Complementary Synthetic Approaches to Constitutionally Diverse N-Aminoalkylated Isoindolinones: Application to the Synthesis of Falipamil and 5-HT_{1A} Receptor Ligand Analogues

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Abstract: Different synthetic approaches for the elaboration of poly and diversely substituted isoindolinones tailed with constitutionally diverse aminoalkylated chains have been developed. The key step is based upon the preliminary assembly of the isoindolinone template equipped with hydroxyalkyl appendages. Subsequent manipulation of the terminal hydroxy functionality afforded the targeted compounds and the synthetic utility of these approaches has been emphasized by the synthesis of the bradycardic agent falipamil and 5-HT_{1A} receptor ligand analogues.

Key words: carbanions, metalation, lactams, ring closure, ring opening

The isoindolinone ring system lies at the heart of a great number of poly and diversely functionalized compounds that have gained considerable attention in the last decade due to their profound physiological and chemotherapeutic properties. Thus, many compounds containing the isoindolinone skeleton are known to exhibit antiviral,[1] antileukemic,[2] anticancer,[3] antipsychotic,[4] antiulcer,[5] and antifibrilogenic[6] properties. Such compounds are also of significant interest for the treatment of neuropsychiatric disorders.[7]

The rationale for developing this ring system, which represents a conformationally constrained variant of the benzamide nucleus, is that the cyclized amide bond may extend in vivo stability without extensive degradation. The benzolactamic nucleus may generally serve as a linker for a variety of pharmacophores,[3c,8] but in most cases, bioactive isoindolinone-centered compounds constitutionally comprise a benzolactam unit tailed with alkyl or aryl chains equipped with appropriate functionalities, namely aminoalkyl moieties, liable to act on the pharmacological profile. Falipamil (**1**)[9] and the piperazine derivatives **2a**,**b**[4b] fall into this class of compounds (Figure 1).

Traditionally, synthesis of compounds structurally related to **1**, **2** relies on the treatment of a lactone[4c,8] or of an *ortho*-bromobenzoyl ester[1a,b,4c,6] with a suitably substituted primary amine. Alternatively, synthetic approaches are based upon the reduction of the carbonyl function either of a phthalimide preequipped with the appropriate aminoalkyl appendage[3c,4b,c] or of a NH-free model with ensuing N-alkylation.[4c] However, these reactions are fraught with difficulties associated with elaboration of the heterobicyclic system with dense functionalities on the benzene nucleus. The lack of generality, accessibility of the appropriate precursors, that is, the polyfunctionalized alkylated amine or aminated alkylating agent required for the above mentioned synthetic strategies, are also some of the main hurdles that must be overcome. Furthermore, the reduction of unsymmetrically substituted phthalimidine is regioselectively compromised. Consequently, the development of synthetic methodologies, which may find generality for constructing a variety of poly and diversely substituted isoindolinones equipped with diverse aminoalkyl appendages constitutes an area of current interest and alternative methods are currently the object of synthetic endeavor.

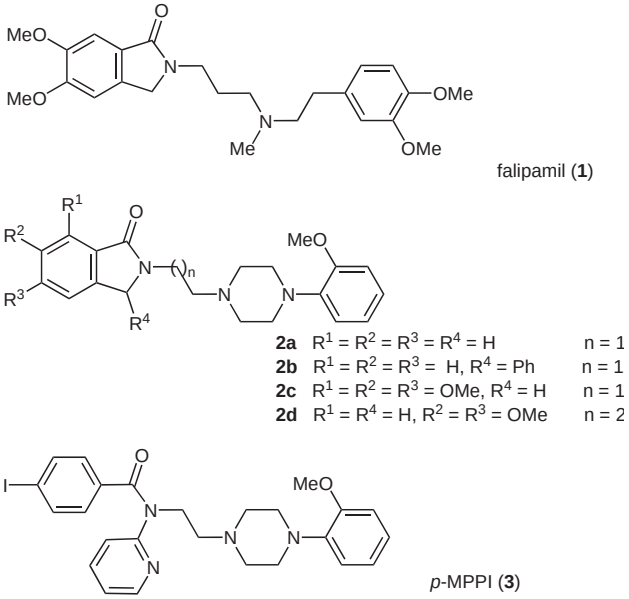

Figure 1 Isoindolinone-centered bioactive compounds

In this context we wish to delineate complementary and tactically new synthetic approaches to these polyaminated isoindolinone derivatives. The feasibility of these routes has been further emphasized by the assembling of the specific embodiment of these aminoalkyl tethered models, **1** and **2a**–**d**. Initially we planned to develop the synthetic

