40 °C to 60 °C, the cross-coupling could be conducted using less reactive bromides instead of iodides (**10i**). By using 3 mol% of the more active catalyst $\text{PEPPSI-}i\text{Pent}^{38}$ at 60 °C, it was possible to react a highly functionalized iodide containing an α,β -unsaturated amide, providing the polyfunctional product **10j** in 57% yield.

A third functionalization was achieved using the 3-ester substituted *N*-heterocycle **10c** (Scheme 6). In this metalation, the bis-base $\text{TMP}_2\text{Zn}\cdot\text{MgCl}_2\cdot 2\text{LiCl}$ (**9**, 0.55–0.65 equiv.), prepared by adding MgCl_2 (1.0 equiv.) and ZnCl_2 (1.0 equiv.) solutions to TMPLi (2.0 equiv.) in THF, yielded the best results. The metalation proceeded selectively in the position 2 and was completed after 30 min at 0 °C, providing the bis-zinc species **18**. This heterocyclic organometallic was then allylated with allyl bromide in the presence of 20 mol% $\text{CuCN}\cdot 2\text{LiCl}$ to

generate the product **11a** in 72% yield. In addition, a series of copper-catalyzed acylations with aromatic, aliphatic and heteroaromatic acyl chlorides was conducted to generate the trisubstituted heterocycles **11b–11e** in 61–81% yield. Finally, a range of Negishi-type cross-couplings catalyzed by 5 mol% $\text{Pd}(\text{PPh}_3)_4$ gave access to the arylated products **11f–11k** in 50–69% yield. The scope of possible coupling partners included electron-deficient (**11f–11h**), electron-rich (**11i**, **11j**) and heterocyclic (**11k**) iodides. The high chemoselectivity of the intermediate zinc species allowed the use of electrophiles containing sensitive functional groups such as an ester (**11f**) or a nitro group (**11c**, **11h**).

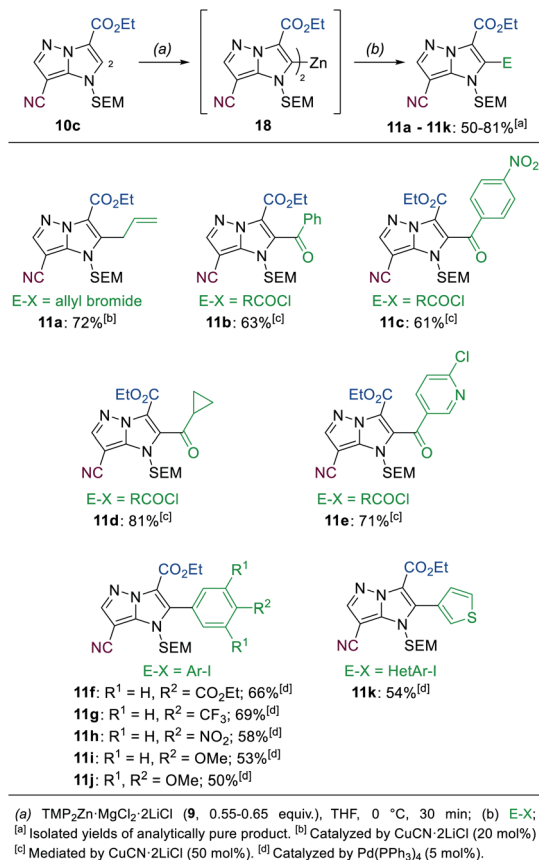
Synthesis and characterization of push-pull dyes of type **14**

Further metalation of the functionalized 1*H*-imidazo[1,2-*b*]pyrazoles of type **11** at the 6-position with $\text{TMP}_2\text{Zn}\cdot\text{MgCl}_2\cdot 2\text{LiCl}$ (**9**, 0.65 equiv., 0 °C, 30–150 min) resulted in a fragmentation of the



