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2-Oxo-1,2-ethylenedioxy group as a linker for solution-, liquid-, and solid-phase syntheses to discover drug-like small molecules

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Abstract—2-Oxo-1,2-ethylenedioxy (2-OED) functionality has been prepared on a soluble MPEG polymer and solid (HM resin and Lanterns) supports as platforms for discovery of drug-like small molecules. The functionality is cleaved either by $Yb(OTf)_3$ or $TMSCHN_2$ in MeOH, or by various amines to release small molecules synthesized on the platform in good yield. Application of these platforms aiming for discovery of potent agonists for growth hormone secretagogue is reported by using the Ugi four-component coupling reaction.

Polymer-supported synthesis is now realized as an efficient strategy to discover drug-like small molecules used for biological study such as chemical genetics where small molecules play a central role.[1] Experimentally, polymer-supported synthesis is used, (1) to realize a small molecules library by means of diversity-oriented organic synthesis[2] as a source of biologically interesting molecules, and (2) to resynthesize hit compounds found from the library by biological screening.[3] Polymers used in these studies are, in most cases, a soluble polymer such as poly(ethylene glycol) (PEG) and an insoluble polystyrene-based cross-linked polymer.

Our strategy for construction of a small molecules library containing thousands of privileged structure, as well as for resynthesis of hit compounds is summarized in Table 1. Process development is at first studied in the solution-phase or in the liquid-phase using PEG[4] to find the best reaction conditions which provide the desired products in good yield. One advantage in using PEG over a solution-phase platform here is that it allows isolation of chemically unstable intermediates such as an imine compound. The same reactions are also attempted on solid-phase using small bead support, and after fine tuning of the reaction conditions, a diverse collection of small molecules can be constructed on the support. For a small size library (less than a thousand), a liquid-phase synthesis may be used. PEG is soluble in most solvents, and hence provides rapid reaction rate, except for ethers such as diethyl ether or *tert*-butyl methyl ether where PEG easily precipitates.[4–6] Once the library is constructed, it is submitted to biological screening. Hit compounds found from the screening are then needed to be synthesized in a larger scale for quantitative evaluation of the activity. This is carried out in either liquid-phase or solid-phase using a bigger support such as SynPhase™ Lanterns so that even chemically unstable intermediates are treated easily.

To develop the chemical studies described above efficiently, a linker of the same chemical structure should be used to reproduce the reactivity of the small molecules even on a different support. Here, we report the application of the ester-type linker, named 2-oxo-1,2-ethylenedioxy (2-OED, Fig. 1) group, on a soluble PEG polymer as well as insoluble cross-linked polystyrene-based polymers, HM resin and Lanterns, aiming for discovery of drug-like small molecules. Though the linker has been used for the synthesis of hydantoin[7] and 1,4-benzodiazepine-2,5-dione[8] derivatives on PEG polymer, mild cleavage conditions have so far not been explored. The cleavage procedures have been established here, and some multi-component coupling products have been prepared on these platforms to discover strong agonists for growth hormone secretagogue (GHS).

In the present study, we used a soluble poly(ethylene glycol) monomethyl ether (MPEG-OH) and an

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Table 1. Chemical strategy aiming for discovery of drug-like small molecules

	Solution-phase	Liquid-phase (PEG support)	Solid-phase (small bead support)[a]	Solid-phase (big Lantern support)[a]
Process development	✓	✓		
Library realization		✓[b]	✓	
Resynthesis of hit compounds		✓		✓

[a] Density of a functional group is <2 nm for one bead and 16 μm for one unit of Lantern in the present study.
[b] Applied for a synthesis of <1000 compounds.

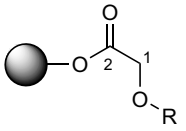


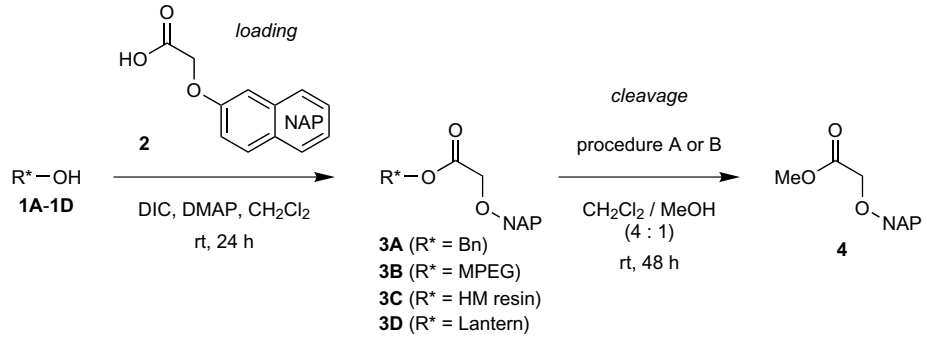
Figure 1. 2-Oxo-1,2-ethylenedioxy (2-OED) linker.

