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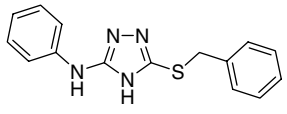
1. Current literature highlights

1.1. An array of 1,2,4-triazole methionine aminopeptidase-2 inhibitors

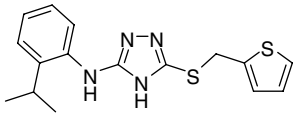
The growth of blood vessels, or angiogenesis, is a key step in the progression of several diseases, including diabetic retinopathy, rheumatoid arthritis and cancer. Pathways that are essential in angiogenesis thus become rational targets in the search for new therapies for these diseases. One such target is methionine aminopeptidase type 2 (MetAP2), an enzyme that has been identified as the target for fumagillin, a potent antiangiogenesis agent. A recent report describes the discovery of an aniline-1,2,4-triazole inhibitor of MetAP2, and the synthesis and iteration of a library of potent inhibitors.[1]

A high throughput screen against the cobaltous form of MetAP2 resulted in the identification of a triazole inhibitor (1) that was both potent ($K_i = 0.5$ nM) and highly selective over MetAP1 ($K_i = 3900$ nM). A parallel array of analogues were approached through a synthetic route that required eight diverse substituted phenylisocyanates that were converted to mercaptotriazoles and then alkylated with 12 commercially available alkyl halides. The alkylation reactions were carried out in a 96-well plate, and a total of 83 compounds were successfully prepared in yields varying from 50% to 90% with >95% purity after reverse phase HPLC purification.



(1)

After screening the array of compounds against MetAP2 a number of SAR trends were apparent. An *ortho*- or *para*-methyl substituent or a *para*-electron-donating group on the aniline phenyl ring increased potency 10-fold. The S-benzyl substituent was replaced with a 2-thienylmethyl group and compound (2) was co-crystallised with MetAP2 demonstrating how the contiguous nitrogens on the triazole ring coordinate to cobalt ions in the active site. The furan derivative (3) was found to be a nanomolar inhibitor of MetAP2 ($K_i = 3$ nM) and a potent inhibitor of human endothelial cell proliferation, as well as blood vessel growth in an aortic tissue model of angiogenesis.



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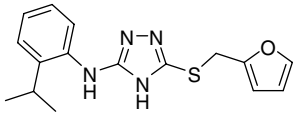
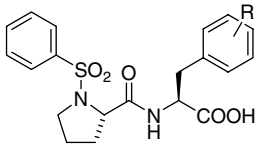


(3)

1.2. A solid-phase route to α2β1 integrin inhibitors

The α2β1 integrin is expressed in a variety of cells and can bind to a number of collagens and laminins. The integrin has been shown to have a role in a range of cellular functions including haemostasis, thrombosis, cancer metastasis, wound healing and angiogenesis. As α2β1 is operative in platelets after their adherence to collagen, this integrin presents a possible safe target for treating thrombosis. Solid-phase synthesis has been used to generate a number of small molecule inhibitors of the α2β1 integrin with potential applications for anticancer and antithrombotic therapy.[2]



(4)

α4β1 antagonist

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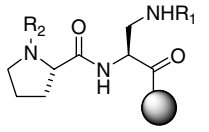
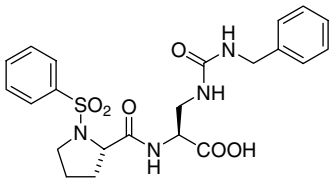


(5)

In the past, benzenesulphonyl-Pro-Phe dipeptides (4) have been developed as inhibitors of the closely related α4β1 integrin. Against the integrin αIIbβ3, 2,3-diaminopropionic acid (DAP) has been shown to occupy a similar role to Phe derivatives. This new publication describes the design and generation of an array of compounds that combine a prolylsulphonamide fragment with DAP derivatives to give selective α2β1 inhibitors. The prolyl-DAP derivatives (5) were prepared on solid support using Wang resin with two positions on the compounds sequentially varied: the 3-position of DAP, and the prolyl amino group. It was found that the most potent and selective inhibitors possessed a urea derivative on DAP with a distal benzyl group, and an aryl sulphonamide group appropriately substituted on the prolyl nitrogen. Compounds such as (6) were shown to be potent integrin α2β1 inhibitors ($IC_{50} = 15$ nM against platelets) and were selective over the related α1β1, α4β1 and α5β1 integrins.



