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Evaluation of 4′-substituted bicyclic pyridones as non-steroidal inhibitors of steroid 5α-reductase

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Abstract—4′-Substituted bicyclic pyridones were prepared and evaluated as non-steroidal inhibitors of type 1 and 2 steroid 5α-reductase (SR). A range of 4′-substituents were incorporated into the bicyclic scaffold to investigate SAR within and across different classes of non-steroidal inhibitors of SR. Bicyclic pyridones containing a 4′-benzoyl or long carbon chain tether showed more potent inhibition against type 1 SR than inhibitors with *N*-substituted acetamide groups in the 4′-position. SAR derived from 4′-substituted bicyclic pyridones reported here do not correlate with SAR derived from known potent 4′-substituted biaryl acid SR inhibitors. A 4′-benzoyl group is favoured by the active site in both isozymes.

Steroid 5α-reductase is an NADPH-dependent enzyme that catalyses the irreversible bioreduction of testosterone to the more potent androgen dihydrotestosterone (DHT). Two isozymes of SR exist, type 1 and type 2, whose tissue distribution and kinetics differs.[1] Major target tissues of DHT include the prostate, skin, scalp and sebaceous gland (see Occhiato et al. and references therein).[2] Elevated levels of DHT are associated with prostate disorders (cancer and benign prostatic hyperplasia)[2] and skin disorders such as androgenetic alopecia (male pattern baldness), acne and hirsutism.[3] Due to the association of DHT with these disorders, there is significant interest in developing SR inhibitors as potential therapeutics. Modification of the natural substrate led to the generation of steroidal inhibitors such as **1**[4] and **2**,[5] but recent work has focussed on developing non-steroidal inhibitors with tricyclic or bicyclic scaffolds that mimic the steroid backbone (e.g., **3**,[6] **4**,[7] **5a**/**5b**[8,9] and **6**[10]). Non-steroidal inhibitors are currently of significant interest as they potentially avoid the well-known side effects associated with steroidal drugs.

Structural diversity is found amongst the different classes of non-steroidal compounds known to inhibit SR. However, a structural feature common to these inhibitors is a lipophilic scaffold incorporating a ring which mimics the geometry and electrostatic properties of the A ring of the proposed enolate intermediate in the bioreduction.[2] The potency and selectivity of non-steroidal inhibitors depends greatly on the nature and position of ring substituents. The number of different classes of non-steroidal SR inhibitors has made the definition of structure–activity relationships (SAR) within and across these classes necessary. In this paper, we report SAR derived from novel compounds with non-steroidal bicyclic scaffolds, 5- and 1-aryl substituted pyridones (e.g., **6** and **7**). As substituents at the 4′-position are known to influence the potency of known bicyclic SR inhibitors, particular substituents were chosen for incorporation at the 4′-position of the bicyclic pyridone scaffolds to examine SAR for this position. Potent inhibitors containing *N*-substituted acetamide or benzoyl substituents at the 4′-position are found within a class of non-steroidal inhibitors consisting of a biaryl acid scaffold (e.g., **5a** and **5b**). These and related moieties were incorporated into the 4′-position of the bicyclic pyridones reported here. The biaryl acids **5a** and **5b** represent non-steroidal derivatives of the steroidal acid **2**, with two of the steroidal rings (B and D) missing. They are also related to the non-steroidal tricyclic aryl acid compound **4** in which the steroidal D ring is absent. The same relationships

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can also be observed for the aza-type compounds **1**, **3** and **5**. To examine SAR for the 4′-position, a series of 4′-substituted 5-arylpyridones (**13**–**15**, **17**, **26** and **27**) were prepared, along with some corresponding 1-arylpyridone derivatives (**20** and **21**), and tested against SR types 1 and 2 expressed in transfected human embryonic kidney cells. SR inhibitors consisting of a substituted 1-arylpyridone scaffold of the type depicted by **7** have not been reported to date and thus present a novel non-steroidal bicyclic scaffold with which to investigate SR inhibition. Compounds **26** and **27** contain a long carbon chain tether which was incorporated to facilitate their potential attachment to a gold surface. Solid supported biologically active compounds provide well-defined systems for investigating biomolecular recognition, such as that between an enzyme and inhibitor. SAR obtained for the compounds reported were compared to SAR derived from inhibitors within the bicyclic pyridone class as well as inhibitors from the biaryl acid class, providing further information about the structural features common to different classes of non-steroidal SR inhibitors (Fig. 1).

