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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†

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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.

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] anticancer,[6,7] anti-inflammatory[8]) 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

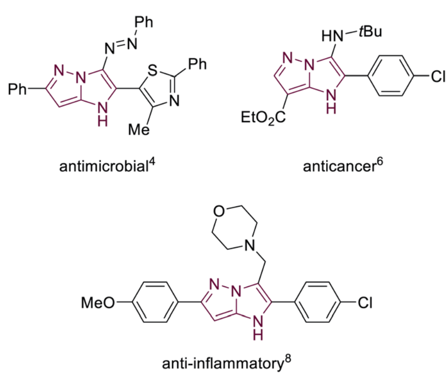

Fig. 1 Examples of 1*H*-imidazo[1,2-*b*]pyrazoles with biological activities.

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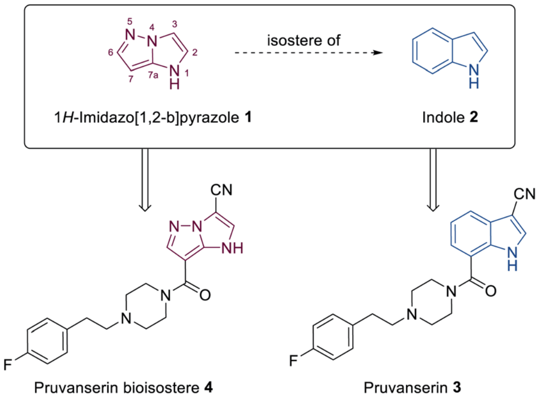
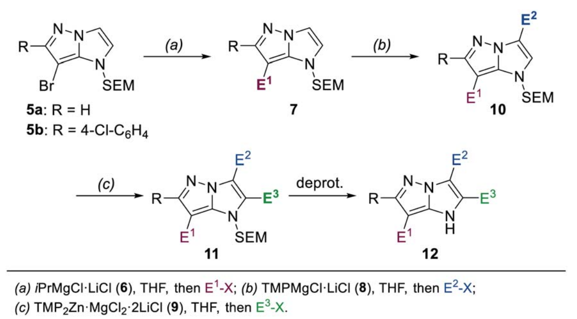
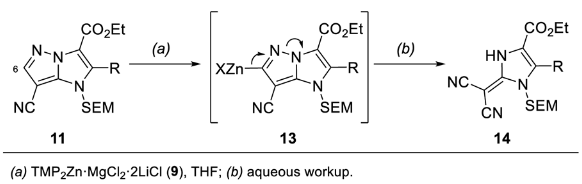


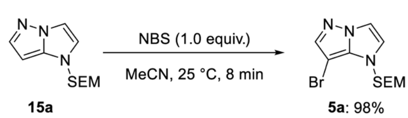
Fig. 2 1*H*-Imidazo[1,2-*b*]pyrazole (**1**) as a potential replacement of indole (**2**) as shown for the 5-HT_{2A} serotonin receptor antagonist pruvanserin (**3**).



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,[22] 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 **5b** [15] (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 $TMP_2Zn\cdot MgCl_2\cdot 2LiCl$ (**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 $TMP_2Zn\cdot MgCl_2\cdot 2LiCl$ (**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**).

