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Solution-phase parallel synthesis of *S*-DABO analogues

Andrea Togninelli, Caterina Carmi, Elena Petricci, Claudia Mugnaini, Silvio Massa, Federico Corelli and Maurizio Botta*

Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via Aldo Moro, 53100 Siena, Italy

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Abstract—A simple and straightforward methodology for the parallel, solution-phase synthesis of a new series of *S*-DABO derivatives **1** and **2**, bearing aromatic substituents at the C2 and C6 positions, has been developed. Starting from potassium ethyl malonates **3**, thiouracil intermediates **5** were prepared through parallel synthesis and isolated as pure products by simple extraction with ethyl acetate. Selective *S*-benzylation of **5** was achieved in few minutes under microwave irradiation to give the title compounds **1**, which were oxidized in parallel to the corresponding sulfones **2**. Some of the new compounds **1** showed potent inhibitory activity against HIV-1 RT.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) include more than 30 structurally different classes of molecules showing high specificity for HIV-1.[1] Among them, nevirapine and efavirenz (Fig. 1) are potent inhibitors of HIV-1 RT used in combination therapy with other drugs for the treatment of AIDS.

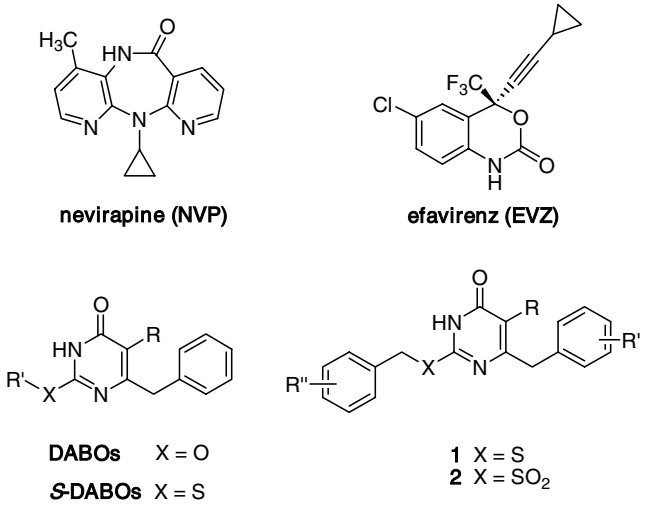

Figure 1.

Dihydro-alkoxy-benzyl-oxopyrimidines (DABOs) (Fig. 1), which were firstly disclosed in 1992[2] and further developed during the following years into *S*-DABOs and related analogues,[3] are an interesting class of NNRTIs active at nanomolar concentration.

Based on previous findings,[4] and with the aim of investigating the influence of the arylalkyl moiety on anti-HIV activity, we selected *S*-DABO derivatives of general structure **1** and **2** as new potential NNRTIs.

Classical methodologies for the synthesis of DABO derivatives usually require long reaction times and lengthy purification procedures.[3b,c,f] Accordingly, during the course of our studies on the synthesis of anti-HIV-1 agents with a pyrimidinone structure, we became interested in developing efficient synthetic methodologies for the preparation of small libraries of the target compounds to be submitted to biological evaluation.[5]

Solution-phase parallel synthesis (SPPS) and microwave-assisted organic synthesis have emerged as powerful and complementary tools for the fast generation of structurally diverse compounds.[6] Therefore, as an extension of our ongoing investigations on the use of the aforementioned techniques in organic synthesis,[7] we decided to combine the advantages of SPPS and microwave irradiation to synthesize a small library of compounds **1** and **2**. The title compounds were synthesized according to Scheme 1.

* Corresponding author. Tel.: +39 0577234306; fax: +39 577234333; e-mail: botta@unisi.it

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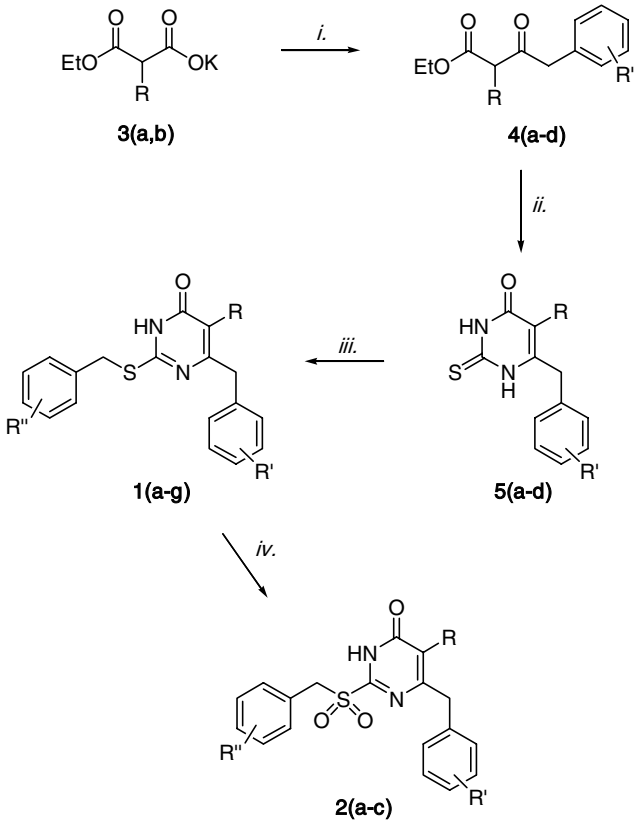