Synthesis. 5-Aryl 1-methyl-2-pyridones **13**–**15** were prepared from the key bicyclic intermediate **9** (Scheme 1), which was synthesised via Suzuki cross coupling of the commercially available pyridine **8** and *p*-methoxyphenyl boronic acid. Acid hydrolysis of **9** was followed by N-methylation and deprotection of the aryl methyl ether to give the phenol **10**. Alkylation of **10** with bromoacetamide **11**[11] or **12** gave target compounds **13** and **14**, respectively. Piperidone **15** was prepared by catalytic hydrogenation of **13**. The synthetic route to pyridone **17** was slightly modified, whereby **8** was converted to 6-fluoropyridin-3-yl boronic acid[12] to facilitate Suzuki cross coupling with benzyl-4-bromophenyl ketone to give the key bicyclic intermediate **16**. Acid hydrolysis of **16** and subsequent N-methylation gave target compound **17**.

1-Aryl 2-methyl 2,3-dihydro-4-pyridones **20** and **21** (Scheme 2) were prepared from racemic key intermediate **18** which was synthesised via aza Diels-Alder methodology using Danishefsky's diene, acetaldehyde and *p*-anisidine.[13] Deprotection of the aryl methyl ether of **18** gave phenol **19** which was alkylated with bromoacetamide **11** or **12** to give target compounds **20** and **21**, respectively.

Long carbon chain tethers containing a terminal olefin (**24** and **25**) were prepared for subsequent attachment to proposed inhibitor **14** using cross metathesis. Compounds **22** and **23** were prepared according to Svedham et al.[14] and coupled to 4-pentenoic acid in the presence of DMAP and EDCI to give tethers **24** and **25**. The inhibitor-tether conjugates **26** and **27** were prepared by reacting proposed inhibitor **14** with tether **24** or **25** in the presence of Grubbs' second generation catalyst (only the *E* isomers were obtained). These long carbon chain tethers were incorporated into compound **14** to facilitate its potential attachment to a gold surface (Scheme 3).

Inhibition of SR type 1 and 2. The inhibitory activity (% inhibition at 10 μM) of compounds reported here (Table 1) against SR type 1 and 2 was evaluated[†] against