(6)

2. A summary of the papers in this month's issue

2.1. Solid-phase synthesis

The $[Ir(COD)Cl]_2$/dppe system effectively catalyses the solid-phase [2 + 2 + 2] cycloaddition of resin-bound dipropargylamine with alkynes under microwave conditions. The reaction results in high purity of isoindoline derivatives with moderate yields.[3]

The use of polymer-supported 2,6-disubstituted-dihydro-2*H*-pyridin-3-one, as the 'polymorphic' core molecule for the formal synthesis of the piperidine alkaloid (±)-prosophylline has been presented.[4]

2.2. Solution-phase synthesis

A convenient single-vessel conversion of primary and secondary alcohols to primary amines has been reported. Use of this method results in substantially cleaner crude products than similar procedures reported in the literature, and a simple work-up makes this procedure ideal for parallel synthesis.[5]

A combinatorial synthetic route yielding imidazo[1,5-*a*]-quinoxalines and pyrazolo[1,5-*a*]quinoxalines has been described. The use of 2-fluoroaniline, 1*H*-imidazole-4-carboxylic acid and 1*H*-pyrazole-3-carboxylic acid in the Ugi-reaction (U-4CR) followed by a nucleophilic aromatic substitution (S_NAr) affords the imidazo- as well as the pyrazolo-[1,5-*a*]quinoxaline moiety in good yield and high diversity.[6]

A convenient synthesis of 4*H*-1,2,4-triazole-3-thiols using di-2-pyridyl-thionocarbonate as the thiocarbonyl transfer reagent has been reported. Using two large sets of amine and hydrazide building-blocks, this method is suitable for microplate parallel synthesis and produces samples in screening-ready condition.[7]

2.3. Scaffolds for combinatorial libraries

Desymmetrisation of pyridazine-3,6-diones by the use of *N*-benzyl protective groups leads to useful starting materials for building polysubstituted pyridazine libraries in a regioselective manner.[8]

2.4. Solid-phase supported reagents

A series of variously-functionalised first-, second-, and third-generation dendrimers have been prepared and linked via a biphenyl core to a bis-styryl moiety suitable for use as a crosslinker in polymerisation. Attachment of titanocene moieties to the first-generation system and copolymerisation with styrene affords polymeric disks that exhibit catalytic properties superior to comparable solution-phase systems in a multicomponent coupling of chlorosilanes with Grignards to give bis-allylic silanes.[9]

2.5. Novel resins, linkers and techniques

Alkylation of secondary sulphonamides by alkyl halides or alcohols (via the Mitsunobu reaction) is an efficient method for secondary amine preparation. A fluorous technique has been proposed to bypass the problem of partial reactions in parallel chemistry. Thus, *o*-nitrobenzenesulphonamides were prepared and alkylated in parallel with various alkyl halides or alcohols. A reactive fluorous alkyl iodide was used to trap unreacted sulphonamide allowing for a rapid and efficient fluorous solid-phase extraction.[10]

New methodology for the solid-phase synthesis of benzothiazoles, benzimidazoles, and benzoxazoles has been developed by using a traceless 4-alkoxyaniline linker. The desired products were released from the polymer support by an imine-exchange process coupled with air oxidation. A combinatorial library consisting of 36 members has been synthesised using this linker.[11]

'Click resins' enable solid phase supported reactions to work under nearly perfect conditions fulfilling the requirements of click chemistry. Utilising the formylpyrrolylmethyltriazole (FPMT) linker, which is readily available via copper(I)-catalysed azide-alkyne cycloaddition, a parallel synthesis of dopaminergic phenylacetylenes has been achieved. A focused library of 20 test compounds revealing three points of diversity has been generated by a four-step SPOS approach including microwave assisted Sonogashira coupling. GPCR-ligand binding assays indicated excellent dopamine D3 and D4 receptor binding affinities.[12]