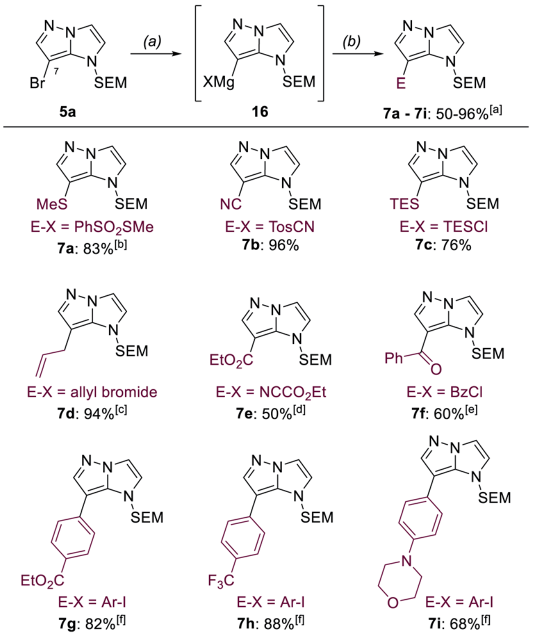
Results and discussion

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 $CuCN\cdot 2LiCl$[35] allowed an allylation in 94% yield (**7d**) and the formation of the ethyl ester **7e** with ethyl cyanoformate in 50% yield. Additional reactions included an acylation with benzoyl chloride catalyzed by $Pd(PPh_3)_4$ (**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*Pr[36] 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).



(a) *i*PrMgCl·LiCl (**6**, 2.1 equiv.), THF, 0 °C to 25 °C, 1 h; (b) E-X; [a] Isolated yields of analytically pure product. [b] Structure confirmed by X-ray diffraction.‡ [c] Catalyzed by CuCN·2LiCl (20 mol%). [d] Mediated by CuCN·2LiCl (1.0 equiv). [e] Catalyzed by Pd(PPh_3)$_4$ (5 mol%). [f] Catalyzed by PEPPSI-*i*Pr (2 mol%).

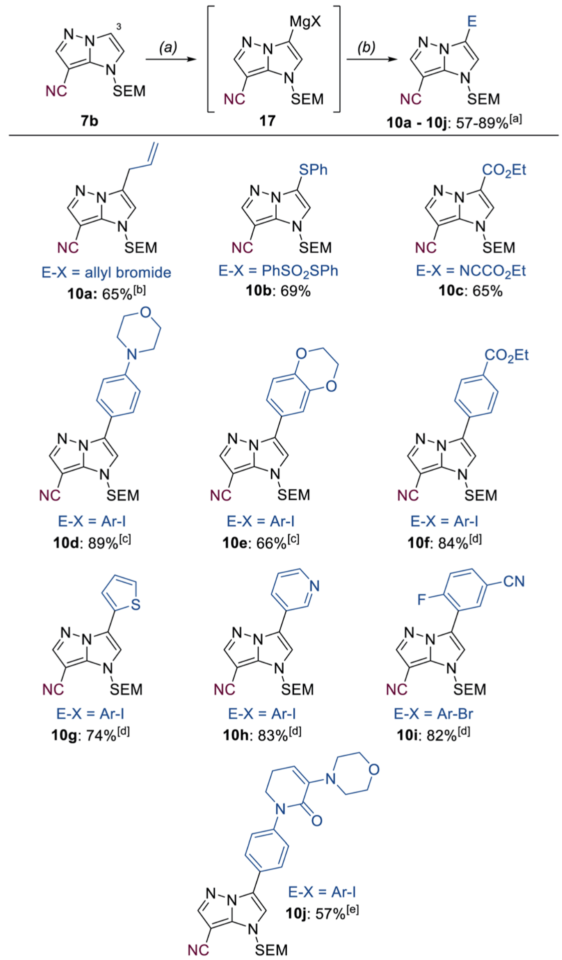
Scheme 4 Selective functionalization of the brominated 1*H*-imidazo[1,2-*b*]pyrazole **5a** *via* Br/Mg-exchange leading to 7-functionalized 1*H*-imidazo[1,2-*b*]pyrazoles of type **7**.

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 (**8c**). 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% Pd(OAc)$_2$ and 10 mol% SPhos[37] gave the best results. However, for electron-deficient and heteroarylic halides (**10f–10i**) the NHC catalyst PEPPSI-*i*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 PEPPSI-*i*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 $TMP_2Zn \cdot MgCl_2 \cdot 2LiCl$ (**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% CuCN·2LiCl 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% Pd(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**).

