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Transition-metal-catalyzed intramolecular cyclization of amido(hetero)arylboronic acid aldehydes to isoquinolinones and derivatives†

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We report an innovative and simple three step high yielding synthesis of a library of 14 chiral isoquinolinone and azepinone derivatives with benzyl, pyridyl and thiophene cores starting from amidoarylboronic acid aldehydes. These products have potential for treating neurodegenerative diseases. The key reaction in this synthetic pathway was an efficient metal-catalyzed (with Rh, Cu and Pd catalysts) intramolecular cyclization. A maximum yield of 87% was obtained using a Rh(I) catalyst.

Introduction

Isoquinolin-1(2*H*)-one derivatives (Fig. 1) are an interesting group of plant alkaloids, which have found many uses in both medicinal and synthetic organic chemistry.[1,2] For instance, (−)-kibdelone C and antinoplanone A, both hexacyclic tetrahydroxanthones and potent anticancer agents isolated from an Australian microbe have the isoquinolin-1(2*H*)-one skeleton (Fig. 1).[3] Dorianine,[4] thalifoline[2c] and pancratistatin[5] (Fig. 1) are other key examples. It is also present in an effective 5-HT3 antagonist, demonstrating much potential for cancer chemotherapy as well as for anxiety and schizophrenia.[6] Several isoquinolin-1(2*H*)-ones and derivatives can inhibit tumor necrosis factor (TNF) production in peripheral blood monocytes.[7] They can also be used as natural base replacements in nucleosides.[8]

The first synthetic approach to these molecules was reported by Gabriel and Colman,[9] and since then many other pioneering synthetic approaches have been developed.[4,10,11] Despite the effectiveness of these methods, some limitations such as long reaction times, low yields, tedious work-up procedures and the use of toxic and expensive reagents or catalysts, including laborious synthetic sequences, were found.

Herein, we report an efficient three-step synthetic approach to isoquinolin-1(2*H*)-one derivatives (**4**) starting from easily accessed acetal substrates (**1**)[12i] (Scheme 1).

Results and discussion

As we are active in this field,[12] and after considering previous literature work[13–15] we set out to study the hitherto unknown

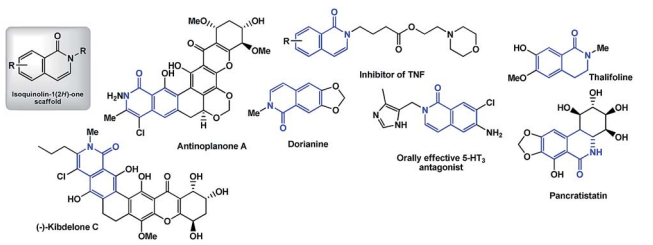
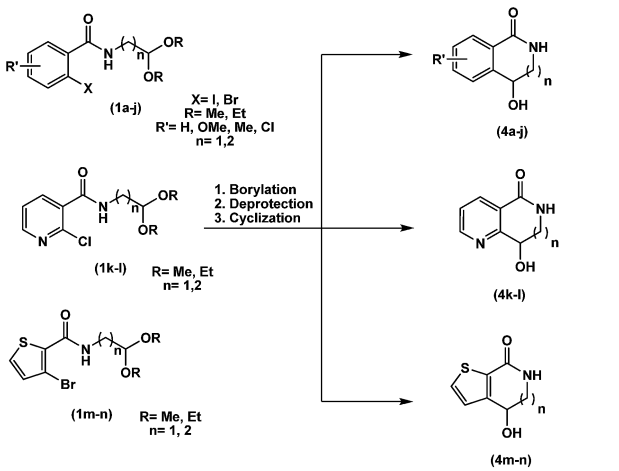


Fig. 1 Examples of biologically active compounds containing the isoquinolin-1(2*H*)-one unit.



Scheme 1 Synthetic route to the isoquinolin-1(2*H*)-one derivatives obtained in this work.