2.6. Library applications

A library of new thalidomide analogues containing an olefin functionality have been synthesised from their aryl halogenated precursor using a Heck cross coupling reaction. All analogues were tested for their ability to inhibit the synthesis of the pro-inflammatory cytokine Tumour Necrosis Factor (TNF).[13]

A novel class of Growth Hormone Secretagogues (GHS), based on a tetrazole template, has been discovered. In vitro SAR and in vivo potency within this new class of GHS are described, and solution and solid phase protocols for the synthesis of tetrazole based GHS have been developed.[14]

Methods appropriate for the parallel synthesis of libraries based on the tricyclic thioxanthen-9-one-10,10-dioxide scaffold have been reported. The novel compounds were synthesised from previously reported 3-chlorothioxanthen-9-one-10,10-dioxide and commercially available 3-carboxylic acid thioxanthen-9-one-10,10-dioxide. The library members were screened for activity in a fluorescence polarisation assay for inhibitors of BRCT domains of breast cancer gene 1 and in cell-based secreted alkaline phosphatase reported replicon system for activity against hepatitis C virus.[15]

A library of new compounds derived from inhibitors of histone deacetylases (HDACs) have been synthesised and their antiproliferative activities towards non small lung cancer cell line H661 evaluated. Their design is based on hybrids between indanones to limit conformational mobility and other known HDAC inhibitors. The synthesis of these new derivatives was achieved by alkylation of appropriate indanones to introduce the side chain bearing a terminal ester group, the latter being a precursor of hydroxamic acid and aminobenzamide derivatives.[16]

An erythromycin analogue, 11,12-di-*O*-*iso*-butyryl-8,9-anhydroerythromycin A 6,9-hemiketal, has been found to be a potential anti-MRSA and anti-VRE agent. The use of copper catalyzed azide–acetylene cycloaddition, and click chemistry, readily provided 10 types of triazole analogues in good to nearly quantitative yield and one library compound exhibited activity against MRSA and VRE bacterial strains.[17]

A versatile parallel synthetic method to obtain three series of non-cyclic analogues of the first drug-like selective angiotensin II (AT_2) receptor agonist has been developed. In all the three series, AT_2 receptor ligands with affinities in the lower nanomolar range were found, and none of the analogues exhibited any affinity for the AT_1 receptor. Several compounds were examined in a neurite outgrowth cell assay and found to exert a high agonistic effect as deduced from their capacity to induce neurite elongation in neuronal cells.[18]

Small constrained non-peptidic molecules consisting of a polyfunctionalised rigid core, carrying appendages corresponding to arginine and aspartic acid side chains, have been recently reported to be promising for drug development. In this work, the 5,6-dihydropyridin-2-one was envisaged as a scaffold to turn into potential integrin ligands, introducing a carboxylic acid and a basic appendage. The synthesis and the antiadhesion activity of a small library of peptidomimetics capable to recognise $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrins has been reported.[19]

To identify the pharmacophore of a phosphoramidate peptidomimetic inhibitor of prostate-specific membrane antigen (PSMA), a small analogue library has been designed and screened for inhibitory potency. The scope of the library was designed to test the importance of various functional groups to the inhibitory potency of the lead phosphoramidate. The IC_{50} for the lead phosphoramidate inhibitor was 35 nM, and the IC_{50} values for the analogue library presented a range from 0.86 nM to 4.1 μM.[20]

