Bioorganic & Medicinal Chemistry Letters 19 (2009) 489–492

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Novel non-carboxylic acid retinoids: 1,2,4-Oxadiazol-5-one derivatives

Julie Charton [a,c,d,e,*], Rebecca Deprez-Poulain [a,c,d,e], Nathalie Hennuyer [b,c,d], Anne Tailleux [b,c,d], Bart Staels [b,c,d], Benoit Deprez [a,c,d,e]

[a] INSERM U761 Biostructures and Drug Discovery, 3 rue du Professeur Laguesse, Lille F-59006, France
[b] INSERM U545, Lille F-59019, France
[c] Faculté de Pharmacie, Université Lille 2, Lille F-59006, France
[d] Institut Pasteur de Lille, Lille F-59021, France
[e] PRIM (www.drugdiscovery-lille.org), Lille F-59006, France

ARTICLE INFO

Article history:
Received 17 September 2008
Revised 12 November 2008
Accepted 12 November 2008
Available online 18 November 2008

Keywords:
1,2,4-Oxadiazol-5-one
Retinoid

ABSTRACT

We have successfully obtained 1,2,4-oxadiazol-5-one bioisoteres of Am580 or Tazarotene-like retinoids. In particular compound **4** displays an EC_{50} of 26 nM on RAR-β.

Natural and synthetic retinoids display pleiotropic effects that have led to their development as therapeutic drugs in a number of applications including acne, psoriasis and cancer.[1] Retinoids have a remarkable range of activities. Indeed, they regulate embryonic development, bone formation, cell differentiation and proliferation, glucose and lipid metabolism, carcinogenesis and immune function.[2–4] The biological activities of retinoids are mediated by two types of nuclear receptors, Retinoic Acid Receptors (RARs or NR1B: RARα, RARβ and RARγ), and Retinoid X Receptors (RXRs or NR2B: RXRα, RXRβ and RXRγ). At the molecular level RARs and RXRs form heterodimers. At the cellular level, these receptors are DNA binding proteins that regulate gene transcription in response to ligand-binding. The success of RAR modulation in the treatment of acute promyelocyticleukaemia (APL)[5] has stimulated considerable interest in the development of RAR and RXR modulators. Most potent retinoids, such as Am580 or Tazarotenic acid have an aromatic carboxylic acid moiety instead of the polyenecarboxylic acid of retinoic acid (ATRA, Fig. 1). In this family, the hydrophobic part and the linker (X) can be varied with retention of high activity. Tazarotene, an RAR-β,γ selective acetylenic retinoid, was chosen for development as a topical agent for psoriasis and acne. Am580 (RAR-α selective) has powerful and selective cyto-differentiating effects on APL.[6,7]

Various acidic heterocycles are classically used by medicinal chemists as carboxylic acid bioisosteres.[8] Tetrazole is a common bioisostere of the carboxylic acid group but in the particular case of retinoids led to loss of activity.[9] On the contrary, thiazolidinedione moiety has been described by Tashima et al. to be an effective replacement of the carboxylic acid (Fig. 2a).[10,11] More recently, bioisosteric replacement of carboxylic acid with a tropolone ring is reported (Fig. 2b).[12,13]

Another example of acidic heterocycle is the 1,2,4-oxadiazol-5-one ring, found in AT1 antagonists[14], COX inhibitors[15], PLA2 inhibitors[16] and modulators of GluR.[17] This heterocycle can replace carboxylic acids but displays geometrically different protomers and slightly different physico-chemical properties. Compounds bearing this heterocycle have different lipophilic properties that may translate into improved bioavailability compared with their carboxylic analogues. Indeed, $\Delta \log D_{7.4}$ between benzoic acid and 3-phenyl-1,2,4-oxadiazol-5-one = 0.7 log unit, the oxadiazolone being more hydrophobic than its carboxylic counterpart.[18] In our project aiming at synthesizing various analogues of pharmacologically active carboxylic acids, we explored the replacement of the carboxylic acid function by the 1,2,4-oxadiazol-5-one moiety in two series of retinoids: analogues of the tazarotene, a RAR-β,γ selective acetylenic retinoid, and Am580, an RAR-α selective retinoid (Fig. 3).

