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Parallel synthesis of 2-alkoxy and 2-acyloxyphenylpropyl amides and amines using dihydrocoumarins as versatile synthons. Application of a novel resin quench-capture method.

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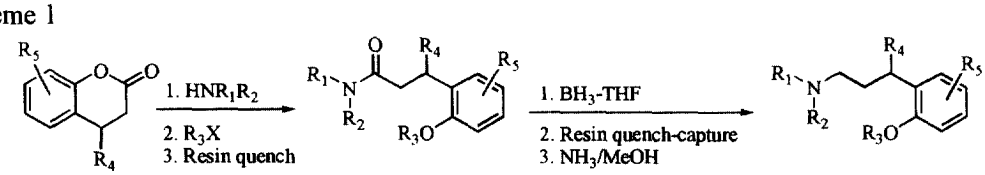
Abstract: A solution phase synthesis for the preparation of libraries of 2-substituted phenylpropyl amines and amides was accomplished using dihydrocoumarins as a useful synthon in parallel synthesis. Resin quench methods were utilized in the purifications of the amides and a resin quench-capture method was utilized in metallo-organic reductions leading to the targeted phenylpropyl amines.

Parallel synthesis has developed into a powerful tool toward the creation of new chemical entites for drug discovery.[1] The ultimate goal is to avoid the disadvantages of synthesizing compound mixtures by rapidly preparing a single compound in solution. Our goal was to produce single-substance libraries using known and dependable chemical transformations. These libraries focused on the preparation of molecules which contain a known pharmacophoric constituent, namely 2-alkoxyphenylpropyl amides **2** and amines **3** (scheme 1). This constituent is prominent in bioactive molecules such as melatonergic agonists,[2] 5 HT1A agonists,[3] anxiolytic agents[4] and agents for the treatment of cognitive disorders.[5]

Scheme 1



1 2 3

Herein, we report the use of dihydrocoumarin and 4-substituted dihydrocoumarins as versatile components in the preparation of diverse libraries which contain 2-alkoxyphenylpropyl amide and amine pharmacophores. We also report the novel use of resin quench-capture in the metal hydride reduction of amides in a parallel array. Resin was used in a tandem process for the synthesis, isolation and purification of the aforementioned amine targets.

Dihydrocoumarins were exploited as versatile synthons in amidation reactions for the synthesis of a variety of secondary and tertiary amides in parallel. Five examples of a 300

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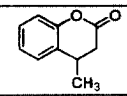
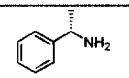
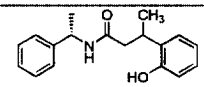
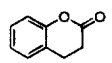
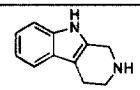
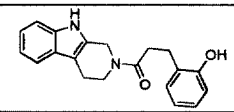
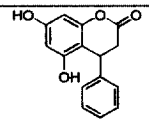
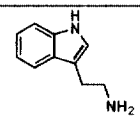
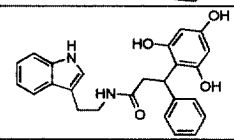
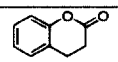
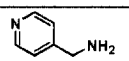
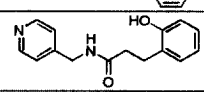
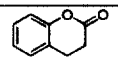
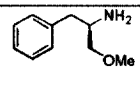
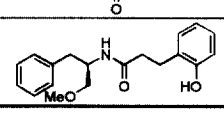
member library are shown in table 1. Rupture of the coumarin lactone enabled further functionalization by unmasking the phenol (table 2). Synthesis and purification of the targeted 2-acyloxy, and 2-alkyloxyphenylpropyl amides was achieved using liquid-liquid extraction or a scavenger, tris(2-aminoethyl)amine, polymer bound WA21J resin.[6] Excess electrophile was easily removed from the reaction mixture by immobilization using resin quench. This process typically afforded >85% pure[7] desired product.

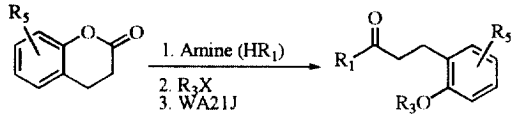
Table 1. Examples of secondary and tertiary amides prepared in parallel.

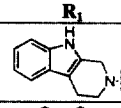
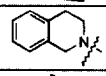
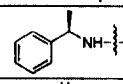
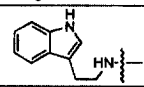
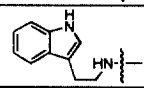
Entry	Coumarin[a]	Amine	Product	% Yield
1				65
2				89
3				62
4				96
5				97

[a]4-Substituted coumarin adducts required purification.

Drawbacks in preparing large numbers of compounds ultimately arise when purification procedures are necessary to obtain pure substances. These problems are amplified when the targeted compounds are water soluble and simple phase extractions are no longer feasible. Using resin capture methods in their preparation, isolation and purification simplifies the task.[8] The amides were reduced to the respective amine targets using diborane (table 3). Typical metallo-organic work-up or quenching procedures discourage the use of diborane in parallel synthesis. Also, many amine products tend to be water soluble and difficult to extract out of the aqueous media. However, we overcame these difficulties with the employment of resin quench-quench. In this novel process, we utilized AG 50W-X2[9] resin as our acid source for metallo-organic quench and as an immobilizer of the basic product. This sulfonic acid-styrene type resin, a product of commerce, has an effective large pore size and a total capacity of 5.2 meq/dry gram. The resin was employed not only to break the boron-amine complex but also to "capture" the product. This allows for rapid and efficient purification of the product amines. By using this quench-capture method,[10] any reagents or unreacted starting materials can be washed away from the resin-amine complex. The amines are released from the resin by treatment with an ammonia solution. All products derived from this method were >95% pure,[7] if not analytically pure.