References

1. Marino, J. P. et al. *J. Med. Chem.* **2007**, *50* (16), 3777–3785.
2. Choi, S. et al. *J. Med. Chem.* **2007**, *50* (22), 5457–5462.
3. Shanmugasundaram, M. et al. *Tetrahedron Lett.* **2007**, *48* (43), 7698–7701.
4. Couladouros, E. A. et al. *Tetrahedron Lett.* **2007**, *48* (46), 8227–8229.
5. Sun, W.; Pelletier, J. C. *Tetrahedron Lett.* **2007**, *48* (44), 7745–7746.
6. Spatz, J. H. et al. *Tetrahedron Lett.* **2007**, *48* (45), 8060–8064.
7. Deprez-Poulain, R. F. et al. *Tetrahedron Lett.* **2007**, *48* (46), 8157–8162.
8. de Araújo-Júnior, J. X. et al. *Tetrahedron Lett.* **2007**, *48* (44), 7817–7820.
9. Berget, P. E. et al. *Tetrahedron Lett.* **2007**, *48* (46), 8101–8103.
10. Baslé, E. et al. *Tetrahedron Lett.* **2007**, *48* (46), 8138–8140.
11. Hioki, H. et al. *Tetrahedron* **2007**, *63* (46), 11315–11324.
12. Loaiza, P. R. et al. *Bioorg. Med. Chem.* **2007**, *15* (23), 7248–7257.
13. Stewart, S. G. et al. *Bioorg. Med. Chem. Lett.* **2007**, *17* (21), 5819–5824.
14. Hernández, A. S. et al. *Bioorg. Med. Chem. Lett.* **2007**, *17* (21), 5928–5933.
15. Lory, P. M. J. et al. *Bioorg. Med. Chem. Lett.* **2007**, *17* (21), 5940–5943.
16. Charrier, C. et al. *Bioorg. Med. Chem. Lett.* **2007**, *17* (22), 6142–6146.
17. Sugawara, A. et al. *Bioorg. Med. Chem. Lett.* **2007**, *17* (22), 6340–6344.
18. Murugaiah, A. M. S. et al. *Bioorg. Med. Chem.* **2007**, *15* (22), 7166–7183.
19. Benfatti, F. et al. *Bioorg. Med. Chem.* **2007**, *15* (23), 7380–7390.
20. Wu, L. Y. et al. *Bioorg. Med. Chem.* **2007**, *15* (23), 7434–7443.

Further reading

Papers on combinatorial chemistry or solid-phase synthesis from other journals

Stazi, F.; Marcoux, D.; Poupon, J.-C.; Latassa, D.; Charette, A. B. Tetraarylphosphonium salts as soluble supports for the

synthesis of small molecules *Angewandte Chemie, International Edition* **2007**, *46* (26), 5011–5014.

Ng, P. Y.; Tang, Y.; Knosp, W. M.; Stadler, H. S.; Shaw, J. T. Synthesis of diverse lactam carboxamides leading to the discovery of a new transcription-factor inhibitor. *Angewandte Chemie, International Edition* **2007**, *46* (28), 5352–5355.

Ludlow, R. F.; Liu, J.; Li, H.; Roberts, S. L.; Sanders, J. K. M.; Sijbren, O. Host-guest binding constants can be estimated directly from the product distributions of dynamic combinatorial libraries. *Angewandte Chemie, International Edition* **2007**, *46* (30), 5762–5764.

Maier, W. F.; Stoewe, K.; Sieg, S. Combinatorial and high-throughput materials science. *Angewandte Chemie, International Edition* **2007**, *46* (32), 6016–6067.

Pflantz, R.; Tielmann, P.; Roessle, M.; Hoenke, C.; Christoffers, J. Eight-membered-ring lactams — new scaffolds for combinatorial chemistry prepared by ring-expansion of 1,4-diketones with primary amines. *European Journal of Organic Chemistry*, **2007**, (19), 3227–3238.

Palimkar, S. S.; Lahoti, R. J.; Srinivasan, K. V. A novel one-pot three-component synthesis of 2,4-disubstituted 3*H*-benzo[b]-[1,4]diazepines in water. *Green Chemistry* **2007**, *9* (2), 146–152.

Kakarla, R.; Li, G.; Gerritz, S. W. Synthesis and applications of a novel polymer-supported EEDQ reagent. *Journal of Combinatorial Chemistry* **2007**, *9* (5), 745–747.