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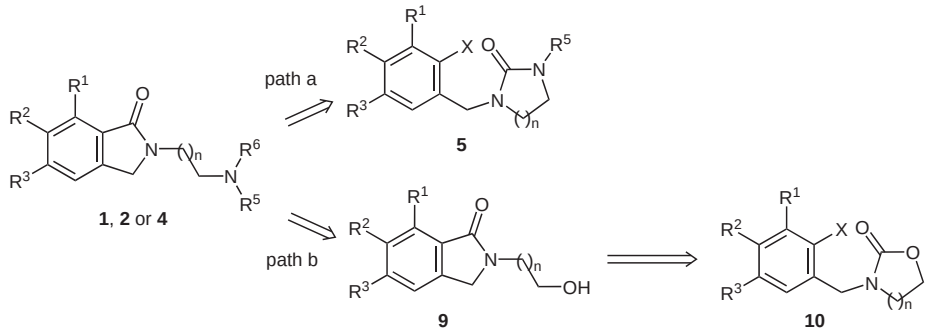


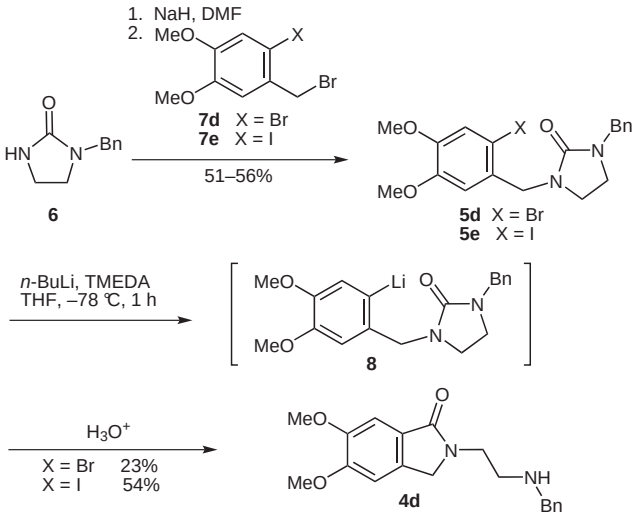
Scheme 1 Retrosynthetic analysis for the synthesis of compounds **1**, **2** or **4**

approach portrayed in retrosynthetic analysis (Scheme 1, path a).

We surmised that the intramolecular interception of the aryllithiated species derived from **5** (X = Br or I) by the imidazolone acting as the internal electrophile would provide the potential for a direct access to the isoindolinone ring system with the concomitant connection of the aminoalkyl appendage, therefore providing the targeted N-alkylaminated models **4**. For this purpose, compound **5d** was initially selected as the model substrate. Assembly of this precursor was readily achieved as depicted in Scheme 2 by coupling the anion of the monoprotected imidazolone **6** with the appropriate benzyl bromide derivative **7d**. The carbanionic Parham type cyclization process[10] was performed upon exposure of the parent compound **5d** to *n*-BuLi at –78 °C in THF in the presence of TMEDA in order to ensure the mandatory bromine–lithium exchange giving rise to **8**. Unfortunately this procedure delivered a rather low yield of the *N*-alkylaminoalkyl compound **4d** along with trace amounts of several unidentified products. Variation of the ethereal solvent, temperature profile, inclusion of anion modifiers had no impact on the efficiency of the process.

To alleviate this problem and to avoid the likely competitive nucleophilic attack by organolithium base on the sensitive urea group we envisioned to take advantage of the very fast rate of metal–iodine exchange and for this purpose the synthesis of the iodinated analogue **5e** was envisaged (Scheme 2). Exposure of **5e** upon the experimental conditions defined above significantly improved the yield for the formation of the annulated compound **4d**, but efficiency of this annulation process remained rather modest (54% vs. 23%). Furthermore, it was anticipated that this synthetic route would not face with problems associated with the assembly of models incorporating a nitrogen atom embedded in a heteroring unit, for example, **2**.