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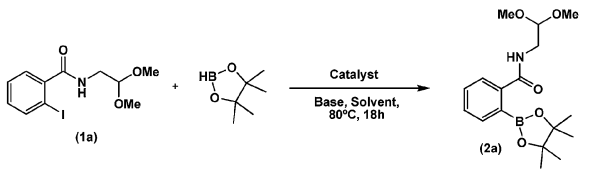
Table 1 Catalytic borylation reaction of *N*-(2,2-dimethoxyethyl)-2-iodobenzamide (**1a**) with HBPin

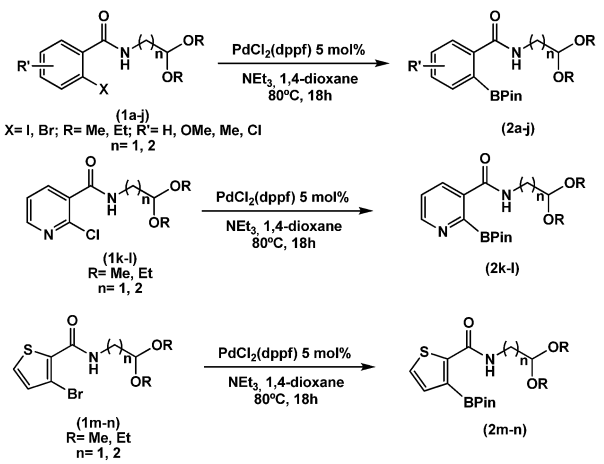


Entry[a]	Catalyst	Base[g]	Yield/%
1	$PdCl_2(dppf)$[b]	KOAc	72
2	$PdCl_2(dppf)$[b]	NEt_3	76
3	$Pd(OAc)_2$[b]/XantPhos[d]	NEt_3	48
4	$Pd(OAc)_2$[e]/RuPhos[e]	NEt_3	40
5	$Pd(OAc)_2$[e]/SPhos[e]	NEt_3	32
6	$Pd(OAc)_2$[e]/CyJohnPhos[e]	NEt_3	20
7[h]	$PdCl_2(dppf)$[b]	KOAc	58
8	$Pd(OAc)_2$[b]/SPhos[c]	K_2CO_3	24
9	$Pd_2(CH_3CN)_2$[f]/SPhos[c]	K_2CO_3	32

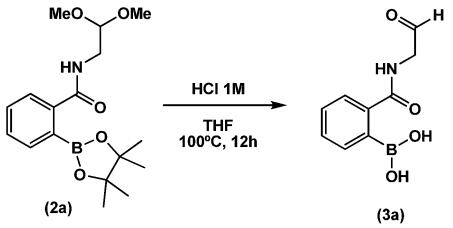
[a] Reaction conducted at 1.5 mmol scale. See ESI for detailed procedures. [b] 5 mol% was used. [c] 3 mol% was used. [d] 10 mol% was used. [e] 15 mol% was used. [f] 6 mol% was used. [g] 3 equivalents of base were used. [h] B_2Pin_2 (1.5 equivalents) was used as borylating agent.

reactivity of arylboronic acid acetal substrates.[16–18] Using the conditions of Masuda,[18e] we began a study on the synthesis of arylboronic esters using Pd catalysts (Table 1). The best yield was obtained using $PdCl_2(dppf)$ as catalyst (Table 1, entries 1 and 2).

The use of NEt_3 (ref. 18e) was observed to be the most effective (Table 1, entry 2). The use of other palladium catalysts, with an additional phosphane ligand, tended to retard the reaction (Table 1, entries 3 to 6), even with high catalyst loadings (see Table 1, entries 4 to 6). Tetra(alkoxo)diboron like, bis(pinacolato)diboron (B_2Pin_2) behave as boron-nucleophiles for palladium-catalyzed cross-coupling reactions with organic halides.[19] We decided to test B_2Pin_2 also in the borylation of (**1a**) with $PdCl_2(dppf)$ and KOAc (Table 1, entry 7). The product yield



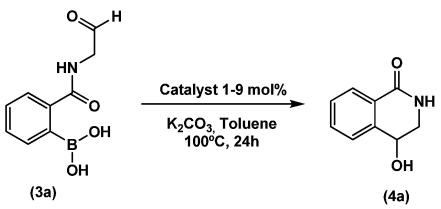
Scheme 2 Palladium cross-coupling borylation reaction of *ortho*-(hetero)arylhalide amide-acetal derivatives (**1**).



