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$FeCl_3 \cdot 6H_2O$-promoted skeleton-rearrangement of 1-substituted-3-benzazepines: substrate extension and product utilization

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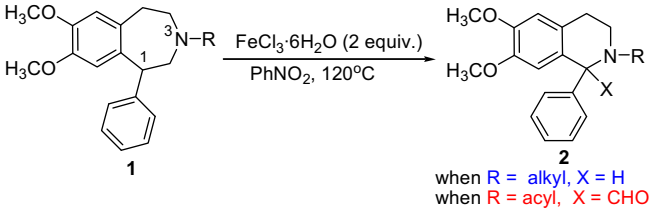
ABSTRACT

$FeCl_3 \cdot 6H_2O$-promoted skeleton-rearrangement of 1-substituted-3-benzazepines was further exploited. Both 1-aryl- and 1-alkyl- or 1-alkenyl-benzazepines underwent this reaction smoothly. The rearrangement products were used to prepare a series of novel derivatives containing both tetrahydroisoquinoline (THIQ) and tetrahydropyrimidin-4(1*H*)-one scaffolds through a Mannich-type process.

1. Introduction

Iron reagents ($FeCl_3$, $FeCl_2$, $FeSO_4$, $Fe(ClO_4)_3$, $Fe(acac)_3$) have attracted increasing interests in organic reactions and synthesis recently due to their low cost and readily availability.[1] We recently reported a novel skeleton-rearrangement of 1-aryl-3-benzazepines with the assistance of 2.0 equiv of $FeCl_3 \cdot 6H_2O$ in $PhNO_2$ (Scheme 1).[2] The *N*-substituents in the benzazepine substrates played a dramatic influence on the structural characters of the products. In the case of *N*-alkylbenzazepines, 1-aryl-tetrahydroisoquinolines (THIQs) were obtained, whereas *N*-acyl-benzazepines yielded a series of *C*1 quaternary 1-aryl-1-formyl-tetrahydroisoquinolines. However, in spite of the simplicity of the protocol and the unique feature of the products, this method suffered from several weakness, especially in view of the substrate limitation (mostly 1-aryl-benzazepines), high loading of $FeCl_3 \cdot 6H_2O$ (2 equiv) and the use of high boiling solvent nitrobenzene, which make the purification of the products troublesome. Accordingly, in the current report we further elaborated this $FeCl_3 \cdot 6H_2O$-initiated rearrangement, with focus on broadening the scope of the substrates to 1-alkyl- or 1-alkenyl-benzazepines, as well as exploring the utility of the rearranged products.



Scheme 1. Our previously reported $FeCl_3 \cdot 6H_2O$-promoted rearrangement.

2. Results and discussion

First, 1-alkyl-*N*-cyclopropanecarbonylbenzazepines **3a**–**c** were prepared according to the literature procedures[3] and subjected to the $FeCl_3 \cdot 6H_2O$-initiated rearrangement. As expected, the corresponding 1-alkyl-1-formyl-tetrahydroisoquinolines (THIQs) **4a**–**c** were obtained in 27–50% yields (Scheme 2). This result confirmed that not only 1-aryl, but also 1-alkylbenzazepines can undergo the $FeCl_3 \cdot 6H_2O$-initiated skeleton rearrangement.

Similarly, we found that 1-alkenylbenzazepines **3d**–**f** also went through the skeleton rearrangement with activation of $FeCl_3 \cdot 6H_2O$ in $PhNO_2$ leading to the corresponding aldehydes **4a**, **4b**, **4f** in 70% yields (Scheme 3). It is of note that the olefinic moiety in benzazepines **3d**–**f** was saturated in the rearranged process, and led to

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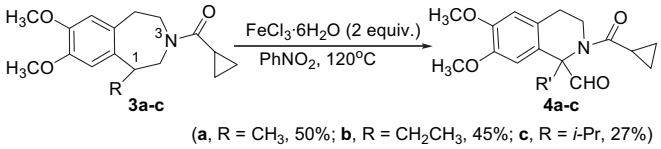
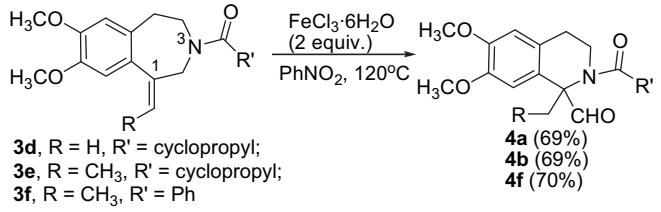


Scheme 2. Rearrangement of 1-alkylbenzazepines.

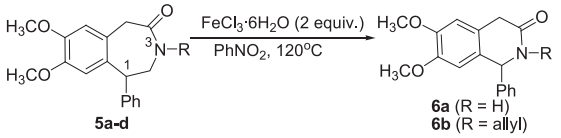
the same products as obtained in Scheme 2. Compared with the 1-alkyl substrates **3a**–**c**, unsaturated compounds **3d**–**f** reacted much quicker and provided the products with higher yields.



Scheme 3. Rearrangement of 1-alkenylbenzazepines.

In the mean time, we examined the rearrangement of benzazepines **5a**–**d**[4] bearing an amide function on the azepine ring instead of as a side chain (Table 1). Interestingly, these substrates did undergo ring-contraction, but the expected aldehydes were not obtained. In the case of **5a**, 1-phenyl-1,2-dihydroisoquinolin-3(4*H*)-one **6a** was produced in 50% yield indicating the endocyclic amide function was not involved in the rearrangement, likely due to the steric effect. This was further evidenced in the case of *N*-allyl substituted **5b**, which also participated in the skeleton rearrangement similarly yielding 1-phenyl-1,2-dihydroisoquinolin-3(4*H*)-one **6b** in 61% yield. In order to generate aldehyde products, imides **5c** and **5d** were prepared and subjected to the same rearrangement reaction. However, the imido moiety mostly failed to survive from the acidic reaction condition, and both reactions yielded *N*-deacylated dihydroisoquinolin-3(4*H*)-ones **6a** as well as recovered *N*-deacylated substrate **5a**.