Carpintero, M.; Cifuentes, M.; Ferritto, R.; Haro, R.; Toledo, M. A. Automated liquid-liquid extraction workstation for library synthesis and its use in the parallel and chromatography-free synthesis of 2-alkyl-3-alkyl-4(3*H*)-quinazolinones. *Journal of Combinatorial Chemistry* **2007**, *9* (5), 818–822.

Marino, J. P., Jr.; Fisher, P. W.; Hofmann, G. A.; Kirkpatrick, R. B.; Janson, C. A.; Johnson, R. K.; Ma, C.; Mattern, M.; Meek, T. D.; Ryan, M. D.; Schulz, C.; Smith, W. W.; Tew, D. G.; Tomazek, T. A., Jr.; Veber, D. F.; Xiong, W. C.; Yamamoto, Y.; Yamashita, K.; Yang, G.; Thompson, S. K. Highly potent inhibitors of methionine aminopeptidase-2 based on a 1,2,4-triazole pharmacophore. *Journal of Medicinal Chemistry* **2007**, *50* (16), 3777–3785.

Choi, S.; Vilaire, G.; Marcinkiewicz, C.; Winkler, J. D.; Bennett, J. S.; DeGrado, W. F. Small molecule inhibitors of integrin α 2β 1. *Journal of Medicinal Chemistry* **2007**, *50* (22), 5457–5462.

Cudic, M.; Mari, F.; Fields, G. B. Synthesis and solid-phase application of suitably protected γ-hydroxyvaline building blocks. *Journal of Organic Chemistry* **2007**, *72* (15), 5581–5586.

Wang, Z.; Zhou, L.; El-Boubbou, K.; Ye, X.-S.; Huang, X. Multi-component one-pot synthesis of the tumor-associated carbohydrate antigen Globo-H based on preactivation of thioglycosyl donors. *Journal of Organic Chemistry* **2007**, *72* (17), 6409–6420.

Angelo, N. G.; Arora, P. S. Solution- and solid-phase synthesis of triazole oligomers that display protein-like functionality. *Journal of Organic Chemistry* **2007**, *72* (21), 7963–7967.

Williams, D. R.; Lee, M.-R.; Song, Y.-A.; Ko, S.-K.; Kim, G.-H.; Shin, I. Synthetic small molecules that induce neurogenesis in skeletal muscle. *Journal of the American Chemical Society* **2007**, *129* (30), 9258–9259.

Ma, Q.; Xu, Z.; Schroeder, B. R.; Sun, W.; Wei, F.; Hashimoto, S.; Konishi, K.; Leitheiser, C. J.; Hecht, S. M. Biochemical evaluation of a 108-member deglycobleomycin library: viability of a selection strategy for identifying bleomycin analogues with altered properties. *Journal of the American Chemical Society* **2007**, *129* (41), 12439–12452.

Aliabiev, S. B.; Bykova, R. V.; Kravchenko, D. V.; Ivachtchenko, A. V. A convenient synthesis of novel substituted isoxazolo-[5,4-d]pyrimidines. *Letters in Organic Chemistry* **2007**, *4* (4), 273–280.

Wallner, F. K.; Spjut, S.; Bostroem, D.; Elofsson, M. Synthesis and evaluation of 2-(2-fluoro-4-hydroxymethyl-5-methoxy-phenoxy)acetic acid as a linker in solid-phase synthesis monitored by gel-phase 19F NMR spectroscopy. *Organic & Biomolecular Chemistry* **2007**, *5* (15), 2464–2471.

Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. Applications of multicomponent reactions for the synthesis of diverse heterocyclic scaffolds. *Organic Letters* **2007**, *9* (21), 4223–4226.

Colombo, A.; De la Figuera, N.; Fernandez, J. C.; Fernandez-Forner, D.; Albericio, F.; Forns, P. A nonacid degradable linker for solid-phase synthesis. *Organic Letters* **2007**, *9* (21), 4319–4322.

Solinas, A.; Taddei, M. Solid-supported reagents and catch-and-release techniques in organic synthesis. *Synthesis*, **2007**, (16), 2409–2453.