Scheme 3 Deprotection of *ortho*-borylated amide-acetal derivatives (**2**).

was lower than that achieved with HBPin under equivalent reaction conditions (Table 1, compare entries 1 and 7). Low yields of the desired borylated compound (**2a**) were achieved using K_2CO_3 as base (see Table 1, entries 8 and 9). A further 13 amide-acetal substrates (**1**) (Scheme 2)[16] were screened. The reactions were monitored using TLC analysis with alizarin dye[20] (see ESI†). ^1H NMR analysis of the crude borylated product (**2a**) (see Scheme 2, R = Me, R′ = H, $n = 1$) was performed, showing

Table 2 Screening of Rh, Pd and Cu catalysts in the intramolecular cyclization of (**3a**)



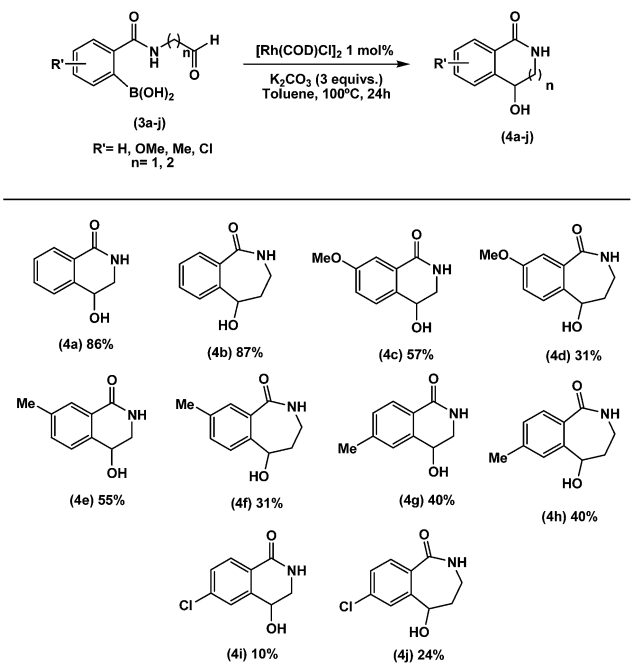
Entry[a]	Catalyst	Yield/%
1	$[Rh(COD)Cl]_2$[b]	86
2	$[Rh(COD)OH]_2$[b]	38
3	$[Rh(nbd)Cl]_2$[b]	27
4	$Rh(COD)_2BF_4$[b]	40
5	$[Rh(C_2H_4)_2Cl]_2$[b]	25
6	$Rh(acac)(C_2H_4)_2$[b]	21
7	$[RhCp^*Cl_2]_2$[b]	13
8	$Pd(OAc)_2$[c]/bpy[d]	52
9	$Pd(OAc)_2$[c]/PCy_3[d]	53
10	$Pd(OAc)_2$[c]/XantPhos[d]	24
11	$Pd(OAc)_2$[c]/RuPhos[d]	52
12	$Pd(OAc)_2$[c]/PPh_3[d]	74
13	$Pd(OAc)_2$[c]/dppf[d]	53
14	$PdCl_2(dppf)$[e]	31
15	$PdCl_2(PPh_3)_2$[e]	43
16	PEPPSI-IPr[e]	47
17	CuF[f]/bpy[g]	40
18	CuCl[f]/bpy[g]	40
19	$CuCl_2$[f]/bpy[g]	48
20	$Cu(OAc)_2$[f]/bpy[g]	40
21	Cu_2O[f]/bpy[g]	40
22	$Cu(CF_3SO_4)_2$[f]/bpy[g]	56
23	$Cu(acac)_2$[f]/bpy[f]	44
24	$CuBr_2$[f]/bpy[g]	44

[a] Reaction conducted at 1.5 mmol scale, with 1–9 mol% of catalyst, 3 equiv. of K_2CO_3 and 2 mL of toluene. See ESI for the detailed procedures. [b] 1 mol% was used. [c] 3 mol% was used. [d] 6 mol% was used. [e] 9 mol% was used. [f] 5 mol% was used. [g] 10 mol% was used.