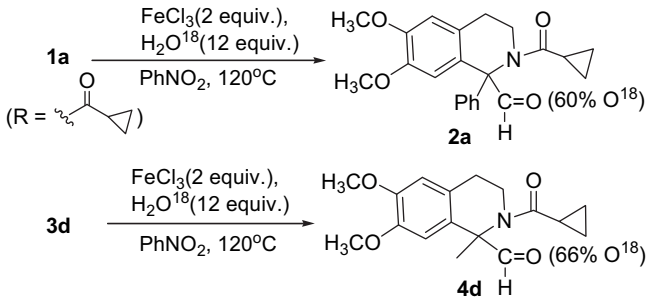
Table 1
Rearrangement of benzazepines **5a**–**d**



Substrate	R	Product (yield)	
5a	H	**6a** (50%)	
5b	Allyl	**6b** (61%)	
5c	Acetyl	**6a** (15%)	**5a** (40%)
5d	Benzoyl	**6a** (20%)	**5a** (40%)

Next, we decide to explore the possibility of reducing the loading of $FeCl_3 \cdot 6H_2O$. Since we have proposed in our previous work[2] that the formyl oxygen in aldehyde products **2** or **4a**–**c** was originated from $FeCl_3 \cdot 6H_2O$ complex, therefore additional water would be needed if we reduce the amount of $FeCl_3 \cdot 6H_2O$. In this regard, we firstly conducted the reaction of benzazepines **1a** and **3d** using in situ prepared iron reagent from anhydrous $FeCl_3$ and 6 equiv of O^{18}-enriched water (H_2O^{18}). As expected, the expected aldehydes **2a** and **4d** were obtained containing 60% and 66% of O^{18}, respectively (Scheme 4), confirming the role of water in $FeCl_3 \cdot 6H_2O$.

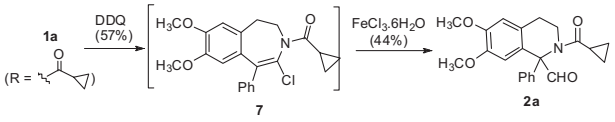
In our previous report,[2] 1 equiv of $FeCl_3 \cdot 6H_2O$ was found unable to ignite the reaction (entries 2 and 3, Table 2) with either high boiling solvent $PhNO_2$ or lower boiling solvent $MeNO_2$. It was found that adding 2 equiv of DDQ as oxidative additive could start this



Scheme 4. Rearrangement of **1a** and **3d** under $FeCl_3$ and H_2O^{18}.

reaction, and adding 100 equiv of water and conducting the reaction in oxygen atmosphere significantly enhanced this reaction providing product **2a** in 50% yield (entry 5). Encouraged by this result, reactions with reduced amount of $FeCl_3 \cdot 6H_2O$ were investigated. It was found that both 0.5 and 0.2 equiv of $FeCl_3 \cdot 6H_2O$ can start this reaction (entries 7 and 8) yielding product **2a** in 49% and 36% yield, respectively. Addition of water can enhance the yield (entry 7 vs 6). These results confirmed that the rearrangement reaction does not necessarily require excessive catalyst, 0.5 or 0.2 equiv were enough to ignite the transformation although the reaction yield was lower. The relative lower yield may be due to the production of chloride **7** that was detected during the catalytic reaction. Compound **7** was structurally confirmed by X-ray analysis (Fig. 1) and can be alternatively prepared by treating benzazepine **1a** with DDQ in 57% yield. Interestingly, conversion of compound **7** to final product **2a** was very sluggish in this reaction but was remarkedly promoted to completion in 2 h (44% yield) with addition of excessive $FeCl_3 \cdot 6H_2O$.

Table 2
Optimization of reaction conditions of benzazepine **1a**



Entry[a]	$FeCl_3 \cdot 6H_2O$ (equiv)	Solvent	H_2O (equiv)	Additive (equiv)	Yield (**2a**)
1	2.0	$PhNO_2$	None	None	66%
2	1.0	$PhNO_2$	None	None	<5%
3	1.0	$MeNO_2$	None	None	0
4	1.0	$MeNO_2$	0	DDQ (2)	38%
5	1.0	$MeNO_2$	100	DDQ (2)	50%
6	0.5	$MeNO_2$	0	DDQ (2)	22%
7	0.5	$MeNO_2$	100	DDQ (2)	49%
8	0.2	$MeNO_2$	100	DDQ (2)	36%
9	0.2	$MeNO_2$	80	DDQ (2)	38%
10	0.2	$MeNO_2$	50	DDQ (2)	29%
11	0.2	$MeNO_2$	10	DDQ (2)	0

[a] All the yields were isolated yields after chromatography.

With the alternative reaction condition described above, the synthetic application of the rearrangement products was explored. Initially, we proposed to prepare compound **10** by treating benzylamine with rearranged product aldehyde **8** through a reductive amination followed by intramolecular Michael addition (Scheme 5). To our surprise, we were not able to obtain compound **10**, instead 1,3-dibenzyl-2-(6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-tetrahydropyrimidin-4(1*H*)-one (**11**) was obtained as the major product. It was further found that compound **11** can be obtained simply by treating aldehyde **8** with benzylamine in the absence of $NaBH_3CN$ in 58% yield.

The structure of compound **11** was determined by all spectroscopic analysis, especially 2D NMR (HMBC, HMQC, $^1H-^1H$ COSY), and finally secured by X-ray analysis (Fig. 2). Several unique characters can be observed from the X-ray structure. Similar to typical 1-arylbenzazepines[5] where the 1-phenyl ring is located in the