First, we investigated the synthesis of tazarotenic acid analogues.[19] Precursors **1** and **2** were synthesized as previously described from the corresponding nitrile in two steps (Scheme 1).[20]

We have recently reported a strategy for solid-phase synthesis of acetylenic derivatives of 3-aryl-1,2,4-oxadiazol-5-one thanks to a Sonogashira reaction.[19] Compound **1** was thus grafted on resin and then reacted with 6-ethynyl-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene **3** to yield compounds **4** (Scheme 2).

* Corresponding author. Tel.: +33 (0) 320 964928; fax: +33 (0) 320 964 709.
E-mail address: julie.charton@univ-lille2.fr (J. Charton).

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.11.040

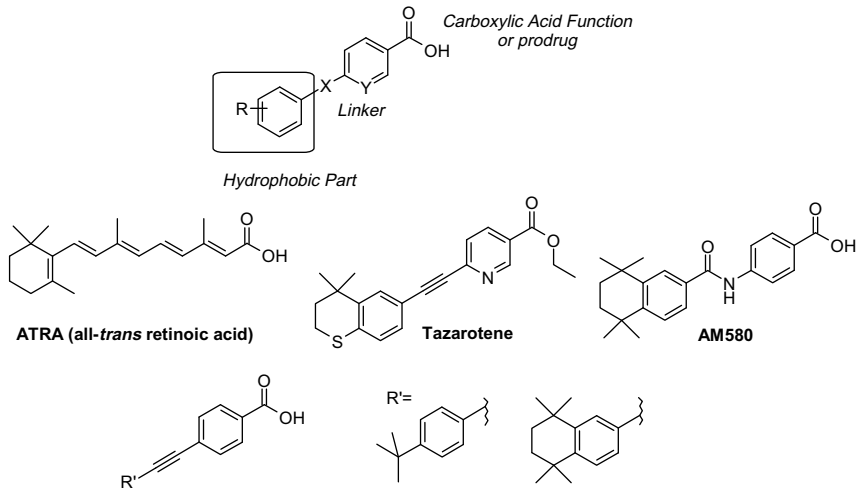


Figure 1. General structure of retinoids and examples.[2]

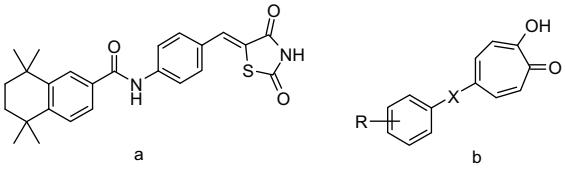


Figure 2. Non-benzoic acid retinoids.

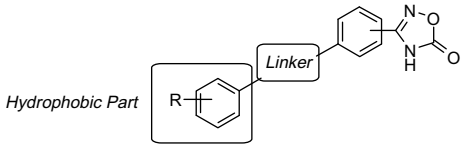
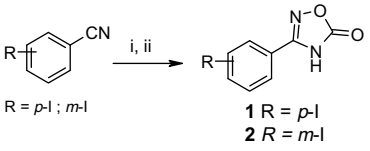
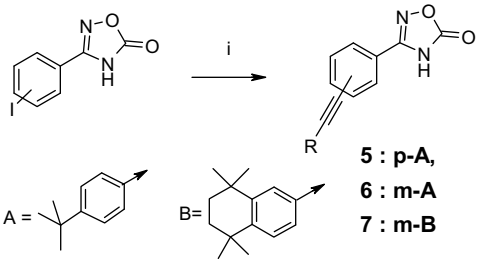


Figure 3. Generic structure of the potential retinoid 1,2,4-oxadiazol-5-one derivatives.

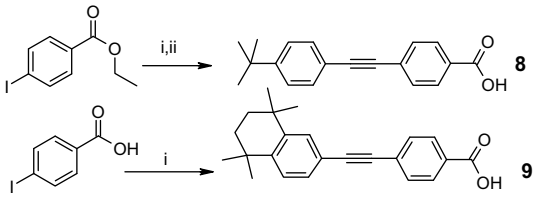


Scheme 1. Reaction conditions: (i) $NH_2OH.HCl$, DIEA, EtOH, reflux, 8 h, (1a: 75%, 2a: 95%). (ii) CDI, DBU, dioxane, 110 °C, 2 h, (1: 80%, 2: 80%).