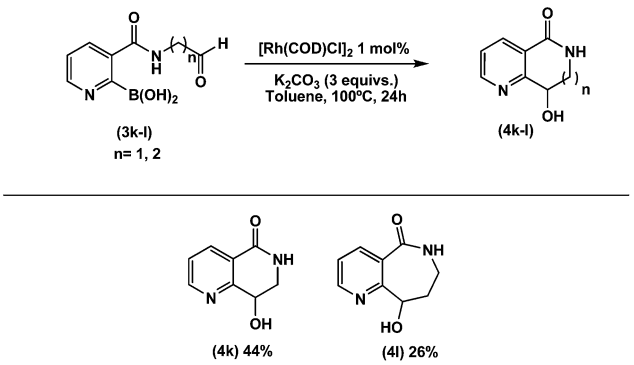
only the presence of unreactive HBPin. We conducted the next step without purification of (**2**).

In order to successfully conduct the intramolecular cyclization of our *ortho*-borylated amide-acetal derivatives (**2**) a deprotection step had to be introduced in the synthetic pathway. We tried unsuccessfully to obtain the final cyclic compounds using the amide-acetal derivatives (**2**) using several transition-metal catalysts. Following a simple method[21] using (**2a**), HCl (1 M) and THF, under reflux we could successfully hydrolyse the pinacol boron ester to the corresponding boronic acid (**3a**) in 85% yield (Scheme 3). ^{1}H NMR analysis of the crude product (**3a**) showed only trace amounts of (**2a**), and we successfully applied this procedure in the case of all the amide-acetal substrates (**2**) (Scheme 3).

We were able to promote the intramolecular cyclization of (**3**) using transition-metal catalysts. Since Miyaura's[22a] pioneering studies on the Rh-catalyzed addition of arylboronic acids to aldehydes, several catalytic systems have been developed, primarily based on Rh[12h,22] and Pd.[12h,23] As far as we are aware, no reports on the intramolecular addition of metal aryl species to aldehydes have been reported to date.[13–15] We started our study with (**3a**) applying literature conditions[24] with Rh, Pd and Cu catalysts.[12h,23,25] The results are shown in Table 2. In the case of the Rh(I)-catalysts, $[Rh(COD)Cl]_2$ gave the best results (86% yield) (Table 2, entry 1). $Pd(OAc)_2$ and PPh_3 afforded the desired compound (**4a**) in 74% yield (Table 2, entry 12), and was the best Pd-catalytic system found. Very similar yields (43–53%) were obtained with almost all the other Pd-systems tested (Table 2, entries 9, 11, 13, and 15) and there was no significant difference between the various phosphane ligands that were used. Both bpy (Table 2, entry 8) and PEPPSI-IPr (Table 2, entry 16) could also be used. Gratifyingly, in the case of Cu-catalysis, despite



Scheme 4 Rh(I)-catalyzed intramolecular cyclization of compounds (**3a–j**) to (**4a–j**).



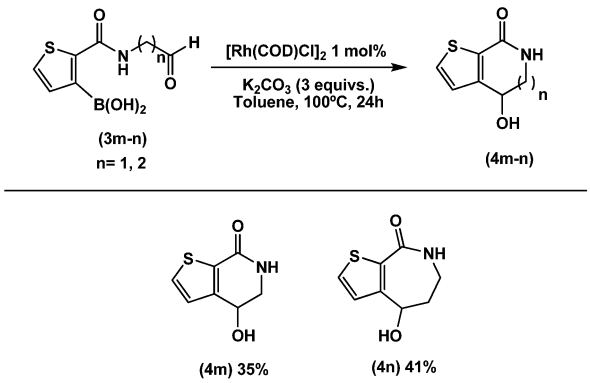
Scheme 5 Rh(I)-catalyzed intramolecular cyclization of (**3k–3l**) to (**4k–4l**).

