Molecular Diversity, **4:** 183–185, 1998.
KLUWER/ESCOM

Parallel solution synthesis of pyridinethiones, pyridinones and thienopyridines

Stephen J. Shuttleworth*, Miguel Quimpère, Nola Lee & Jeancarlo DeLuca
Biochem Pharma Inc., 275 Armand-Frappier Boulevard, Laval, Québec, Canada H7V 4A7

Received 26 May 1999; Accepted 15 June 1999

Key words: library-from-library, parallel synthesis, 'privileged templates'

Summary

The parallel solution synthesis of three classes of heterocycles is described. Arrays of pyridinethiones, pyridinones and thienopyridines were prepared using one-step chemistry starting from readily accessible building blocks. The latter class of compounds was accessed by utilising a library-from-library approach.

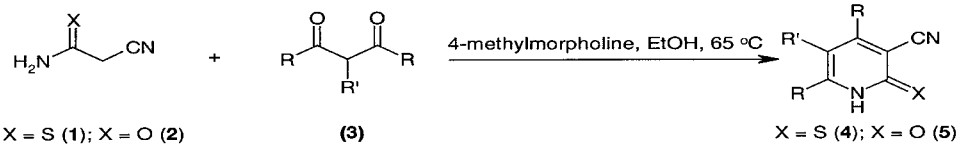
Combinatorial parallel synthesis has become firmly established within the pharmaceutical industry as a means of rapidly producing large numbers of compounds for biological assays in a time- and resource-effective manner [1,2]. Whilst most of the literature focused upon combinatorial parallel synthesis has outlined the use of solid phase chemistry [3], the preparation of compound libraries in solution has, for many years [4], been an accepted approach, and is now beginning to receive deserved literature attention [5].

Pyridinethiones, pyridinones and thienopyridines are 'privileged templates', being present in a number of biologically active compounds. Indeed, pyridinethiones and pyridinones are collectively cited on 847 occasions in the MDDR [6], and thienopyridines are listed 136 times. Pyridinethiones and pyridinones have been examined as activators of CAMP-dependent protein kinase [7a], as $5HT_2$ antagonists [7b], and as inhibitors of HIV reverse transcriptase [7c], whilst thienopyridines have been evaluated as calcium regulators [7d], as 5-lipoxygenase inhibitors [7e], and as carbonic anhydrase inhibitors [7f]. Owing to their apparent calibre as drug-like compounds, we have examined the parallel synthesis of arrays of pyridinethiones, pyridinones and thienopyridines. The preparation of each array was suited to reliable, one-step solution chemistry using readily accessible monomers, and a library-from-library approach was adopted to facilitate the preparation of the thienopyridine array.

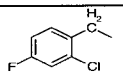
Synthesis of pyridinethiones and pyridinones was accomplished using the method described by Frolova [8] which makes use of 2-cyanothioacetamide and 2-cyanoacetamide [9]. The facile preparation of pyridinethiones (**4**) and pyridinones (**5**) is illustrated in Scheme 1, and representative examples of compounds prepared are listed. Typically, a solution of 2-cyanothioacetamide (**1**), or 2-cyanoacetamide (**2**), in five volumes of ethanol was treated with 1,3-diketone (**3**) (1.0 equiv) and 4-methylmorpholine (2.3 equiv). After 16 h at 65 °C, precipitation of the desired products was observed in most cases. For the synthesis of some pyridinones, heating over longer periods was required to enable the reactions to go to completion. In instances where precipitation did not occur, solvent was simply removed under reduced pressure, and the residue was triturated with the minimum volume of ethanol. All products were isolated by parallel filtration, and purities exceeding 90% as determined by LC-MS and NMR were observed in all cases. Isolated yields were moderate.

The array of thienopyridines was prepared using an equally straightforward approach (Scheme 2). Pyridinethiones (**4**) were treated with a series of secondary α-bromoketones (**6**) (1.0 equiv) in the presence of potassium hydroxide (2.1 equiv) at 65 °C in ethanol. As for the pyridinethiones and pyridinones discussed above, thienopyridines (**7**) were collected by filtra-

* To whom correspondence should be addressed. E-mail: ShuttleS@biochempharma.com.



X = S (**1**); X = O (**2**) (**3**) X = S (**4**); X = O (**5**)

Entry	R	R'	X	TheoreticalMass	Observed Mass [M+1]	Yield (%)
1	Me	CO_2Me	S	222.27	223.2	66
2	Me		S	306.79	307.2	58
3	Me	O-Ph	S	256.33	257.2	57
4	Me	Me	O	148.17	149.2	67
5	Me	$(CH_2)_4Me$	O	218.33	219.4	67

Scheme 1. Representative set of pyridinethiones and pyridinones.

tion; structures were confirmed by LCMS, and by NMR sampling (10% of set). Several hundred thienopyridines, possessing a breadth of functionality, were synthesised, and representative examples are shown in Scheme 2. Aromatic α-bromoketones were seen to give the cleanest products, whilst reactions with ethyl bromopyruvate were less successful.

The synthesis, isolation and purification of all compounds was accomplished using equipment routinely employed in our laboratories for parallel synthesis. A 48-position Bohdan RAM block was used for compound preparation; isolation of precipitated/triturated products was accomplished using a 20-channel vacuum manifold from Varian, fitted with Varian bond-elut reservoirs; and solvent removal was effected using a GeneVac Atlas HT-8 vacuum centrifuge.