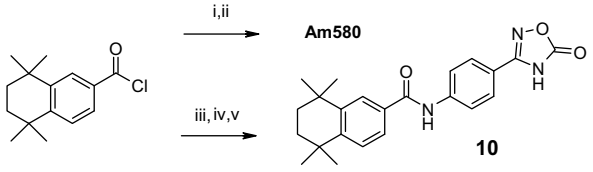
In the search of a more cost-effective synthesis, we also developed the first solution Sonogashira coupling with an unprotected 1,2,4-oxadiazol-5-one ring. Such strategy has been used for Suzuki–Miyaura reactions [21] and successfully applied for the synthesis of compounds **5**–**7** (Scheme 3).



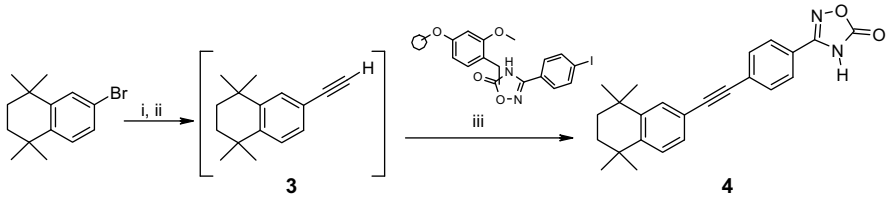
Scheme 3. Reaction conditions: (i) **1** or **2**, $PdCl_2(PPh_3)_2$, CuI, NEt_3, DMF, 80 °C, 7 h, (**5**: 50%, **6**: 83%, **7**: 56%).



Scheme 4. Reaction conditions: (i) Alkyne (1.2 equiv), $PdCl_2(PPh_3)_2$ (0.05 equiv), CuI (0.1 equiv), NEt_3, DMF, 80 °C, 5 h, **8a**: 52%, **9**: 20%, (ii) NaOH (2 equiv), EtOH, **8**: 100%.



Scheme 5. Reaction conditions: (i) $H_2N–C_6H_4–CO_2Et$, NEt_3, THF, rt, 3 h, 85%. (ii) NaOH, EtOH, H_2O, 40 °C, 12 h, 90%. (iii) $H_2N–C_6H_4–CN$, NEt_3, THF, rt, 12 h, **10a**: 98%. (iv) $NH_2OH.HCl$, DIEA, EtOH, reflux, 6 h, **10b**: 91%. (v) CDI, DBU, dioxane, 110 °C, 2 h, **10**: 44%.



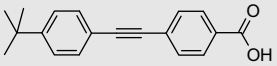
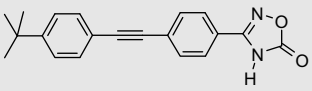
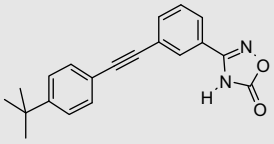
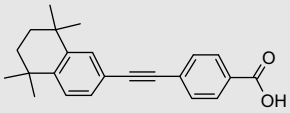
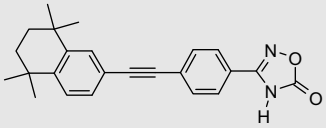
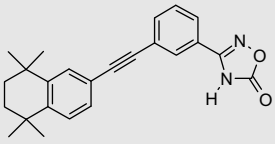
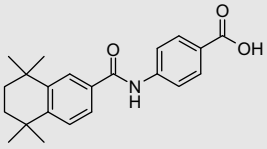
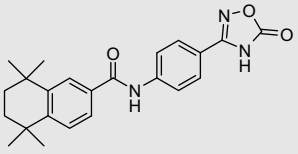
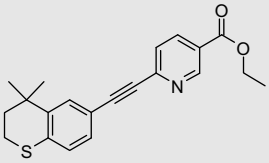
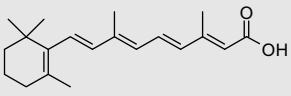
Scheme 2. Reaction conditions: (i) trimethylsilylacetylene (1.3 equiv), $PdCl_2(PPh_3)_2$ (0.05 equiv), CuI (0.1 equiv), NEt_3, 70 °C, 12 h (ii) KOH (0.1 N), Isopropanol, 12 h, rt (iii) alkyne (10 equiv), $PdCl_2(PPh_3)_2$ (1.1 equiv), CuI (2.2 equiv), DIEA (30 equiv), DMF, rt, 3 h then 5% TFA/CH_2Cl_2, rt, 3 h.