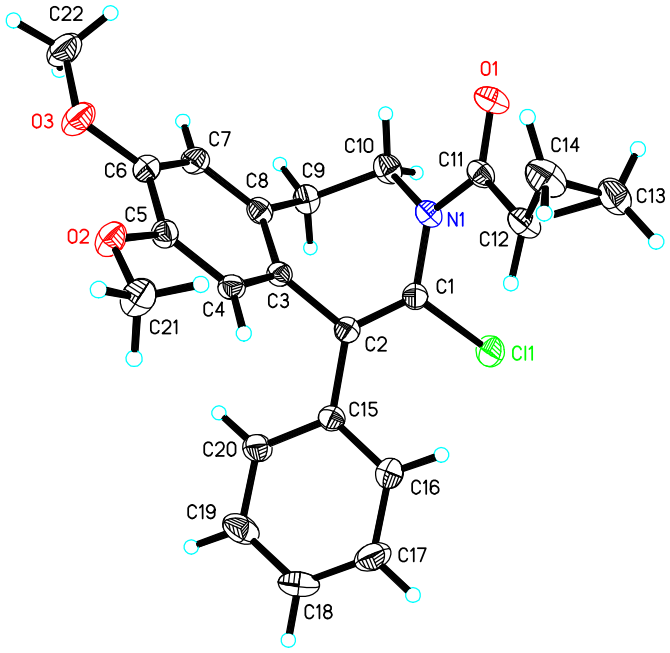
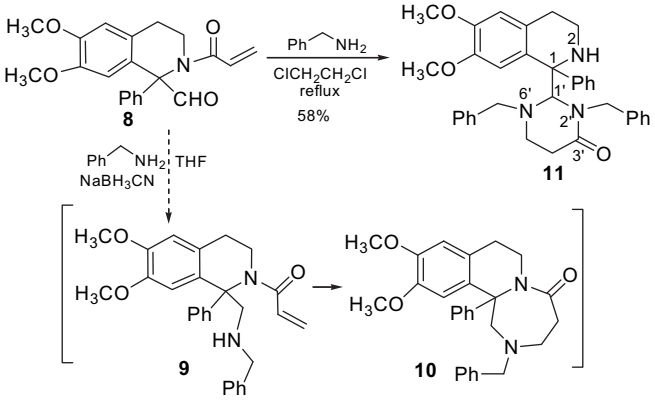


Fig. 1. Structure of compound **7**.



Scheme 5. Reaction of aldehyde **8** with benzylamine.

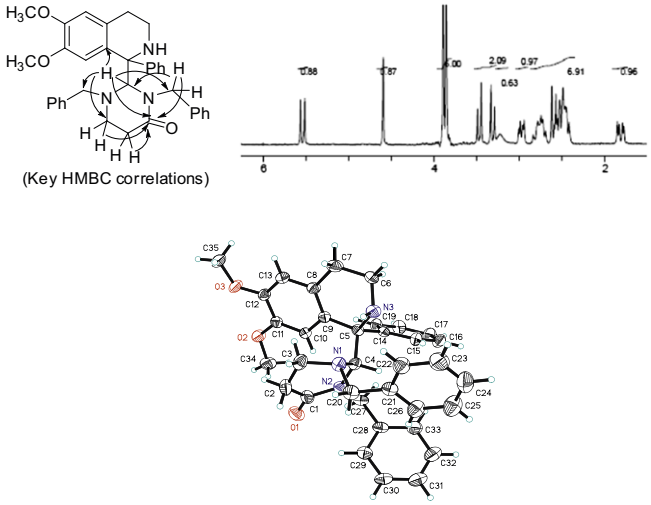


Fig. 2. Structure determination of compound **11**.

equational orientation, the newly formed tetrahydropyrimidin-4(1*H*)-one ring is also positioned in the equational orientation, which pushes both benzyl moieties to the east side of the molecule. Therefore, the three phenyl ring (1-phenyl, 2′- and 6′-*N*-benzyl) formed a sandwich-like conformation, thus the chemical shifts of benzyl methylene protons shifting to high field (2.5–3.5 ppm, Fig. 2), whereas the α-H in the 2′-*N*-benzylic methylene unit showed a unique chemical shift of 5.5 ppm due to the spatial neighboring interaction with the carbonyl group (Fig. 2).

To rationale the formation of compound **11**, a Mannich-type mechanism was proposed. As illustrated in Fig. 3, a Michael addition would occur upon treating aldehyde **8** with benzylamine forming intermediate **I**. Compound **I** may subsequently undergo a Mannich-type condensation with one additional molecule of benzylamine to form [1,4]diazepino[2,1-*a*]isoquinolin-5(12b*H*)-one network **II** in which intramolecular nucleophilic attack of the secondary amino function to the amide carbonyl moiety would then occur to release the high ring-tension, and yield pyrimidione **11**.

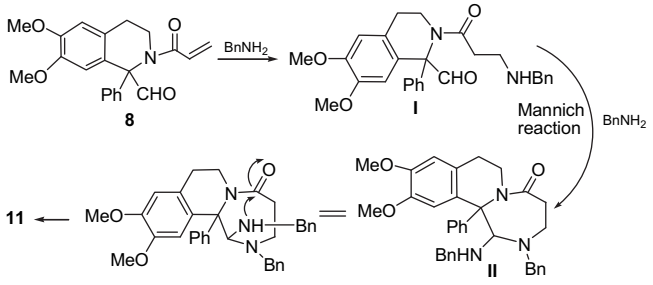
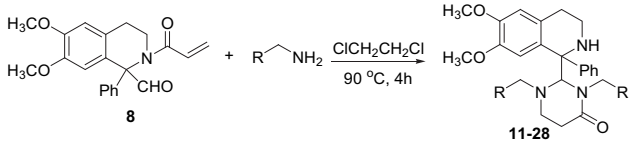


Fig. 3. Proposed mechanism for production of compound **11**.

Since both THIQ[6] and pyrimidin-4(1*H*)-one[7] are important pharmacophores in many biologically active compounds, this method may provide a practical technique to prepare compounds like **11** bearing both pharmacophores. Therefore, generality of this method was evaluated by employing a variety of primary amines to react with aldehyde **8**.

From the results summarized in Table 3, all the primary amines participated in this reaction smoothly and yielded products **11**–**28**

Table 3
Reaction of aldehyde **8** with primary amines



Entry	R	Product	Yield[a]
1	Ph	**11**	58%
2	2-Cl–Ph	**12**	58%
3	4-Cl–Ph	**13**	43%
4	3-Cl–Ph	**14**	47%
5	4-F–Ph	**15**	51%
6	3-F–Ph	**16**	41%
7	4-MeO–Ph	**17**	30%
8	2-MeO–Ph	**18**	30%
9	4-Tolyl	**19**	52%
10	3-Tolyl	**20**	55%
11	2-Tolyl	**21**	50%
12	3-CF_3–Ph	**22**	56%
13	1-Naphthyl	**23**	55%
14	2-Furyl	**24**	48%
15	$PhCH_2$	**25**	52%
16	3-MeO–$PhCH_2$	**26**	41%
17	$PhCH_2CH_2$	**27**	49%
18	CH_3CH_2	**28**	50%

[a] Isolated yield after chromatography.

in 30–58% isolated yields. The relatively lower yields were partially due to the difficulty in isolating the products from excessive polar substrates amines. The electronic nature, size, and location of the substituent in arylmethyl amine substrates did not play significant effects on the yields. Much bulky amines, 1-naphthylmethyl amine (entry 13) and heteroarylmethyl amine, 2-furylmethylamine (entry 14) also participated in this transformation very well and delivered corresponding products **23** and **24** in 55% and 48% yield, respectively. Extension of the alkyl chain to arylethylamines (entries 15 and 16) and arylpropylamine (entry 17) all went through the reaction smoothly and provided corresponding products **25**–**27** in 41–52% yield. Simple alkylamine, e.g., propylamine (entry 18) also underwent the reaction and yielded product **28** in 50% yield. All the results above confirmed the generality of this protocol in preparation of THIQ substituted tetrahydropyrimidin-4(1*H*)-ones.