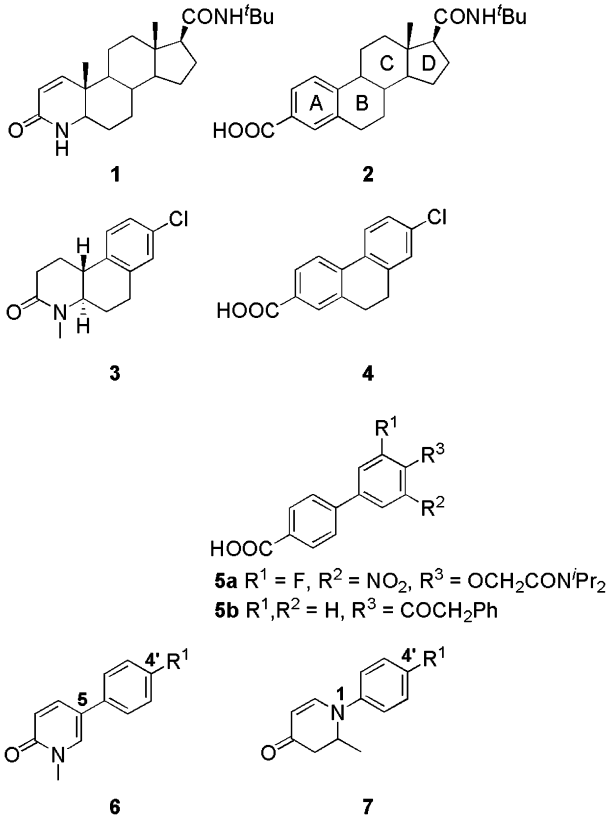
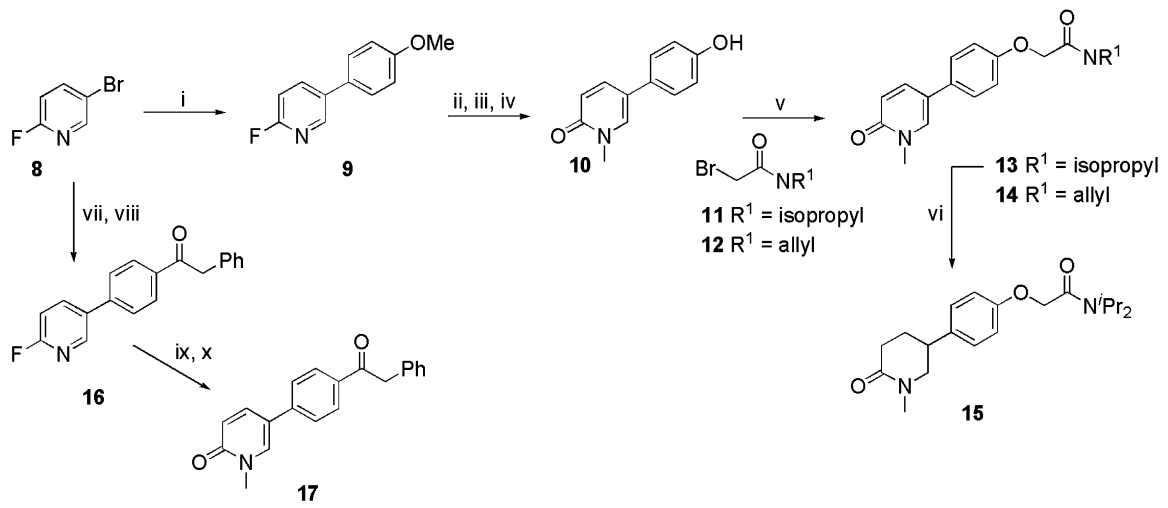
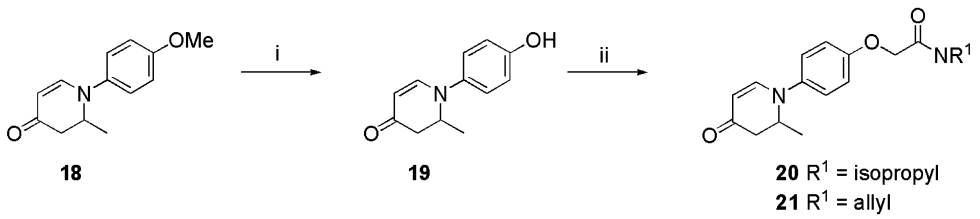


Figure 1. Some known steroidal inhibitors (**1** and **2**) of SR and related non-steroidal tricyclic (**3** and **4**) and bicyclic inhibitors (**5** and **6**). Structure **7** represents a novel scaffold for the inhibition of SR as reported here.