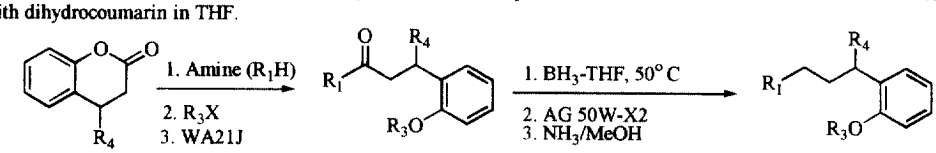
Table 2. Examples of representative alkylations and acylations of the phenol derived from the reaction of an amine with dihydrocoumarin in THF.

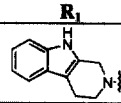
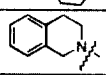
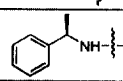
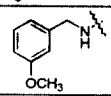
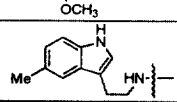


Entry	R_1	R_3	R_5	Yield[a]
1		CH_3	H	54
2		Ac	H	78
3		CH_3	H	77
4		$-CH_2(CH)_2CO_2CH_3$	H	78
5		4-NitroBz	H	67

[a]Overall yields.

Table 3. Examples of representative alkylations, acylations and subsequent reductions of the amides derived from the reaction of an amine with dihydrocoumarin in THF.



Entry	R_1	R_3	R_4	% Yield[a]
1		H	H	84
2		H	H	73
3		CH_3	CH_3	51
4		H	CH_3	79
5		H	H	81

[a]Overall yields.

In summary, we have demonstrated an effective synthesis of a large number of defined compounds using commercially available dihydrocoumarins as a useful element in the production of diverse libraries in parallel synthesis. We have also demonstrated that the employment of metal-hydride reductions can be amenable to parallel synthesis using resin quench-capture methods. Moreover, we have shown that the resins described herein

can be utilized to trap electrophiles, quench metallo-organic aggregates derived from metal hydride reductions, and to capture the resultant products in rapid parallel fashion.

References and notes:

1. Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chemie* **1996**, *35*, (20), 2289.
2. Takaki, K.S.; Karageorge, G.N.; Keavy, D.J.; Parker, M.F.; Watson, B.T. Eur. Patent Appl. EP 95-402197 950929.
3. (a) Kitamura, Y. *Jpn J. Pharmacol* **1997**, *73* (suppl.1), 354. (b) Kogami,Y. and Mochizuki, D. World Patent, **1994**, WO 9415930;940721.
4. Kogami, Y. World Patent, **1996**, WO 9601816.
5. Hayashi, K. and Linuma, M. Eur. Patent Appl. EP 515917.
6. (a) Booth, R.J.; Hodges, J.C. *J. Am. Chem. Soc.* **1997**, *119*, 4882. (b) Dianion WA21J resin purchased from Supelco.
7. As confirmed by ^{1}H-NMR analysis and Hewlett Packard 1100 MSD LC-MS [Zorbax 2.1 x 50 mm phenyl column eluting with a gradient mixture of acetonitrile and 0.1% aqueous TFA (80:20 to 20:80) monitored at 254 nm].
8. (a) Fiorini, M.T.; Abell, C. *Tetrahedron Lett.* **1998**, *39*(13), 1827. (b) Chen, C.; Mcdonald, I.A.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*(3/4), 217. (c) Brown, S.D.; Armstrong, R.W. *J. Org. Chem.* **1997**, *62*(21), 7076. (d) Brown, S.D.; Armstrong, R.W. *J. Am. Chem. Soc.* **1996**, *118*(26), 6331.
9. Large pore, polystyrene sulfonic acid resin, 100-200 mesh, purchased from Bio-Rad Laboratories.
10. General procedure: Dihydrocoumarin (1.169, 7.89 mmol, 1.1 equ.) and 10 mL of THF were added to the 50 mL reaction vessel. 3-Methoxybenzylamine (0.95 mL, 7.17 mmol, 1 equ.) was added and the reaction was shaken for 8 hours. A 1M solution of diborane in THF (10 mL, 1.4 equ.) was added to this reaction mixture and the reaction was warmed to 50°C for 4 hrs. The reaction was cooled to room temperature and ion exchange resin, AG 50W-X210 (20 grams, 20 fold mass of starting amine), water (5 mL) and MeOH (5 mL) was added. The mixture was shaken for 30 minutes, filtered, and the resin was washed with H_2O (100 mL) and MeOH (100 mL). The filtrate was discarded and the resin was suspended in ammonia (100 mL, 2 M in MeOH), agitated for 30 minutes, and filtered. Concentration of the filtrate yielded the secondary amine (1.0333 g, 53%) analytically pure. Calculated for $C_{17}H_{21}NO_2$ x 0.2 H_2O: 74.26% C; 7.70% H; 5.07% N. Found: 74.60% C; 7.70% H; 5.07% N.