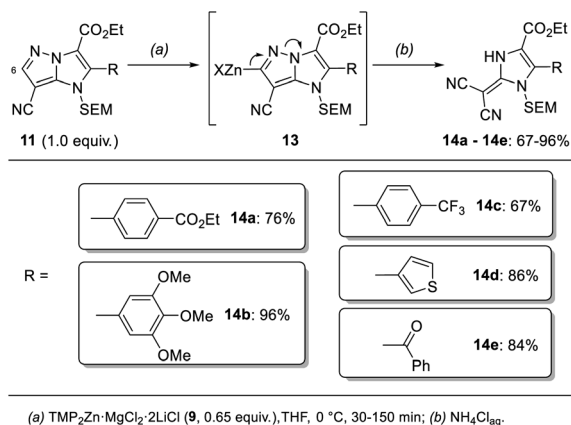
Scheme 5 Selective metalation of the 1*H*-imidazo[1,2-*b*]pyrazole **7b** using $\text{TMPMgCl}\cdot\text{LiCl}$ (**8**) followed by electrophile trapping leading to 3-substituted 1*H*-imidazo[1,2-*b*]pyrazoles of type **10**.





Scheme 6 Selective metalation of the 1*H*-imidazo[1,2-*b*]pyrazole **10c** using $\text{TMP}_2\text{Zn} \cdot \text{MgCl}_2 \cdot 2\text{LiCl}$ (**9**) followed by electrophile trapping leading to 2-substituted 1*H*-imidazo[1,2-*b*]pyrazoles of type **11**.

pyrazole ring (Scheme 7). This reaction presumably proceeded *via* a zincated intermediate of type **13**. The shift of an electron pair to the bridgehead nitrogen then led to the formation of a second nitrile. After an aqueous work-up a series of push-pull dyes of type **14** containing a (1,3-dihydro-2*H*-imidazol-2-ylidene) malononitrile core were isolated in 67–96% yield. The reaction



Scheme 7 Fragmentation of 1*H*-imidazo[1,2-*b*]pyrazoles of type **11** after treatment with $\text{TMP}_2\text{Zn} \cdot \text{MgCl}_2 \cdot 2\text{LiCl}$ (**9**) leading to push-pull dyes of type **14**.

was successfully performed with a range of different functionalized aryl (**14a–14c**), a 3-thienyl (**14d**) and a benzoyl substituent (**14e**) in the 2-position of the 1*H*-imidazo[1,2-*b*]pyrazole scaffold.

In contrast to previously reported (1,3-dihydro-2*H*-imidazol-2-ylidene)malononitriles, for which no special optical properties were described,^{28,29} the compounds of type **14** displayed a distinct fluorescence in solution when irradiated with UV-light. These compounds can be classified as push-pull dyes, as they contain electron donor and electron acceptor groups connected *via* an organic π -system.³⁰ The optoelectronic properties in these dyes result from an intramolecular charge-transfer (ICT), which leads to the formation of a new low-energy molecular orbital. The band gap between such a charge-transferred state and the neutral ground state is significantly lower and thus an excitation of electrons between them can often be achieved using lower energy visible light. Therefore, push-pull dyes have become highly sought after for applications in devices such as organic field-effect transistors (OFET),³⁹ organic light-emitting diodes (OLED)^{40–42} and organic photovoltaic cells (OPVC).⁴³ In addition, some push-pull compounds found application in metal-free photoredox-catalysis.^{44,45}

The main donor-acceptor (D-A) interaction in the compounds of type **14** is presumably happening between the malononitrile group, which is widely considered one of the strongest natural electron-withdrawing groups in organic chemistry,^{46,47} and the proaromatic electron-donor 2-methylene-2,3-dihydro-1*H*-imidazole. This group is comparable to the widely explored 1,3-dithiol-2-ylidene (dithiafulvene). The strong donor properties of these heterocycles can be attributed to the fact that the ICT in these molecules results in the formation of a resonance stabilized 6 π -aromatic system.^{48–51} The ester substituent can also function as a second, albeit weaker acceptor group. The ICT between these groups can be described using several resonance structures (Fig. 3). Overall, the (1,3-dihydro-2*H*-imidazol-2-ylidene)malononitriles of type **14** can be characterized as quadrupolar donor-acceptor systems (A- π -D- π -A), as they contain a donor group, which is connected to two acceptor groups *via* a π -system.³⁰