insoluble cross-linked polymer bearing a hydroxymethyl (HM) functional group, namely HM resin and hydroxymethylated SynPhase™ Lanterns,[9] since it is one of the simplest and hence is inexpensive, and in addition, it is reusable.

Introduction of small molecules onto polymers via the 2-OED linker was effected by direct acylation with phenoxyacetic acid derivatives. The results for loading 2-naphthol on various supports via the 2-OED linker are summarized in Table 2. Supports used were benzyl alcohol (solution-phase experiments (run 1)), MPEG-OH (run 2), HM resin (run 3), and Lanterns (run 4).[10] Generally, yields for the loading reaction were found to be satisfactorily good (87–100% yield) with (2-naphthoyl)oxyacetic acid (**2**) by the use of 1,3-diisopropylcarbodiimide (DIC) and DMAP in CH_2Cl_2 at rt for 24 h.[11]

Cleavage reaction to release small molecule **4** was next attempted. As had been expected from our earlier study with the alkoxyacetyl (AAc) linker,[6] the cleavage by $Yb(OTf)_3$ (procedure A) proceeded quantitatively in both solution and liquid-phases using CH_2Cl_2–MeOH (4:1) as a solvent (runs 1 and 2).[12] For solid-phase cleavage from **3C** and **D** (runs 3 and 4), the yields were lower than the homogeneous reaction probably because these insoluble supports are not swollen sufficiently in the solvent system employed. In comparison with $Yb(OTf)_3$, the cleavage was effected in better yield satisfactorily by the use of $TMSCHN_2$ (procedure B); it was quantitative for both solution and liquid-phases (runs 1 and 2), and the yields were around 90% for cleavage from the solid-phase (runs 3 and 4).[13] The cleavage is also effected by various amines. Thus, by treatment of the polymer **3** with $EtNH_2$ in water at rt for 40 h, *N*-ethyl (2-naphthyl-

Table 2. Loading and cleavage yields of 2-naphthol on various support, via the 2-OED linker

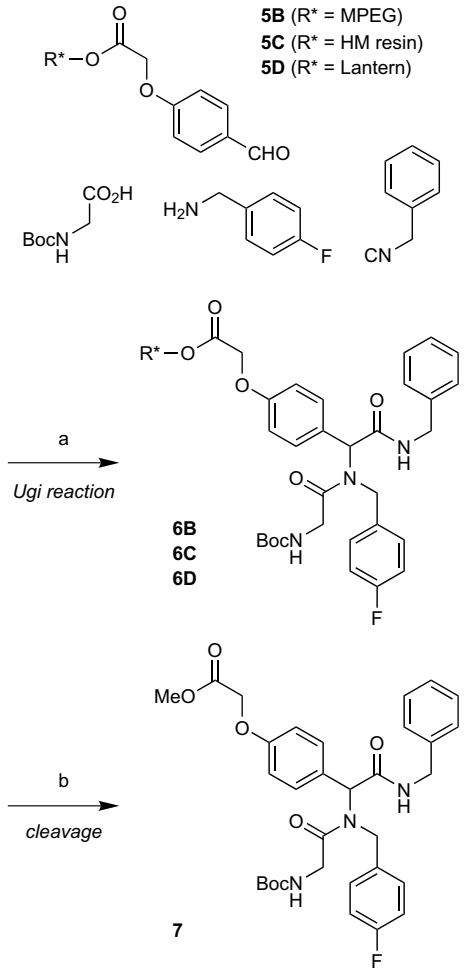


Run	Phase	R*-OH	Product and loading yield (%)	Cleavage yield for **4** (%)[d]	
				Procedure A[e]	Procedure B[f]
1	Solution	Benzyl alcohol (**1A**)	**3A** (93)[a]	>99[a]	>99[a]
2	Liquid	MPEG-OH (**1B**)	**3B** (>99)[b]	>99[g]	>99[g]
3	Solid	HM resin (**1C**)	**3C** (87)[c]	84[g]	91[g]
4	Solid	Lantern (**1D**)	**3D** (>99)[c]	61 (90)[g,h]	89[g]