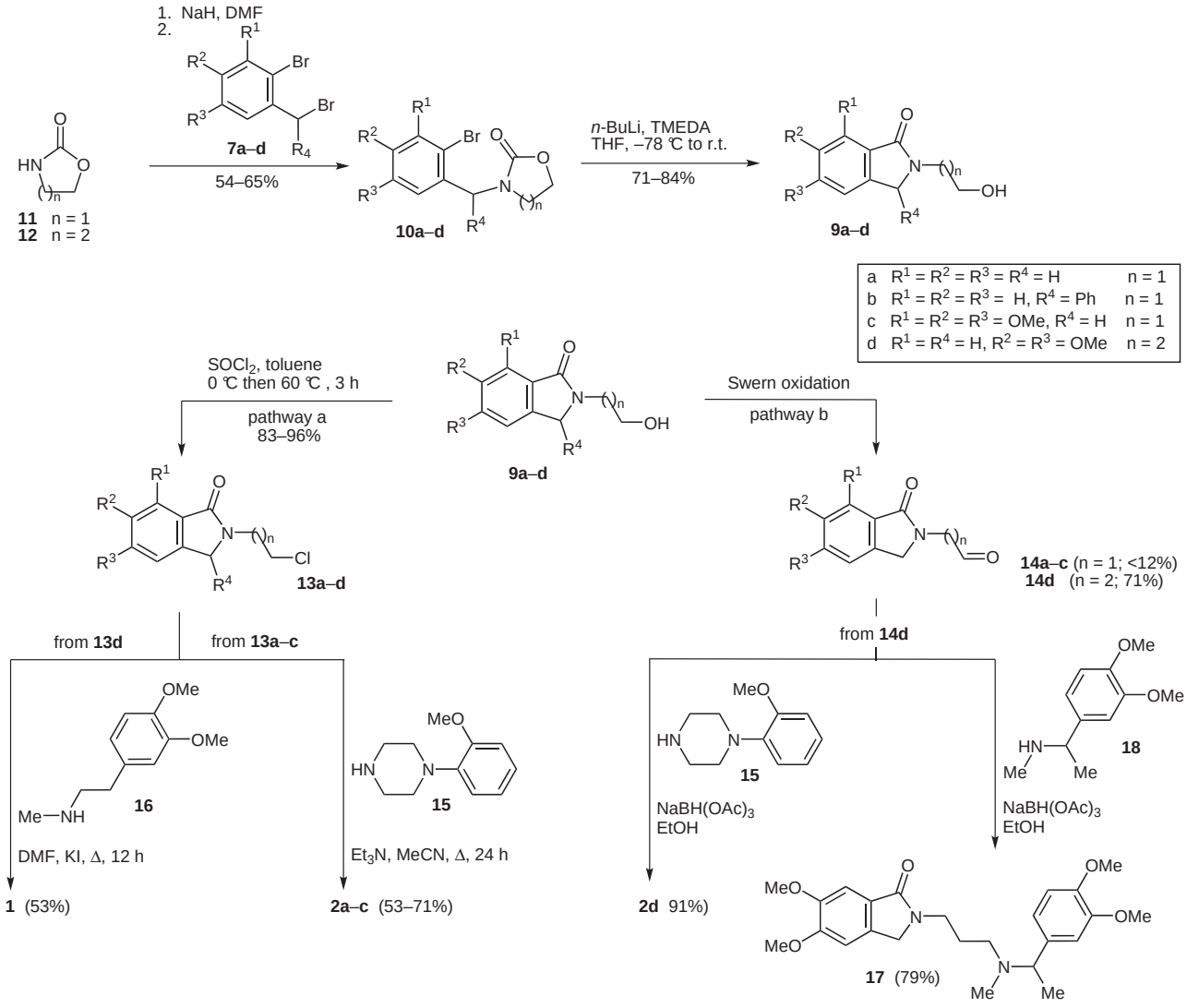
We then decided to switch our plans and set out to achieve an alternative synthetic strategy to secure the formation of a variety of structurally and constitutionally diverse N-aminoalkylated isoindolinones. The key step of the new synthetic route, which is depicted in retrosynthetic Scheme 1 (path b) hinges upon the preliminary construction of the *N*-hydroxyalkyl tethered isoindolinones **9** that should allow for later structural divergence. Indeed such



Scheme 2 Synthesis of **4d**

compounds can be regarded as excellent candidates for the elaboration of models bearing terminal carbonyl or alkylating functions as well and we conjectured that ensuing manipulation of these functional groups should lend to the assembling of the targeted compounds **1**, **2a**–**d**. The diversely substituted hydroxyethyl and hydroxypropyl tethered isoindolinones **9a**–**d** were readily obtained upon exposure to a lithiated base of the parent compounds **10a**–**d**[10b] easily assembled by coupling the bromobenzyl bromides **7a**–**d** with oxazolidin-2-one (**11**) and oxazinan-2-one (**12**) (Scheme 3).

According to the synthetic routes depicted in Scheme 3, we began evaluating synthetic pathway a. Nucleophilic displacement of the halogen atom of **13a** by the *N*-arylpiperazine **15** proceeded uneventfully to afford excellent yield of the 5-HT_{1A} receptor ligand **2a**. It is worth noting that this approach allowed access to the constitutionally unsymmetrical model **2c** from the suitably substituted precursor **13c** and to the C-3 arylated analogue **2b** incorporating a diarylmethylene carboxamide unit, a valuable pharmacophore endowed with a wide range of biological activities.[11] Compounds **2a**,**b** have been shown to display high in vitro binding affinity for 5-HT_{1A} receptors, which exceeds that of the lead compound in this series, that is, *p*-MPPI (**3**).[4b]



Scheme 3 Synthesis of falipamil (**1**) and related compounds

The potential of this process, which offers, at least, complementary and, at best, significant advantages over the classical methodologies was further demonstrated by the conceptually new synthesis of the bradycardic agent falipamil (**1**). Falipamil (**1**) is endowed with a rather unique biological profile. It reduces heart rate specifically but is not a β-blocker,[12] it does not interfere with the cardiac conducting system at therapeutic doses,[13] and its benefit in myocardial ischemia has been shown in a number of animal models[14] and in human studies.[15] For this purpose installation of the requisite *N*-methyl-*N*-dimethoxyphenethylamino moiety was readily secured by coupling the *N*-chloropropylisoindolinone **13d** with *N*-methylhomoveratrylamine **16** under basic conditions to afford a satisfactory yield of the targeted compound **1**.