To characterize the optical properties of the (1,3-dihydro-2*H*-imidazol-2-ylidene)malononitriles of type **14** we measured their UV/vis (Fig. 4) as well as photoluminescence (PL) spectra (Fig. 5) in 50 μM solutions. These measurements revealed that the compound **14e** with a benzoyl substituent on the heterocycle differs significantly from the compounds **14a–14d**. While the latter mainly absorb in the UV range and only show a weak absorption up to approximately 450 nm, the former possesses

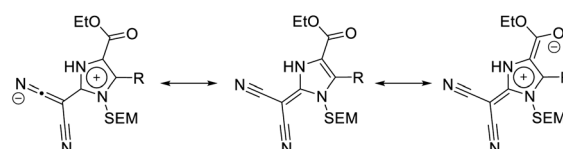


Fig. 3 Resonance structures visualizing the ICT in the push-pull dyes of type **14**.

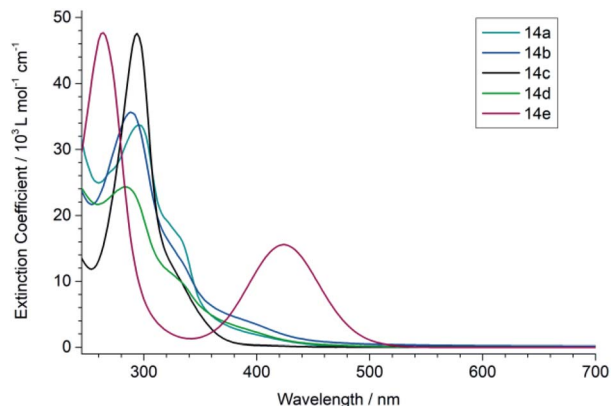


Fig. 4 UV/vis spectrum of the push-pull dyes of type 14.

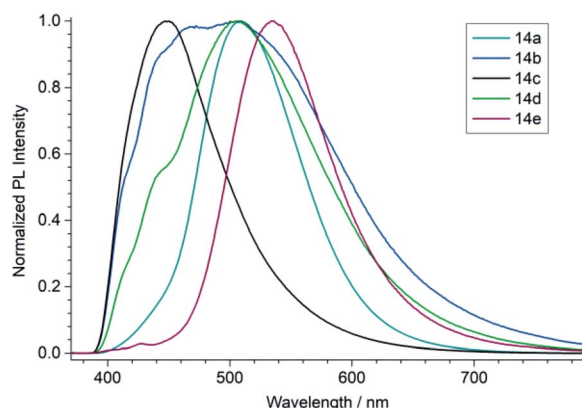


Fig. 5 PL spectrum of the push-pull dyes of type 14.

a very pronounced second absorption band in the high-energy part of the visible spectral region with a peak absorption at 430 nm, accompanied by an overall red shift of the absorption onset. This is consistent with the colour of the compounds: **14a–14d** only exhibit a very slight yellow to orange colour, while **14e** is intensely yellow. A similar effect can also be seen in the PL spectrum, where the photoluminescence of **14e** is significantly

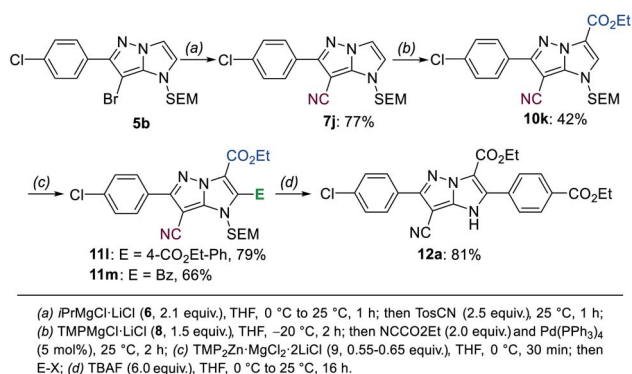
red shifted compared to the other compounds. A possible explanation for these observations lies within the strong acceptor properties of the benzoyl group, leading to a stronger D–A character. Thus, the (1,3-dihydro-2*H*-imidazol-2-ylidene) malononitrile **14e** can be seen as an octupolar ((A– π)₃–D), instead of a quadrupolar push-pull system.³⁰