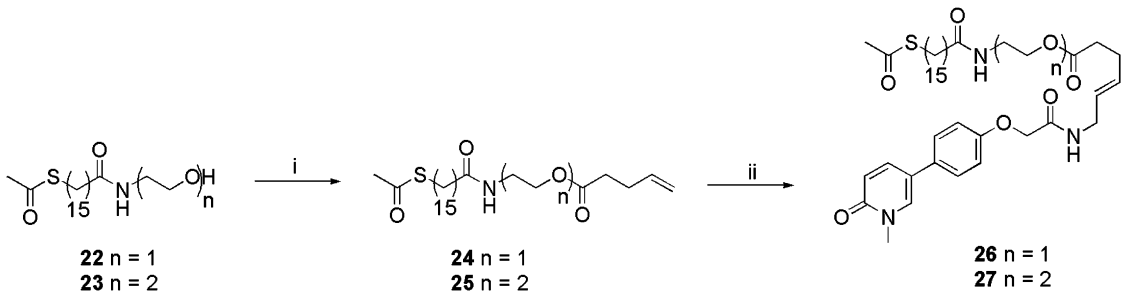
[†] *Assay procedure:* SR type 1 and 2 transfected HEK293 cells were washed with PBS buffer and harvested in cold homogenate buffer (Tris–HCl, EDTA and sucrose). Cells were homogenised on ice. Test compound solutions (10 μM in DMSO) were incubated with cell homogenate (total volume 500 μL using Tris–HCl buffer, EDTA). This high test compound concentration was used as inhibitory activity could not be detected at lower concentrations. The incubation mixture included $NADP^+$, glucose-6-phosphate, glucose-6-phosphate dehydrogenase, androstenedione (AD) (500 nM with 3.2 μCi [1β-^{3}H]-AD) and 2% MeOH. Androstenedione was used as the substrate as it has a higher affinity for SR type 1 compared to testosterone (androstenedione and testosterone have similar affinities for SR type 2). The K_m values for androstenedione in the cell-free homogenate are 852 nM (type 1) and 57 nM (type 2). K_m values for testosterone are 1–5 μM (type 1) and 4–50 nM (type 2).[2] Addition of the enzyme preparation to the test compound solution started the reaction, which was stopped by extracting the steroids with cold diethyl ether. Collection of the ether layer after centrifugation gave the steroids which were dissolved in 50 μL MeOH for HPLC analysis. HPLC analysis was carried out with Agilent 1100 series, Agilent Chemstation for LC 3D. The dissolved steroids (AD and androstanedione, 12.5 μL) were injected. Radioactivity was measured with a Berthold radioflow monitor LB509. Methanol/water (65:35) was used as the mobile phase with a flow of 0.35 mL min^{-1}, and additive flow of 1 mL for scintillator (quickszint flow 302) and RP 18 Nucleodur column. Baseline separation of steroidal substrates and products was achieved within 15 min. Results are expressed as the amount of androstanedione formed as a percentage of control values.



Scheme 1. Reagents and conditions: (i) *p*-methoxyphenyl boronic acid, $Pd(PPh_3)_4$, KOH, *n*-Bu_4NBr, THF, reflux, 19 h (82%); (ii) 4 M HCl in dioxane, H_2O, reflux, 24 h (quant.); (iii) LiH, DMF, 50 °C, 1.5 h then MeI, 16 h (68%); (iv) HBr in AcOH, reflux, 16 h (83%); (v) 2 M aq KOH, DMF, 80 °C, 1.5 h, then **11** or **12**, 16 h [**13** (46%), **14** (79%)]; (vi) H_2, Pd/C, 40 bar, EtOH, rt (63%); (vii)[12]; (viii) benzyl-4-bromophenyl ketone, $Pd(PPh_3)_4$, 2 M aq Na_2CO_3, EtOH, PhMe, reflux, 18 h (85%); (ix) as for step (ii); (x) LiH, DMF, rt, 1 h, then MeI, 16 h (52%).



Scheme 2. Reagents and conditions: (i) HBr in AcOH, 80 °C, 8 h (66%); (ii) 2 M aq KOH, DMF, 80 °C, 1 h, then **11** or **12**, 16 h [**20** (43%), **21** (30%)].



Scheme 3. Reagents and conditions: (i) DMAP, 4-pentenoic acid, EDCI, CH_2Cl_2, rt, 3 h [**22** (49%), **23** (62%)]; (ii) 20 mol% Grubbs' 2nd generation catalyst, 1,1,2-trichloroethane, rt, 16 h [**26** (30%), **27** (52%)].