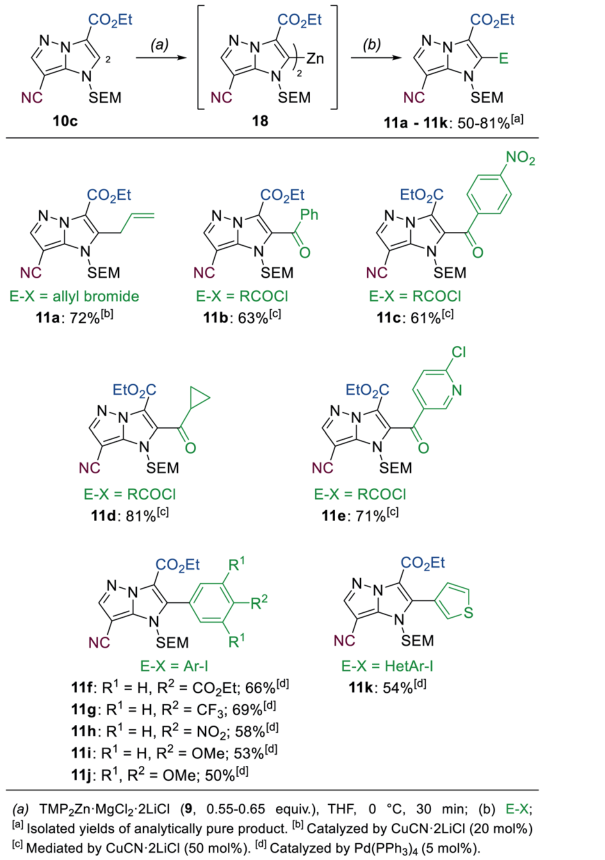
Synthesis and characterization of push–pull dyes of type 14

Further metalation of the functionalized 1*H*-imidazo[1,2-*b*]pyrazoles of type **11** at the 6-position with $TMP_2Zn \cdot MgCl_2 \cdot 2LiCl$ (**9**, 0.65 equiv., 0 °C, 30–150 min) resulted in a fragmentation of the



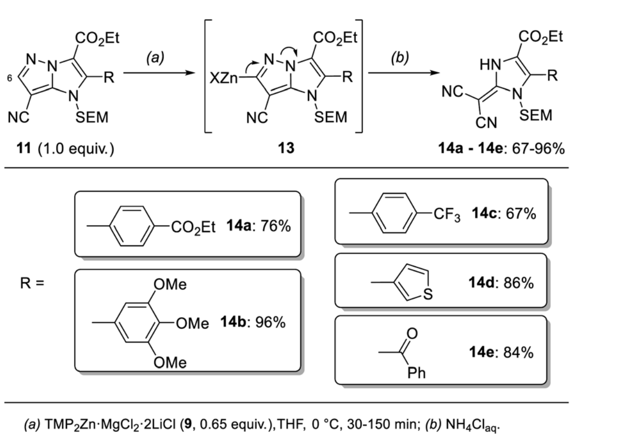
(a) TMPMgCl·LiCl (**8**, 1.5 equiv.), THF, −20 °C, 2 h; (b) E-X; [a] Isolated yields of analytically pure product. [b] Catalyzed by CuCN·2LiCl (20 mol%). [c] Transmetalated using $ZnCl_2$ (1.5 equiv.) and catalyzed by Pd(OAc)$_2$ (5 mol%) and SPhos (10 mol%). [d] Transmetalated using $ZnCl_2$ (1.5 equiv.) and catalyzed by PEPPSI-*i*Pr (2 mol%). [e] Transmetalated using $ZnCl_2$ (1.5 equiv.) and catalyzed by PEPPSI-*i*Pent (3 mol%).

Scheme 5 Selective metalation of the 1*H*-imidazo[1,2-*b*]pyrazole **7b** using TMPMgCl·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 $TMP_2Zn\cdot MgCl_2\cdot 2LiCl$ (**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 $TMP_2Zn\cdot MgCl_2\cdot 2LiCl$ (**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 6π-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

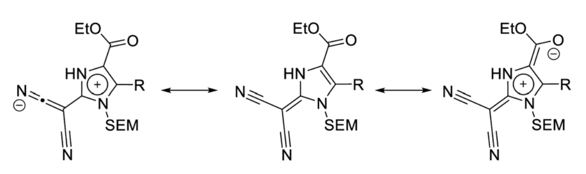


Fig. 3 Resonance structures visualizing the ICT in the push–pull dyes of type **14**.

