Synthesis of Diverse Benzo[1,4]oxazin-3-one-Based Compounds Using 1,5-Difluoro-2,4-dinitrobenzene

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This paper discusses the synthesis of benzo[1,4]oxazin-3-one-based compounds from 1,5-difluoro-2,4-dinitrobenzene (**1**), including benzo[1,4]oxazin-3-ones (**5**−**11**) and five novel benzo[1,4]oxazin-3-one-based tricycles: 6-hydroxy-4H-1-oxa-4,5,8-triazaanthracen-3-one (**14**), 3,8-dihydro-5-oxa-1,3,8-triazacyclopenta-[b]-naphthalene-7-one (**15**, **17**, **21**), 3,8-dihydro-5-oxa-1,2,3,8-tetraazacylopenta[b]-naphthalene-7-one (**16**, **20**), 3,8-dihydro-1H-5-oxa-1,3,8-triazacyclopenta[b]-naphthalene-2,7-dione (**18**, **22**), and 5,8-dihydro-4H-1-oxa-4,5,8-triazaanthracene-3,6,7-trione (**19**). Finally, a chemical library based on **15** was synthesized in parallel solution-phase reactions.

Introduction

Benzo[1,4]oxazin-3-one-based compounds have shown various biological activities, such as being anti-inflammatory,[1] antiulcer,[2] antipyretic,[3] antihypertensive,[4] and antifungal.[5] Some of them also act as 5-HT ligands,[6] DP receptor antagonists,[7] integrin antagonists,[8] platelet fibrinogen receptor antagonists,[9] calmodulin antagonists,[4] inhibitors of the transforming growth factor β (TGF-β) signaling pathway,[10] soybean lipoxygenase,[11] and Janus kinase (JAK) and other protein kinases.[12] Furthermore, benzo[1,4]oxazin-3-one analogs are presenting as potassium channel openers,[13] immunomodulating reagents,[5] etc. Therefore, the benzo[1,4]-oxazin-3-one scaffold can be viewed as a "privileged structure"[14] among pharmaceutical compounds. The benzo-[1,4]oxazin-3-one scaffold has been generated by several methods[15−18] (Scheme 1). A library was also synthesized by Caliendo et al.[19] All of these methods involved two key intermediates, namely, 2-aminophenol and 2-nitrophenol, with limited diversity points. In contrast to these methods, we herein used 1,5-difluoro-2,4-dinitrobenzene (DFDNB, **1**) to synthesize benzo[1,4]oxazin-3-one derivatives and benzo-[1,4]oxazin-3-one-based tricycles that permitted us to introduce great molecular diversity, including substitution diversity and skeleton diversity.

Results and Discussion

After the quantitative nucleophilic replacement of one fluorine atom of **1**,[20] the remaining fluorine atom was systematically substituted from **2** by various α-hydroxy acetates (**1′**, Figure 1) in the presence of K_2CO_3 (Scheme 2). The product, **3**, was then conveniently reduced by Pd/$HCOONH_4$ to give benzo[1,4]oxazin-3-one (**4**). For those compounds containing hydrogen-sensitive groups or potential catalyst-poisoning groups, $Na_2S_2O_4/K_2CO_3$ was used instead.[20b]

Preparation of Benzo[1,4]oxazin-3-ones. Scheme 2 outlines the synthesis of benzo[1,4]oxazin-3-one using 1,5-difluoro-2,4-dinitrobenzene (**1**). The intermediate **4** was stable under experimental conditions, unlike other intermediates from **1**[20c] and thus was easily substituted on the 6-amino group by various methods. Sixty-six compounds have been synthesized in a parallel manner in the solution phase (Tables 1−4).

The Pd/C−$HCOONH_4$ reduction went smoothly in most cases. Only one impurity was observed as **5i** (Table 2), which was formylated by formic acid resulting from the decomposition of excess $HCOONH_4$. The reduction using the $Na_2S_2O_4/K_2CO_3$ method took a longer reaction time, and sometimes, microwave assistance was required to promote the ring closure. The detectable corresponding hydroxylamine was sometimes detected by our fast LC−MS analysis system during the process of reduction; however, it could be completely converted into **4** with a longer reaction time.

To synthesize versatile benzo[1,4]oxazin-3-one analogs, we selected acylation, sulfonation, urea or thiourea formation, reductive alkylation, biguanide formation, and the Ugi-4cc reaction to derivatize the free 6-amino group of **4**. All of these reactions not only introduce tremendous diversity, but also create a diverse range of pharmacophores on benzo-[1,4]oxazin-3-one. Microwave assistance[21] was used in our experiments to accelerate some reactions. For instance, urea **7** or thiourea **8** (Table 2) formation completed within 2−90 min using 1.0 equiv of isocyanate or isothiocyanate without any observed impurities. The desired ureas or thioureas were usually precipitated from the reaction mixture. Acylation was also totally completed within 30−60 min by using 3.0 equiv of acetic anhydride in anhydrous DCM (Table 2). Sulfamide **6** was obtained from 1.0 equiv of sulfonyl chloride and 1.1 equiv of pyridine within 60−120 min under microwave assistance[22] (Table 2). In the case of **5g**, the corresponding formyl chloride was used in the same way as the sulfonation reaction.

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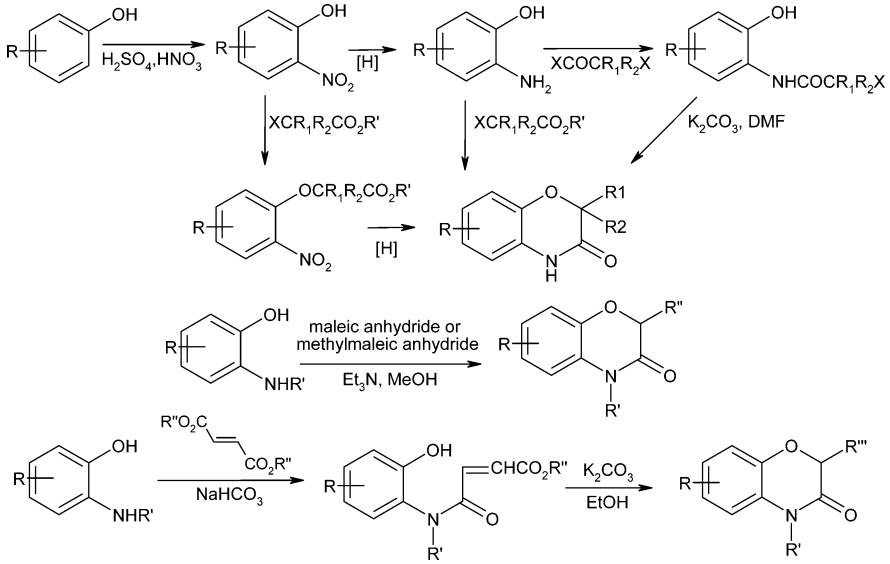
Scheme 1. Literature Methods for Synthesis of Benzo[1,4]oxazin-3-ones



$Na(OAc)_3BH$ was the reagent of choice for the reductive alkylation[23] to synthesize compound **9** (Table 3) in this paper. The reductive alkylation was fast at room temperature in the presence of 5% AcOH and completed within 30 min. Bialkylation was the major side reaction indicated by the LC−MS analysis.

Scheme 3 is an alternative route for synthesis of sulfoxide and sulfone derivatives at the 7-position of **5**, **6**, **7**, and **9**. The corresponding intermediates **6b** and **7b** could be easily oxidized using UHP/$(CF_3CO)_2O$ to yield **6c** and **7c**, respectively (Table 2). The oxidation completely finished within 5 h at room temperature. However, to obtain the sulfoxide derivatives, which are known as the intermediates to sulfone in high yield, the oxidative capacity of this reagent must be reduced to a proper level. Replacement of $(CF_3CO)_2O$ with $(CH_3CO)_2O$[24] could achieve this goal. We are currently studying the mechanism of UHP oxidation aided by $(CF_3CO)_2O$ and $(CH_3CO)_2O$. Following the reactions by LC−MS, we found that the electron-withdrawing property at the 6-position of benzo[1,4]oxazin-3-one would delay the reaction. For example, 75.1% of **9c** was converted into **9d** (Table 3) in 2.5 h. However, it took at least 10 h to convert 73.1% of **5b** to **5c** (Table 2). Trace amounts of the corresponding sulfone compounds were also detected by LC−MS analysis. Therefore, careful selection of reactants and frequent following of the reaction can give high yields of sulfoxide compounds by this method.