very few reports in the literature,[25] the desired product (**4a**) was obtained in satisfactory yields (40–56%) using commercial Cu(I)- and Cu(II)-catalysts (Table 2, entries 17 to 24). Bpy could be used with various Cu pre-catalysts.[26]

All of our substrates (**3**) were tested (Schemes 4–6). In the case of the Rh(I)-catalyzed intramolecular cyclization of compounds (**3a–j**) the best yields (86 and 87%) were obtained for compounds (**4a**) and (**4b**), *i.e.* obtained from substrates with no substituents in the aromatic ring (Scheme 4). When electron donating groups like methoxyl and methyl were present in the aromatic ring, a slight decrease in the yield was observed (see **4c–h**, Scheme 4). No significant difference was noted regarding the position of the methyl group in the aromatic ring (compare for instance compound (**4e**) with (**4g**), Scheme 4). When electron withdrawing groups, like Cl were present, the yield dropped significantly (**4i** and **4j**, Scheme 4). This is hard to explain, but it seems that the presence of electron-donating groups in the *para*-position relative to the boronic acid unit disfavour some key step in the catalytic cycle. In fact, Gallego and Sarpong have demonstrated that the presence in their system of a fluorine in the *para*-position (see discussion below) gives better yields over the non-substituted derivative.[27] This is most likely an indication that electron-withdrawing groups in the *para*-position promote the transmetallation step. When a chlorine or a methyl is present in the *meta*-position the yields are lower than the non-substituted case, implying that electron-withdrawing and electron-donating groups inhibit some steps in the reaction. Although quite puzzling, each substituent is possibly affecting disparate steps in the catalytic cycle. Presumably the methyl group inhibits the transmetallation step *via* an inductive-electron-donating effect, whilst the chlorine group inductively deactivates the 1,2-addition step to the carbonyl group (see the mechanistic discussion below). Gratifyingly there were no differences in the yields for the formation of either six- or seven-member rings, testimony to the applicability and robustness of the method.

In the case of (**3k–3l**), low to moderate yields were obtained (Scheme 5), lower than for the normal aryl substrates (**4a–4b**, Scheme 4).

Finally, *S*-heteroaromatic derivatives – thiophene type (**3m–3n**) were tested in this Rh(I)-catalytic intramolecular cyclization



Scheme 6 Rh(I)-catalyzed intramolecular cyclization of (3m) and (3n) to (4m) and (4n).

reaction (Scheme 6). Moderate yields were obtained for the thiophene-derivatives (**4m–4n**), with a maximum of 41% for the azepinone (**4n**) (Scheme 6).

Regarding the reaction mechanism and the catalytic cycle, there are a number of reports in the literature on very similar systems that we believe to be analogous to ours. In 2012, Gallego and Sarpong reported on a Rh(I)-catalyzed intramolecular arylation on aryl pinacolboronic ester ketones.[27] In their catalytic method they used $[Rh(COD)(MeCN)_2]BF_4$ and a tertiary amine base or $[Rh(cod)(OH)]_2$ and a chiral diphosphane ligand (the latter system gave better yields). Based on a previous account by Feringa, Minnard and coworkers,[28] they proposed that the base promotes the transmetallation step to give a Rh–aryl intermediate, followed by coordination of the Rh centre to the carbonyl group and then a migratory insertion step, which is then followed by the 1,2-addition to the ketone giving a Rh–alkoxide that suffers transmetallation from another boronate ester precursor molecule giving the cycloalkanolboronate (which is hydrolyzed to the product) with regeneration of the Rh–aryl intermediate. Our mechanism should be equivalent to this. Of note was that in our case the $[Rh(COD)(OH)]_2$ catalyst did not give the best yields. In 2006 Liu and Lu reported a Pd catalyzed intramolecular arylation with aryl pinacolboronic acid ketones using a cationic Pd(II) complex in the presence of basic Amberlite IRA-400(OH).[29] The Pd(II) complex was purported to afford a Pd(I) active complex. The mechanism for our Pd-catalyzed reactions is probably somewhat analogous to this. Again we would imagine that there is transmetallation of Pd with the arylboronic acid to give an aryl–Pd species, followed by coordination of the Pd to the aldehyde oxygen, 1,2-addition (migratory insertion) to the aldehyde which we believe should undergo either: (1) a transmetallation step with an available arylboronic acid substrate molecule and regeneration of the active aryl–Pd species and formation of the product *via* hydrolysis of the cycloalkanolboronate during work-up or (2) hydrolysis *via* the boronic acid derivative (for example $XB(OH)_2$ or its salt) furnished in the initial transmetallation step with regeneration of the active Pd(I) species. However, (1) seems the most plausible. In the case of the Cu-catalyzed cyclizations, a similar mechanism is proposed. We purport that the active Cu(I) catalyst (in the case of the Cu(II) salt/bpy reactions, the Cu is reduced to Cu(I) with the phosphane ligand[30]) suffers transmetallation leading to an aryl–Cu species that suffers a 1,2-addition to give a Cu–arylcycloalkanolate followed by possible direct transmetallation with an available aryl boronic acid substrate molecule to give the active aryl–Cu species and the product after hydrolysis.