isozymes expressed separately by transfected human embryonic kidney (HEK) cells.[15] HEK-I (expressing type 1 SR) and HEK-II (type 2 SR) cell-free homogenates were used. Weak inhibition against the type 1 isozyme was observed for compounds with 4′-*N*-substituted acetamide compounds **13**–**15**, **20** and **21**. More potent inhibition of type 1 SR was observed for compounds **26** and **27** which have long carbon chain tethers attached to the 4′-acetamide, and also **17** which has a 4′-benzoyl substituent. This finding provides further evidence that large hydrophobic groups are tolerated in a region of the active site not involved in the enzymatic reaction. Similar inhibitory activities against type 1 SR are observed for compounds with an *N*-methylated lactam ring (**13** and **14**) compared to those with a 2-methyl 2,3-dihydro-4-pyridone ring (**20** and **21**) (cf **13/20**, and **14/21**). A benzoyl group clearly enhances the potency of **17** when compared to inhibitors containing *N*-substituted acetamide groups (**13**, **14**, **20** and **21**). This observation correlates with that reported by Hartmann et al. who noted that the presence of bulky ketones at the 4′-position of 5-aryl pyridones enhanced inhibitory potency compared to compounds with amides at the 4′-position.[16] Inhibition against the type 2 isozyme was only observed for compound **21** which also inhibited type 1 SR very weakly.

Table 1. Inhibition of type 1 and 2 SR

Compound	Type 1[a] (% inhibition at 10 μM)	Type 2[b] (% inhibition at 10 μM)
13	8	—
14	6	—
15	6	—
17	61	
20	3	—
21	8	12
26	43	—
27	33	—
Finasteride (**9f**)	453[c]	25[c]

[a] HEK-I cell homogenate.
[b] HEK-II cell homogenate.
[c] IC_{50} (nM).

The substituent present at the 4′-position of non-steroidal bicyclic inhibitors is influential on both type 1 and 2 SR inhibition potencies. Potent biaryl acid compound **5a** (IC_{50} = 9.8 nM)[8] contains an OCH_2 linker between the aromatic ring and *N*-diisopropylamide group at the 4′-position. This linker was incorporated into the 4′-position of the 5-aryl 1-methyl-pyridone scaffold reported here to give novel compounds **13** and **15** with 4′-*N*-substituted acetamides. However the presence of the OCH_2 linker in **13** and **15** did not result in potent inhibitory activity for these compounds (6% and 8% inhibition of type 1 activity, respectively). This is a significant result for defining SAR across different classes of SR inhibitors. For the pyridone inhibitors, SAR for 4′-substituents do not correlate with SAR derived from the biaryl acid class.

Inhibitor **17** was based on known potent compound **5b** (K_i = 60 nM for type 2 SR)[9] which possesses a benzoyl group at the 4′-position of the biaryl acid scaffold. Due to its influence on potency, this benzoyl group was incorporated into the 4′-position of the 5-aryl 1-methyl-pyridone scaffold reported here to give **17** (61% inhibition of type 1 SR activity at 10 μM). Whilst not as potent as **5b**, the inhibitory activity of **17** suggests that the benzoyl group is tolerated by the enzyme active site of both isozymes.

The presence of a long carbon chain tether enhanced the inhibitory activity of compounds **26** and **27** (43% and 33% inhibition of type 1 activity, respectively) in comparison to **14** (6% inhibition of type 1 activity). This result provides further evidence for the presence of a lipophilic pocket in the enzyme active site that tolerates bulky hydrophobic groups at the terminus of the inhibitor which is not interacting with residues responsible for the enzyme catalysed reduction. These compounds also suggest a way forward for gold surface attachment to facilitate potential biomolecular recognition studies.

The results reported here reveal important information on the correlation between SAR from 4′-substituted bicyclic pyridones (as described here) and SAR derived from known 4′-substituted biaryl acids, in particular **5a** and **5b**. We can conclude for the bicyclic pyridone inhibitors, SAR for 4′-substituents do not correlate with SAR for 4′-substituents derived from the biaryl carboxylic acid inhibitors. In addition, a novel type of non-steroidal scaffold for inhibiting SR has been reported, which may allow further development of more potent non-steroidal inhibitors of SR. The bicyclic pyridones reported here are related to the tricyclic benzo[*f*]quinolinone **3**, all of which are non-steroidal mimics of the aza-steroid inhibitor **1**. The biaryl acid SR inhibitors discussed (e.g., **5a/5b**) are related to the tricyclic aryl acid **3** and are non-steroidal mimics of steroidal inhibitor **2**. The inhibitory activities reported here provide further evidence that the nature of the substituent at the 4′-position of non-steroidal bicyclic inhibitors has a profound effect on potency and selectivity against SR types 1 and 2.