Scheme 1. Reagents and conditions: (i) $MgCl_2$, Et_3N, substituted phenylacetic acid, *N*,*N*′-carbonyldiimidazole, CH_3CN, rt, overnight, 360 rpm; (ii) thiourea, EtONa, EtOH, reflux, 16 h, 360 rpm; (iii) substituted benzyl halides, K_2CO_3, dry DMF, MW, 130 °C, 5 min; (iv) MCPBA, dry CH_2Cl_2, rt, 16 h, 360 rpm.

Potassium ethyl malonates **3**(**a**,**b**)[8] (5.04 mmol) were partitioned in four separate reaction vessels and reacted with substituted phenylacetyl imidazolides (2.67 mmol) in a Büchi Syncore® synthesizer[9] in the presence of $MgCl_2$ (6 mmol) and Et_3N (7.67 mmol) in CH_3CN, according to the Clay et al.'s procedure.[10] Ketoesters **4**(**a**–**d**) were obtained as pure products after a simple extraction with ethyl acetate.

Compounds **4**(**a**–**d**) (2.27 mmol) were then condensed in parallel with thiourea (3.18 mmol) in the presence of EtONa (4.55 mmol) in boiling ethanol, to give thiouracils **5**(**a**–**d**) in excellent yield and good purity after neutralization with acetic acid followed by extractions in parallel with ethyl acetate. The spectroscopic and analytical data of **5**(**a**–**d**) are in agreement with those reported in the literature.[3f]

In order to accelerate the reaction and improve the yield, compounds **5**(**a**–**d**) were selectively *S*-benzylated under microwave irradiation. Thus, **5**(**a**–**d**) (0.3 mmol) were irradiated either in a closed or open vessel at 130 °C for 5 min in the presence of the appropriate substituted benzyl halide (0.3 mmol) and K_2CO_3 (0.3 mmol) in DMF.[11] Compounds **1** (Table 1) were obtained in good yield and purity in only 5 min instead of 16 h as required when conventional heating was used.

Table 1. Chemical and physical data for the new compounds **1** and **2**

Compound	R	R′	R″	Mp[a] (°C)	Yield (%)
1a	H	2,6-diCl	H	230–231	70
1b	CH_3	2,6-diCl	H	236–237	50
1c	CH_3	2,6-diCl	4-OCH_3	219	67
1d	CH_3	2,6-diCl	4-F	205–206	50
1e	CH_3	2,6-diF	3,5-diOCH_3	228–230	60
1f	CH_3	2,6-diF	4-NO_2	248–250	57
1g	CH_3	4-F	4-NO_2	246	56
2a	CH_3	2,6-diCl	4-OCH_3	241–244	50
2b	CH_3	2,6-diF	4-NO_2	253–255	62
2c	CH_3	4-F	4-NO_2	251–252	58

[a] All the compounds were recrystallized from CH_3CN.

Finally, sulfides **1c**,**f**, and **g** (0.2 mmol) were oxidized to the corresponding sulfones **2**(**a**–**c**) in a parallel way with *m*-chloroperbenzoic acid (0.6 mmol).[12,13] All sulfides **1** and sulfones **2** were obtained in more than 95% purity after recrystallization, as shown by HPLC–MS analysis (Table 1).

The *S*-alkylation reactions performed using microwave irradiation were compared in separate experiments with the corresponding reactions carried out by conventional heating. While similar results were obtained in terms of yield, the MW-assisted procedure afforded the target compounds in a far faster way. The combination of this advantage with the easiness of execution of the parallel synthesis opens up the route to a combinatorial approach for the preparation of larger libraries of compounds **1** and **2**. In fact, the number of sulfides **1** can be increased using a larger number of malonates **3** (functionalization at position 5), phenylacetyl imidazolides (functionalization at position 6) and benzyl halides (functionalization at position 2) in order to amplify the chemical diversity within the libraries.