Some carboxylic acid analogues described in literature were also synthesized like compounds **8** and **9** in order to compare retinoidal activity of our oxadiazolone derivatives with known retinoic compounds (Scheme 4).

Am580 and its 1,2,4-oxadiazol-5-one analog **10** were synthesized as described in Scheme 5.

The retinoidal activities of the synthesized compounds were examined in terms of potency and efficacy and results are presented in Table 1. Chimeric receptors RAR-Gal4 where RAR ligand-binding domain (LBD) fused to the DNA binding domain (DBD) of the yeast transcription factor GAL4 and reporter gene containing a GAL4 response element–driven luciferase activity have

Table 1
Transcriptional activation assay data[a]

Compound		RAR-α		RAR-β		RAR-γ	
		EC_{50} (nM)	Eff (%)	EC_{50} (nM)	Eff (%)	EC_{50} (nM)	Eff (%)
8		>1000	—[b]	10.0	35[c]	10.0	44[c]
5		>1000	—[b]	820.0	34	>1000	—[b]
6		>1000	—[b]	>1000	—[b]	>1000	—[b]
9		0.6	53	0.3	83	0.6	125
4		>1000	—[b]	26.0	50	91.0	48
7		>1000	—[b]	>1000	—[b]	>1000	—[b]
Am580		0.3	43	8.6	46	13.0	43
10		520.0	40	>1000	—[b]	>1000	—[b]
Tazarotene		63.0	54	0.8	57	40.0	72
ATRA		17.0	100	12.0	100	0.2	100

[a] The data are expressed as averages of % efficacy and EC_{50}. Eff.: efficacy is relative to ATRA defined as 100%.
[b] <10% at 10 μM.
[c] Efficacy is relative to Tazarotene defined as 100%.

been transiently transfected. Mammalian cells did not contain GAL, only the transfected RAR-GAL4 chimeric receptors can activate the reporter gene, eliminating interference from endogenous nuclear receptors.[22]

Tazarotene and its analogue **8** are RAR-β,γ selective acetylenic retinoids, whereas analogue **9** is very active on the three subtypes. Interestingly, 1,2,4-oxadiazol-5-one **4** and **5** activities differ from their carboxylic acids analogues. Indeed, compound **5** is slightly active on RAR-β. Compound **4**, though nanomolar on RAR-β (EC_{50} = 26 nM), is less active than **9** but displays a better selectivity on RAR-β,γ subtypes and an efficacy comparable with tazarotene. As expected, bended analogue **7** is not active since it is not linear enough to fit the RAR pharmacophore. In the second series, compound **10** is active on RAR-α with a similar efficacy to that of Am580 (40 versus 43%). In the light of these results, both compounds **4** and **10** could be good starting points for further optimization.

All these compounds were checked for cross-reactivity with the retinoid X receptor (RXR α, β, γ) and found to be inactive.

In conclusion, we have described the solid-phase or solution-phase syntheses of a new series of non-carboxylic acid RAR ligands. We have shown that the 1,2,4-oxadiazol-5-one moiety can act as a bioisostere of the carboxylic acid function in retinoid structures. In particular the retinoidal activity of compound **4** (RAR-β,γ selective) is significant, considering that replacement of the carboxylic acid in retinoid structures with bioisosteric functional groups is generally ineffective. These non-carboxylic acid type RAR ligands may exhibit different pharmacological behaviors from classical carboxylic acid compounds, as well as unique biological activity, and they may provide further scope for clinical applications.

Acknowledgments

We are grateful to the Institutions that support our laboratory (Inserm, Université de Lille2 and Institut Pasteur de Lille). Data management was performed using Pipeline Pilot™ from Scitegic. We thank also the following Institutions or companies: CAMPLP and VARIAN.inc. This project was supported by the Fondation pour la Recherche Medicale (FRM) - Nord-Pas-de-Calais.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.11.040.

