Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 13, pp. 1483-1486, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00253-3

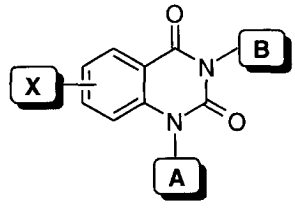
An Efficient Solid Phase Synthetic Route to 1,3-Disubstituted 2,4(1*H*,3*H*)-Quinazolinediones Suitable for Combinatorial Synthesis

Adrian L. Smith,* Christopher G. Thomson, and Paul D. Leeson

Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, United Kingdom. FAX: +44 1279 440390. Email: smithad@merck.com

Abstract: Novel, efficient solid phase chemistry has been developed for the synthesis of 1,3-disubstituted quinazolinediones. Anthranilic acids are linked to a chloroformate resin through the nitrogen, amines are coupled to the free carboxylic acid, and thermal cyclization leads to heterocycle formation and concommitant resin release resulting in traceless linkage. Copyright © 1996 Elsevier Science Ltd

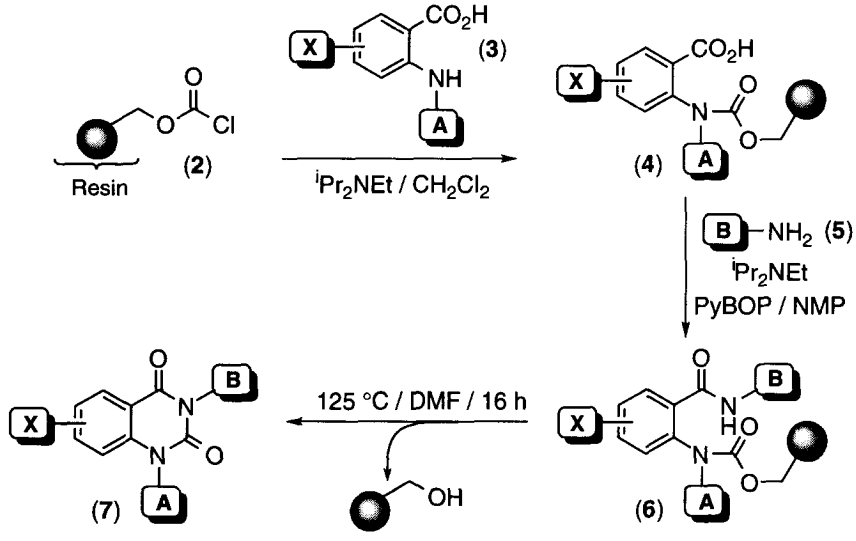
In recent years there has been an explosion of interest in the synthesis and screening of combinatorial libraries for lead generation in the drug discovery process.[1] Whilst much of the early work was devoted to the synthesis of peptide and smaller peptide-like (peptoidal) libraries, there is an increasing realization that 'small molecule' libraries based upon heterocyclic templates are more likely to produce quality leads with the physicochemical / pharmacokinetic properties necessary to make a drug.[2] This is especially true when seeking molecules with activity in the central nervous system (CNS), where the highly polar nature of peptides / peptoids prevents them from easily crossing the blood-brain barrier. There is therefore a need for practical and efficient new methodologies in this area. The quinazolinedione template occurs in a large number of bioactive molecules including serotonergic, dopaminergic and adrenergic receptor ligands and inhibitors of aldose reductase, lipoxygenase, cyclooxygenase, collagenase and carbonic anhydrase.[3] A combinatorial library based upon this template would therefore be expected to provide lead compounds in a wide range of bioassays. We wish to describe here a novel, highly practical and efficient solid phase synthetic approach for the construction of the quinazolinedione template which we have used to build structurally diverse 'small molecule' combinatorial libraries of generic structure (**1**).



(**1**)

Our primary aim at the outset of this work was to devise a solid phase synthetic approach to 1,3-disubstituted quinazolinediones which would not leave an extraneous polar resin-tethering substituent on the resulting molecules which might compromise CNS penetration. We also wanted to be able to incorporate the **A** and **B** substituents in the form of primary amines since there are approximately 8000 suitable commercially available primary amines, and this would provide considerable scope for structural diversity within a library. Experimentation with existing solution phase methods for the synthesis of 1,3-disubstituted quinazolinediones[4]

revealed serious shortcomings when trying to adapt them to solid phase. Particular problems were encountered with the ambident nucleophilicity of anthranilamide systems (e.g. *O*- rather than *N*-acylation) which gave unpredictable results. We therefore developed a new approach to the construction of the quinazolinedione template (**Scheme 1**) which is experimentally very simple, reliable and efficient, and which is eminently suitable for the solid phase construction of combinatorial libraries. Furthermore, the nature of the chemistry results in a traceless solid phase linkage.[2a,2e,2k,5]



Scheme 1. Solid phase synthesis of 1,3-disubstituted quinazolinediones.