In conclusion, a simple and efficient procedure for the synthesis of a small family of 6-arylmethyl-2-(arylmethylthio)-5-methylpyrimidin-4(3*H*)-ones **1** and 6-arylmethyl-2-(arylmethylsulfonyl)-5-methylpyrimidin-4(3*H*)-ones **2** has been developed. These new *S*-DABO analogues were obtained in an easy, rapid, and profitable way using solution-phase parallel synthesis and MW-assisted organic synthesis. The products obtained in each step did not require any further purification before undergoing the subsequent transformation. The whole methodology shows combinatorial potential to the synthesis of larger libraries of compounds which is ongoing in our laboratories. Finally, it is interesting to note that some of the reported compounds showed high inhibitory activity against wild type enzyme without showing cytotoxicity (e.g., **1c**: $IC_{50/wt} = 0.0038$ μM; $CC_{50} = 32$ μM and **2a**: $IC_{50/wt} = 0.006$ μM; $CC_{50} = 2.8$ μM), thus favorably comparing with inhibitors belonging to the same structural class already reported in the literature.[3b,c]

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References and notes

1. (a) De Clercq, E. *Chem. Biodivers.* **2004**, *1*, 44–64; (b) De Clercq, E. *Antiviral Res.* **1998**, *38*, 153–179.
2. Botta, M.; Artico, M.; Massa, S.; Gambacorta, A.; Marongiu, M. E.; Pani, A.; La Colla, P. *Eur. J. Med. Chem.* **1992**, *27*, 251–257.
3. (a) Ragno, R.; Frasca, S.; Manetti, F.; Brizzi, A.; Massa, S. *J. Med. Chem.* **2005**, *48*, 200–212; (b) Mai, A.; Artico, M.; Ragno, R.; Sbardella, G.; Massa, S.; Musiu, C.; Mura, M.; Marturana, F.; Cadeddu, A.; Maga, G.; La Colla, P. *Bioorg. Med. Chem.* **2005**, *13*, 2065–2077; (c) Ragno, R.; Mai, A.; Sbardella, G.; Artico, M.; Massa, S.; Musiu, C.; Mura, M.; Marturana, F.; Cadeddu, A.; La Colla, P. *J. Med. Chem.* **2004**, *47*, 928–934; (d) Rizzo, R. C.; Udier-Blagovic, M.; Wang, D. P.; Watkins, E. K.; Kroeger Smith, M. B.; Smith, R. H., Jr.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2002**, *45*, 2970–2987; (e) Botta, M.; Corelli, F.; Maga, G.; Manetti, F.; Renzulli, M.; Spadari, S. *Tetrahedron* **2001**, *57*, 8357–8367; (f) Mai, A.; Sbardella, G.; Artico, M.; Ragno, R.; Massa, S.; Novellino, E.; Greco, G.; Lavecchia, A.; Musiu, C.; La Colla, M.; Murgioni, C.; La Colla, P.; Loddo, R. *J. Med. Chem.* **2001**, *44*, 2544–2554; (g) Nizi, E.; Botta, M.; Corelli, F.; Manetti, F.; Messina, F.; Maga, G. *Tetrahedron Lett.* **1998**, *39*, 3307–3310.
4. Parlato, M. C.; Mugnaini, C.; Renzulli, M. L.; Corelli, F.; Botta, M. *Arkivoc* **2004**, *V*, 349–363.
5. (a) Radi, M.; Petricci, E.; Maga, G.; Corelli, F.; Botta, M. *J. Comb. Chem.* **2005**, *7*, 117–122; (b) Petricci, E.; Radi, M.; Corelli, F.; Botta, M. *Tetrahedron Lett.* **2003**, *44*, 9181–9184.
6. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
7. (a) Petricci, E.; Mugnaini, C.; Radi, M.; Corelli, F.; Botta, M. *J. Org. Chem.* **2004**, *69*, 7880–7887; (b) Paolini, L.; Petricci, E.; Corelli, F.; Botta, M. *Synthesis* **2003**, 1039–1042; (c) Petricci, E.; Botta, M.; Corelli, F.; Mugnaini, C. *Tetrahedron Lett.* **2002**, *43*, 6507–6509.
8. Box, V. G. S.; Marinovich, N.; Yiannikouros, G. P. *Heterocycles* **1991**, *32*, 245–251.
9. Büchi Syncore® Polyvap was used for parallel synthesis, filtration, and evaporation.
10. Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290–292.
11. Microwave reactions were carried out using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC).
12. Petricci, E.; Renzulli, M.; Radi, M.; Corelli, F.; Botta, M. *Tetrahedron Lett.* **2002**, *43*, 9667–9670.
13. Obrecht, D.; Abrecht, C.; Grieder, A.; Villalgordo, J. M. *Helv. Chim. Acta* **1997**, *80*, 65–71.