The biguanidine group was also introduced at the 6-position of the benzo[1,4]oxazin-3-one skeleton. Compounds **10a** and **10b** (Table 3) were synthesized by the method of Shridhar et al.[25] in 26.7 and 34.5% yields, respectively. This reaction was always incomplete even under microwave assistance with harsh conditions, such as high temperature and high pressure.

The Ugi-4cc condensation[26] is a frequently used method for introducing molecular diversity. In this paper, we explored fourteen such reactions at the 6-amino group of **4**. MeOH is a favorite solvent according to the Nakamura research group.[27] Aldehyde was added to a solution of **4** in MeOH, followed by the addition of acid and isocyanide. The condensation was monitored by LC−MS analysis until the material was exhausted. The reaction period was determined mainly by the R_1 substitution groups and the physical properties of the aldehydes. In all our experiments, most Ugi reactions completed within 12 h at room temperature. However, the investigation of different building blocks indicated that aromatic aldehydes and large R_1 substitution groups slowed down the reaction extremely, for example, to go completion 4-fluorobenzaldehyde took 7 days, *N*-cyclohexyl-*N*-methylamine of R1 took 5 days, and 1-(2,4-dimethylphenyl)piperazine of R1 took 4 days. This was possibly caused by the stability of their corresponding Schiff bases and steric hindrance effect,[26] respectively. A mixture of isomers (Table 4) were received since a new chiral center was created. In all of our successful experiments, two impurities were detected as **11f′** and **11g′** (Figure 2). Two Ugi-4cc reactions totally failed (**11c** and **11i** in Table 4). The former was believed to be caused by the 4-morpholinecarbaldehyde used. This aldehyde was more like a substituted formylamine than an aldehyde and could not form a Schiff base with the amine. The latter reaction might have failed because of the 9-acridinecarboxylic acid with an unknown reason.

Preparation of Benzoxazin-3-one-Based Tricycles. There has always been considerable effort placed on the integration of privileged structures into one molecule for drug design. Adibendan,[28] Quazolast,[29] Icopezil,[30] and Tomoxiprole,[31] Furodazole[32] (Figure 3) are successful cases. As indicated,

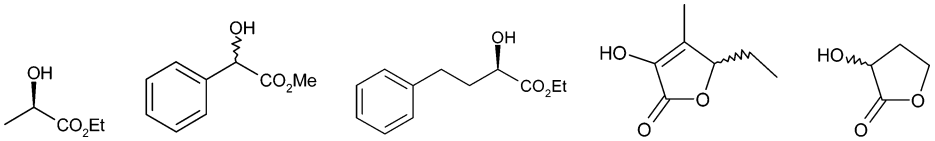
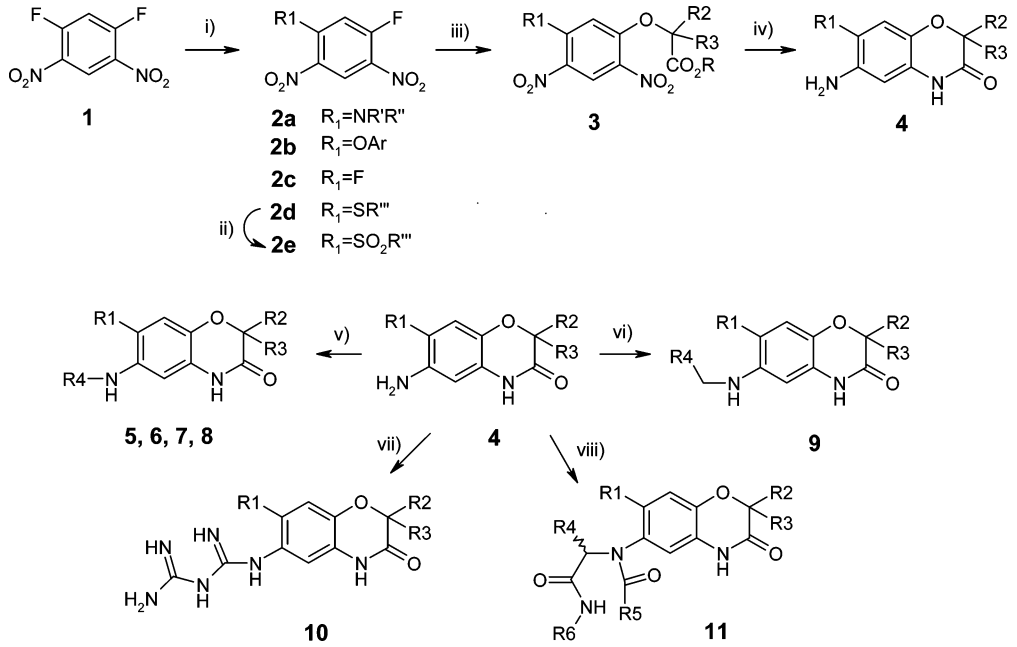


Figure 1. α-Hydroxy acetate (**1′**) used in this paper.

Scheme 2. Synthetic Routes of Benzoxazine Analogs[a]



[a] (i) R′R″NH, DIPEA, THF, 1−3 h; ArOH, K_2CO_3, acetone, 24−72 h; or R‴SH, DIPEA, THF, 2 h; (ii) UHP/$(CF_3CO)_2O$, CH_3CN, 2 h; (iii) $R_2C(OH)$-R_3CO_2R, K_2CO_3, acetone, 12−36 h; (iv) Pd/C, $HCOONH_4$, EtOH + THF, 1−6 h or $Na_2S_2O_4$, K_2CO_3, EtOH + THF + H_2O, 1−12 h; (v) $(R_4CO)_2O$ or R_4CO_2Cl, R_4SO_2Cl, pyridine, R_4NCO or R_4NCS, DCM, microwave irradiation (150 W, 100 psi, 80 °C, 2−90 min); (vi) (1) R_4CHO, AcOH, DCM, (2) $Na(OAc)_3BH$, 15 min−2 h; (vii) (1) HCl (12M), EtOH, (2) dicyanamide, water, microwave irradiation (250 W, 250 psi, 105 °C, 10 h); (viii) R_4CHO, R_5COOH, R_6NC, MeOH, 4 h−7 d (according to the R_1 and R_4CHO).

with the aim of increasing compound diversity through the integration of diverse skeletons,[33] we report herein studies on the preparation of benzo[1,4]oxazine-3-one-based tricycles. Treatment of **1** offered a new compound **14** or the intermediate **14′** (Scheme 4) by reaction of an α-amino acid ester or primary amine replacement, followed by secondary substitution with α-hydroxy acetate and reduction, with or without further dehydrogenation steps. Then **14′**, in a reaction with aldehyde, carbon disulfide, triphosgene, sodium nitrite, or oxalyl chloride, generated additional skeletons of 1H-benzoimidazole, 1,3-dihydrobenzoimidazol-2-one, 1H-benzotriazole, or 1,4-dihydroquinoxaline-2,3-dione, respectively. Thus, five novel tricycles were obtained. They are 6-hydroxy-4H-1-oxa-4,5,8-triazaanthracen-3-one (**14**), 3,8-dihydro-5-oxa-1,3,8-triazacyclopenta[b]naphthalen-7-one (**15**, **17**), 3,8-dihydro-5-oxa-1,2,3,8-tetraazacyclopenta-[b]naphthalen-7-one (**16**), 3,8-dihydro-1H-5-oxa-1,3,8-triazacyclopenta[b]naphthalene-2,7-dione (**18**), and 6-hydroxy-5,8-dihydro-4H-1-oxa-4,5,8-triazaanthracene-3,6,7-trione (**19**).

The slow dehydrogenation of **13** was the rate-determining step to generate **14**. The addition of excess Pd/C or heating of the reactants assisted the dehydrogenation after the reduction and ring-closing steps. Moreover, microwave assistance also significantly accelerated the ring-closing and dehydrogenation steps, which finished in 30 min. Typical compounds were characterized after purification by silica gel chromatography. The total yields of the four reaction steps ranged from 40 to 71% (Table 5).

As discussed in our previous paper,[20c] **14′** was unstable when it was exposed to air. Therefore, continuous reactions were carried out to synthesize **15**, **16**, and **17**. The typical compounds are listed in Tables 6−8, respectively. It is recommended that the solvent, THF, for synthesis of these compounds is freshly redistilled over $LiAlH_4$ before use because a byproduct could be detected, for example as **15′** (Figure 4). THF might contain an impurity of 2,3-dihydrofuran, a oxidative product of THF, which resulted in additive and dehydrogenation reactions with **14′**. When the synthesis of the library is considered, such treatment of THF would significantly improve the quality of the library.