Evaluation of a proposed alternative approach (pathway b) was next envisaged. Since interest in designing efficient synthetic procedures is to allow structure–activity relationship studies and to find analogues with improved biological activities we set out to achieve the assembly of **2d** and **17** structurally related to the biologically active compounds, **2a** and **1**, respectively. For this purpose the propionaldehyde derivative **14d** was allowed to react with the arylated piperazine **15** and with the *N*-methylmethylbenzylamine **18** under reductive amination conditions. This operation delivered excellent yields of the homologated analogue of **2a**, that is, **2d**, and of the isomeric falipamil **17**. Curiously the synthesis of compound **17** seemed to be precedented,[16] but closer analysis of the purported structure of the synthetic material led to the conclusion that the structure should be revised from **17** to **1**. Thus, the synthesis of the C-methyl isomeric model **17** can arguably be deemed as the first total synthesis of this falipamil analogue. It is noteworthy that this synthetic route could not be applied to the synthesis of **2a**–**c** due to the hardly explainable low efficiency of the Swern oxidation process applied to **9a**–**c** that furnished only trace amounts of the required aldehydes **14a**–**c** (e.g., **14a**–**c**: yield 12%).

The analytical and spectral data of all the new synthesized compounds are listed in Table 1 and Table 2.

Table 1 Spectroscopic and Physical Data of Imidazolinones **5d**,**e** and Oxazolidinones **10a**,**b**

Product[a]	Mp (°C)	^{1}H NMR ($CDCl_3$/TMS); δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS); δ
5d	90–91 (pale yellow crystals)	3.06–3.19 (m, 4 H, 2 × NCH_2), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.33 (s, 2 H, NCH_2Ph), 4.42 (s, 2 H, $ArCH_2N$), 6.87 (s, 1 H_{arom}), 6.91 (s, 1 H_{arom}), 7.19–7.27 (m, 5 H_{arom})	42.1 (CH_2), 42.2 (CH_2), 47.6 (CH_2), 48.3 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 112.7 (C), 113.9 (CH), 115.1 (CH), 127.4 (2 × CH), 128.0 (CH), 128.4 (2 × CH), 128.5 (C), 137.1 (C), 148.8 (C), 148.9 (C), 160.9 (C=O)
5e	95–96 (white crystals)	3.07–3.20 (m, 4 H, 2 × NCH_2), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.35 (s, 2 H, NCH_2Ph), 4.40 (s, 2 H, $ArCH_2N$), 6.86 (s, 1 H_{arom}), 7.13 (s, 1 H_{arom}), 7.19–7.29 (m, 5 H_{arom})	42.1 (CH_2), 42.3 (CH_2), 48.3 (CH_2), 56.1 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 87.4 (C), 112.1 (CH), 121.2 (CH), 127.4 (CH), 128.1 (2 × CH), 128.6 (2 × CH), 132.0 (C), 137.2 (C), 148.9 (C), 149.7 (C), 160.9 (C=O)
10a	51–52 (white crystals)	3.44 (t, *J* = 8.0, 2 H, CH_2N), 4.27 (t, *J* = 8.0, 2 H, OCH_2), 4.52 (s, 2 H, $ArCH_2N$), 7.12 (td, *J* = 2.0, 7.5, 1 H), 7.23–7.33 (m, 2 H_{arom}), 7.47 (d, *J* = 7.9, 1 H)	44.1 (CH_2), 48.1 (CH_2), 62.0 (CH_2), 123.7 (C), 128.0 (CH), 129.6 (CH), 129.9 (CH), 133.0 (CH), 135.0 (C), 158.5 (C=O)
10b	111–112 (white crystals)	3.13–3.32 (m, 2 H, NCH_2), 4.27 (t, *J* = 7.9, 2 H, CH_2O), 6.42 (s, 1 H, ArC*H*Ph), 6.99 (dd, *J* = 1.8, 7.8, 1 H_{arom}), 7.06–7.13 (m, 3 H_{arom}), 7.17–7.30 (m, 4 H_{arom}), 7.53 (dd, *J* = 1.4, 7.8, 1 H_{arom})	43.3 (CH_2), 60.6 (CH_2), 62.3 (CH), 124.9 (C), 127.5 (CH), 127.8 (CH), 127.9 (2 × CH), 128.8 (2 × CH), 129.7 (CH), 129.9 (CH), 133.6 (CH), 137.9 (C), 138.2 (C), 157.8 (C=O)

[a] Satisfactory microanalyses obtained: C ± 0.24, H ± 0.27, N ± 0.22.