3. Conclusions

In summary, $FeCl_3\cdot 6H_2O$-promoted skeleton-rearrangement of 1-substituted-3-benzazepines was further exploited. Both 1-aryl- and 1-alkyl- or 1-alkenylbenzazepines can undergo this reaction providing corresponding aldehydes in reasonable yields. Further, the rearrangement products were used to prepare tetrahydroisoquinoline (THIQ)-substituted tetrahydropyrimidin-4(1*H*)-ones through a Mannich-type process and a total 18 analogues were prepared in moderate yields.

4. Experimental section

4.1. General procedure for the rearrangement of compounds 3a–f, 5a–d

A mixture of benzazepine substrate (1.0 equiv) and $FeCl_3\cdot 6H_2O$ (2.0 equiv) in nitrobenzene (10 mL) was stirred at 120 °C under O_2 atmosphere for about 2–10 h until the starting material was consumed. Then the dark mixture was cooled to rt, diluted with CH_2Cl_2 and washed with 10% HCl aqueous solution. The aqueous solution was further extracted with CH_2Cl_2 twice. The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. The crude product was concentrated and chromatographed on silica gel column (CH_2Cl_2, then CH_2Cl_2/EtOAc) to give the corresponding rearrangement product.

*4.1.1. 2-(Cyclopropanecarbonyl)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-1-carbaldehyde (**4a**).* Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91 (s, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 4.43 (dd, *J*=2.4, 10.8 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.38 (dt, *J*=3.3, 12.6 Hz, 1H), 3.09 (m, 1H), 2.80 (m, 1H), 1.85 (m, 1H), 1.68 (s, 3H), 1.11 (m, 1H), 0.92 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 172.5, 148.4, 148.0, 127.5, 123.9, 111.1, 110.3, 67.2, 55.9, 55.8, 40.4, 29.9, 19.6, 11.6, 7.9, 7.6; EI-MS *m*/*z*: 303 (M^+); HR-MS calcd for $C_{17}H_{21}NO_4$ (M^+) 303.1471, found: 303.1475.

*4.1.2. 2-(Cyclopropanecarbonyl)-1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbaldehyde (**4b**).* Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (s, 1H), 6.62 (s, 1H), 6.61 (s, 1H), 4.48 (m, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.43 (dt, *J*=3.3, 12.6 Hz, 1H), 2.98 (m, 1H), 2.78 (dt, *J*=2.7, 15.6 Hz, 1H), 2.37 (m, 2H), 1.87 (m, 1H), 1.00 (m, 2H), 0.80 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 172.5, 148.3, 148.2, 128.7, 121.9, 111.0, 110.0, 70.7, 55.8, 55.7, 42.1, 30.0, 26.1, 11.8, 8.7, 7.6, 7.5; EI-MS *m*/*z*: 317 (M^+); HR-MS calcd for $C_{18}H_{23}NO_4$ (M^+) 317.1627, found: 317.1633.

*4.1.3. 2-(Cyclopropanecarbonyl)-1-isopropyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbaldehyde (**4c**).* Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (s, 1H), 6.62 (s, 1H), 6.61 (s, 1H), 4.51 (m, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.51 (m, 1H), 3.04 (m, 2H), 2.78 (m, 1H), 1.87 (m, 1H), 1.03 (m, 5H), 0.84 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 172.7, 148.4, 148.2, 128.6, 122.9, 111.2, 110.5, 73.0, 55.9, 55.8, 42.4, 34.9, 30.2, 19.7, 19.0, 12.0, 7.6, 7.4; EI-MS *m*/*z*: 331 (M^+); HR-MS calcd for $C_{19}H_{25}NO_4$ (M^+) 331.1784, found: 331.1792.

*4.1.4. 2-Benzoyl-1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbaldehyde (**4f**).* Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.20 (s, 1H), 7.46 (m, 5H), 6.72 (s, 1H), 6.62 (s, 1H), 4.07 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.39 (m, 1H), 2.94 (m, 1H), 2.67 (m, 2H), 2.48 (m, 1H), 0.95 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 171.0, 148.6, 148.5, 135.4, 130.2, 128.7, 126.9, 121.6, 111.2, 110.0, 71.0, 56.0, 55.8, 44.9, 30.1, 26.0, 8.8; EI-MS *m*/*z*: 353 (M^+); HR-MS calcd for $C_{21}H_{23}NO_4$ (M^+) 353.1627, found: 353.1623.

*4.1.5. 6,7-Dimethoxy-1-phenyl-1,2-dihydroisoquinolin-3(4H)-one (**6a**).* Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 4H), 7.07 (m, 2H), 6.52 (br s, 1H), 6.48 (s, 1H), 4.44 (dd, *J*=6.3, 2.1 Hz, 1H), 3.91 (m, 4H), 3.74 (s, 3H), 3.60 (m, 1H).

*4.1.6. 2-Allyl-6,7-dimethoxy-1-phenyl-1,2-dihydroisoquinolin-3(4H)-one (**6b**).* Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 5H), 7.06 (m, 2H), 6.45 (s, 1H), 5.60 (m, 1H), 5.15 (d, *J*=10.2 Hz, 1H), 5.04 (d, *J*=17.1 Hz, 1H), 4.44 (d, *J*=7.2 Hz, 1H), 4.31 (dd, *J*=4.8, 15.0 Hz, 1H), 3.91 (m, 4H), 3.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 166.7, 153.4, 148.4, 141.2, 137.7, 131.8, 129.0, 128.7, 127.7, 127.6, 118.9, 113.2, 111.4, 56.0, 51.0, 49.9, 48.8; EI-MS *m*/*z*: 323 (M^+); HR-MS calcd for $C_{20}H_{21}NO_3$ (M^+) 323.1521, found: 323.1517.