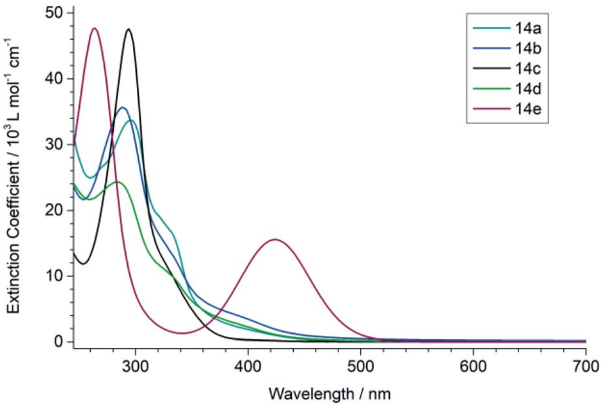


Fig. 4 UV/vis spectrum of the push–pull dyes of type 14.

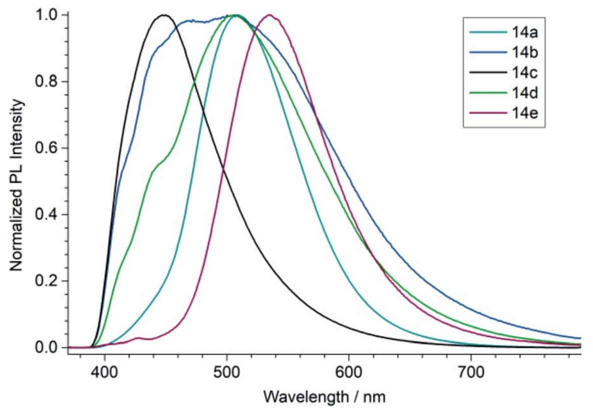
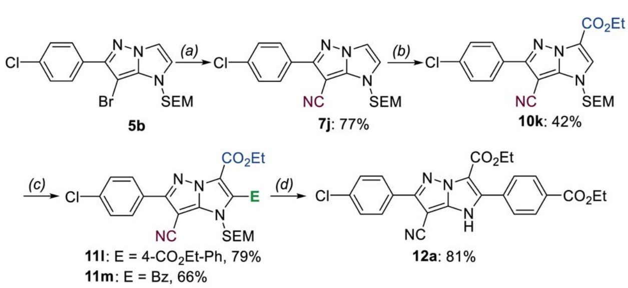


Fig. 5 Pl spectrum of the push–pull dyes of type 14.

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]



(a) *i*PrMgCl·LiCl (**6**, 2.1 equiv.), THF, 0 °C to 25 °C, 1 h; then TosCN (2.5 equiv.), 25 °C, 1 h; *(b)* TMPMgCl·LiCl (**8**, 1.5 equiv.), THF, −20 °C, 2 h; then NCCO2Et (2.0 equiv.) and Pd(PPh$_3$)$_4$ (5 mol%), 25 °C, 2 h; *(c)* TMP$_2$Zn·MgCl$_2$·2LiCl (9, 0.55-0.65 equiv.), THF, 0 °C, 30 min; then E-X; *(d)* TBAF (6.0 equiv.), THF, 0 °C to 25 °C, 16 h.