N,N-Diisopropyl-2-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)acetamide (**13**). ^{1}H NMR (CD_3OD, 500 MHz) δ 1.24 (d, 6H, J = 6.4 Hz, (CH_3)$_2$), 1.39 (d, 6H, J = 6.4 Hz, (CH_3)$_2$), 3.43 (m, 1H, $CH(CH_3)_2$), 3.61 (s, 3H, NCH_3), 4.09 (m, 1H, $CH(CH_3)_2$), 4.72 (s, 2H, CH_2), 6.59 (d, 1H, J = 9.3 Hz, COCH=CH), 7.00 (d, 2H, J = 8.8 Hz, ArH), 7.43 (d, 2H, J = 8.8 Hz, ArH), 7.80 (dd, 1H, J = 2.4, 9.3 Hz, COCH=CH), 7.86 (d, 1H, J = 2.4 Hz, NCH_3CH). HRMS (M+H). Found: 343.2032 (Calcd for $C_{20}H_{27}N_2O_3$: 343.2022).

N-Allyl-2-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)acetamide (**14**). ^{1}H NMR (CD_3OD, 500 MHz) δ 3.65 (s, 3H, NCH_3), 3.89 (d(br), 2H, J = 5.4 Hz, $NHCH_2$), 4.55 (s, 2H, OCH_2), 5.13 (m, 2H, CH=CH_2), 5.85 (m, 1H, CH=CH_2), 6.62 (d, 1H, J = 9.3 Hz, COCH=CH), 7.06 (d, 2H, J = 8.8 Hz, ArH), 7.48 (d, 2H, J = 8.8 Hz, ArH), 7.83 (dd, 1H, J = 2.4, 9.3 Hz, COCH=CH), 7.90 (d, 1H, J = 2.4 Hz, NCH_3CH). HRMS (M+H). Found: 299.1390 (Calcd for $C_{17}H_{19}N_2O_3$: 299.1396).

N,N-Diisopropyl-2-(4-(1-methyl-6-oxopiperidin-3-yl)phenoxy)acetamide (**15**). ^{1}H NMR (CD_3OD, 500 MHz) δ 1.24 (d, 6H, J = 6.4 Hz, (CH_3)$_2$), 1.38 (d, 6H, J = 6.8 Hz, (CH_3)$_2$), 2.02 (m, 2H, NCH_3CH_2), 2.46 (m, 2H, $COCH_2CH_2$), 2.94 (s, 3H, NCH_3), 3.09 (m, 1H, NCH_3CH_2CH), 3.41 (m, 2H, $COCH_2CH_2$), 3.54 (m, 1H, $CH(CH_3)_2$), 4.09 (m, 1H, $CH(CH_3)_2$), 4.67 (s, 2H, OCH_2), 6.92 (d, 2H, J = 8.8 Hz, ArH), 7.23 (d, 2H, J = 8.3 Hz, ArH). HRMS (M+H). Found: 347.2327 (Calcd for $C_{20}H_{31}N_2O_3$: 347.2335).

1-Methyl-5-(4-(2-phenylacetyl)phenyl)pyridin-2(1H)-one (**17**). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.62 (s, 3H, NCH_3), 4.49 (s, 2H, CH_2), 6.61 (d, 1H, J = 9.8 Hz, COCH=CH), 7.38 (m, 5H, ArH), 7.85 (d, 2H, J = 8.3 Hz, ArH), 8.02 (dd, 1H, J = 2.7, 9.7 Hz, COCH=CH), 8.18 (d, 1H, J = 8.3 Hz, ArH), 8.41 (d, 1H, J = 2.9 Hz, NCH_3CH). HRMS (M+H). Found: 304.1340 (Calcd for $C_{20}H_{18}NO_2$: 304.1338).