4.2. General procedure for the rearrangement of compounds 1a and 3d under $FeCl_3$ and H_2O[18]

To a mixture of compound **1a** or **3d** (1.0 equiv), H_2O^{18} (97% O^{18}-enriched, 12.0 equiv) and $FeCl_3$ (2.0 equiv) under O_2 atomosphere was added nitrobenzene (distilled over anhydrous $CaCl_2$) via syringe, then the mixture was allowed to stir under 100 °C for 1 or 4 h. After standard work-up, a mixture of labled and unlabled product was obtained. The relative amounts of oxygen-18 labled and unlabled products were determined by mass spectrometry (see copies of the MS spectra in Supplementary data).

4.3. General procedure for the catalytic version of the rearrangement

A mixture of compound **1a**, $FeCl_3\cdot 6H_2O$, H_2O (as indicated in Table 2) and DDQ in nitromethane was refluxed under O_2 atmosphere for 4 h. Then it was cooled down and filtered. The filtrate was concentrated, and dissolved in CH_2Cl_2, which was further washed with saturated Na_2CO_3 aqueous solution, brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was chromatographied (pet. ether/EtOAc=1:1) to give the desired compound **2a**, with compound **7** as side product.

*4.3.1. (4-Chloro-7,8-dimethoxy-5-phenyl-1H-benzo[d]azepin-3(2H)-yl)(cyclopropyl)methanone (**7**).* White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (m, 5H), 6.76 (s, 1H), 6.29 (s, 1H), 4.76 (dt, *J*=5.4, 13.8 Hz, 1H), 3.90 (s, 3H), 3.74 (dd, *J*=8.1, 13.8 Hz, 1H), 3.63 (s, 3H), 3.16 (dt, *J*=6.9, 14.1 Hz, 1H), 2.69 (dd, *J*=5.4, 13.8 Hz, 1H), 2.06 (m, 1H), 0.87 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 149.0, 147.7, 140.6, 138.1, 131.8, 131.5, 130.0, 128.5, 128.1, 125.4, 112.5, 111.6, 56.1, 55.9, 53.5, 31.3, 13.4, 9.1, 8.2; EI-MS *m*/*z*: 383 (M^+); HR-MS calcd for $C_{22}H_{22}ClNO_3$ (M^+) 383.1288, found: 383.1285.

*4.3.2. 2-(Cyclopropanecarbonyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbaldehyde (**2a**).* Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.38 (m, 2H), 7.29 (m, 3H), 6.73 (s,

1H), 6.41 (s, 1H), 4.29 (m, 1H), 3.91 (s, 3H), 3.66 (s, 3H), 3.41 (dt, *J*=3.0, 12.9 Hz, 1H), 3.17 (dt, *J*=5.1, 15.9 Hz, 1H), 2.88 (dt, *J*=15.6, 2.7 Hz, 1H), 1.77 (m, 1H), 1.14 (m, 1H), 0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1, 172.1, 148.8, 147.6, 139.6, 130.2, 129.0, 127.8, 127.7, 121.9, 112.3, 111.0, 72.4, 55.9, 55.8, 40.1, 29.5, 11.8, 7.8, 7.6; EI-MS *m*/*z*: 365 (M^+); HR-MS calcd for $C_{22}H_{23}NO_4$ (M^+) 365.1627, found: 365.1626.

4.4. 2-Acryloyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbaldehyde (8)

This compound was synthesized from 1-(7,8-dimethoxy-1-phenyl-4,5-dihydro-1*H*-benzo[*d*]azepin-3(2*H*)-yl)prop-2-en-1-one by following our previously reported literature procedure[2] in 65% yield or the catalytic reaction condition (DDQ and $FeCl_3\cdot 6H_2O$ in nitromethane) as described above in 56% yield. Yellow liquid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.44 (m, 2H), 7.31 (m, 3H), 6.72 (s, 1H), 6.58 (dd, *J*=10.8, 16.8 Hz, 1H), 6.41 (s, 1H), 6.37 (dd, *J*=2.1, 16.8 Hz, 1H), 5.78 (dd, *J*=1.8, 10.8 Hz, 1H), 4.06 (m, 1H), 3.91 (s, 3H), 3.66 (s, 3H), 3.38 (dt, *J*=3.3, 12.6 Hz, 1H), 3.13 (m, 1H), 2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 165.4, 148.9, 147.8, 139.5, 130.3, 129.6, 128.8, 128.0, 127.9, 127.2, 121.8, 112.4, 111.0, 55.9, 55.8, 40.5, 29.5; EI-MS *m*/*z*: 351 (M^+); HR-MS calcd for $C_{21}H_{21}NO_4$ (M^+) 351.1471, found: 351.1474.

4.5. General procedure for reaction of compound 8 with primary amines

A mixture of **8** (1.0 equiv) and an appropriately substituted primary amine (3.0 equiv) in $ClCH_2CH_2Cl$ was refluxed at 90 °C for 4 h, then it was cooled down and concentrated. The obtained residue was chromatographed on silica gel column to give the corresponding products **11**–**28**.

*4.5.1. 1,3-Dibenzyl-2-(6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)tetrahydropyrimidin-4(1H)-one (**11**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 10H), 7.00 (m, 2H), 6.85 (m, 3H), 6.63 (s, 1H), 5.54 (d, *J*=14.1 Hz, 1H), 4.59 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.46 (d, *J*=12.9 Hz, 1H), 3.31 (d, *J*=12.9 Hz, 1H), 2.96 (m, 1H), 2.74 (m, 2H), 2.61 (m, 7H), 1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 147.6, 146.6, 145.8, 137.3, 129.8, 129.1, 129.0, 128.3, 128.2, 128.0, 127.5, 127.4, 127.2, 112.6, 112.2, 82.1, 64.4, 57.5, 55.8, 55.6, 46.0, 40.8, 37.9, 30.5, 26.4; EI-MS *m*/*z*: 547 (M^+); HR-MS calcd for $C_{35}H_{37}N_3O_3$ (M^+) 547.2835, found: 547.2838.