To obtain **16**, **14′** was reacted with sodium nitrite[34] smoothly in acetic acid at room temperature. LC−MS analysis at the wavelength of 254 nm indicated that a high purity crude compound was obtained. Typical compounds were characterized, as shown in Table 7, after chromatogram purification.

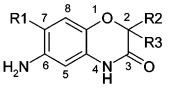
Compound **17** was made directly from **14′** treated with carbon disulfide.[34] Such compounds precipitated from the reaction solution, which allowed us to characterize them (Table 8) by ^1H NMR directly. An additional diversity point was then introduced by reaction of **17** with α-halogen ketones or α-halogen alkanes under microwave assistance to yield **21** in 25 min without detectable impurities.

Compounds **18** and **19** were synthesized by using triphosgene[35] in redistilled THF and oxalyl chloride in dried toluene, respectively, after evaporation of the solvents of the reduction reaction. Compound **18** was obtained in good yield; however, **19** had a very low yield because of the low purity of the oxalyl chloride used (Table 9).

We also attempted to derivatize the amide-NH of **16b** and **18a** using NaH/RX (see compounds **20a** and **22a** in Tables 7 and 9, respectively). **16b** produced a good yield of the desired compound, **20a**; however, **18a** was not selectively methylated either at the 4- or the 6-position. Only dimethylated **22a** was obtained.

Preparation of the Library. A library of template **15** was

Table 1. Structure, Melting Point, Yield, and LC−MS of **4**



Entry	R_1	R_2	R_3	mp (℃)	Yield [a] (%)	LC-MS
4a		-CH_3	-H	291.6–292.6	62.1	277.4[b] 278.1[c]
4b		-CH_3	-H	226.0–228.7	28.8	366.5 367.1
4c		-CH_3	-H	90.1–92.3	43.0	238.3 239.0
4d[d]		-Ph	-H	159.0–160.5	35.7	300.4 301.0
4e		-CH_3	-H	132.0–132.9	48.3	249.3 250.1
4f		-CH_3	-H	170.7–171.9	18.1	270.3 271.0
4g		-CH_3	-H	197.0–199.0	52.9	261.3 262.3
4h[d]	 		/	56.0–58.1	37.7	333.4 334.5
4i[d]	 		-H	139.5–141.5	42.8	293.3 293.9
4j[d]		-Ph	-H	181.6–184.0	15.7	360.4 360.9
4k		-C_2H_4Ph	-H	124.1–125.2	38.7	423.5 424.3
4l		-CH_3	-H	136.7–138.2	49.1	289.4 290.2
4m	F	-CH_3	-H	226.7–228.4	19.7	196.2 197.0
4n		-CH_3	-H	185.0–187.0	32.5	298.3 299.1
4o[d]		-Ph	-H	249.6–251.4	32.3	323.4 324.2

[a] Purified yields from **1**. [b] Calculated molecular weight. [c] Found molecular weight by positive-ion scanning using electrospray ionization (see details in the experiment section). [d] A mixture of two enantiomers.

eventually synthesized in a parallel manner in solution phase (Figure 5). The building blocks (Figure 6) were carefully selected from our stock reagents. Three rules were considered; the selected building blocks were not randomly combined: (1) the maximum diversity of molecules, (2) the compatibility with the Pd/C−$HCOONH_4$ reduction, and (3) the easy removal by the scavenger amino-resin. Therefore, this library finally included 1040 members.

Compounds **13′** were previously prepared. Compounds of **13′** in THF and EtOH were distributed into the reaction tubes in equal molar ratios. A certain amount of Pd/C and $HCOONH_4$ was then added to each reaction tubes to carry out reaction 1 (see Figure 5) in parallel manner on the H+P Labortechnik GmbH parallel synthesizer. After the reductions were complete, the Pd/C and excess $HCOONH_4$ were filtered off. The filtrates were added directly to the tubes containing aldehydes in EtOH to perform reaction 2 overnight (Figure 5). Then enough amino-resin was added to scavenge the excess aldehydes (reaction 3). A fast LC−MS analysis was used to randomly spot-check the reactions. After the resin was filtered off, the filtrates were concentrated, washed with saturated sodium bicarbonate solution, and extracted with DCM using phase separators. Evaporation of the organic layers to dryness gave the library members individually. All final products were analyzed by a LC−MS analysis and an LC−ELSD tandem system. The UV wavelength is 254 nm. The analytical results indicated that 80% of the members of the library were over 80% pure (Figure 7). Incompletely removed aldehydes were the major impurities.

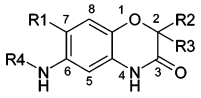
Conclusion

This paper has developed methods that synthesize benzo[1,4]oxazin-3-ones (**5**−**11**) from 1,5-difluoro-2,4-dinitrobenzene (**1**). Meanwhile, five novel benzo[1,4]oxazin-3-one-based tricycles were described, including 6-hydroxy-4H-1-oxa-4,5,8-triazaanthracen-3-one (**14**), 3,8-dihydro-5-oxa-1,3,8-triazacyclopenta[b]naphthalen-7-one (**15**, **17**), 3,8-dihydro-5-oxa-1,2,3,8-tetraazacyclopenta[b]naphthalen-7-one (**16**), 3,8-dihydro-1H-5-oxa-1,3,8-triazacyclopenta[b]naphthalene-2,7-dione (**18**), and 6-hydroxy-5,8-dihydro-4H-1-oxa-4,5,8-triazaanthracene-3,7-trione (**19**). Eventually, a chemical library of scaffold **15** was prepared in a parallel manner in solution phase.

Experimental Section

General Information. All chemical reagents were purchased from Acros Organics (Geel, Belgium) and used without further purification. THF, DCM, and toluene were redistilled using the standard drying procedure.[36] Acetone was dried with anhydrous K_2CO_3. Aminomethyl polystyrene resin (1.3 mmol/g, 1% DVB cross-linked, 100−200 mesh) was purchased from TianJin HeCheng Corporation (Tianjin, China). HPLC analysis was performed on a Shimadzu HPLC system equipped with an SPD-10A VP detector, an LC-10AT VP pump, a DGU-12A degasser, and Gilson HPLC system equipped with a Gilson 322 pump, Gilson UV−VIS-152 detector, and a Gilson 215 liquid handler. The automatic LC−MS analysis was performed on a Thermo Finigan LCQ-Advantage mass spectrometer equipped with an Agilent HPLC system and an eluent splitter (5% eluent was split into the MS system). A Kromasil C18 column (4.6 μm, 4.6 mm × 50 mm) from DIKMA was employed. The eluent was a mixture of acetonitrile and water containing 0.05% TFA with a linear gradient from 5:95 v/v acetonitrile−H_2O to 95:5% acetonitrile−H_2O within 5 min at 1 mL/min. The UV detection wavelength was 254 nm. Mass spectra were recorded in either positive- or negative-ion mode using electrospray ionization. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Varian Mercury 300, 400, or Inova 500 MHz NMR spectrometer. Parallel synthesis was conducted on an H+P Labortechnik GmbH parallel synthesizer. Microwave-assistance synthesis was carried out on a CEM microwave synthesizer equipped with an Explorer automatic handle and a Discover vessel. Melting points were determined on a Yamato micromelting-point apparatus