A chloroformate-functionalized polystyrene resin (**2**) (loading: ~0.30 mmol/g)[6] was treated individually with a wide range of substituted anthranilic acids (**3**) (3 equiv.) in the presence of Hünig's base (CH_2Cl_2, 20 °C, 1 h) to give the urethane-linked system (**4**). Structurally diverse primary amines (2 x 3 equiv.) were readily double-coupled (individually) to the free carboxylic acid using standard PyBOP conditions (2 x 1h) to give the anthranilamide (**6**). In the final key step of the synthesis, heating this system in DMF at 125 °C for 16 h caused the amide nitrogen to cyclize onto the urethane to generate the 1,3-disubstituted quinazolinedione template and simultaneously liberate the molecule from the resin into solution. Filtration and solvent removal (SpeedVac) then gave the final products lacking any extraneous tethering substituents. Since the molecule is only released into solution if all synthetic steps have worked, the products obtained are of very high purity (>95% in the vast majority of cases). The final cyclization / cleavage conditions were optimized for all combinations of **A** = Me, Ph, Bn and **B** = Ph, Bn, chosen as a representative range of reactivities.[7] Heating at 125 °C for 16 h gave a uniform yield of 0.20 mmol/g for all six permutations of substituents, and purities (HPLC) were in excess of 95%. These yields and purities have been reproduced for a large structurally diverse range of anthranilic acids and amines including the representative examples shown in **Figure 1**.[8,9] This is especially important in library synthesis where it is essential that uniform amounts of each component in a mixture are obtained. At 100 °C, substantially reduced yields were obtained for **B** = Ph (probably a steric factor).[9]

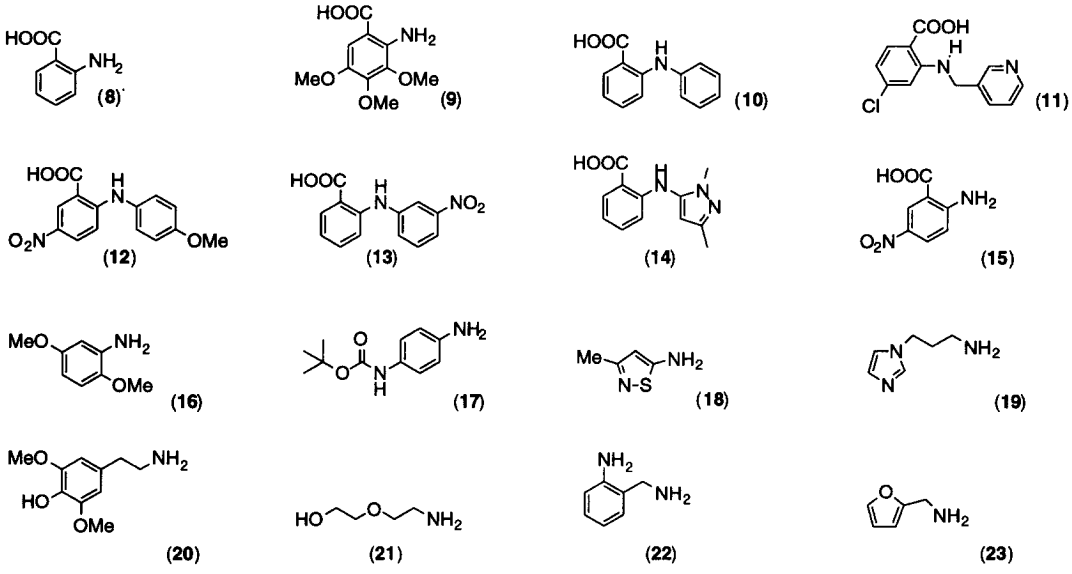
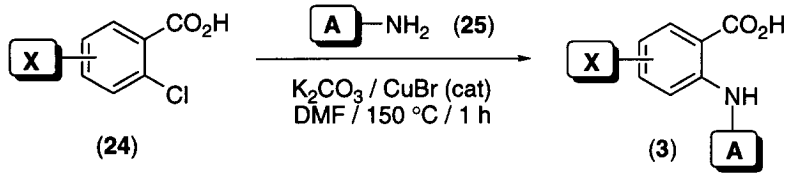


Figure 1. Representative examples of anthranilic acids (**8** → **15**) and primary amines (**16** → **23**) demonstrated to undergo the described chemistry efficiently.