*4.5.2. 1,3-Bis(2-chlorobenzyl)-2-(6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)tetrahydropyrimidin-4(1H)-one (**12**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 12H), 6.95 (d, *J*=6.9 Hz, 1H), 6.84 (s, 1H), 6.62 (s, 1H). 5.11 (d, *J*=15.9 Hz, 1H), 4.83 (s, 1H), 4.01 (d, *J*=13.8 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.79 (d, *J*=13.8 Hz, 1H), 3.33 (d, *J*=15.9 Hz, 1H), 2.94 (m, 1H), 2.64 (m, 7H), 1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 147.7, 146.1, 145.9, 135.2, 134.7, 134.0, 133.4, 130.8, 130.0, 129.9, 129.8, 129.6, 128.9, 128.7, 128.4, 128.2, 128.1, 127.2, 126.6, 126.4, 112.7, 112.3, 84.4, 65.1, 55.9, 55.6, 45.9, 40.6, 38.0, 30.6, 26.8; EI-MS *m*/*z* 615 (M^+); HR-MS calcd for $C_{35}H_{35}Cl_2N_3O_3$ (M^+) 615.2055, found: 615.2060.

*4.5.3. 1,3-Bis(4-chlorobenzyl)-2-(6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)tetrahydropyrimidin-4(1H)-one (**13**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 9H), 6.89 (d, *J*=8.4 Hz, 2H), 6.77 (d, *J*=5.7 Hz, 3H), 6.64 (s, 1H), 5.45 (d, *J*=14.1 Hz, 1H), 4.48 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.44 (d, *J*=13.8 Hz, 1H), 3.27 (d, *J*=13.8 Hz, 1H), 2.96 (m, 1H), 2.78 (m, 2H), 2.45 (m, 6H), 1.82 (d, *J*=17.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 147.7, 146.5, 145.8, 135.8, 135.5, 133.5, 133.2, 130.4, 130.2, 129.9, 128.9, 128.8, 128.5, 128.1, 128.0, 127.4, 112.7, 112.2, 81.6, 64.4, 56.7, 55.8, 55.6, 45.3, 41.5, 37.9, 30.5, 26.4; EI-MS *m*/*z* 615 (M^+); HR-MS calcd for $C_{35}H_{35}Cl_2N_3O_3$ (M^+) 615.2055, found: 615.2029.

*4.5.4. 1,3-Bis(3-chlorobenzyl)-2-(6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)tetrahydropyrimidin-4(1H)-one (**14**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 9H), 6.85 (m, 5H), 6.63 (s, 1H), 5.48 (d, *J*=14.1 Hz, 1H), 4.50 (s, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.46 (d, *J*=14.4 Hz, 1H), 3.30 (d, *J*=14.4 Hz, 1H), 3.00 (m, 1H), 2.81 (m, 2H), 2.52 (m, 5H), 1.87 (d, *J*=18.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 147.7, 146.1, 145.1, 139.2, 139.0, 134.1, 134.1, 129.0, 128.9, 128.2, 127.9, 127.6, 127.3, 127.0, 126.9, 112.7, 111.9, 81.7, 64.4, 57.0, 55.7, 55.6, 45.4, 41.5, 37.9, 30.4, 26.4; EI-MS *m*/*z* 615 (M^+); HR-MS calcd for $C_{35}H_{35}Cl_2N_3O_3$ (M^+) 615.2055, found: 615.2053.

*4.5.5. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(4-fluorobenzyl) tetrahydropyrimidin-4(1H)-one (**15**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 5H), 6.93 (m, 6H), 6.79 (m, 3H), 6.64 (s, 1H), 5.45 (d, *J*=14.1 Hz, 1H), 4.51 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.43 (d, *J*=12.9 Hz, 1H), 3.27 (d, *J*=12.6 Hz, 1H), 2.96 (m, 1H), 2.77 (m, 2H), 2.51 (m, 5H), 1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 163.5, 163.2, 161.2, 160.8, 147.6, 146.5, 145.7, 133.2, 132.7, 130.8, 130.7, 130.6, 130.5, 129.8, 128.9, 128.1, 127.8, 127.3, 115.3, 115.2, 115.1, 115.0, 112.5, 112.0, 81.4, 64.2, 56.5, 55.8, 55.6, 45.1, 41.2, 37.8, 30.5, 26.4; ESI-MS *m*/*z* 584 (M+H); HR-MS calcd for $C_{35}H_{35}F_2NaN_3O_3$ (M+Na) 606.2544, found: 606.2538.

*4.5.6. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(3-fluorobenzyl) tetrahydropyrimidin-4(1H)-one (**16**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 7H), 6.92 (m, 2H), 6.71 (m, 6H), 5.48 (d, *J*=15.0 Hz, 1H), 4.52 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.43 (d, *J*=12.9 Hz, 1H), 3.26 (d, *J*=12.6 Hz, 2.98, 1H), 2.97 (m, 1H), 2.78 (m, 2H), 2.51 (m, 5H), 1.84 (d, *J*=18.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 163.8, 161.4, 147.8, 146.3, 145.7, 139.7, 129.9, 129.8, 129.7, 129.6, 128.9, 128.2, 128.0, 127.4, 124.6, 124.4, 116.0, 115.8, 115.6, 114.7, 114.5, 114.3, 112.7, 112.0, 81.9, 64.4, 57.0, 55.7, 55.6, 45.5, 41.3, 37.8, 30.4, 26.4; EI-MS *m*/*z* 583 (M^+); HR-MS calcd for $C_{35}H_{35}F_2N_3O_3$ (M^+) 583.2646, found: 583.2652.

*4.5.7. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(4-methoxybenzyl) tetrahydropyrimidin-4(1H)-one (**17**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 5H), 6.92 (d, *J*=9.0 Hz, 2H), 6.77 (m, 7H), 6.62 (s, 1H), 6.45 (d, *J*=15.0 Hz, 1H), 4.60 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.37 (d, *J*=14.1, 1H), 3.24 (d, *J*=12.9 Hz, 1H), 2.95 (m, 1H), 2.65 (m, 2H), 2.50 (m, 5H), 1.75 (d, *J*=18.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 158.9, 158.7, 147.5, 146.5, 145.6, 130.2, 129.7, 129.4, 129.3, 128.9, 128.0, 127.2, 113.6, 113.4, 112.5, 112.2, 81.5, 64.2, 56.7, 55.7, 55.5, 55.1, 45.3, 40.6, 37.8, 30.4, 26.3; EI-MS *m*/*z* 607 (M^+); HR-MS calcd for $C_{37}H_{41}N_3O_5$ (M^+) 607.3046, found: 607.3047.