Table 2. Structure, Melting Point, Yield, and LC−MS of **5**−**8**



Entry	R_1	R_2	R_3	R_4	mp (℃)	Yield (%)	LC-MS
5a		-CH_3	-H	-COC_2H_4-C O_2H	139.0–141.4	81.2[a]	349.5[b] 350.1[c]
5b		-CH_3	-H	-$COCH_3$	185.3–187.0	83.5[d]	280.4 281.0
5c[e]		-CH_3	-H	-$COCH_3$	210.3–212.0	58.2[f]	296.4 297.0
5d		-CH_3	-H	-$COCH_3$	251.8–252.7	87.7[d]	312.4 313.2
5e		-C_2H_4Ph	-H	-$COCH_3$	172.9–174.4	50.8[a]	395.5 396.2
5f	F	-CH_3	-H	-$COCF_3$	196.7–198.7	86.7[d]	292.2 290.7
5g[g]		-Ph	-H		197.0–199.0	68.9[d]	509.5 509.8
5h		-CH_3	-H	-$COCH_3$	186.9–187.6	45.5[a]	408.5 409.2
5i		-CH_3	-H	-CHO	147.7–149.1	1.62[h]	305.4 306.0
6a		-CH_3	-H		199.3–199.8	38.8[i]	431.5 432.0
6b[g]		-Ph	-H		72.5–73.9	81.8[a]	454.6 455.2
6c[g]		-Ph	-H		147.6–149.1	81.8[f]	486.6 485.2
6d		-C_2H_4Ph	-H		56.1–58.5	96.9[a]	581.7 581.9
6e[g]		-Ph	-H		131.1–133.7	94.1[a]	518.4 518.9
7a[g]		-Ph	-H		> 300	65.4[d]	472.6 473.2
7b[g]		-Ph	-H		239.1–240.2	74.0[j]	461.6 462.0
7c[g]		-Ph	-H		197.0–199.0	89.4[f]	493.6 493.9
7d		-CH_3	-H		197.0–199.0	92.1[d]	473.4 474.1
7e	F	-CH_3	-H		214.4–216.1	90.4[d]	407.4 407.8
7f[g]		-Ph	-H		197.7–199.0	65.2[d]	493.6 494.3
7g		-C_2H_4Ph	-H		228.5–229.7	90.9[d]	610.6 611.4
8a		-CH_3	-H		185.7–187.6	81.0[a]	546.6 547.1
8b		-CH_3	-H		166.4–167.4	78.4[a]	426.6 427.1
8c		-CH_3	-H		191.5–192.8	84.3[d]	509.5 510.2
8d		-CH_3	-H		190.5–192.3	80.3[a]	519.6 520.3
8e		-CH_3	-H		167.3–170.2	80.0[a]	442.6 443.1
8f		-CH_3	-H		164.1–165.7	87.1[d]	402.5 403.0
8g		-CH_3	-H		167.8–170.1	93.2[d]	402.5 403.0
8h[g]		-Ph	-H		239.1–240.2	90.9[d]	465.6 466.3
8i		-C_2H_4Ph	-H		105.4–107.0	72.2[a]	538.7 539.4
8j[g]		-Ph	-H		222.8–224.2	71.0[d]	523.6 523.8
8k		-C_2H_4Ph	-H		56.1–58.5	68.6[a]	626.7 627.0

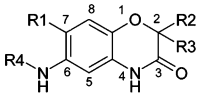
[a] Silica gel chromatography purification yields from **4**. [b] Calculated molecular weight. [c] Found molecular weight by positive- or negative-ion scanning using electrospray ionization (see details in the experiment section). [d] Yields by filtration from **4**. [e] A mixture of two diastereomers. [f] Purified yields for one oxidization step from the corresponding thioether. [g] A mixture of two enantiomers. [h] Byproduct of the reduction. [i] Purified yields from **1**. [j] Collection yields for 1 h using microwave assistance with a 90% conversion rate.

without correction. Phase separators were purchased from Argonaut Inc. (Mid Glamorgan, U.K.).

Preparation of 2a, 2d, and 12′. A solution of 1.0 equiv of nucleophilic reagent (primary/secondary amine or ethenethiol) in 90 mL of THF was added dropwise within 1 h at room temperature to a vigorously stirred solution of 1,5-difluoro-2,4-dinitrobenzene **1** (DFDNB, 8 mmol) and diisopropylethylamine (DIPEA, 8.8 mmol) in 30 mL of THF. The reaction mixture was continuously stirred for an additional 1 h. The solvent was removed under reduced pressure, and water was added to precipitate **2a**, **2d**, or **12′**, which was then filtered, washed thoroughly with water, and dried in desiccators for the next step without further purification. A typical compound of **2a**, 1-(5-fluoro-2,4-dinitrophenyl)-piperidine, was purified with a silica gel column, eluting with EtOAc−petroleum ether = 1:2, in a yield of 92%. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 8.601 (d, 1H, J = 8.4 Hz), 7.338 (d, 1H, J = 14.7 Hz), 3.245 (brs, 4H), 1.622 (brs, 6H).

Preparation of 2b. DFDNB **1** (4 mmol) was dissolved in acetone (10 mL), followed by addition of 1.0 equiv of phenol and 5.0 equiv of anhydrous K_2CO_3. The reaction mixture was mechanically shaken at room temperature until the total disappearance of **1**, as determined by TLC (EtOAc−petroleum ether = 1:2). Then, the reaction mixture containing

Table 3. Structure, Melting Point, Yield, and LC−MS of **9**−**10**



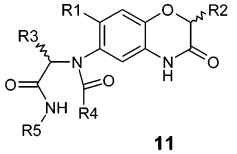
Entry	R_1	R_2	R_3	R_4	mp (℃)	Yield (%)	LC-MS
9a		-CH_3	-H		172.1–174.0	72.4[a]	385.2[b] 386.0[c]
9b		-CH_3	-H		125.5–127.2	64.4[a]	457.6 458.0
9c		-CH_3	-H		118.4–119.6	87.1[d]	346.4 346.9
9d[e]		-CH_3	-H		28.9–30.0	48.3[f]	362.4 363.0
9d'		-CH_3	-H		207.7–208.2	4.9[g]	378.4 376.8
9e[h]		-Ph	-H		124.8–126.4	59.8[a]	388.5 389.1
9f[h]			no		34.9–36.5	25.3[a]	480.6 481.1
9g[h]			-H		63.1–65.2	77.9[a]	413.5 414.5
9h	F	-CH_3	-H		209.1–211.3	99.5[d]	330.3 330.4
9i[h]		-Ph	-H		163.4–165.5	90.7[d]	540.5 540.7
10a[h]		-Ph	-H		257.6–260.0	26.7[a]	444.5 445.3
10b		-CH_3	-H		228.2–230.9	34.5[a]	382.4 383.2

[a] Silica gel chromatography purification yields from **4**. [b] Calculated molecular weight. [c] Found molecular weight by positive-ion scanning using electrospray ionization (see details in the experiment section). [d] Yields by filtration from **4**. [e] A mixture of two diastereomers. [f] Purified yields for one oxidization step from the corresponding thioether. [g] Byproduct of the oxidation of the thioether to sulfoxide compound. [h] A mixture of two enantiomers.

2b went to the next step directly, as described in the general procedure for the second substitution.

Preparation of 2e. Ten equivalents of $(CF_3CO)_2O$ was added dropwise to a mixture of **2d** (3 mmol) in CH_3CN (30 mL) with 15 equiv of UHP at 0 °C. The reaction mixture was kept for an additional 10 min at 0 °C, and then, it was shaken mechanically at room temperature until the absence of **2d** was confirmed by LC−MS analysis. The reaction mixture was then neutralized to pH 8 by saturated sodium bicarbonate solution and extracted with DCM (15 mL × 3). The organic layers were combined and washed with saturated sodium chloride (15 mL × 2) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure produced **2e**, 1-(ethylsulfonyl)-5-fluoro-2,4-dinitrobenzene, as a light yellow solid, which was purified by silica gel chromatography eluting with EtOAc−EtOH = 2:1. Yield: 89%. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 9.038 (d, 1H, J = 6.3 Hz) 8.350 (d, 1H, J = 10.2 Hz) 3.691 (q, 2H, J = 7.5 Hz) 1.269 (t, 3H, J = 7.5 Hz).

Table 4. Structure, Melting Point, Yield, and LC−MS Data of the Ugi-4CC Reaction



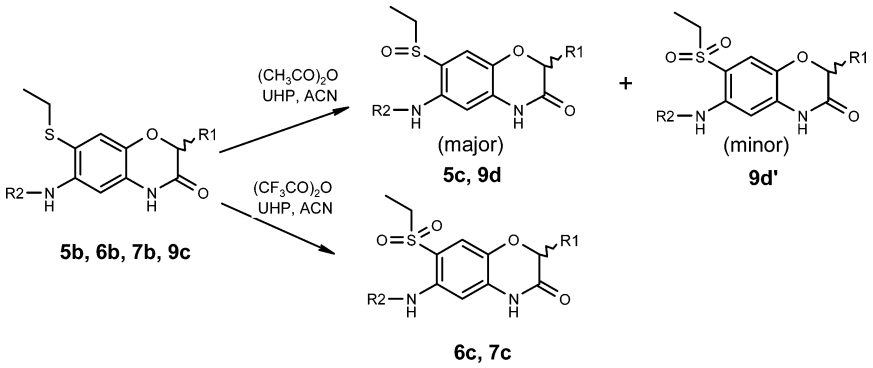
11

Entry	R_1	R_2	R_3	R_4	R_5	mp (°C)	Yield (%)	LC–MS
11a[a]		–CH_3		–CH_3		194.4–195.9	94.6	432.6[b] 433.0[c]
11b[d]		–CH_3				191.3–192.5	81.1	735.9 736.3
11c		–Ph				/	/	Failed
11c'[d]		–Ph				87.9–90.5	53.2	587.8 588.3
11d[a]		–CH_3				127.1–131.3	82.4	570.7 571.0
11e[e]		–Ph				/	/	622.8 623.2
11f[a]		–CH_3				96.5–99.1	25.8	667.9 668.4
11g[a]		–CH_3				127.1–131.3	32.4	586.7 587.2
11h[a]		–CH_3				54.0–56.5	27.6	701.9 702.2
11i	F	–CH_3				/	/	Failed
11i'[a]	F	–CH_3				120.2–123.7	90.6	510.6 511.0
11j[a]		–C_2H_4Ph		–CH_3		88.5–92.2	84.9	606.8 607.3
11k[a]		–CH_3				139.4–143.8	85.1	582.7 582.9
11l[a]		–CH_3				101.5–104.8	57.0	605.7 605.9

