Bioorganic & Medicinal Chemistry Letters, Vol.2, No.9, pp. 1085-1088, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

SYNTHESIS OF TETRAZOL-1-YL ANALOGS OF HMG-COA REDUCTASE INHIBITOR BMS180431 (FORMERLY BMY21950)

S. Y. Sit*, Rex A. Parker and J. J. Wright

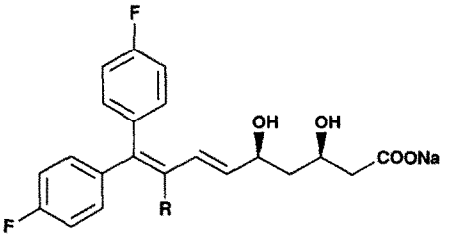
Bristol-Myers Squibb Pharmaceutical Research Institute
5 Research Parkway, Wallingford, CT 06492-7660

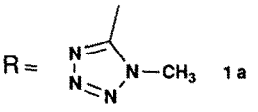
(*Received* 19 *May* 1992)

Abstract : A series of tetrazol-1-yl analogs were prepared and compared with the corresponding parent tetrazol-5-yl HMGCO-A reductase inhibitors. The generally weaker enzyme inhibitory activity of **2a** may be attributed to the shorter distance between the heterocycle and the backbone of the molecule. The corresponding unsubstituted tetrazole parent compound (**2c**) becomes the most active in this series.

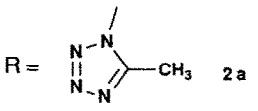
We recently reported a series of 9,9-bis(aryl)-3,5-dihydroxy-8-(alkyltetrazol-5-yl)-6,8-nonadienoic acid derivatives to be HMG-CoA reductase inhibitors[1]. The 1-methyltetrazol-5-yl compound **1a** is a potent and tissue specific inhibitor of the enzyme HMG-CoA reductase (IC_{50} values in liver; spleen; testes; bovine occular and adrenal cell preparations were 21; 3200; 1800; 3000; and 1600 nM respectively)[2]. The high potency and tissue specificity prompted us to look into the unique structural feature of **1a** which might be responsible for its extraordinary biological profile.

We wish to report here on a series of very closely related analogs of **1a**. In this series of compounds, the orientation of the crucial tetrazole ring was altered so that the N_1 atom of the tetrazole ring is connected to the nonadienoic acid backbone of the parent molecule. This design introduces a slightly shorter (1.36Å) sp^2 C-N bond in comparison to the original (1.48Å) sp^2 carbon-sp^2 carbon bond in **1a**. Due to the shorter bond length, the conformation of the 6,8-nonadienoic acid should be more sensitive to any substituent attached to the C_5 position of the tetrazole ring in **2a**. The idea of introducing a slightly modified tetrazole ring stemmed from the rather narrow SAR available to us in terms of optimizing both potency and specificity in **1a** by modifying this tetrazole moiety. We therefore sought suitable active candidates with which we may be able to probe this narrow window.





1a



2a

The preparation of the title compounds required the synthesis of the tetrazole intermediates **6**. Compounds of type **6** are generally prepared by a dipolar cycloaddition of a suitable nitrile and a vinyl azide, or by reacting an organic azide with an iminochloride[3]. The existing methodologies involve the manipulation of small molecular weight organic