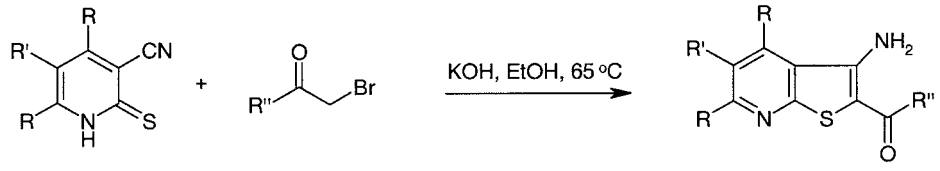
In summary, this paper outlines a convenient parallel solution synthesis leading to three classes of heterocyclic templates. All three templates boast an established biological profile. The library-from-library strategy adopted allows for the use of a range of monomers, and permits the introduction of a breadth of functional groups into the target compounds.

Acknowledgement

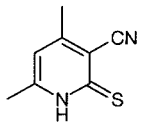
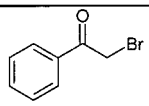
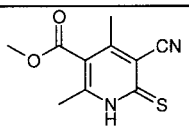
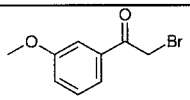
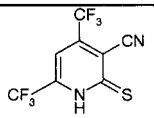
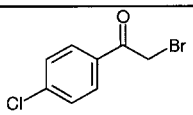
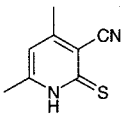
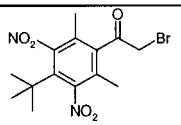
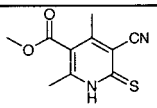
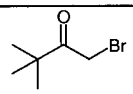
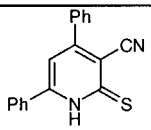
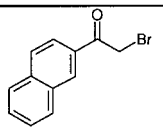
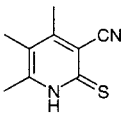
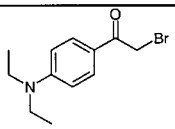
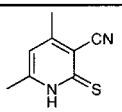
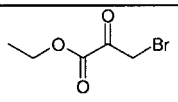
We would like to thank Dr Richard Storer for his comments.

References

1. Shuttleworth, S.J., *Synthesis of Compound Libraries at Biochem Pharma Inc.*, presented at 'NMHCC 2nd Annual Emerging Directions in Combinatorial Chemistry' Conference, San Diego, CA, USA, September 14–16, 1998.
2. Borman, S., *Combinatorial chemistry,* Chem. Eng. News, (1998) 47–67.
3. Brown, A.R., Hermkens, P.H.H., Ottenheijm, H.C.J. and Rees, D.C., *Solid phase synthesis*, Synlett., (1998) 817–827.
4. Coe, D.M. and Storer, R., *Solution-phase combinatorial chemistry*, Mol. Div., 4 (1999) 31–38.
5. Doffin, D.L., *Solution phase combinatorial synthesis*, Tetrahedron Symposia in Print No. 70, 54 (1998) 3955–4150.
6. MDL Drug Data Report from Molecular Design Inc.
7. a. Murray, K.J., Porter, R.A., Prain, H.D. and Warrington, B.H., WO 9117987; 911128.
   b. Berger, J. and Clark, R.D., EP485962; 920520.
   c. Chen, S.S.T., Hsu, A., Doss, G.A., Goldman, M.E., Balani, S.K., Theoharides, A.D., Hoffman Jr., J.M., Pitzenberger, S.M. and Ramjit, H.G., EP 481802; 920422.
   d. Ohe, T., Akagi, T., Chiba, K. and Amano, Y., WO 9203427; 920305.
   e. Baker, R.K., US 4904672; 900227.
   f. Hoffman Jr., J.M. and Shepard, K.L., US 4731368; 880315.
8. Frolova, N.G., Zav'yalova, V.K. and Litvinov, V.P., *Synthesis of 4,5,6-trisubstituted 3-cyano-2(1H)-pyridinethiones from α-substituted β-diketones*, Izv. Akad. Nauk, Ser. Khim., 11 (1996) 2719–2721.
9. Riad, B.Y., Negm, A.M., Abdou, S.E. and Daboun, H.A., *Chemistry of α-cyanothioacetamide*, Heterocycles, 26 (1987) 205–238.
10. As determined by HPLC at 215 nM.
11. For product from entry 1, Scheme 2: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.1 (2H, 2d), 7.7 (1H, dd), 7.5 (2H, 2dd), 6.9 (1H, s), 2.45 (3H, s), 2.1 (3H, s). M+1 for $C_{16}H_{14}N_2SO$ = 283.2 (calculated M^+ = 282.37).



(4) (6) (7)

Entry	Pyridinethione (4)	α–Bromoketone (5)	Theoretical Mass	Observed Mass [M+1]	Purity (%)[10]
1[11]			282.37	283.2	90
2			370.43	371.3	95
3			424.75	425.4	82
4			456.54	457.5	90
5			320.41	321.3	50
7			456.57	457.5	41
8			367.52	368.2	75
9			278.33	279.1	23

Scheme 2. Representative set of thienopyridines.