*4.5.8. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(2-methoxybenzyl) tetrahydropyrimidin-4(1H)-one (**18**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (s, 2H), 7.22 (m, 7H), 6.88 (m, 4H), 6.75 (d, *J*=7.8 Hz, 1H), 6.61 (s, 1H), 5.15 (s, 1H), 4.88 (d, *J*=15.0 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.68 (m, 2H), 3.64 (s, 3H), 3.21 (d, *J*=14.7 Hz, 1H), 2.91 (m, 3H), 2.48 (m, 4H), 1.62 (d, *J*=16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 157.9, 157.4, 147.6, 145.8, 131.0, 130.5, 129.1, 128.5, 128.2, 127.8, 126.9, 126.2, 124.9, 120.3, 119.9, 112.5, 112.4, 110.6, 110.2, 109.7, 84.6, 65.2, 56.0, 55.6, 55.1, 54.6, 52.5, 43.9, 39.4, 38.0, 30.5, 26.5; EI-MS *m*/*z* 607 (M^+); HR-MS calcd for $C_{37}H_{41}N_3O_5$ (M^+) 607.3046, found: 607.3027.

*4.5.9. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(4-methylbenzyl) tetrahydropyrimidin-4(1H)-one (**19**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5H), 7.04 (m, 4H), 6.83 (m, 5H),

6.62 (s, 1H), 5.49 (d, *J*=15.0 Hz, 1H), 4.61 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.41 (d, *J*=13.2 Hz, 1H), 2.27 (d, *J*=13.2 Hz, 1H), 2.95 (m, 1H), 2.85 (m, 2H), 2.52 (m, 5H), 2.33 (s, 3H), 2.31(s, 3H), 1.77 (dd, *J*=6.9,18.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 147.6, 146.6, 145.7, 137.1, 137.0, 134.3, 134.2, 129. 8, 129.1, 129.0, 129.0, 128.9, 128.0, 127.2, 112.5, 112.3, 82.0, 64.3, 57.2, 55.8, 55.6, 45.7, 40.6, 37.9, 30.5, 26.3, 21.1; EI-MS *m*/*z* 575 (M^+); HR-MS calcd for $C_{37}H_{41}N_3O_3$ (M^+) 575.3148, found: 575.3113.

*4.5.10. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(3-methylbenzyl) tetrahydropyrimidin-4(1H)-one (**20**).* ^{1}H NMR (300 MHz, CD_3OD): δ 6.99 (m, 9H), 6.59 (s, 2H), 6.47 (s, 3H), 6.34 (s, 1H), 5.23 (d, *J*=14.1 Hz, 1H), 4.45 (s, 1H), 3.63 (s, 3H), 3.53 (s, 3H), 3.21 (m, 3H), 2.62 (m, 3H), 2.39 (m, 3H), 2.18 (m, 2H), 2.09 (s, 3H), 2.01 (s, 3H), 1.51 (d, *J*=25.5 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 172.7, 150.0, 147.8, 139.8, 139.4, 139.0, 138.4, 132.1, 131.5, 131.2, 130.7, 130.2, 129.7, 129.2, 128.0, 127.5, 114.7, 114.5, 82.5, 66.4, 58.9, 56.8, 56.8, 47.6, 43.3, 39.5, 31.3, 27.8, 22.05, 22.02; EI-MS *m*/*z* 575 (M^+); HR-MS calcd for $C_{37}H_{41}N_3O_3$ (M^+) 575.3148, found: 575.3154.

*4.5.11. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(2-methylbenzyl) tetrahydropyrimidin-4(1H)-one (**21**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (s, 2H), 7.24 (m, 7H), 7.14 (m, 3H), 6.79 (d, *J*=10.5 Hz, 2H), 6.61 (s, 1H), 5.23 (d, *J*=15.9 Hz, 1H), 4.79 (s, 1H), 3.87 (s, 3H), 3.84 (d, *J*=13.5 Hz, 1H), 3.81 (s, 3H), 3.67 (d, *J*=13.5 Hz, 1H), 3.20 (d, *J*=16.2 Hz, 1H), 2.8 (m, 5H), 2.50 (m, 3H), 2.24 (s, 3H), 1.93 (dd, *J*=5.4, 8.1 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 147.6, 146.4, 145.9, 137.6, 136.2, 135.4, 134.0, 130.6, 130.4, 129.5, 128.6, 128.1, 127.6, 126.9, 126.7, 125.6, 112.6, 112.0, 83.5, 64.9, 56.3, 55.8, 55.6, 44.6, 40.5, 38.0, 30.4, 26.5, 19.2, 18.7; EI-MS *m*/*z* 575 (M^+, 2%), 576 (M+1, 12%); HR-MS calcd for $C_{37}H_{41}N_3O_3$ (M^+) 575.3148, found: 575.3170.

*4.5.12. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(3-(trifluoromethyl) benzyl)tetrahydropyrimidin-4(1H)-one (**22**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (m, 2H), 7.34 (m, 8H), 7.22 (d, *J*=15.6 Hz, 1H), 7.09 (s, 1H), 6.95 (d, *J*=8.4 Hz, 1H), 6.81 (s, 1H), 6.66 (s, 1H), 5.60 (d, *J*=15.0 Hz, 1H), 4.45 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.57 (d, *J*=13.5 Hz, 1H), 3.36 (d, *J*=13.5 Hz, 1H), 2.95 (m, 1H), 2.79 (m, 2H), 2.57 (m, 5H), 1.86 (dd, *J*=7.5, 18.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 147.8, 146.4, 145.9, 138.1, 138.0, 132.2, 131.9, 130.8, 130.7, 130.5, 130.4, 130.0, 128.9, 128.7, 128.3, 127.9, 127.5, 125.8, 125.3, 124.6, 124.4, 122.6, 112.8, 111.9, 81.9, 64.3, 57.0, 55.8, 55.6, 45.4, 41.6, 37.8, 30.5, 26.4; EI-MS *m*/*z* 683 (M^+); HR-MS calcd for $C_{37}H_{35}F_6N_3O_3$ (M^+) 683.2583, found: 683.2566.