Whilst there are approximately 50 commercially available anthranilic acids suitable for inclusion in a combinatorial library, much greater structural diversity would be achieved if the **A** substituents could be incorporated from primary amines. Fortunately, the modified literature procedure[10] for the synthesis of anthranilic acids shown in **Scheme 2** is ideal for this purpose since the pure anthranilic acid is almost invariably obtained simply by dilution of the reaction mixture with water, filtration, washing and drying. No subsequent purification is necessary. This means that a large number of reactions can be rapidly carried out in parallel.



Scheme 2. Synthesis of anthranilic acids (**3**)

We have successfully used this methodology for the construction of a number of combinatorial libraries based upon the quinazolinedione template using the resin-archived split / mix approach for the generation of combinatorial mixtures.[11] Further modifications of (**6**) prior to cyclization / cleavage are possible, for example by addition of extra subunits to **A**, **B** and **X**. This has been used to synthesize larger libraries making the described chemistry an extremely practical and versatile addition to the repertoire of the combinatorial chemist.

Acknowledgements. The authors thank Mr Steven Thomas for mass spectrometry assistance, Dr Richard Herbert for NMR assistance, and Dr Howard Broughton for helpful discussions concerning the use of topological similarity searching for the selection of structurally dissimilar subunits.

References and Notes

1. (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233 - 1251. (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385 - 1401.

2. (a) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R; Pavia, M. R. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909 - 6913. (b) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997 - 10998. (c) Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4708 - 4712. (d) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306 - 3307. (e) Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47 - 50. (f) Pátek, M.; Drake, B.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 2227 - 2230. (g) Boojamra, C. G.; Burow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 5742 - 5743. (h) Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 5744 - 5745. (i) Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 5748 - 5749. (j) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819 - 7822. (k) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937 - 940.

3. Data obtained from the MDDR database, Molecular Designs Ltd, 2132 Farallon Drive, San Leandro, CA 94577.

4. (a) Jacobs, R. L. *J. Heterocycl. Chem.* **1970**, *7*, 1337 - 1345. (b) Gadekar, S. M.; Kotsen, A. M.; Cohen, E. *J. Chem. Soc.* **1964**, 4666 - 4668. (c) Taub, B.; Hino, J. B. *J. Org. Chem.* **1961**, *26*, 5238 - 5239. (d) Cortez, R.; Rivero, I. A.; Aguirre, G.; Ramirez, F.; Hong, E.; Somanathan, R. *Synthetic Commun.* **1991**, *21*, 285 - 292.

5. (a) Camps, E.; Cartells, J.; Pi, J. *Anales de Quimica* **1974**, *70*, 848 - 849. (b) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006 - 6007. (c) Chenera, B.; Finkelstein, J. A.; Veber, D. F *J. Am. Chem. Soc.* **1995**, *117*, 11999 - 12000. (d) Han, Y.; Walker, S. D.; Young, R. N. *Tetrahedron Lett.* **1996**, *37*, 2703 - 2706.

6. This was conveniently and reproducibly prepared immediately prior to use by reaction of aminomethyl polystyrene resin (1.0 mmol/g) with triethyleneglycol bis chloroformate (3 equiv.), Hünig's base (3 equiv.), CH_2Cl_2, 1 h, 20 °C. Loading was estimated gravimetrically after subsequent reaction, with the difference in loadings being attributed to cross-linking. The resulting resin has good solvation properties in the solvents used, whilst giving no PEG contamination in products unlike chloroformate-functionalized commercial PEG-grafted polystyrene resins. Reactions were typically carried out on 100 mg - 5 g of resin.

7. Compound identity was confirmed by ^{1}H-NMR, ^{13}C-NMR and MS analysis.

8. All subunits are validated by single compound synthesis and analysis (yield / HPLC / MS) prior to library construction. Virtually all anthranilic acids (**3**) tested worked efficiently (~80), as did a large proportion of the amines (**5**) (>400). The corresponding benzoxazinedione was never observed. Reactions were typically carried out on 10 - 100 mg of resin.

9. Substantially reduced yields (~0.02 mmol/g) were observed for secondary alkyl amines such as cyclohexylamine under the given cyclization conditions (125 °C, 16 h) due to incomplete reaction in the final step. This suggests that steric congestion is impeding the reaction in these cases.

10. Brennan, S. T.; Colbry, N. L.; Leeds, R. L.; Leja, B.; Priebe, S. R.; Reily, M. D.; Showalter, H. D. H.; Uhlendorf, S. E.; Atwell, G. J.; Denny, W. A. *J. Heterocyclic Chem.* **1989**, *26*, 1469 - 1476.

11. Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487 - 493.

(*Received in Belgium* 19 *April* 1996; *accepted* 30 *May* 1996)