References and notes

1. Altucci, L.; Leibowitz, M. D.; Ogilvie, K. M.; de Lera, A. R.; Gronemeyer, H. *Nat. Rev. Drug Discov.* **2007**, *6*, 793.
2. Thacher, S. M.; Vasudevan, J.; Chandraratna, R. A. *Curr. Pharmcol. Des.* **2000**, *6*, 25.
3. Altucci, L.; Gronemeyer, H. *Nat. Rev. Cancer* **2001**, *1*, 181.
4. de Lera, A. R.; Bourguet, W.; Altucci, L.; Gronemeyer, H. *Nat. Rev. Drug Discov.* **2007**, *6*, 811.
5. Lengfelder, E.; Saussele, S.; Weisser, A.; Büchner, T.; Hehlmann, R. *Crit. Rev. Oncol./Hematol.* **2005**, *56*, 261.
6. Kagechika, H.; Kawachi, E.; Hashimoto, Y.; Shudo, K.; Himi, T. *J. Med. Chem.* **1988**, *31*, 2182.
7. Gianni, M.; Li Calzi, M.; Terao, M.; Guiso, G.; Caccia, S.; Barbui, T.; Rambaldi, A.; Garattini, E. *Blood* **1996**, *87*, 1520.
8. Wermuth, C. G. In *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed., second ed.; Academic Press: London, 2003; pp 189–214.
9. Dawson, M. I.; Hobbs, P. D.; Kuhlmann, K.; Fung, V. A.; Helmes, C. T.; Chao, W.-R. *J. Med. Chem.* **1980**, *23*, 1013.
10. Tashima, T.; Kagechika, H.; Tsuji, M.; Fukasawa, H.; Kawachi, E.; Hashimoto, Y.; Shudo, K. *Chem. Pharm. Bull. (Tokyo)* **1997**, *45*, 1805.
11. Ebisawa, M.; Kawachi, E.; Fukasawa, H.; Hashimoto, Y.; Itai, A.; Shudo, K.; Kagechika, H. *Biol. Pharmacol. Bull.* **1998**, *21*, 547.
12. Ebisawa, M.; Ohta, K.; Kawachi, E.; Fukasawa, H.; Hashimoto, Y.; Kagechika, H. *Chem. Pharmacol. Bull. (Tokyo)* **2001**, *49*, 501.
13. Kagechika Hiroyuki Nerima-Ku, EP 1 357 104 A1.
14. Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. *J. Med. Chem.* **1996**, *39*, 5228.
15. Boschelli, D. H.; Connor, D. T. U.S. Patent 5,114,958, May 19, **1992**.
16. Dong, C.-Z.; Ahamada-Himidi, A.; Plocki, S.; Aoun, D.; Touaibia, M.; Meddad-Bel Habich, N.; Huet, J.; Redeuilh, C.; Ombetta, J.-E.; Godfroid, J.-J. *Bioorg. Med. Chem.* **2005**, *13*, 1989.
17. Valgeirsson, J.; Nielsen, E. O.; Peters, D.; Mathiesen, C.; Kristensen, A. S.; Madsen, U. *J. Med. Chem.* **2004**, *47*, 6948.
18. Measured with shake-flash method, UV detection.
19. U.S. Patent 5,349,105, Allergan, issued 20th September 1994.
20. Charton, J.; Cousaert, N.; Bochu, C.; Willand, N.; Deprez, B.; Deprez-Poulain, R. *Tetrahedron Lett.* **2007**, *48*, 1479.
21. Stansfield, I.; Pompei, M.; Conte, I.; Ercolani, C.; Migliaccio, G.; Jairaj, M.; Giuliano, C.; Rowley, M.; Narjes, F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5143.
22. *Cell culture.* Cos-7 cells were obtained from ATCC (CRL-1651). Cells were maintained in standard culture conditions (Dulbecco's modified Eagle's minimal essential medium supplemented with 10% fetal calf serum at 37 °C in a humidified atmosphere of 5% CO_2/95% air). Medium was changed every 2 days.Effect of compounds on RARs transcriptional activity using chimaeric protein constructs.Cos-7 cells were seeded in 60 mm dishes in DMEM supplemented with 10% FCS and incubated at 37 °C for 16 h prior transfection. Cells were transfected in DMEM 10% FCS, using jetPEI™ transfection reagent, with reporter (pGal5-TK-pGl3) and expression plasmids (pGal4-hRARα, γor β). Cells were incubated at 37 °C. After 24 h, cells were trypsinised and seeded in 96-well plates and incubated for 6 h in DMEM containing 0.2% FCS. Cells were then incubated 16h in DMEM 0.2% FCS and increasing concentrations of the compounds tested or vehicle (DMSO). At the end of the experiments, cells were washed once with PBS and the luciferase and the β-galactosidase assays were performed.