Functionalization of the substituted heterocycle **5b**

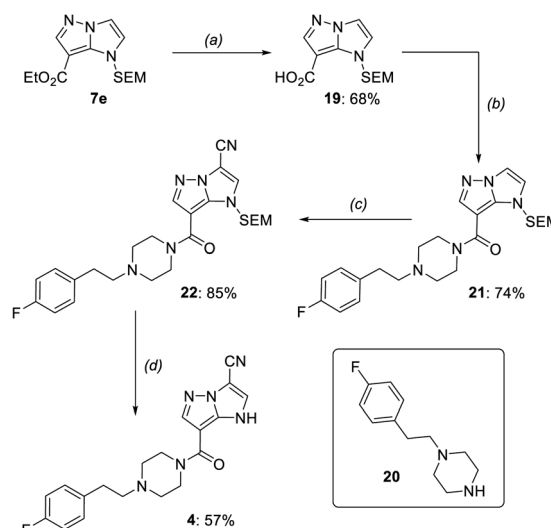
Since the fragmentation of the pyrazole ring prevented a full functionalization of the 1*H*-imidazo[1,2-*b*]pyrazole scaffold *via* metalation, we have prepared a new starting material with a substituent in the 6-position following a literature procedure.¹⁵ A SEM-protection and bromination with NBS resulted in the formation of the compound **5b**, which was then submitted to the previously optimized functionalization sequence (Scheme 8). The Br/Mg-exchange of **5b** followed by the tosylation proceeded smoothly and provided the heterocyclic nitrile **7j** in 77% yield. The first metalation with TMPMgCl·LiCl (**8**) then gave access to the ester **10k** in 42% yield after trapping with ethyl cyanoformate. The second metalation with TMP₂Zn·MgCl₂·2LiCl (**9**) was followed by a Negishi-type cross-coupling, as well as an acylation to generate the products **11l** and **11m** in 66–79% yield. Finally, the SEM-deprotection of **11l** was achieved using TBAF (6.0 equiv.) in THF, leading to the tetra-functionalized 1*H*-imidazo[1,2-*b*]pyrazole **12a** in 81% yield.

Synthesis and assays of the pruvanserine isostere **4**

With these methods in hand, we have performed a synthesis of the pruvanserine isostere **4** (Scheme 9). In a first step, the ester **7e** (Scheme 4) was saponified with aqueous NaOH in MeOH to generate the free acid **19** in 68% yield. This was followed by an



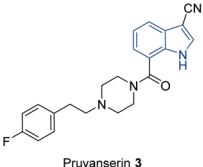
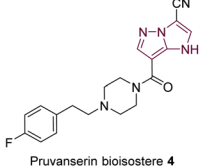
Scheme 8 Full functionalization of the 1*H*-imidazo[1,2-*b*]pyrazole **5b** followed by a SEM-deprotection leading to the tetra-substituted product **12a**.



Scheme 9 Synthesis of the pruvanserine isostere **4**.



Table 1 Physicochemical properties of the 5-HT_{2A} serotonin receptor antagonist pruvanserin (**3**) and the 1*H*-imidazo[1,2-*b*]pyrazole analogue (**4**)

		
	Pruvanserin 3	Pruvanserin bioisostere 4
Physicochemical property measured	3	4
log <i>D</i> @ pH = 7.4	3.5 = log <i>P</i>	2.0 (log <i>P</i> ≈ 2.4) ^a
Solubility @ pH = 6.8 (μM)	17	226
p <i>K</i> _a	6.4	7.3

^a Given the acidic p*K*_a at 7.3, the log *P* was extrapolated.

amide coupling with the amine **20** using bis(pentafluorophenyl) carbonate (BPC) as a coupling reagent,⁵² affording the amide **21** in 74% yield. The previously optimized conditions for the metalation of the 1*H*-imidazo[1,2-*b*]pyrazole scaffold in the 3-position (TMPCl·LiCl (**8**, 1.5 equiv.), −20 °C, 2 h) allowed the formation of the nitrile **22** in 85% yield. Finally, the SEM-group was deprotected using a combination of caesium fluoride (5.0 equiv.) and the phase-transfer catalyst 18-crown-6 (1.0 equiv.) in acetonitrile to generate the pruvanserin isostere **4** in 57% yield.†