*4.5.13. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(naphthalen-1-ylmethyl)tetrahydropyrimidin-4(1H)-one (**23**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (m, 4H), 7.65 (m, 2H), 7.44 (m, 7H), 7.26 (m, 3H), 7.16 (t, *J*=7.2 Hz, 1H), 6.99 (s, 1H), 6.89 (d, *J*=6.6 Hz, 1H), 6.61 (s, 1H), 6.47 (d, *J*=6.6 Hz, 1H), 6.13 (d, *J*=15.0 Hz, 1H), 4.75 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.76 (d, *J*=10.8 Hz, 1H), 3.41 (t, *J*=12.6 Hz, 2H), 2.71 (m, 4H), 2.46 (m, 3H), 1.92 (d, *J*=12.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 147.6, 146.4, 145.9, 133.8, 133.6, 132.8, 132.2, 131.9, 131.6, 129.7, 129.1, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.0, 126.8, 126.2, 125.8, 125.7, 125.5, 124.8, 124.7, 124.2, 123.8, 112.6, 112.5, 82.5, 64.7, 55.8, 55.5, 44.6, 40.6, 38.0, 30.5, 26.7; EI-MS *m*/*z* 647 (M^+); HR-MS calcd for $C_{43}H_{41}N_3O_3$ (M^+) 647.3148, found: 647.3140.

*4.5.14. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(furan-2-ylmethyl) tetrahydropyrimidin-4(1H)-one (**24**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (s, 2H), 7.28 (m, 5H), 6.85 (s, 1H), 6.63 (s, 1H), 6.27 (s, 2H), 5.99 (m, 2H), 5.34 (d, *J*=15.0 Hz, 1H), 4.83 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.53 (s, 2H), 2.99 (d, *J*=13.2 Hz, 1H), 2.82 (m, 1H), 2.68 (d, *J*=15.6 Hz, 1H), 2.47 (m, 5H), 1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 151.0, 150.2, 147.8, 145.8, 142.6, 142.3, 129.8, 129.1, 128.1, 127.5, 112.5, 112.0, 110.2, 110.1, 109.4, 109.1, 81.7, 64.3, 55.8, 55.6, 50.3, 41.1, 39.8, 37.7, 30.1, 26.4; EI-MS *m*/*z* 527 (M^+); HR-MS calcd for $C_{31}H_{33}N_3O_5$ (M^+) 527.2420, found: 527.2402.

*4.5.15. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-diphenethyl tetrahydropyrimidin-4(1H)-one (**25**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (s, 2H), 7.22 (m, 11H), 6.92 (d, *J*=7.2 Hz, 2H), 6.74 (s, 1H), 6.62 (s, 1H), 4.64 (s, 1H), 3.88 (s, 3H), 3.80 (s, 4H), 2.78 (m, 7H), 2.43 (m, 6H), 2.22 (m, 1H), 1.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 147.7, 145.8, 139.3, 138.3, 129.6, 128.8, 128.7, 128.3, 128.1, 127.4, 126.2, 112.5, 111.9, 85.5, 64.5, 55.8, 55.6, 55.5, 46.5, 40.3, 37.5, 34.8, 33.3, 30.2, 26.3; EI-MS *m*/*z* 575 (M^+); HR-MS calcd for $C_{37}H_{41}N_3O_3$ (M^+) 575.3148, found: 575.3175.

*4.5.16. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(3-methoxyphenethyl) tetrahydropyrimidin-4(1H)-one (**26**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.25 (m, 5H), 7.05 (t, *J*=8.4 Hz, 1H), 6.74 (m, 4H), 6.62 (s, 2H), 6.50 (d, *J*=7.8 Hz, 1H), 6.45 (s, 1H), 4.61 (s, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 2.78 (m, 8H), 2.44 (m, 7H), 2.23 (m, 1H), 1.68 (d, *J*=12.9, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 159.6, 159.5, 147.7, 145.8, 141.0, 139.9, 129.8, 129.4, 129.2, 129.0, 128.1, 127.4, 121.3, 121.1, 114.7, 114.2, 112.6, 111.9, 111.4, 85.7, 64.4, 55.9, 55.6, 55.2, 55.1, 46.6, 40.5, 37.6, 35.4, 33.1, 30.3, 29.7, 26.4; EI-MS *m*/*z* 635 (M^+); HR-MS calcd for $C_{39}H_{45}N_3O_5$ (M^+) 635.3359, found: 635.3364.

*4.5.17. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-bis(3-phenylpropyl) tetrahydropyrimidin-4(1H)-one (**27**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 2H), 7.21 (m, 10H), 7.02 (d, *J*=7.5 Hz, 2H), 6.78 (s, 1H), 6.65 (s, 1H), 4.66 (s, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 2.98 (dd, *J*=5.1, 12.9 Hz, 1H), 2.70 (m, 5H), 2.47 (m, 9H), 2.11 (m, 1H), 1.95 (m, 2H), 1.82 (m, 1H), 1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 147.7, 146.5, 145.8, 141.6, 141.4, 129.9, 128.6, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.2, 126.0, 125.8, 112.6, 112.1, 84.1, 64.2, 55.9, 55.6, 53.5, 44.5, 41.3, 37.7, 33.4, 33.1, 30.5, 30.2, 28.3, 26.5; EI-MS *m*/*z* 603 (M^+); HR-MS calcd for $C_{39}H_{45}N_3O_3$ (M^+) 603.3461, found: 603.3463.

*4.5.18. 2-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-dipropyl tetrahydropyrimidin-4(1H)-one (**28**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (s, 2H), 7.25 (d, *J*=4.8 Hz, 3H), 6.75 (s, 1H), 6.64 (s, 1H), 4.71 (s, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.70 (m, 1H), 2.99 (dd, *J*=5.1, 12.6 Hz, 1H), 2.81 (t, *J*=15.3 Hz, 1H), 2.55 (m, 6H), 1.65 (m, 4H), 1.30 (m, 4H), 0.98 (t, *J*=7.2 Hz, 3H), 0.55 (t, *J*=7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.0, 147.7, 145.8, 129.7, 128.7, 128.0, 127.2, 112.5, 112.1, 83.7, 64.2, 55.9, 55.8, 55.6, 45.9, 41.0, 37.7, 30.4, 26.3, 21.6, 19.7, 11.7, 11.0; EI-MS *m*/*z* 451 (M^+); HR-MS calcd for $C_{27}H_{37}N_3O_3$ 451.2835, found: 451.2817.

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Supplementary data

Supplementary data related to this article can be found online version, at doi:10.1016/j.tet.2010.12.038. These data include MOL files and InChIKeys of the most important compounds described in this article.

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