[a] Yield for chromatographically pure compound.
[b] Determined by ^1H NMR (500 MHz).
[c] Determined by weight gain of the polymer after the reaction.
[d] In all cases, R*-OH (**1A**–**D**) were recovered after the cleavage quantitatively.
[e] 30 mol% of $Yb(OTf)_3$ was used.
[f] 10 equiv of $TMSCHN_2$ (hexane solution) was used.
[g] Cleaved **4** from the polymer was pure (>95%) as judged from ^1H NMR (500 MHz).
[h] In parentheses is a combined yield after second cleavage.

oxy)acetamide was obtained in 80% and >99% yields for **3C** and **D**, respectively (data not shown).[14]

With these results in hand, we carried out multi-component coupling reactions to show the usefulness of these platforms in construction of a small molecules library. The reaction demonstrated here is a Ugi reaction which is a four-component coupling reaction between aldehyde, amine, isonitrile, and carboxylic acid to synthesize α-(acylamino)carboxylic acid amide.[15] *N*-Boc-glycine, 4-fluorobenzylamine, and benzyl isocyanide were independently treated with 4-substituted benzaldehyde immobilized onto MPEG (0.18 mmol/g), HM resin (1.32 mmol/g), and Lanterns (16 μm/unit), prepared by acylation of **1B**–**D** with 2-(4-formylphenoxy)acetic acid in >94% yield. The optimized conditions and the result for each platform are shown in Scheme 1. A standard solvent, MeOH, gave a reasonable result (82% yield) for MPEG-immobilized aldehyde **5B**. For HM resin **5C** and Lantern **5D**, CH_2Cl_2, and THF were needed as co-solvents to swell the polymer, respectively. In these solvent systems, the reaction proceeded in a comparable



Scheme 1. Reagents and conditions: (a) (for **5B**) MeOH, rt, 24 h, 82%; (for **5C**) MeOH–CH_2Cl_2 (4:1), 40 °C, 48 h, 81%; (for **5D**) MeOH–THF (2:1), 50 °C, 24 h, 62%, (b) $Yb(OTf)_3$ (30 mol%), MeOH–CH_2Cl_2 (1:4), rt, 48 h, 99% from **6B**, 80% from **6C**, and 62% from **6D**; $TMSCHN_2$ (10 equiv), MeOH–CH_2Cl_2 (1:4), rt, 48 h, 99% from **6B**, 90% from **6C**, and 52% from **6D**.

yield (81%) for HM resin and in a lower but an acceptable yield (62%) for Lantern. The reaction temperature was specific to the polymer supports; the reaction proceeded smoothly at rt in the liquid-phase (**5B**), whereas heating up to 40–50 °C was required for HM resin **5C** and Lantern **5D**, respectively, to lead the reaction to completion. As for the reaction time, the reaction was completed within 24–48 h for MPEG **5B** and HM resin **5C**, respectively. In contrast to this, the Ugi reaction with Lantern-immobilized aldehyde **5D** stopped after 24 h, and prolonged reaction time did not improve the yield.

Release of small molecule **7** from the polymer supports was effected by the same two procedures, A and B, shown in Table 2. In both cases, the cleavage proceeded in the range of good (Lanterns) to excellent (MPEG) yields. In view of the operational efficiency, the procedure using $TMSCHN_2$ is advantageous over $Yb(OTf)_3$, since the reagent can be easily removed under reduced pressure after the reaction.

Our attention then moved to a practical application of these strategies to discover biologically active small molecules. The privileged scaffold shown in Figure 2 has been recently discovered as a potent agonist for growth hormone secretagogue (GHS) which controls the release of growth hormone from somatotrophs in the pituitary gland at the low-micromolar level.[16] With this significantly different structure from known GHS agonists, we have determined to construct an appendage diverted library to discover more potent GHS agonists. Though the structure was shown to be readily accessible by the Ugi reaction, details for synthetic work are not reported. Our strongest concern was to realize the Ugi reaction between such heavily functionalized components on the polymer support. Here, two aldehydes immobilized on HM resin (**5C** and its *meta*-isomer) were used for the aldehyde component in combination with two carboxylic acids (5-phenyl-2-pyrrolecarboxylic acid and 5-(2-methoxyphenyl)-2-pyrrolecarboxylic acid)[17] and two amines (3-(diethylamino)propylamine and *N*-(3-aminopropyl)diethanolamine). In all reactions, cyclohexyl isocyanide was used. Efficient reaction conditions, which provide the scaffold in Figure 2 by the Ugi reaction were at first explored using the aldehyde **5C** immobilized on HM resin, since our first goal is construction of a GHS agonist library comprising thousands of small molecules. Though the same reaction conditions used for the synthesis of **6C** (Scheme 1) gave the product in only a trace amount (<20% yield), we found that addition of a catalytic amount of perchloric acid was effective for improvement of the yield after several experiments. With the optimized reaction conditions,