Table 2 Spectroscopic and Physical Data of N-Alkyl-Functionalized Isoindolinones

Product	Mp (°C)	^{1}H NMR ($CDCl_3$/TMS); δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS); δ
4d	125–126 (fawn crystals)[a]	2.86 (t, *J* = 6.1, 2 H, CH_2N), 3.66 (t, *J* = 6.1, 2 H, NCH_2), 3.76 (s, 2 H, NCH_2Ph), 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.25 (s, 2 H, $ArCH_2N$), 6.81 (s, 1 H_{arom}), 7.12–7.27 (m, 6 H_{arom})	42.4 (CH_2), 47.5 (CH_2), 50.4 (CH_2), 53.4 (CH_2), 56.2 (CH_3), 56.3 (CH_3), 104.9 (CH), 105.2 (C), 125.0 (CH), 127.1 (CH), 128.2 (2 × CH), 128.4 (2 × CH), 134.9 (C), 139.6 (C), 149.6 (C), 152.4 (C), 163.9 (C=O)
9b	111–112 (yellow crystals)[a]	2.86–2.95 (m, 1 H, NCH_2), 3.54–3.68 (m, 2 H, CH_2OH), 3.74–3.82 (m, 1 H, NCH_2), 4.40 (br s, 1 H, OH), 5.55 (s, 1 H, ArC*H*Ph), 6.95–7.00 (m, 3 H_{arom}), 7.13–7.27 (m, 5 H_{arom}), 7.63–7.66 (m, 1 H_{arom})	43.4 (CH_2), 60.9 (CH_2), 65.8 (CH), 123.1 (CH), 123.3 (CH), 127.7 (2 × CH), 128.2 (CH), 128.7 (2 × CH), 129.1 (CH), 131.2 (C), 131.9 (CH), 136.8 (C), 146.7 (C), 169.6 (CO)
13a	79–80[b] (white crystals)	3.74 (t, *J* = 5.6, 2 H, CH_2Cl), 3.90 (t, *J* = 5.8, 2 H, NCH_2), 4.52 (s, 2 H, $ArCH_2N$), 7.38–7.41 (m, 2 H_{arom}), 7.43–7.52 (m, 1 H_{arom}), 7.80 (d, *J* = 7.4, 1 H_{arom}).	42.7 (CH_2), 44.6 (CH_2), 51.4 (CH_2), 122.8 (CH), 123.6 (CH), 128.1 (CH), 131.6 (CH), 132.2 (C), 141.4 (C), 168.8 (C=O)
13b	90–91 (yellowish crystals)	3.06–3.15 (m, 1 H, CH_2Cl), 3.41–3.48 (m, 1 H, CH_2Cl), 3.59–3.68 (m, 2 H, NCH_2), 5.59 (s, 1 H, ArC*H*Ph), 7.01–7.06 (m, 3 H_{arom}), 7.18–7.25 (m, 3 H_{arom}), 7.30–7.37 (m, 2 H_{arom}), 7.78–7.81 (m, 1 H_{arom})	42.3 (2 × CH_2), 65.6 (CH), 123.1 (CH), 123.6 (CH), 127.7 (2 × CH), 128.4 (CH), 128.9 (CH), 129.3 (2 × CH), 131.0 (C), 132.1 (CH), 136.7 (C), 146.5 (C), 168.6 (C=O)
13c	114–115 (white crystals)	3.71 (t, *J* = 5.8, 2 H, CH_2Cl), 3.78–3.80 (m, 2 H, NCH_2), 3.81 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.39 (s, 2 H, $ArCH_2N$), 6.63 (s, 1 H_{arom})	42.5 (CH_2), 44.4 (CH_2), 50.7 (CH_3), 56.2 (CH_2), 61.3 (CH_3), 62.5 (CH_3), 101.3 (CH), 116.7 (C), 130.9 (C), 141.4 (C), 151.2 (C), 157.1 (C), 167.0 (C=O)
13d	110–111 (white crystals)	2.14 (quint, *J* = 6.7, 2 H, CH_2), 3.58 (t, *J* = 6.5, 2 H, CH_2Cl), 3.72 (t, *J* = 6.9, 2 H, NCH_2), 3.91 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.32 (s, 2 H, $ArCH_2N$), 6.90 (s, 1 H_{arom}), 7.27 (s, 1 H_{arom})	31.4 (CH_2), 40.2 (CH_2), 42.3 (CH_2), 50.3 (CH_2), 56.2 (2 × CH_3), 104.9 (CH), 105.2 (CH), 124.9 (C), 134.6 (C), 149.6 (C), 152.5 (C), 169.1 (C=O)
14a	118–119 (white crystals)[a]	4.51–4.53 (m, 4 H, 2 × CH_2), 7.46–7.51 (m, 2 H_{arom}), 7.56–7.59 (m, 1 H_{arom}), 7.87–7.90 (m, 1 H_{arom}), 9.74 (s, 1 H, CHO)	50.8 (CH_2), 52.4 (CH_2), 122.9 (CH), 124.0 (CH), 128.2 (CH), 131.6 (C), 131.9 (CH), 141.5 (C), 169.2 (C=O), 196.8 (CHO)
14d	122–123 (white crystals)[a]	2.85 (t, *J* = 6.2, 2 H, CH_2CO), 3.82 (s, 1 H, NCH_2), 3.84 (s, 1 H, NCH_2), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.30 (s, 2 H, $ArCH_2N$), 6.84 (s, 1 H_{arom}), 7.22 (s, 1 H_{arom}), 9.79 (s, 1 H, CHO)	36.0 (CH_2), 42.9 (CH_2), 50.3 (CH_2), 56.0 (CH_3), 56.1 (CH_3), 104.8 (CH), 104.9 (CH), 124.4 (C), 134.9 (C), 149.4 (C), 152.3 (C), 168.8 (C=O), 197.7 (CHO)