Following the synthesis of pruvanserin (**3**)⁵³ and the 1*H*-imidazo[1,2-*b*]pyrazole analogue **4**, we analysed the physicochemical properties of the matched pair in order to understand the impact of incorporating an indole replacement (Table 1). Interestingly, the 1*H*-imidazo[1,2-*b*]pyrazole analogue **4** showed a lowering in the log *D*, or lipophilicity, which translated into a significant improvement in aqueous solubility compared to pruvanserin (**3**). The p*K*_a measured at 6.4 for pruvanserin (**3**) corresponds to protonation of the piperazine tertiary amine, whereas the p*K*_a measured at 7.3 for the 1*H*-imidazo[1,2-*b*]pyrazolo analogue **4** likely corresponds to the deprotonation of the core NH, which is considerably lower than the expected p*K*_a for an indole NH. Overall, the results indicated that 1*H*-imidazo[1,2-*b*]pyrazoles could be promising core morphs worth further investigation in light of their enhanced solubility compared to indoles. Such investigations could include direct bioassay studies in order to compare the biological activity of the analogues and the original indolyl drugs. In particular, deprotonation of the 1*H*-imidazo[1,2-*b*]pyrazole in physiological medium might lead to a change in receptor interactions and cell membrane permeability. Additionally, studies regarding cytochrome P450 oxidation would be necessary in order to determine the metabolic stability of the analogues.

Conclusions

In summary, we developed a sequence for the selective functionalization of the 1*H*-imidazo[1,2-*b*]pyrazole scaffold starting from SEM-protected and brominated compounds of type **5**. The

functionalizations were achieved using various magnesiated and zincated organometallics, which were generated either *via* a Br/Mg-exchange or *via* regioselective metalations using TMP-bases. A range of different trapping reactions were possible, including cross-couplings, allylations, acylations, cyanations and carboxylations. A final deprotection of the SEM-group allowed the isolation of tetra-functionalized N-heterocycles of type **12**.

In addition, we reported a fragmentation of the pyrazole ring in 1*H*-imidazo[1,2-*b*]pyrazoles of type **11**, which was induced by a metalation at the 6-position. This gave access to push-pull dyes of type **14** containing a proaromatic (1,3-dihydro-2*H*-imidazol-2-ylidene)malononitrile core. The optical properties of these dyes were explored and it was found that a benzoyl substituent resulted in a significant red shift of both the absorption as well as the photoluminescence.

Finally, we have prepared a non-classical isostere (**4**) of the indolyl drug pruvanserin (**3**) in a concise manner using the previously established methodologies. The physicochemical properties of this new isostere were compared to those of the original drug and it was found that a substitution of the indole ring with a 1*H*-imidazo[1,2-*b*]pyrazole led to a significant decrease in the lipophilicity (log *D*). This translated into an increased solubility in aqueous media. Thus, further investigations of 1*H*-imidazo[1,2-*b*]pyrazoles as potential replacements of indoles in drug molecules might lead to compounds with a higher bioavailability.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.† Crystallographic data for **7a** has been deposited at the CCDC under 2097280 and can be obtained from <http://www.ccdc.cam.ac.uk>.

Author contributions

K. S. and P. K. conceived the project and designed the synthetic experiments. D. B. and T. B. designed the experiments for the optical characterization. F. L. and C. E. B. designed the physico-chemical assays. K. S. and S. K. R. conducted the synthetic experiments. D. B. conducted the experiments for the optical characterization. K. K. conducted the X-ray crystallography. K. S., S. K. R., D. B., C. E. B. and K. K. analysed the data. K. S. and P. K. wrote the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the LMU Munich, the Cluster of Excellence e-conversion and the DFG for financial support. We thank Albe-marle (Hoechst, Germany) for the generous gift of chemicals. We acknowledge the skilled support of Dominik Ruffle, Daniel Gosling, Stephane Rodde, Guillaume Ngo and Damien Hubert



(Novartis, Basel) in the final purification and profiling of pruvanserin and its isostere.

Notes and references

‡ A deprotection with TBAF in THF was also successful; however it proved difficult to separate the product 4 from the tetra-*n*-butylammonium salts.

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