N,N-Diisopropyl-2-(4-(2-methyl-4-oxo-3,4-dihydropyridin-1(2H)-yl)phenoxy) acetamide (**20**). ^{1}H NMR (CD_3OD, 500 MHz) δ 1.25 (d, 3H, J = 6.3 Hz, $NCHCH_3$), 1.25 (d, 6H, J = 6.3 Hz, $CH(CH_3)_2$), 1.40 (d, 6H, J = 6.8 Hz, $CH(CH_3)_2$), 2.30 (dd, 1H, J = 3.2, 16.6 Hz, $COCH_aH_b$),

3.00 (dd, 1H, J = 6.8, 16.6 Hz, $COCH_aH_b$), 3.56 (m, 1H, $CH(CH_3)_2$), 4.08 (m, 1H, $CH(CH_3)_2$), 4.37 (m, 1H, $NCHCH_3$), 4.72 (s, 2H, OCH_2), 5.09 (d, 1H, J = 7.8 Hz, $COCH{=}CH$), 7.01 (d, 2H, J = 9.3 Hz, Ar**H**), 7.24 (d, 2H, J = 8.8 Hz, Ar**H**), 7.53 (d, 1H, J = 7.8 Hz, $COCH{=}CH$). HRMS (M+H). Found: 345.2188 (Calcd for $C_{20}H_{29}N_2O_3$: 345.2178).

N-Allyl-2-(4-(2-methyl-4-oxo-3,4-dihydropyridin-1(2H)-yl)phenoxy)acetamide (**21**). ^{1}H NMR (CD_3OD, 500 MHz) δ 1.25 (d, 3H, J = 6.4 Hz, $CHCH_3$), 2.31 (dd, 1H, J = 2.9, 16.6 Hz, $COCH_aH_b$), 3.01 (dd, 1H, J = 6.4, 16.6 Hz, $COCH_aH_b$), 3.88 (d(br), 2H, J = 4.9 Hz, $NHCH_2$), 4.39 (m, 1H, $CHCH_3$), 4.55 (s, 2H, OCH_2), 5.10 (d, 1H, J = 7.3 Hz, $COCH{=}CH$), 5.12 (m, 2H, $CH_2CH{=}CH_2$), 5.84 (m, 1H, $CH_2CH{=}CH_2$), 7.06 (d, 2H, J = 8.8 Hz, Ar**H**), 7.26 (d, 2H, J = 9.2 Hz, Ar**H**), 7.54 (d, 1H, J = 7.8 Hz, $COCH{=}CH$). HRMS (M+H). Found: 301.1546 (Calcd for $C_{17}H_{21}N_2O_3$: 301.1552).

2-(16-(Acetylthio)hexadecanamido)ethyl 6-(2-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)acetamido)hex-4-enoate (**26**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.29 (m(br), 22H, $(CH_2)_{11}$), 1.56 (m, 4H, $(CH_2)_2$), 2.16 (t, 2H, J = 7.5 Hz, CH_2), 2.30 (s, 3H, CH_3CO), 2.40 (m, 4H, $COCH_2CH_2$), 2.83 (t, 2H, J = 7.1 Hz, CH_2), 3.48 (m, 2H, $NHCH_2CH_2$), 3.60 (s, 3H, NCH_3), 3.90 (t, 2H, J = 5.9 Hz, $NHCH_2CH{=}CH$), 4.14 (t, 2H, J = 5.2 Hz, $NHCH_2CH_2$), 4.50 (s, 2H, OCH_2CO), 5.56 (m, 2H, $CH_2CH{=}CH$), 5.96 (s(br), 1H, $NHCH_2CH_2$), 6.64 (d, 1H, J = 9.5 Hz, $COCH{=}CH$), 6.71 (s(br), 1H, $NHCH_2CH{=}CH$), 6.95 (d, 2H, J = 8.7 Hz, Ar**H**), 7.34 (d, 2H, J = 8.7 Hz, Ar**H**), 7.44 (d, 1H, J = 2.4 Hz, NCH_3CH), 7.57 (dd, 1H, J = 2.4, 9.5 Hz, $COCH{=}CH$). HRMS (M+H). Found: 726.4182 (Calcd for $C_{40}H_{60}N_3O_7S$: 726.4152).