Table 2 Spectroscopic and Physical Data of N-Alkyl-Functionalized Isoindolinones (continued)

Product	Mp (°C)	^{1}H NMR ($CDCl_3$/TMS); δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS); δ
2a	117–118 (yellowish crystals)[a]	2.58–2.62 (m, 6 H, 3 × CH_2), 2.93–2.99 (m, 4 H, 2 × CH_2), 3.66 (t, *J* = 6.4, 2 H, CH_2N), 3.72 (s, 3 H, OCH_3), 4.39 (s, 2 H, ArCH_2N), 6.71–6.74 (m, 1 H_{arom}), 6.78–6.81 (m, 2 H_{arom}), 6.85–6.90 (m, 1 H_{arom}), 7.28–7.33 (m, 2 H_{arom}), 7.39–7.42 (m, 1 H_{arom}), 7.71–7.74 (m, 1 H_{arom})	39.4 (CH_2), 50.6 (2 × CH_2), 50.8 (CH_2), 53.5 (2 × CH_2), 55.3 (CH_3), 56.7 (CH_2), 111.2 (CH), 118.1 (CH), 120.9 (CH), 122.7 (CH), 122.9 (CH), 123.5 (CH), 127.8 (CH), 131.1 (CH), 132.8 (C), 141.2 (C), 141.5 (C), 152.2 (C), 168.4 (C=O)
2b	168–169 (yellowish crystals)[a]	2.36–2.64 (m, 6 H, 3 × CH_2), 2.90–2.99 (m, 5 H, 2 × CH_2 + 1 H NCH_2), 3.72 (s, 3 H, OCH_3), 3.96–4.04 (m, 1 H, NCH_2), 5.67 (s, 1 H, ArC*H*Ph), 6.72–6.90 (m, 4 H_{arom}), 7.04–7.06 (m, 3 H_{arom}), 7.21–7.23 (m, 3 H_{arom}), 7.30–7.33 (m, 2 H_{arom}), 7.78–7.81 (m, 1 H_{arom})	37.1 (CH_2), 50.7 (2 × CH_2), 53.4 (2 × CH_2), 55.4 (CH_3), 57.0 (CH_2), 65.4 (CH), 111.2 (CH), 118.1 (CH), 121.0 (CH), 122.9 (CH), 123.0 (CH), 123.5 (CH), 127.5 (CH), 128.2 (2 × CH), 128.6 (CH), 129.1 (2 × CH), 131.2 (CH), 131.5 (C), 137.3 (C), 141.3 (C), 146.7 (C), 152.2 (C), 168.6 (C=O)
2c	118–119 (white crystals)[a]	2.56–2.62 (m, 6 H, 3 × CH_2), 2.93–3.02 (m, 4 H, 2 × CH_2), 3.61 (t, *J* = 6.3, 2 H, CH_2N), 3.75 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 4.31 (s, 2 H, ArCH_2N), 6.62 (s, 1 H_{arom}), 6.74–6.76 (m, 1 H_{arom}), 6.80–6.83 (m, 2 H_{arom}), 6.88–6.91 (m, 1 H_{arom})	39.3 (CH_2), 50.3 (CH_2), 50.7 (2 × CH_2), 53.4 (2 × CH_2), 55.3 (CH_3), 56.2 (CH_3), 56.7 (CH_2), 61.4 (CH_3), 62.6 (CH_3), 101.2 (C), 111.1 (CH), 117.5 (CH), 118.0 (CH), 120.9 (CH), 122.9 (CH), 139.1 (C), 141.2 (C), 141.5 (C), 151.3 (C), 152.2 (C), 156.8 (C), 166.8 (C=O)
2d	56–57 (fawn crystals)[a]	1.86 (quint, *J* = 7.5, 2 H, CH_2), 2.45 (t, *J* = 7.2, 2 H, CH_2), 2.63 (br s, 4 H, $H_{piperazine}$), 3.01 (br s, 4 $H_{piperazine}$), 3.55 (t, *J* = 7.3, 2 H, CH_2), 3.72 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.22 (s, 2 H, ArCH_2N), 6.72–6.74 (m, 1 H_{arom}), 6.78–6.81 (m, 3 H_{arom}), 6.85–6.90 (m, 1 H_{arom}), 7.18 (s, 1 H_{arom})	25.4 (CH_2), 40.4 (CH_2), 49.6 (CH_2), 50.0 (2 × CH_2), 53.2 (2 × CH_2), 55.2 (CH_3), 55.5 (CH_3), 56.1 (CH_2), 56.1 (CH_3), 105.0 (2 × CH), 111.1 (CH), 118.1(CH), 120.9 (C), 123.0 (CH), 124.8 (CH), 134.7(C), 140.8 (C), 149.4 (C), 152.0 (C), 152.3 (C), 168.8 (C=O)
17	207–208 (white crystals)[a]	1.20 (d, *J* = 6.6, 3 H, NCHCH_3), 1.64-1.73 (m, 2 H, CH_2), 2.11 (s, 3 H, NCH_3), 2.17–2.24 (m, 1 H, NCH_2), 2.29–2.35 (m, 1 H, NCH_2), 3.32–3.37 (m, 1 H, NCH_2), 3.40–3.52 (m, 2 H, NCH_2 + N*CH*Me), 3.71 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.03 (br s, 2 H, ArCH_2N), 6.61–6.70 (m, 2 H_{arom}), 6.77 (s, 1 H_{arom}), 6.80 (s, 1 H_{arom}), 7.16 (s, 1 H_{arom})	23.5 (CH_3), 29.5 (CH_2), 39.4 (CH_2), 49.6 (CH_3), 51.0 (CH_2), 55.6 (CH_3), 56.0 (CH_3), 56.1 (CH_2), 56.1 (CH_3), 56.3 (CH_3), 65.7 (CH), 104.8 (CH), 105.1 (CH), 110.7 (CH), 111.6 (CH), 121.3 (CH), 123.9 (C), 126.2 (C), 135.0 (C), 149.3 (C), 149.4 (C), 149.8 (C), 152.5 (C), 169.2 (C=O)