[a] A mixture of two diastereomers. [b] Calculated molecular weight. [c] Found molecular weight by positive-ion scanning using electrospray ionization (see details in the experiment section). [d] A mixture of four diastereomers. [e] This product could not been separated from a byproduct having a molecular weight less than the desired one and was confirmed only by LC−MS.

Preparation of 12. DIPEA (10 mmol) and $MeO_2CCH(R_1)NH_2$•HCl (4 mmol) were added to a vigorously stirred solution of DFDNB **1** (4 mmol) in THF (30 mL). The reaction mixture was continuously stirred at room temperature until all of the DFDNB **1** was converted to the anticipated compound **12**, as confirmed by HPLC analysis. The solvent was evaporated, and water was added to precipitate **12**, which was then filtered, washed thoroughly with water, and dried in a desiccator for use without further purification. A typical compound of **12b**, methyl 2-(5-fluoro-2,4-dinitroanilino)-3-methylpentanoate, was purified by silica gel column, eluting with EtOAc−petroleum ether = 1:9, with a yield of 95%. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 8.872 (d, 2H, J = 8.1 Hz), 7.254 (d, 1H, J = 14.7 Hz), 4.785 (dd,

Scheme 3. Oxidation of Aromatic Thioether to Corresponding Sulfoxide or Sulfone Derivatives, Respectively



1H, $J = 4.5$ Hz, $J = 8.4$ Hz), 3.745 (s, 3H), 2.019 (m, 1H), 1.532 (m, 1H), 1.335 (m, 1H), 0.918 (m, 6H).

General Procedure for the Second Substitution. 2a, **2c**−**e,** or **12**, **12′** (3 mmol) was dissolved in acetone (10 mL), followed by the addition of 1.2 equiv of α-hydroxy acetate and 5.0 equiv of anhydrous K_2CO_3. For **2b**, the α-hydroxy acetate and K_2CO_3 were added directly into the reaction mixture above to carry out the reaction in one pot. The reaction mixture was then shaken mechanically at room temperature. When all reactions were finished, as shown by HPLC, enough water was added to precipitate the products, and **3**, **13**, and **13′** were collected to perform the reduction reaction directly by filtration after they were thoroughly washed and properly dried. A typical compound of **3a**, ethyl 2-(2,4-dinitro-5-piperidinophenoxy)-4-phenylbutanoate, was purified in a 93% yield by silica gel chromatography, eluting with EtOAc−petroleum ether = 1:10. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 8.566 (s, 1H), 7.248 (m, 5H), 6.555 (s, 1H), 5.415 (t, 1H, $J = 5.55$ Hz), 4.143 (q, 2H, $J = 6.75$ Hz), 3.144 (m, 4H), 2.797 (m, 2H), 2.246 (m, 2H), 1.585 (m, 6H), 1.169 (t, 3H, $J = 7.05$ Hz).

Pd/C and $HCOONH_4$ Method for Synthesis of 4 and 14′. Refer to the method in ref 20c method. Herein, the solvent was THF−EtOH (v/v = 1:1).

$Na_2S_2O_4$/K_2CO_3 Method for Synthesis of 4 and 14′. This method was slightly modified according to ref 20b. The aromatic dinitro compound (1 mmol) was dissolved in THF (15 mL), and then the same volume of EtOH was added. After the addition of 10 equiv of K_2CO_3 and 20 equiv of $Na_2S_2O_4$, water was added dropwise with vigorous stirring until the mixture turned red and clear. Then, the solution was heated below 50 °C for 12 h. The organic layer was separated, and the water layer was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated sodium chloride (30 mL × 2) and dried over anhydrous Na_2SO_4. The solvent was finally removed under reduced pressure. The residual **4** was further purified by silica gel column chromatography, eluting with EtOAc and petroleum ether. **14′** was directly used for the next reactions because of its unstable nature. The listed compounds of **4** were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

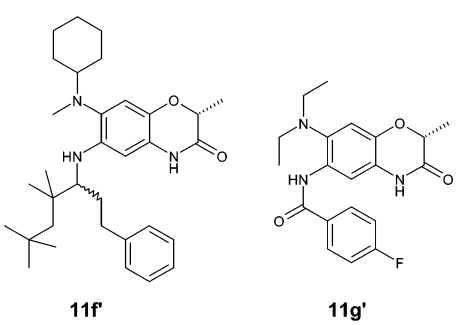


Figure 2. Structures of Ugi-4cc byproducts.

Preparation of 5. Three milliliters of DCM was added to a reaction tube containing 0.2 mmol **4**, followed by the addition of 3.0 equiv of acetic anhydride. The microwave-assisted reaction conditions were set as follows: power, 150 W; pressure, 100 psi; temperature, 80 °C; hold time, 30 min. After the reaction was finished, the solvent was evaporated. The residue was sonicated in 4 mL of petroleum ether for 10 min. The light yellow powder was finally collected and washed thoroughly with petroleum ether. Characterization of the listed compound **5** by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds is indicated in the Supporting Information.

Preparation of 6. Three milliliters of DCM was added to a reaction tube containing 0.2 mmol **4**, followed by the addition of 1.1 equiv of pyridine and 1.0 equiv of sulfonyl chloride. The microwave-assisted conditions were set the same as above. A saturated copper sulfate solution was then added to the reaction mixture after the sulfonation was finished. The organic layer was separated and the water layer was extracted with DCM (3 mL × 3). The combined organic layers were washed with brine (3 mL × 3) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel chromatography, eluting with EtOAc and petroleum ether. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

Preparation of 7 and 8. Four milliliters of DCM was added to a reaction tube containing 0.2 mmol **4**, followed by the addition of 1.0 equiv of isocyanate or isothiocyanate. The microwave-assisted conditions were set the same as above. Usually, a white precipitate of the anticipated compound was obtained, which was collected after filtration and thoroughly washed with petroleum ether and then characterized directly by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds. For those which were not precipitated, after removal of solvent, the residues were