2-(2-(16-(Acetylthio)hexadecanamido)ethoxy)ethyl 6-(2-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenoxy)acetamido)hex-4-enoate (**27**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (m(br), 20H, $(CH_2)_{10}$), 1.58 (m, 6H, $(CH_2)_3$), 2.16 (t, 2H, J = 7.5 Hz, CH_2), 2.31 (s, 3H, CH_3CO), 2.40 (m, 4H, $COCH_2CH_2$), 2.84 (t, 2H, J = 7.5 Hz, CH_2), 3.43 (m, 2H, $NHCH_2CH_2$), 3.53 (t, 2H, J = 5.2 Hz, $NHCH_2CH_2$), 3.61 (s, 3H, NCH_3), 3.63 (t, 2H, J = 4.8 Hz, OCH_2), 3.92 (t, 2H, J = 5.9 Hz, $NHCH_2CH{=}CH$), 4.21 (t, 2H, J = 4.8 Hz, OCH_2), 4.51 (s, 2H, OCH_2CO), 5.57 (m, 2H, $CH_2CH{=}CH$), 5.95 (s(br), 1H, $NHCH_2CH_2$), 6.64 (d, 1H, J = 9.5 Hz, $COCH{=}CH$), 6.67 (s(br), 1H, $NHCH_2CH{=}CH$), 6.96 (d, 2H J = 8.7 Hz, Ar**H**), 7.35 (d, 2H, J = 8.7 Hz, Ar**H**), 7.44 (d, 1H, J = 2.8 Hz, NCH_3CH), 7.57 (dd, 1H, J = 2.8, 9.5 Hz, $COCH{=}CH$). HRMS (M+H). Found: 770.4426 (Calcd for $C_{42}H_{64}N_3O_8S$: 770.4414).

References and notes

1. Jenkins, E. P.; Andersson, S.; Imperato-McGinley, J.; Wilson, J. D.; Russell, D. W. *J. Clin. Invest.* **1992**, *89*, 293.
2. Occhiato, E. G.; Guarna, A.; Serio, M. *J. Steroid Biochem. Mol. Biol.* **2004**, *88*, 1.
3. Deplewski, D.; Rosenfield, R. L. *Endocr. Rev.* **2000**, *21*, 363.
4. Rasmusson, G. H.; Reynolds, G. F.; Steinberg, N. G.; Walton, E.; Patel, C. F.; Liang, T.; Cascieri, M. A.; Cheung, A. H.; Brooks, J. R.; Berman, C. *J. Med. Chem.* **1986**, *29*, 2298.
5. Lamb, J. C.; Levy, M. A.; Johnson, R. K.; Issacs, J. T. *Prostate* **1992**, *21*, 15.
6. Jones, C. D.; Audia, J. E.; Lawhorn, D. E.; McQuaid, L. A.; Neubauer, B. L.; Pike, A. J.; Pennington, P. A.; Stamm, N. A.; Toomey, R. E.; Hirsch, K. R. *J. Med. Chem.* **1993**, *36*, 421.
7. Abell, A. D.; Brandt, M.; Levy, M. A.; Holt, D. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 481.
8. Lesuisse, D.; Gourvest, J.-F.; Albert, E.; Doucet, B.; Hartmann, C.; Lefrancois, J.-M.; Tessier, S.; Tric, B.; Teutsch, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1713.
9. Holt, D. A.; Yamashita, D. S.; Konalian-Beck, A. L.; Leungo, J. I.; Abell, A. D.; Bergsma, D. J.; Brandt, M.; Levy, M. A. *J. Med. Chem.* **1995**, *38*, 13.
10. Picard, F.; Schulz, T.; Hartmann, R. W. *Bioorg. Med. Chem.* **2002**, *10*, 437.
11. Park, L.; Keum, G.; Kang, S. B.; Kim, K. S.; Kim, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, *24*, 4462.
12. Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885.
13. Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309.
14. Svedham, S.; Hollander, C.-A.; Shi, J.; Konradsson, P.; Liedberg, B.; Svensson, S. C. T. *J. Org. Chem.* **2001**, *66*, 4494.
15. Reichert, W.; Hartmann, R. W.; Jose, J. *J. Enzyme Inhib.* **2001**, *16*, 47.
16. Hartmann, R. W.; Reichert, M. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *335*, 145.