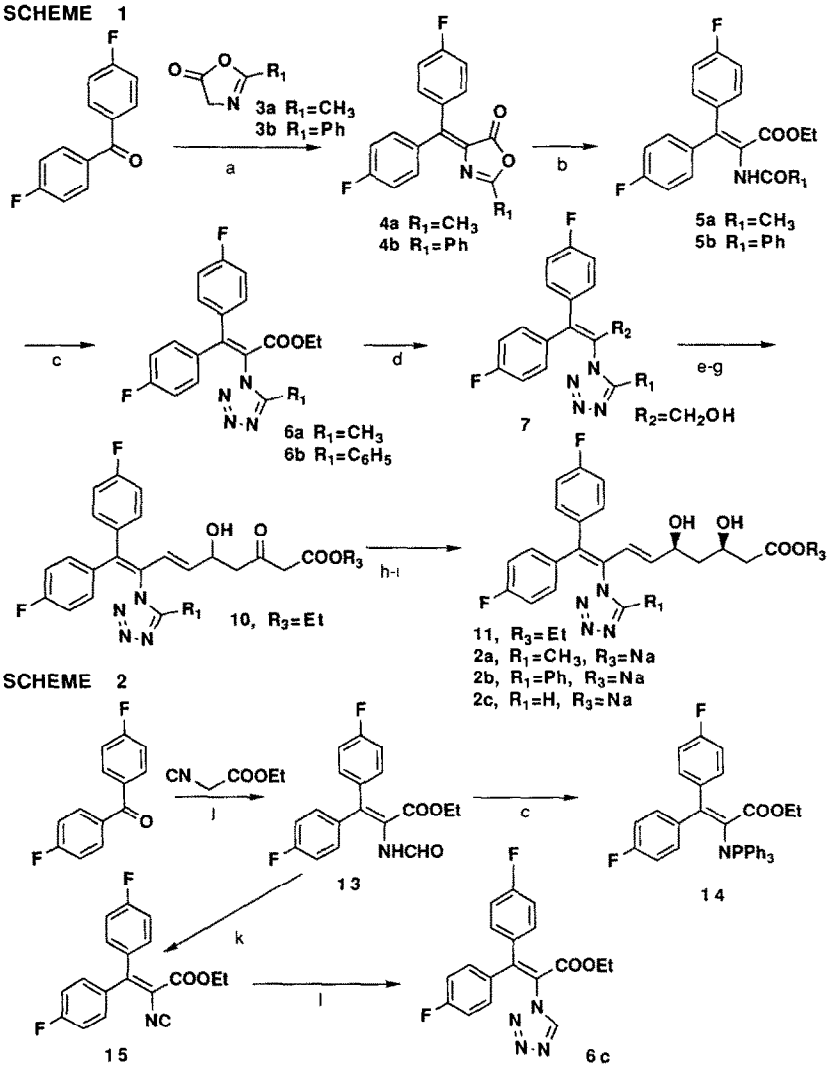
azides and are unsatisfactory for large scale preparation. The present procedure avoids the handling of organic azides and therefore provides a safer and a viable alternative.

The substituted azlactones **3a** and **3b**[4] condensed very efficiently with 4,4-difluorobenzophenone in conditions reported previously[5] to give **4a** (54%, m.p.=135.5-137.3°C) and **4b** (81%, m.p.=141-143°C). The oxazolone ring was opened in absolute ethanol in the presence of a catalytic amount of NaOEt at room temperature to provide the ethyl esters **5a** and **5b**. Each of these was subjected to Appel's[6] conditions (Ph_3P/CCl_4) in anhydrous acetonitrile under nitrogen at room temperature to give a dark reddish solution[7]. To this homogeneous solution was added NaN_3 (solid) and a phase transfer catalyst ($n\text{-}Bu_4NBr$, 10 mol %)[8], the resulting suspension was then stirred at R.T. for 30 minutes. During this period, the color smoothly faded into pale brownish yellow and a heavy precipitate of NaCl was formed. The mixture was filtered after three hours, the solution concentrated and the desired products purified by crystallization to afford **6a** (88%, m.p.=102.9-103.5°C) and **6b** (69%, m.p.=148.6-150.1°C). The rest of the synthesis of the final target compounds **2** from **6** was straightforward and is summarized[9] in scheme 1.

The synthesis of the unsubstituted **6c** was slightly different since the unsubstituted oxazolone **3c** (R_1=H) is not readily available. The formamide **13** was prepared by condensing 4,4-difluorobenzophenone with ethyl isocyanoacetate[10] in the presence of NaH in THF (80% yield, m.p.=174.1-175.7°C). The preparation of the unsubstituted tetrazole **6c** was also different from that of **6a** and **6b** since iminophosphorane **14** (m.p.=205-206°C) was produced in a yield of over 80% when **13** was subjected directly to Appel's conditions.[11] Compound **13** was dehydrated ($COCl_2$, Et_3N in $CHCl_3$) to give the isocyanide **15**, which was generally used without purification.[12] However, an analytically pure sample of **15** was obtained by a recrystallization in EtOAc-Hexanes (m.p.=92-95°C) (Scheme 2). The isocyanide **15** was treated under conditions identical to those described above to give **6c** in 25% yield (m.p.=117.8-119.2°C)[13] along with over 60% of recovered **13**.