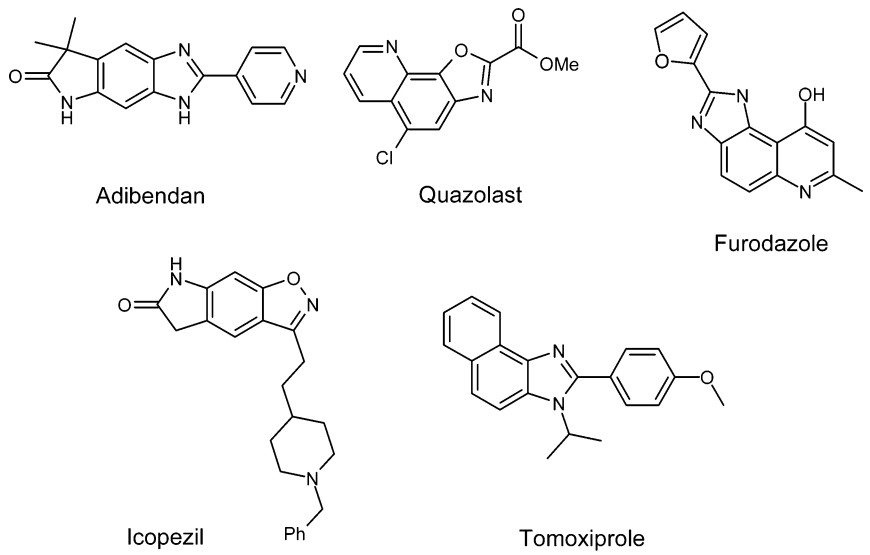
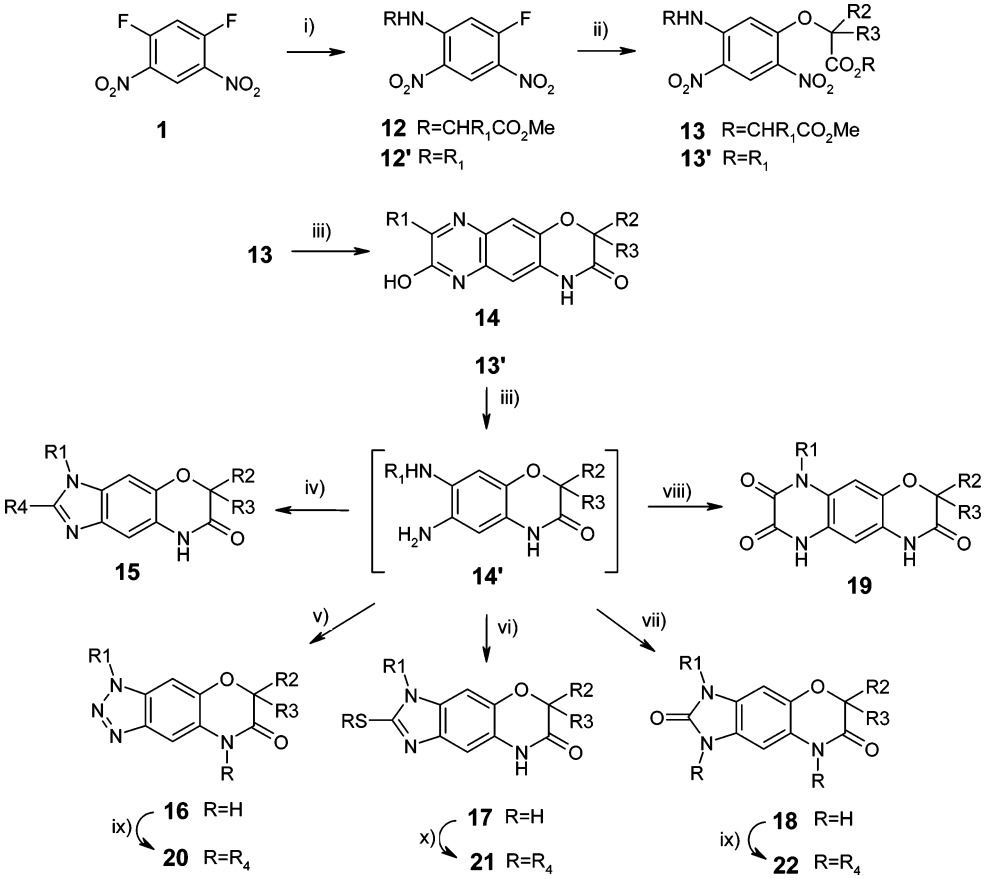


Figure 3. Representative drugs for integration of privileged structures into one molecule.

Scheme 4. Synthetic Route of Tricycles Based on Benzo[1,4]oxazine-3-one[a]

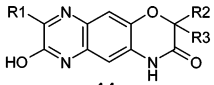


[a] (i) $MeO_2CCH(R_1)NH_2$·HCl or R_1NH_2, DIPEA, THF, 1−10 h; (ii) $R_2C(OH)R_3CO_2R$, K_2CO_3, acetone, 12−36 h; (iii) Pd/C, $HCOONH_4$, EtOH + THF, 1−6 h or $Na_2S_2O_4$, K_2CO_3, EtOH + THF + H_2O, 1−12 h, microwave assistance was used to accelerate the ring closing and dehydrogenation (250 W, 250 psi, 150 °C, 30−45 min); (iv) (1) R_4CHO, AcOH, EtOH, 30 min−4 h, (2) PS−NH_2 resin, DCM, 6−24 h; (v) $NaNO_2$, AcOH, H_2O, 15 min−4 h; (vi) CS_2, EtOH, H_2O, 2−6 h; (vii). triphosgene, DIPEA, THF, 3−5 h; (viii) $(COCl)_2O$, DIPEA, toluene, 24 h; (ix) (1) NaH, xylene, reflux, 5 h, (2) R_4X, 12 h; (x) R_4X, microwave condition (100 W, 100 psi, 60 °C, 25 min).

purified by silica gel chromatography, eluting with EtOAc and petroleum ether. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}NMR for typical compounds, see the Supporting Information.

Preparation of 9. One equivalent of aldehyde and 300 μL of AcOH (6% v/v) was added to a mixture of 0.2 mmol **4** in 5 mL of DCM. Ten minutes later, 2.0 equiv of$Na(OAc)_3BH$ was added. The reaction mixture became a light yellow. When colorlessness occurred, saturated sodium bicarbonate solution was added to neutralize the AcOH (pH 8). The organic layer was separated, and the water layer was extracted with DCM (3 mL × 3). The combined organic layers were washed with saturated sodium chloride (3 mL × 2) and dried over anhydrous sodium sulfate. After removal

Table 5. Structure, Melting Point, Yield, and LC−MS for Some Representatives of **14**

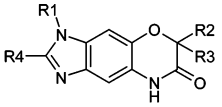


14

Entry	R_1	R_2	R_3	mp (℃)	Yield (%)	LC-MS
14a[a]	$-CH(CH_3)_2$		/	210.2–211.8	71.0	343.4[b] 344.0[c]
14b[a]	$-CH(CH_3)_2$	-H	-Ph	282.0–282.4	47.8	335.4 336.2
14c[a]	$-CH(CH_3)C_2H_5$	-H	-Ph	260.1–262.1	40.2	349.4 350.1

[a] A mixture of two enantiomers. [b] Calculated molecular weight. [c] Found molecular weight by positive-ion scanning using electrospray ionization (see details in the experiment section).

Table 6. Structure, Melting Point, Yield, and LC−MS for Some Representatives of **15**



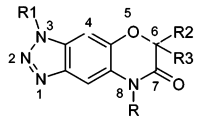
Entry	R_1	R_2	R_3	R_4	R	mp (°C)	Yield (%)[a]	LC–MS
15a		–CH_3	–H		–H	197.0–199.0	29.6[b]	355.5[c] 356.0[d]
15b		–CH_3	–H		–H	213.4–215.1	22.1[b]	367.4 368.0
15c		–CH_3	–H		–H	177.5–199.2	65.9	469.5 470.2
15d		–CH_3	–H		–H	259.7–261.5	71.2[e]	459.6 460.2
15e[f]		–Ph	–H		–H	61.0–63.0	45.5	471.6 472.0
15f		–C_2H_4Ph	–H		–H	237.0–239.2	41.9	489.6 490.1

[a] Purified yields for four steps from **1**. [b] The low yield was the result of the existence of byproducts. [c] Calculated molecular weight. [d] Found molecular weight by positive-ion scanning using electrospray ionization (see details in the experiment section). [e] Purified by crystallization. [f] A mixture of two enantiomers.

of solvent in vacuo, the residue was purified by silica gel chromatography, eluting with EtOAc and petroleum ether. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

Preparation of 10. The method in ref 25 was used with some slight modification. HCl (12 M) was added to **4** (0.2 mmol) in ethanol until the pH was 4. The solution was then concentrated to dryness. The residual 6-aminobenzoxazinone hydrochloride (0.2 mmol) was mixed with dicyanodiamide (0.2 mmol) in water (5 mL) and reacted under microwave-assisted conditions as follows: power, 250 W; pressure, 250 psi; temperature, 105 °C; hold time, 10 h. The reaction solution was then neutralized with saturated sodium bicarbonate solution to pH 8 and extracted with DCM (5 mL × 3). The combined organic layers were washed with saturated sodium chloride (5 mL × 2) and dried over anhydrous sodium sulfate. After removal of the solvent in vacuo, the residue was purified by silica gel chromatography eluting with MeOH/DCM. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

Table 7. Structure, Melting Point, Yield, and LC−MS for Some Representatives of **16** and **20**



Entry	R_1	R_2	R_3	R	mp (°C)	Yield(%)[a]	LC–MS
16a		–CH_3	–H	–H	230.8–232.9	50.7	246.3[b] 247.1[c]
16b		–CH_3	–H	–H	208.6–210.2	43.7	272.3 273.0
16c		–CH_3	–H	–H	137.8–140.2	43.2	322.4 323.2
16d[d]		–Ph	–H	–H	149.9–151.2	83.9	430.5 430.9
16e		–C_2H_4Ph	–H	–H	Oil	61.8	394.5 395.0
20a		–CH_3	–H	–CH_3	47.0–48.7	54.6	286.3 287.1

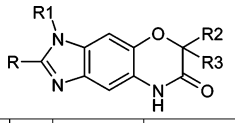
[a] Purified yields for four steps from **1**. [b] Calculated molecular weight. [c] Found molecular weight by positive-ion scanning using electrospray ionization (see details in the experiment section). [d] A mixture of two enantiomers.