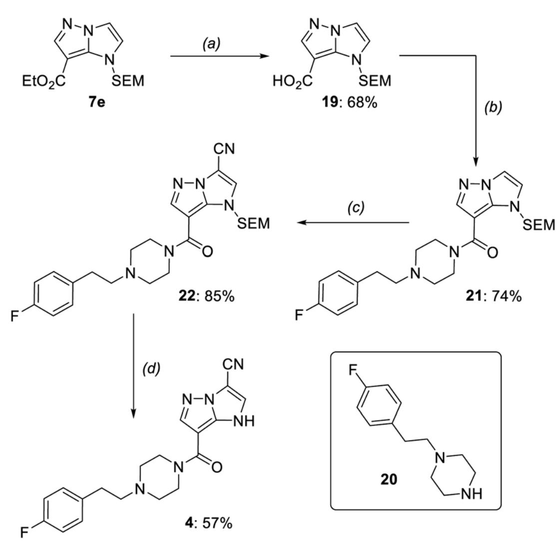
Scheme 8 Full functionalization of the 1*H*-imidazo[1,2-*b*]pyrazole **5b** followed by a SEM-deprotection leading to the tetra-substituted product **12a**.

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 TMP$_2$-Zn·MgCl$_2$·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 pruvanserin isostere 4

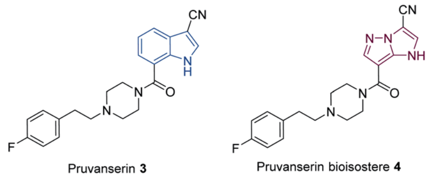
With these methods in hand, we have performed a synthesis of the pruvanserin isostere **4** (Scheme 9). In a first step, the ester **7e** (Scheme 4) was saponified with aqueous NaOH in MeOH to generate the free acid **19** in 68% yield. This was followed by an



(a) NaOH (32%), MeOH, 50 °C, 40 h; *(b)* BPC (1.1 equiv.), NEt$_3$ (1 0 equiv.), MeCN/DMF, −20 °C, 50 min, then **20** (5.0 equiv.), NEt$_3$ (1.0 equiv.), 25 °C, 21 h; *(c)* TMPMgCl·LiCl (**8**, 1.5 equiv.), THF, −20 °C, 50 min, then TosCN (1.0 equiv.), CuCN·2LiCl (1.0 equiv.),25 °C, 2 h; *(d)* CsF (5.0 equiv), 18-crown-6 (1.0 equiv.),MeCN, reflux, 26 h.

Scheme 9 Synthesis of the pruvanserin 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**)



Physicochemical property measured	3	4
log *D* @ pH = 7.4	3.5 = log *P*	2.0 (log *P* ≈ 2.4)[a]
Solubility @ pH = 6.8 (μM)	17	226
pK_a	6.4	7.3

[a] Given the acidic pK_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 (TMPMgCl·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 pK_a measured at 6.4 for pruvanserin (**3**) corresponds to protonation of the piperazine tertiary amine, whereas the pK_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 pK_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 synthetical 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 synthetical 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.

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(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.