Conclusions

In conclusion, we report a high-yielding innovative method to afford isoquinolinone and azepinone derivatives. We are currently developing an asymmetric version of this reaction and investigating the mechanism of this reaction.

Experimental

General considerations

All the reagents were obtained from Aldrich, Fluka, Acros and Alfa Aeser. The solvents used were dried using current laboratory techniques.[31] All the reagents applied in this work were used as received. All reactions with transition metals were conducted under a nitrogen atmosphere. Column chromatography was carried out on silica gel (sds, 70–200 μm). Thin layer chromatography (TLC) analysis was carried out on aluminium backed Kiselgel 60 F254 plates (Merck). Plates were visualized either by UV light or with phosphomolybdic acid in ethanol. ^{1}H and ^{13}C NMR spectra was recorded on a Bruker Avance III at 400 and 100 MHz, respectively, and the chemical shifts were quoted in parts per million (ppm) referenced to the appropriate non-deuterated solvent peak relative to 0.0 ppm for tetramethylsilane. Mass spectra (MS) using the ESI-TOF technique were obtained from the University of Vigo, C.A.C.T.I., Spain. The detailed procedures for the synthesis of compounds (**1**), (**2**) and (**3**) described in ESI.†

General procedure for the synthesis of isoquinolinone and azepinone derivatives (4)

The reactions were performed under a nitrogen atmosphere using a Radleys® carousel reactor. The tubes were filled with the appropriate transition-metal catalyst (according to Table 2), amido(hetero)arylboronic acid aldehyde (un-purified) (**3a–p**), K_2CO_3 (3 equiv.) and dry toluene. The reaction performed at 100 °C for 24 h. After completion, the mixture was allowed to cool to room temperature. Then HCl (3 N) and CH_2Cl_2 were added and the organic phase was separated, dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave the crude product which was submitted to column chromatography using Et_2O as eluent.

4-Hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one (4a). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.59–3.62 (m, 2H, CH_2), 5.15 (t, J = 4.8 Hz, 1H, CH), 6.48 (br s, 1H, NH), 7.37–7.47 (m, 2H, ArH), 7.76–7.78 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.2 (CH_2), 98.3 (CH), 127.1 (CH), 128.6 (2× CH), 131.5 (CH), 134.5 (C), 140.1 (C), 167.6 (HNC=O). MS (ESI-TOF) m/z: 164.16 (M^+ + H).

5-Hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (4b). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.87–1.91 (m, 2H, CH_2), 3.55–3.59 (m, 2H, CH_2), 5.17 (t, J = 4.8 Hz, 1H, CH), 7.21 (br s, 1H, NH), 7.21–7.46 (m, 2H, ArH), 7.74–7.77 (m, 1H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.6 (CH_2), 35.8 (CH_2), 100.6 (CH), 126.8 (2× CH), 128.5 (CH), 131.3 (CH), 134.8 (C), 167.0 (HNC═O). MS (ESI-TOF) *m*/*z*: 178.20 (M^+ + H).