[a] Satisfactory microanalyses obtained: C ± 0.22, H ± 0.26, N ± 0.28.
[b] Lit.[24] mp 81–82 °C.

In summary, complementary and tactically new synthetic approaches to aminoalkyl-tethered isoindolinones with a variety of bridging units have been developed. The main synthetic route hinges upon the assembling of the poly and diversely substituted benzolactam units tailed with hydroxyalkyl chains, which allow for sufficient versatility for further tailor-made structural modifications. We believe that the methodology established for the synthesis of the exemplary representatives may find utility for abbreviated synthesis of structurally related congeners of pharmaceutical interest.

THF was predried with anhyd Na_2SO_4 and distilled over sodium benzophenone ketyl under argon before use. CH_2Cl_2, Et_3N, and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembled under dry argon. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μm; 230–400 mesh ASTM) was used. Melting points were obtained on a Reichert-Thermopan apparatus and are not corrected. Elemental analyses were obtained using a Carlo-Erba CHNS-11110 equipment. NMR spectra were recorded on a Bruker AM 300 (300 MHz and 75 MHz, for ^{1}H, and ^{13}C), $CDCl_3$ as solvent, TMS as internal standard. The *o*-bromobenzyl bromides **7a**,[17] **7b**,[18] **7c**,[19] **7d**,[20] and *o*-bromobenzyl iodide **7e**[21] were prepared according to reported procedures. Amines **15** and **16** are commercially available and amine **18**[22] was synthesized following literature methods.

N-Substituted Imidazolinones 5d,e, 6, Oxazolidinones 10a–c and Oxazinanone 10d; General Procedure

A solution of the parent heterocycle (4 mmol) in THF (10 mL) was added to a stirred suspension of pentane-prewashed NaH (108 mg, 4.5 mmol, from a 60% suspension in mineral oil) in THF (20 mL) under argon. The mixture was stirred for 1 h at r.t. and a solution of benzyl bromide or *o*-halobenzyl bromide derivative **7a–e** (4.5 mmol) in THF (10 mL) was then added dropwise. The mixture was refluxed overnight and after cooling, H_2O (20 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under vacuum affording a crude solid residue, which was purified by flash column chromatography on silica gel using EtOAc–hexanes–CH_2Cl_2 (30:20:50) as eluent for **5d** (824 mg, 51%); EtOAc–hexanes (40:60) as eluent for **5e** (1.01 g, 56%); EtOAc–hexanes–CH_2Cl_2 (30:20:50) as eluent for **10a** (601 mg, 59%), EtOAc–hexanes (50:50) as eluent for **10b** (715 mg, 54%). Compounds **6**[23] (649 mg, 92%), **10c**[10b] (814 mg, 59%), **10d**[10b] (855 mg, 65%) were purified according to literature (Table 1).

Isoindolinones 4d and 9a–d; General Procedure

A solution of *n*-BuLi (2 M in hexane, 1.50 mL, 3.0 mmol) and TMEDA (350 mg, 3.0 mmol) in anhyd THF (4 mL) was carefully degassed by three freeze-thaw cycles and stirred at –78 °C under dry deoxygenated argon. A solution of compound **5d**, **10a**–**d** (1.0 mmol) in degassed THF (15 mL) was then added dropwise through a cannula. The mixture was stirred at –78 °C for 30 min. After quenching with aq sat. NH_4Cl (5 mL) and dilution with H_2O (30 mL), THF was removed under vacuum in a rotary evaporator and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under vacuum to leave the isoindolinone as a solid residue, which was purified by flash column chromatography on silica gel using acetone–hexanes–Et_3N (80:15:5) as eluent for **4d** (75 mg, 23%); acetone–hexanes (80:20) as eluent for **9a** (126 mg, 71%),[4b,24] **9c** (214 mg, 80%),[10b] **9d** (198 mg, 79%);[10b] and acetone–hexanes (60:40) as eluent for **9b** (213 mg, 84%) (Table 2).