1 R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845.
2 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
3 W. R. Pitt, D. M. Parry, B. G. Perry and C. R. Groom, *J. Med. Chem.*, 2009, **52**, 2952.
4 A. O. Abdelhamid, K. A. Abdelall and Y. H. Zaki, *J. Heterocycl. Chem.*, 2010, **47**, 477.
5 M. V. Murlykina, M. N. Kornet, S. M. Desenko, S. V. Shishkina, O. V. Shishkin, A. A. Brazhko, V. I. Musatov, E. V. Van der Eycken and V. A. Chebanov, *Beilstein J. Org. Chem.*, 2017, **13**, 1050.
6 A. T. Baviskar, C. Madaan, R. Preet, P. Mohapatra, V. Jain, A. Agarwal, S. K. Guchhait, C. N. Kundu, U. C. Banerjee and P. V. Bharatam, *J. Med. Chem.*, 2011, **54**, 5013.
7 S. Grosse, V. Mathieu, C. Pillard, S. Massip, M. Marchivie, C. Jarry, P. Bernard, R. Kiss and G. Guillaumet, *Eur. J. Med. Chem.*, 2014, **84**, 718.
8 A. H. Shridhar, G. Banuprakash, H. H. Joy and Y. T. Vijaykumar, *Int. Res. J. Pharm.*, 2017, **8**, 25.
9 T. Wang, Z. Yin, Z. Zhang, J. A. Bender, Z. Yang, G. Johnson, Z. Yang, L. M. Zadhura, C. J. D`Arienzo, D. D. Parker, C. Gesenberg, G. A. Yamanaka, Y.-F. Gong, H.-T. Ho, H. Fang, N. Zhou, B. V. McAuliffe, B. J. Eggers, L. Fan, B. Nowicka-Sans, I. B. Dicker, Q. Gao, R. J. Colonno, P.-F. Lin, N. A. Meanwell and J. F. Kadow, *J. Med. Chem.*, 2009, **52**, 7778.
10 G. D. Bartoszyk, C. van Amsterdam, H. Böttcher and C. A. Seyfried, *Eur. J. Pharmacol.*, 2003, **473**, 229.
11 R. Adamec, K. Creamer, G. D. Bartoszyk and P. Burton, *Eur. J. Pharmacol.*, 2004, **504**, 79.
12 B. R. Teegarden, H. Al Shamma and Y. Xiong, *Curr. Top. Med. Chem.*, 2008, **8**, 969.
13 ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Identifier NCT00259311, Efficacy Study of LY2422347 to treat Insomnia. Nov 29, 2005; https://clinicaltrials.gov/ct2/show/NCT00259311 (accessed June 21, 2021).
14 E. Vanotti, F. Fiorentini and M. Villa, *J. Heterocycl. Chem.*, 1994, **31**, 737.
15 P. Seneci, M. Nicola, M. Inglesi, E. Vanotti and G. Resnati, *Synth. Commun.*, 1999, **29**, 311.
16 J. Khalafy, A. P. Marjani and F. Salami, *Tetrahedron Lett.*, 2014, **55**, 6671.
17 N. N. Kolos, B. V. Kibkalo, L. L. Zamigaylo, I. V. Omel'chenko and O. V. Shishin, *Russ. Chem. Bull.*, 2015, **64**, 864.
18 A. Krasovskiy and P. Knochel, *Angew. Chem. Int. Ed.*, 2004, **43**, 3333; *Angew. Chem.*, 2004, **116**, 3396.
19 D. S. Ziegler, B. Wei and P. Knochel, *Chem. – Eur. J.*, 2019, **25**, 2695.
20 A. Krasovskiy, V. Krasovskaya and P. Knochel, *Angew. Chem. Int. Ed.*, 2006, **45**, 2958; *Angew. Chem.*, 2006, **118**, 3024.
21 S. H. Wunderlich and P. Knochel, *Angew. Chem. Int. Ed.*, 2007, **46**, 7685; *Angew. Chem.*, 2007, **119**, 7829.
22 K. Schwärzer, C. P. Tüllmann, S. Graßl, B. Górski, C. E. Brocklehurst and P. Knochel, *Org. Lett.*, 2020, **22**, 1899.
23 A. Kremsmair, J. H. Harenberg, K. Schwärzer, A. Hess and P. Knochel, *Chem. Sci.*, 2021, **12**, 6011.
24 M. Takahashi, T. Mamiya, H. Hasegawa, T. Nagai and H. Wakita, *J. Heterocycl. Chem.*, 1986, **23**, 1363.
25 M. Schlosser, J.-N. Volle, F. Leroux and K. Schenk, *Eur. J. Org. Chem.*, 2002, 2913.
26 A. Bunnell, C. O'Yang, A. Petrica and M. J. Soth, *Synth. Commun.*, 2006, **36**, 285.
27 V. L. Blair, D. C. Blakemore, D. Hay, E. Hevia and D. C. Pryde, *Tetrahedron Lett.*, 2011, **52**, 4590.
28 G. Mlostoń, M. Jasiński, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, 2006, **89**, 1304.
29 A. V. Kutasevich, A. S. Efimova, M. N. Sizonenko, V. P. Perevalov, L. G. Kuz'mina and V. S. Mityanov, *Synlett*, 2020, **31**, 179.
30 F. Bureš, *RSC Adv.*, 2014, **4**, 58826.
31 J. P. Whitten, D. P. Matthews and J. R. McCarthy, *J. Org. Chem.*, 1986, **51**, 1891.
32 C. Despotopoulou, L. Klier and P. Knochel, *Org. Lett.*, 2009, **11**, 3326.
33 N. Fugina, W. Holzer and M. Wasicky, *Heterocycles*, 1992, **34**, 303.
34 K. Fujiki, N. Tanifuji, Y. Sasaki and T. Yokoyama, *Synthesis*, 2002, **3**, 343.
35 P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, *J. Org. Chem.*, 1988, **53**, 2390.
36 M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien and C. Valente, *Chem. – Eur. J.*, 2006, **13**, 150.
37 T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685.
38 M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi and A. J. Lough, *Angew. Chem. Int. Ed.*, 2009, **48**, 2383; *Angew. Chem.*, 2009, **121**, 2419.
39 P. Devibala, R. Dheepika, P. Vadivelu and S. Nagarjan, *ChemistrySelect*, 2019, **4**, 2339.
40 S. Gong, Y. Chen, J. Luo, C. Yang, C. Zhong, J. Qin and D. Ma, *Adv. Funct. Mater.*, 2011, **21**, 1168.
41 J. Ye, Z. Chen, M.-K. Fung, C. Zheng, X. Ou, X. Zhang, Y. Yuan and C.-S. Lee, *Chem. Mater.*, 2013, **25**, 2630.
42 W.-C. Chen, Y. Yuan, S.-F. Ni, Z.-L. Zhu, J. Zhang, Z.-Q. Jiang, L.-S. Liao, F.-L. Wong and C.-S. Lee, *ACS Appl. Mater. Interfaces*, 2017, **9**, 7331.
43 A. W. Hains, Z. Liang, M. A. Woodhouse and B. A. Gregg, *Chem. Rev.*, 2010, **110**, 6689.
44 Y. Zhao, C. Zhang, K. F. Chin, O. Pytela, G. Wei, H. Liu, F. Bureš and Z. Jiang, *RSC Adv.*, 2014, **4**, 30062.
45 Z. Hloušková, M. Klikar, O. Pytela, N. Almonasy, A. Růžička, V. Jandová and F. Bureš, *RSC Adv.*, 2019, **9**, 23797.