4-Hydroxy-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (4c). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.59–3.61 (m, 2H, CH_2), 3.78 (s, 3H, OMe), 5.16 (t, J = 4.8 Hz, 1H, CH), 6.27 (br s, 1H, NH), 6.79–6.82 (m, 1H, ArH), 7.07–7.08 (m, 1H, ArH), 7.42–7.44 (m, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.3 (CH_2), 55.7 (OMe), 98.1 (CH), 109.6 (C), 114.8 (CH), 117.9 (CH), 134.4 (C), 138.5 (C), 159.0 (7 C), 167.5 (HNC═O). MS (ESI-TOF) *m*/*z*: 194.20 (M^+ + H).

5-Hydroxy-8-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (4d). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.90–1.95 (m, 2H, CH_2), 3.58–3.63 (m, 2H, CH_2), 3.79 (s, 3H, OMe), 5.17 (t, J = 4.8 Hz, 1H, CH), 6.71 (br s, 1H, NH), 6.80 (dd, J = 3.2 and 8.8 Hz, 1H, ArH), 7.09 (d, J = 3.2 Hz, 1H, ArH), 7.44 (d, J = 8.8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.8 (CH_2), 36.0 (CH_2), 55.7 (OMe), 100.2 (CH), 109.5 (C), 114.8 (CH), 117.8 (CH), 134.3 (CH), 138.8 (C), 139.9 (C), 159.0 (C), 167.2 (HNC═O). MS (ESI-TOF) *m*/*z*: 208.23 (M^+ + H).

4-Hydroxy-7-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (4e). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.39 (s, 3H, CH_3), 3.60–3.63 (m, 2H, CH_2), 5.16 (t, J = 4.8 Hz, 1H, CH), 6.35 (br s, 1H, NH), 729–7.31 (m, 1H, ArH), 7.54–7.57 (m, 1H, ArH), 7.62 (br s, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5 (CH_3), 44.3 (CH_2), 98.4 (CH), 124.0 (CH), 127.9 (CH), 132.3 (CH), 134.5 (C), 138.5 (C), 167.8 (HNC═O). MS (ESI-TOF) *m*/*z*: 178.20 (M^+ + H).

5-Hydroxy-8-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (4f). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.64 (s, 1H, OH), 1.90–1.94 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 3.58–3.62 (m, 2H, CH_2), 5.21 (t, J = 4.8 Hz, 1H, CH), 7.16 (br s, 1H, NH), 729–7.31 (m, 1H, ArH), 7.55–7.57 (m, 1H, ArH), 7.61 (br s, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5 (CH_3), 34.7 (CH_2), 35.9 (CH_2), 100.9 (CH), 123.9 (CH), 127.7 (CH), 132.1 (CH), 134.9 (C), 138.4 (C), 167.1 (HNC═O). MS (ESI-TOF) *m*/*z*: 192.11 (M^+ + H).

4-Hydroxy-6-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (4g). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.38 (s, 3H, CH_3), 3.60–3.62 (m, 2H, CH_2), 5.15 (t, J = 4.8 Hz, 1H, CH), 6.35 (br s, 1H, NH), 721–7.23 (m, 1H, ArH), 7.67–7.70 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6 (CH_3), 44.2 (CH_2), 98.4 (CH), 127.1 (2× CH), 129.3 (CH), 131.2 (C), 142.8 (C), 167.5 (HNC═O). MS (ESI-TOF) *m*/*z*: 178.20 (M^+ + H).

5-Hydroxy-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (4h). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.79–1.93 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 3.57–3.61 (m, 2H, CH_2), 5.20 (t, J = 4.8 Hz, 1H, CH), 7.12 (br s, 1H, NH), 721–7.23 (m, 2H, ArH), 7.66 (br s, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5 (CH_3), 34.7 (CH_2), 35.8 (CH_2), 100.8 (CH), 126.9 (2× CH), 129.3 (CH), 132.1 (C), 141.7 (C), 166.9 (HNC═O). MS (ESI-TOF) *m*/*z*: 192.23 (M^+ + H).