The enzyme inhibitory activity of compounds **2** was determined using the protocols established previously[2] and the results are summarized in Table 1. In contrast to the tetrazol-5-yl series, the shorter C-N bond renders this series more sensitive towards tetrazole ring substitution, hence the unsubstituted **2c** becomes the most active while the phenyl analog **2b** was found to be almost three orders of magnitude less potent. The results in the HepG2 also agree very well with that reported for **1a** and it further confirms that tissue specificity is attributed to the local hydrophilicity of these molecules. We are currently completing the synthesis of an extensive series of azole analogs, and expanding the scope of coverage for more SAR information. Issues regarding steric versus electronic effects remained to be explored

SCHEME 1



SCHEME 2

Reaction Conditions: (a) $TiCl_4/CCl_4$/THF/Pyridine @ -78°C then to R.T., (b) Absolute EtOH/EtONa @ R.T., (c) $CCl_4/PPh_3/CH_3CN$ then n-Bu_4NBr/NaN_3 R.T., (d) Dibal-H/CH_2Cl_2, (e) PCC/CH_2Cl_2, (f) $Ph_3PCHCHO$/Benzene @ reflux, (g) Dianion of Ethyl Acetoacetate, (h) $Et_3B/NaBH_4$/MeOH, (i) NaOH/H_2O/THF, (j) NaH/THF @ 0°C, (k) $COCl_2/CHCl_3/Et_3N$ @ 0°C, (l) NaN_3/n-Bu_4NBr/catalytic Et_3N HCl

TABLE 1

	Isolated Enzyme IC_{50} (nM)	Rat Hepatocyte IC_{50} (nM)	HepG2 IC_{50} (nM)	Ratio of HEPG2 to Hepatocyte
Mevinolin	27	32	39	1.2
1a	43	21	1340	62
2a (CH_3)	630	100	1290	13
2b (Ph)	>100μM	Not Tested	Not Tested	Not Compared
2c (H)	120	20	1720	86

These results, coupled with the established[2d,2e] *in vitro* and *in vivo* data of BMY21950, sufficiently validated a novel and potent HMG-CoA reductase inhibitor (**2c**) with augmented tissue specificity.

Acknowledgement : We thank the Bristol-Myers Squibb Analytical Research Department for assistance in obtaining spectral and elemental combustion data

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7. It is uncertain whether the colored species in CH_3CN is the iminochloride or a reactive ionic intermediate. However, the intense reddish color in this case strongly suggests the latter.
8. The initial phase of the cycloaddition was exothermic.
9. For details of this general transformation from esters **6** to the final product **2**, refer to reference 1e
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12 The use of isocyanides and hydrazoic acid to produce a tetrazole has been reported, see Zimmerman, D.M. and Olofson, R.A. *Tet Lett* , **1969**, *58*, 5081. However, the present procedure avoids the handling of hydrazoic acid, which is explosive.
13. (All are racemic unless specified.) H-NMR data [300 MHz, $CDCl_3$, δ(ppm), J(Hz),] and elemental analyses for selected compounds: **6a** 7.23 (2H, dd, J=5.3, 8.7), 7 10 (2H, dd, J=8.3, 10 2), 6.88 (4H, d, J=7.1), 4.04 (2H, q, J=7.1), 2.20 (3H, s,), 0.96 (3H, t, J=7 1), Calc CHN 61.62, 4 35, 15 13; found CHN 61.39, 4.36, 15 02; **6b** 7.3-7.5 (5H, m), 7 0-7 2 (4H,m), 6 7 (2H, t, J=7 5), 6 35-6 45 (2H, m), 4 1 (2H, q, J=7.2), 1.0 (3H, t, J=7.2), Calc CHN 66.66, 4 20, 12.96; found CHN 65.91, 4.26, 12 82; **6c** 8.33 (1H, s), 7.20-7.25 (2H, m), 7.05-7.16 (2H, m), 6.83-6 92 (4H, m), 4.06 (2H, q, J=7.1), 0.98 (3H, t, J=7.1), Calc CHN 60.67, 3.96, 15 72; found CHN 60 65, 3 89, 15 82