Preparation of 11. One equivalent of aldehyde was added with stirring at room temperature to 0.2 mmol of **4** in 5 mL of anhydrous MeOH. Fifteen minutes later, 1.0 equiv of carboxylic acid and 1.0 equiv of isocyanide were added. The reaction mixture was stirred vigorously at room temperature. After the reaction was finished, as monitored by LC−MS, the solvent was evaporated. The crude product **11** was further purified by crystallization or silica gel chromatography, eluting with EtOAc and petroleum ether. The listed compounds, except for **11b**, a mixture of four isomers, were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

Preparation of 14. Compound 14 was obtained after the reduction of **13** by the Pd/C−$HCOONH_4$ or $Na_2S_2O_4/KCO_3$ method. The reaction was monitored by LC−MS. The control step of dehydrogenation was accelerated and totally completed within 30 min with microwave assistance (power, 250 W; pressure, 250 psi; temperature, 150 °C). After evaporation of the solvent, crude **14** was purified by silica gel column chromatography eluting with EtOAc and petroleum ether. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

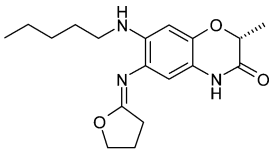
Preparation of 15. Aldehyde (1.5 equiv) in 2 mL of anhydrous EtOH was quickly added to compound **14′** in THF and ethanol (3 mL, v/v = 1:1), followed by the addition of 150 μL of acetic acid. The reaction mixture was stirred at

Table 8. Structure, Melting Point, Yield, and LC−MS for **17** and **21**



Entry	R_1	R_2	R_3	R	mp (°C)	Yield (%)	LC–MS
17a		$-CH_3$	–H	–SH	291.6–292.6	86.4[a]	305.4[b] 306.2[c]
17b		$-CH_3$	–H	–SH	269.0–270.5	93.3[a]	335.4 336.1
17c[d]		$-CH_3$	–H	–SH	144.2–145.7	72.9[a]	333.5 334.1
17d		$-CH_3$	–H	–SH	> 300	67.9[a]	303.4 304.2
17e		$-CH_3$	–H	–SH	> 300	86.4[a]	339.4 340.1
17f[d]		–Ph	–H	–SH	249.6–251.4	46.8[a]	339.4 340.1
17g		$-C_2H_4Ph$	–H	–SH	201.5–203.4	61.6[a]	425.6 425.9
21a		$-CH_3$	–H		147.1–149.5	85.4[e]	467.6 468.2
21b[d]		$-CH_3$	–H		164.0–165.9	70.7[e]	469.6 470.1
21c		$-CH_3$	–H		82.7–83.4	60.2[e]	453.6 454.2
21d[d]		$-CH_3$	–H	$-SCH_3$	71.6–73.0	62.5[e]	347.5 348.1

[a] Collected yields for four steps from **1**. [b] Calculated molecular weight. [c] Found molecular weight by positive-ion scanning using electrospray ionization (see details in the experiment section). [d] A mixture of two enantiomers. [e] Purified yields for deriving the mercapto groups.



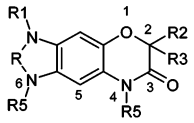
15'

Figure 4. Structure of the byproducts of **15′**.

room temperature for at least 4 h. Then, 5.0 equiv of aminomethyl polystyrene resin was added to scavenge the excess aldehyde. The resin was filtered off and washed with DCM and EtOH until the aldehyde was completely removed, as determined by LC−MS. The combined filtrates were evaporated in vacuo to give **15**, which was purified by silica gel column chromatography, eluting with EtOAc/petroleum ether or DCM/MeOH. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

Preparation of 16. One milliliter of AcOH was added to compound **14′** in THF and ethanol (3 mL, v/v = 1:1),

Table 9. Structure, Melting Point, Yield, and LC−MS for **18**, **19**, and **22**



Entry	R_1	R_2	R_3	R	R_5	mp (°C)	Yield (%)[a]	LC–MS
18a		$-CH_3$	–H	–CO–	–H	251.6–253.5	65.0	289.3[b] 290.2[c]
18b[d]		$-CH_3$	–H	–CO–	–H	264.3–264.5	74.4	303.3 304.1
18c		$-CH_3$	–H	–CO–	–H	210.0–211.1	84.4	305.3 306.1
18d[d]		–Ph	–H	–CO–	–H	232.2–234.0	77.4	445.5 445.9
18e		$-C_2H_4Ph$	–H	–CO–	–H	177.4–180.0	96.9	379.5 380.0
22a		$-CH_3$	–H	–CO–	$-CH_3$	72.3–73.9	50.9	317.4 318.2
19a		$-CH_3$	–H	-COCO-	–H	230.0–232.0	20.5	289.3 290.1
19b		$-CH_3$	–H	-COCO-	–H	208.7–212.1	19.2	315.3 316.0

[a] Purified yields for four steps from **1**. [b] Calculated molecular weight. [c] Found molecular weight by positive-ion scanning using electrospray ionization (see details in the experiment section). [d] A mixture of two enantiomers.

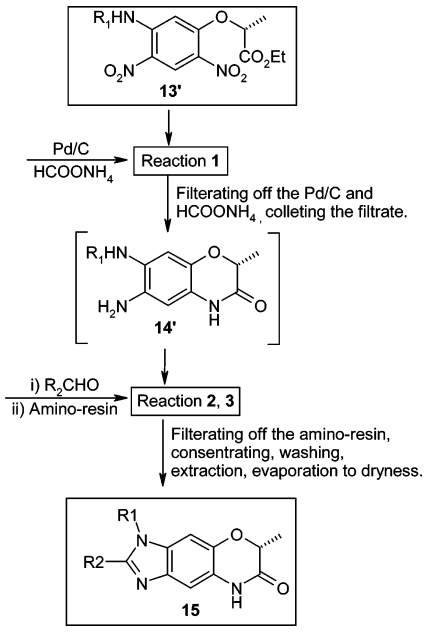
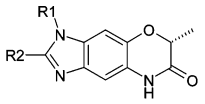


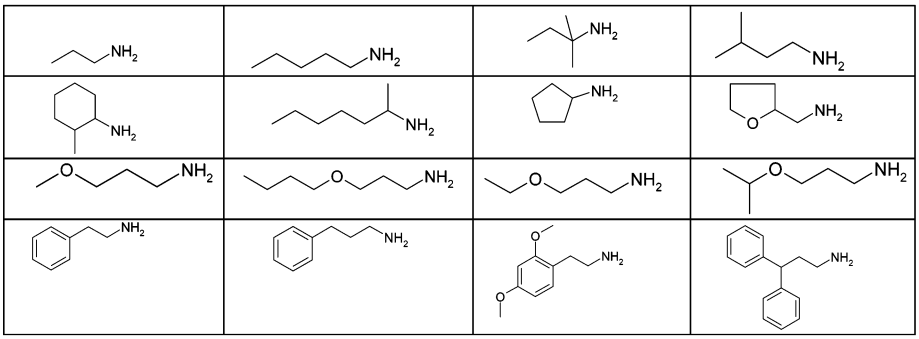
Figure 5. Flow chart of the library synthesis of scaffold **15**.

followed by the addition of 3.0 equiv of $NaNO_2$ in 1 mL of water. The reaction solution quickly turned red. After approximately 30 min or longer, the reaction solution was neutralized with saturated sodium bicarbonate to pH 8 and extracted with EtOAc (4 mL × 3). The organic layer was separated and washed with saturated sodium chloride (4 mL × 2), and then it was dried over anhydrous Na_2SO_4. The