6-Chloro-4-hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one (4i). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.58–3.60 (m, 2H, CH_2), 5.14 (t, J = 4.8 Hz, 1H, CH), 6.45 (br s, 1H, NH), 7.36–7.39 (m, 1H, ArH), 7.71–7.73 (m, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.3 (CH_2), 98.3 (CH), 128.6 (2× CH), 128.8 (CH), 132.8 (C), 137.8 (C), 166.5 (HNC═O). MS (ESI-TOF) *m*/*z* (%): ^{35}C: 198.04 (M^+ + H, 75); ^{37}C: 200.03 (M^+ + H, 25).

7-Chloro-5-hydroxy-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (4j). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.79 (br s, 1H, OH), 1.90–1.93 (m, 2H, CH_2), 3.56–3.61 (m, 2H, CH_2), 5.19 (t, J = 4.8 Hz, 1H, CH), 7.17 (br s, 1H, NH), 7.32–7.40 (m, 2H, ArH), 7.69–7.71 (m, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.5 (CH_2), 36.0 (CH_2), 100.8 (CH), 128.3 (CH), 128.9 (CH), 133.3 (C), 137.6 (C), 139.5 (CH), 140.9 (C), 165.9 (HNC═O). MS (ESI-TOF) *m*/*z* (%): ^{35}C: 212.06 (M^+ + H, 75); ^{37}C: 214.03 (M^+ + H, 25).

8-Hydroxy-7,8-dihydro-1,6-naphthyridin-5(6*H*)-one (4k). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.60–3.62 (m, 2H, CH_2), 5.14 (t, J = 4.8 Hz, 1H, CH), 6.75 (br s, 1H, NH), 7.31 (dd, J = 4.8 and 7.6 Hz, 1H, ArH), 8.06 (dd, J = 2.0 and 7.6 Hz, 1H, ArH), 8.43 (dd, J = 2.0 and 4.8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.4 (CH_2), 97.9 (CH), 122.8 (CH), 131.3 (C), 139.8 (CH), 147.3 (C), 151.0 (CH), 164.8 (HNC═O). MS (ESI-TOF) *m*/*z*: 195.16 (M^+ + H).

9-Hydroxy-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-5-one (4l). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88–1.92 (m, 2H, CH_2), 3.56–3.61 (m, 2H, CH_2), 5.14 (t, J = 4.8 Hz, 1H, CH), 7.29 (dd, J = 4.8 and 7.6 Hz, 1H, ArH), 7.37 (br s, 1H, NH), 8.06 (dd, J = 2.0 and 7.6 Hz, 1H, ArH), 8.39 (dd, J = 2.0 and 4.8 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.5 (CH_2), 36.2 (CH_2), 100.2 (CH), 122.8 (CH), 131.5 (C), 139.8 (CH), 147.3 (C), 150.8 (CH), 164.4 (HNC═O). MS (ESI-TOF) *m*/*z*: 179.20 (M^+ + H).

4-Hydroxy-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one (4m). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.63–6.65 (m, 2H, CH_2), 5.18 (t, J = 4.4 Hz, 1H, CH), 7.02 (d, J = 5.2 Hz, 1H, ArH), 7.27 (br s, 1H, NH), 7.43 (d, J = 5.2 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.9 (CH_2), 98.0 (CH), 128.9 (C), 130.3 (CH), 132.2 (CH), 135.1 (C), 160.6 (HNC═O). MS (ESI-TOF) *m*/*z*: 170.20 (M^+ + H).

4-Hydroxy-6,7-dihydro-4*H*-thieno[2,3-*c*]azepin-8(5*H*)-one (4n). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.90–1.94 (m, 2H, CH_2), 3.57–3.63 (m, 2H, CH_2), 5.17 (t, J = 4.4 Hz, 1H, CH), 7.00 (d, J = 5.2 Hz, 1H, ArH), 7.40 (d, J = 5.2 Hz, 1H, ArH), 7.99 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.8 (CH_2), 36.0 (CH_2), 100.3 (CH), 108.5 (C), 129.9 (CH), 132.2 (CH), 135.4 (C), 160.4 (HNC═O). MS (ESI-TOF) *m*/*z*: 184.23 (M^+ + H).

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