46 M. C. Zerner, C. Reidlinger, W. M. F. Fabian and H. Junek, *J. Mol. Struct.: THEOCHEM*, 2001, **543**, 129.
47 M. Hornum, J. Kongsted and P. Reinholdt, *Phys. Chem. Chem. Phys.*, 2021, **23**, 9139.
48 R. Andreu, M. J. Blesa, L. Carrasquer, J. Garín, J. Orduna, B. Villacampa, R. Alcalá, J. Casado, M. C. Ruiz Delgado, J. T. López Navarrete and M. Allain, *J. Am. Chem. Soc.*, 2005, **127**, 8835.
49 S. Alías, R. Andreu, M. J. Blesa, S. Franco, J. Garín, A. Gargera, J. Orduna, P. Romero, B. Villacampa and M. Allain, *J. Org. Chem.*, 2007, **72**, 6440.
50 R. Andreu, M. A. Cerdán, S. Franco, J. Garín, A. B. Marco, J. Orduna, D. Palomas, B. Villacampa, R. Alicante and M. Allain, *Org. Lett.*, 2008, **10**, 4963.
51 R. Andreu, E. Galán, J. Orduna, B. Villacampa, R. Alicante, J. T. López Navarrete, J. Casado and J. Garín, *Chem. – Eur. J.*, 2011, **17**, 826.
52 K. Lombar, U. Grošelj, G. Dahmann, B. Stanovnik and J. Svete, *Synthesis*, 2015, **47**, 497.
53 A. Bathe, H. Böttcher, H. Crassier, U. Eckert and S. Emmert, *Ger. Pat.*, 2002, DE10102944A1.