15

R_1 primary amines



R_2 aldehydes

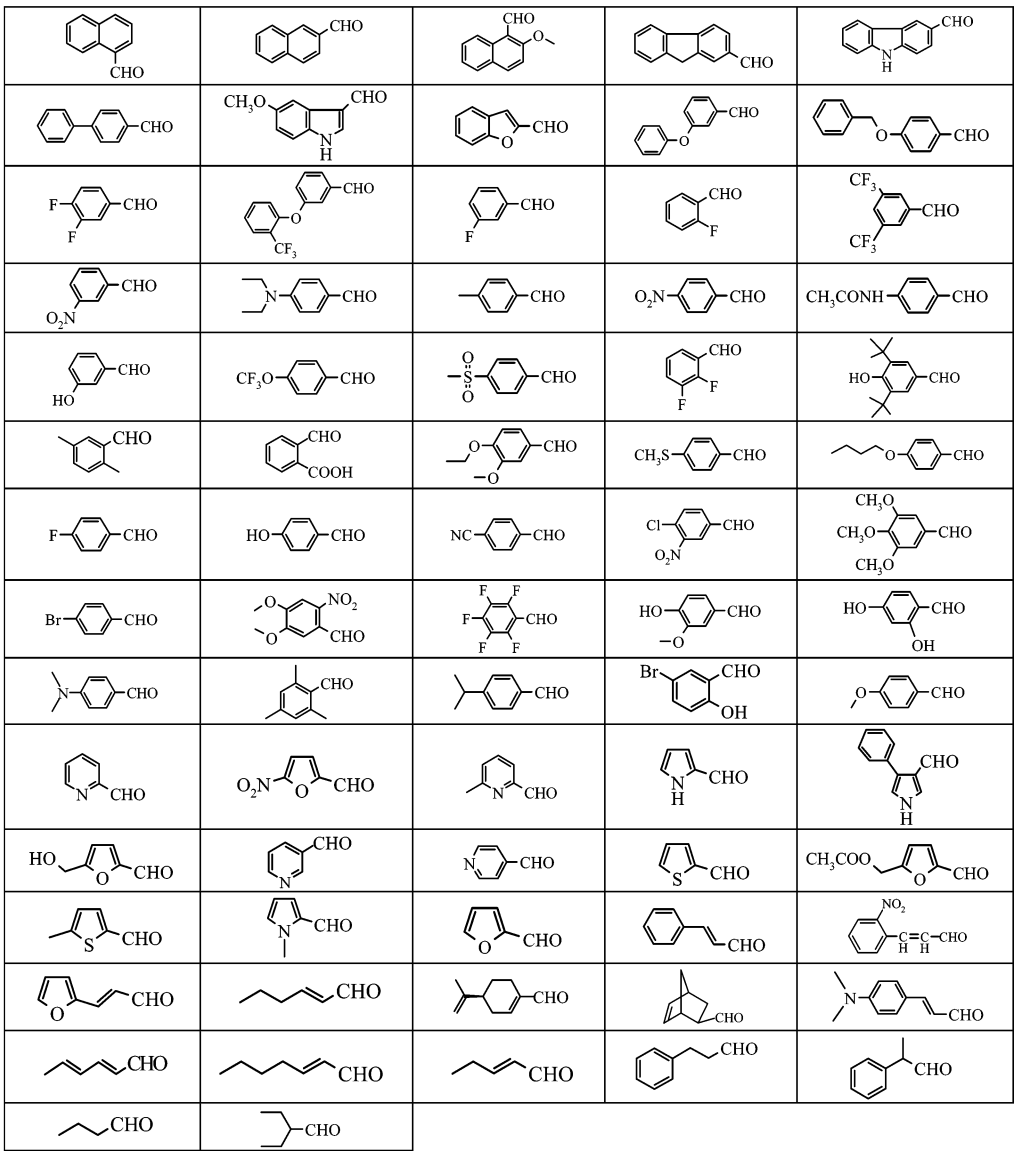


Figure 6. Building blocks of the 3,8-dihydro-5-oxa-1,3,8-triazacyclopenta[b]naphthalen-7-one library.

solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography, eluting with EtOAc and petroleum ether. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

Preparation of 17. Two milliliters of water was added to

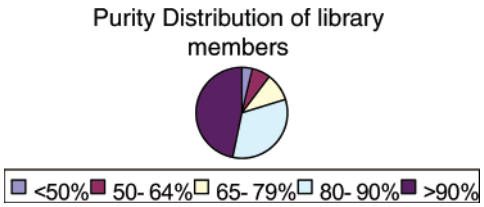


Figure 7. Purity distribution of library members.

compound **14′** in THF and ethanol (3 mL, v/v = 1:1), followed by the addition of 15 equiv of CS_2. The reaction solution was stirred vigorously at room temperature. The mixture was continuously stirred for an additional 3 h at room temperature after a pink to deep purple precipitate appeared. The precipitate, **17**, was collected by filtration and washed thoroughly with water. After it was dried, the precipitate was directly characterized by ^{1}H NMR for all compounds and ^{12}C NMR for typical compounds, see the Supporting Information.

Preparation of 18. Two equivalents of DIPEA and 1/3 equiv of triphosgene were added to compound **14′** in THF (3 mL). The reaction solution immediately turned bright purple. The reaction solution was continuously stirred at room temperature for at least 5 h. The white salt was filtered off, and the filtrate was concentrated under reduced pressure. The crude sample was purified by silica gel chromatography, eluting with EtOAc and petroleum ether. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

Preparation of 19. One equivalent of $(COCl)_2$ and 3.0 equiv of DIPEA in 10 mL of toluene were added dropwise to compound **14′** in 1,4-dioxane (3 mL) at room temperature within 1 h. The reaction solution was then refluxed at 130 °C for 24 h under argon protection. The solvent was removed under reduced pressure, and water was added to the residue. The anticipated compound was extracted with DCM (15 mL × 3) and then washed with brine (15 mL × 2). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated in vacuo to give crude product **19**, which was purified by silica gel chromatography, eluting with MeOH and DCM. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

Alkylation of the Amide-NH of 16e and 18a. Compound **16e** (or **18a**, 0.1 mmol) was dissolved in toluene (10 mL), followed by the addition of a 10 molar excess of NaH. The reaction mixture was vigorously stirred at 130 °C for 5 h. After the white turbid solution was naturally cooled to room temperature, 1.0 equiv (or 2.0 equiv) of alkyl halide was added. The mixture was continuously stirred at room temperature for 2 h and then heated to 130 °C for at least 10 h. The solvent was removed under reduced pressure, and water was added to the residue. The mixture was extracted with EtOAc (15 mL × 3) and washed with brine (15 mL × 2). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated in vacuo. The crude product **20a** (or **22a**) was purified by silica gel chromatography, eluting with EtOAc and petroleum ether. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

Preparation of 21. Three milliliters of EtOAc was added to a reaction tube containing **17** (0.2 mmol), followed by the addition of 1.0 equiv of alkyl halide or α-halogen ketone. The microwave-assisted conditions were set as follows: power, 100 W; pressure, 100 psi; temperature, 60 °C; hold time, 25 min. Evaporation of the solvent gave **21**, which was purified by silica gel chromatography, eluting with EtOAc and petroleum ether. The listed compounds were characterized by ^{1}H NMR for all compounds and ^{13}C NMR for typical compounds, see the Supporting Information.

General Procedure for Library Synthesis. One hundred milligrams of $HCOONH_4$ and 200 mg of Pd/C were added with vigorous magnetic stirring to the solution of **13′** (0.05 mmol) in 1 mL of THF and 1 mL of anhydrous EtOH. The catalyst and excess undissolved $HCOONH_4$ were filtered off as soon as the mixture turned colorless using our parallel filtering apparatus.[37] The filtrates were filtered into additional reaction vessels containing 0.075 mmol of coded aldehyde and 150 μL of AcOH in 1 mL of EtOH. All the reaction vessels were stirred and heated overnight at 40 °C by an H+P Labortechnik GmbH parallel synthesizer. Then, 150 mg of aminomethyl polystyrene resin was added to each reaction vessel, and the mixtures were continuously stirred at 40 °C until the excess of aldehyde was completely removed, as shown by LC−MS detection. The resin was then filtered and washed with DCM and EtOH using our parallel filtering apparatus again. The combined filtrates of each vessel were concentrated under reduced pressure using an HT-4 series Genevac evaporator. Three milliliters of DCM and 5 mL of saturated $NaHCO_3$ were then added to each residue and fully mixed. The organic layers were collected using 5 mL phase separators and then completely evaporated. All the compounds were finally analyzed by LC−MS and LC−ELSD.

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR characterization of synthetic compounds (**4**−**22**). This material is available free of charge via the Internet at http://pubs.acs.org.

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