2-(2-Benzylaminoethyl)-5,6-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one (4d) Starting from 5e; Improved Procedure

A solution of *o*-iodobenzyl derivative **5e** (452 mg, 1.0 mmol) and TMEDA (203 mg, 2.2 mmol) in anhyd THF (20 mL) was carefully degassed by three freeze-thaw cycles and stirred at –78 °C under dry deoxygenated argon. A solution of *n*-BuLi (2 M in hexane, 1.1 mL, 2.2 mmol) was then added dropwise. The mixture was stirred for 30 min at –78 °C, then treated as described above to afford **4d** (176 mg, 54%); fawn crystals.

N-(Chloroalkyl)isoindolinones 13a–d; General Procedure

$SOCl_2$ (400 mg, 3.4 mmol) was added dropwise to an ice-water cooled solution of *N*-hydroxyalkylisoindolinone **9a–c** (3.0 mmol) in toluene (50 mL). The reaction mixture was allowed to stand at r.t. for 4 h with occasional swirling, then the mixture was heated at 60 °C for 3 h. The toluene and the excess $SOCl_2$ were removed by distillation under vacuum and the hot residue was poured into hexanes (50 mL) to afford a brown solid. After filtration, the solid was dissolved in refluxing toluene (20 mL). The solution was filtered hot, and the hot filtrate was poured into hexanes (30 mL) with stirring. The precipitate was filtered, washed with hexanes, and dried in a vacuum oven to afford **13a**–**d** as white solid, which was used without further purification. Yield of crude products: **13a** (557 mg, 95%), **13b** (717 mg, 88%), **13c** (823 mg, 96%), **13d** (671 mg, 83%) (Table 2).

2-(3-{[2-(3,4-Dimethoxyphenyl)ethyl]methylamino}propyl)-5,6-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one [Falipamil (1)]

A solution of chloropropylisoindolinone **13d** (428 mg, 1.6 mmol), methylhomoveratrylamine (**16**) (818 mg, 4.2 mmol), and KI (catalytic amount) in DMF (30 mL) was refluxed under argon for 12 h. After cooling, the resulting mixture was filtered, then the solvent was evaporated under reduced pressure, and H_2O (10 mL) was added. The mixture was extracted with EtOAc (3 × 30 mL), the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to give an oily residue, which was purified by flash column chromatography on silica gel using acetone–hexanes–Et_3N (50:45:5) as eluent, yield: 842 mg (53%). A sample of the product **1** was dissolved in acetone and the hydrochloride was precipitated by the addition of ethereal HCl. Analytical and spectral data of **1**·HCl matched with those previously reported in the literature.[9]

Piperazine Derivatives 2a–c; General Procedure

A solution of chloroethylisoindolinone **13a**–**c** (1.0 mmol), 1-(2-methoxyphenyl)piperazine (**15**; 192 mg, 1.0 mmol), Et_3N (121 mg, 1.2 mmol) in MeCN (10 mL) was refluxed under argon for 24 h. After cooling and filtration, the solution was diluted with EtOAc (20 mL), washed with aq sat. K_2CO_3 (5 mL) and brine (5 mL), and dried ($MgSO_4$). Evaporation of the solvent in vacuo left an oily residue, which was purified by flash column chromatography on silica gel using acetone–hexanes–Et_3N (40:55:5) as eluent; yield: **2a** (249 mg, 71%), **2b** (260 mg, 61%), **2c** (234 mg, 53%) (Table 2).

Aldehydes 14a,d by Oxidation of 9a,d

Anhyd DMSO (351 mg, 4.5 mmol) was added dropwise to a solution of oxalyl chloride (280 mg, 2.2 mmol) in anhyd CH_2Cl_2 (15 mL) at –78 °C under argon. The mixture was stirred at –78 °C for 30 min and a solution of **9a**,**d** (1.1 mmol) in CH_2Cl_2 (25 mL) was added slowly. After stirring for 1 h, Et_3N (606 mg, 6 mmol) was added and the reaction mixture was allowed to warm to r.t. over 2 h. H_2O (20 mL) was added and the mixture concentrated under vacuum. The residue was redissolved in CH_2Cl_2 (30 mL) and the solution was washed with H_2O (3 × 10 mL) and brine (10 mL). The solution was dried ($MgSO_4$) and evaporated under vacuum. Purification of the solid residue by flash column chromatography using acetone–hexanes (80:20) as eluent afforded **14a** (22 mg, 12%) and **14d** (195 mg, 71%), respectively (Table 2).

Reductive Amination Reaction Involving 14d; General Procedure

$NaBH(OAc)_3$ (297 mg, 1.4 mmol) was added portionwise to a solution of **14d** (249 mg, 1.0 mmol) and amine **15** or **18** (1.0 mmol) in 1,2-dichloroethane (10 mL) followed by AcOH (60 mg, 1.0 mmol). The mixture was stirred at r.t. under argon for 24 h, then quenched by addition of aq 1 N NaOH (10 mL). CH_2Cl_2 (10 mL) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). The solvent was evaporated to give the crude free base; yield: **2d** (387 mg, 91%), **17** (338 mg, 79%) (Table 2).

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