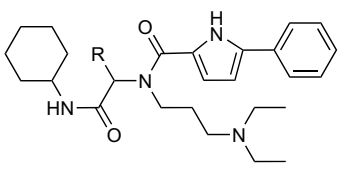
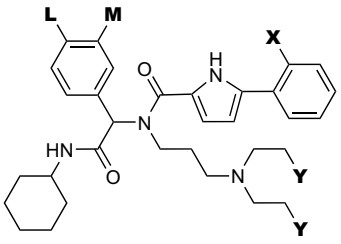


Figure 2. A GHS agonist scaffold (R = alkyl, aryl).[16]

Table 3. Preparation of GHS agonist candidates on the HM resin[a,b]



		Y	
		H	OH
X	OMe	90%[c]	>99%[d]
	H	60%[c]	>99%[d]

[a] For experimental procedures, see Scheme 1. In all cases, a catalytic amount of perchloric acid was added to the reaction mixture. Cleavage was effected by $TMSCHN_2$.

[b] Yields are for two steps including Ugi and cleavage reactions, and were determined by LC–MS.

[c] HM resin-immobilized aldehyde **5C** was used for an aldehyde component. **L** = –O–CH_2COOMe, **M** = H.

[d] The *meta*-substituted aldehyde corresponding to **5C** was used for an aldehyde component. **L** = H, **M** = –O–CH_2COOMe.

we have successfully synthesized the appendage-diverse GHS agonist candidates in good yield on the platform comprising HM resin and 2-OED linker (Table 3). To the best of our knowledge, this is the first example for perchloric acid-assisted solid-phase Ugi reaction.[18]

We have thus shown that the 2-OED linker on the HM resin is an efficient platform to synthesize the GHS agonist candidates rapidly. We are now applying the method to construct a library comprising thousands of the drug candidates on the platform. We have also shown the usefulness of the linker in combination with MPEG and Synphase™ Lanterns for resynthesizing hit compounds to be found from biological evaluation of the library. The 2-OED linker will be widely used for discovery of drug-like small molecules through both liquid-phase and solid-phase organic syntheses because of its (1) ready availability on various polymer supports, (2) chemical stability, (3) chemospecific reactivity under cleavage conditions, and (4) ability to provide moderate to excellent reactivity to small molecules loaded on both soluble and insoluble cross-linked polymers.

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9. MPEG-OH, HM resin, and SynPhase™ Lanterns were purchased from Aldrich Co. (catalog no. 20251-7), Advanced ChemTech, Inc. (catalog no. SA5020), and Mimotopes Pty Ltd (catalog no. SP-PS-L-HOM-015), respectively.
10. Polymers were recovered after the reactions by precipitation using diethyl ether for the liquid-phase synthesis, and by a simple washing in a stopcock-connected column for the solid-phase synthesis.
11. A stepwise reaction comprising acylation with bromoacetic acid followed by nucleophilic addition of phenol-type nucleophile is also effective. For the synthesis of **3B** (MPEG) and **3C** (HM resin), the loading proceeded in good yield (89%) and in poor yield (25%), respectively. The low yields are due to low reactivity of phenols toward alkyl bromide on the cross-linked polymer. Since various derivatives can be commercially available for phenol, we are now investigating high yield loading procedure via nucleophilic addition of phenol derivatives.
12. As can be seen in run 1, (2-naphthyloxy)acetyl group is potentially useful for an efficient protecting group of hydroxy functionality. For phenoxyacetyl group for protection of secondary alcohol, see; Shimada, K.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 4048–4049.
13. Since the reaction takes place by the nucleophilic attack of MeOH used as a solvent in the presence of basic $TMSCHN_2$, the cleavage in various solvents is under investigation.
14. Other amines such as $MeNH_2$, $^nPrNH_2$, $^nBuNH_2$, allylamine, ethylenediamine, and piperidine were also effective for the cleavage.
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