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REACTION OF 3-PHENYL-1,2,4-TRIAZIN-5(4*H*)-ONE UNDER ACYLATING CONDITIONS WITH NATURAL ALCOHOLS CONTAINING AN ASYMMETRIC CARBON ATOM

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This study describes the reactions of natural chiral alcohols such as borneol, isoborneol, cholesterol, and dihydrocholesterol with 3-phenyl-1,2,4-triazin-5(4H)-one in the presence of carboxylic acid anhydrides.

Keywords: borneol, cholesterol, dihydrocholesterol, 1,2,4-triazines, nucleophilic addition reactions.

Chiral azines have recently attracted a close attention. Studies have been carried out on the synthesis of bornyl derivatives of bipyridines [1, 2], terpyridines [3-5], and also bispyridylamine [6] as catalysts for asymmetric synthesis. In addition, examples are known of bornyl and isobornyl derivatives of azines exhibiting antiviral activity [7]. It was also of interest to modify azines introducing cholesterol residues since functionalization of the A ring of the polycyclic cholesterol system can lead to compounds which modify the properties of cell membranes [8].

In this work, we have studied the possible asymmetric synthesis of the products of addition of O-nucleophiles to the C=N bond of the aromatic azine [9] using readily available natural alcohols. Employing nucleophiles which contain an optically active center could lead to formation of diastereomerically enriched products. There is example in the literature of the stereoselective addition of nucleophiles to the C=N double bond of azirines involving an isobornyl residue [10]. It has been shown previously that in the reaction of 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) with (-)-menthol, addition products were obtained with diastereoselectivity *de* 20-70% depending on the type of anhydride used [11].

We have used the readily available racemic isoborneol (**2**) and borneol (**3b**) and also the optically pure borneol (**3a**), dihydrocholesterol (**4**), and cholesterol (**5**) as nucleophiles in an addition reaction to the C=N double bond of the 3-phenyl-1,2,4-triazin-5(4*H*)-one **1**. The non-activated triazinone **1** is unreactive towards nucleophiles. There are two routes for converting it to an active azinium salt which involve either carrying out reactions in the presence of acids (route A) or in the presence of acid anhydrides (route B) [12, 13] where it

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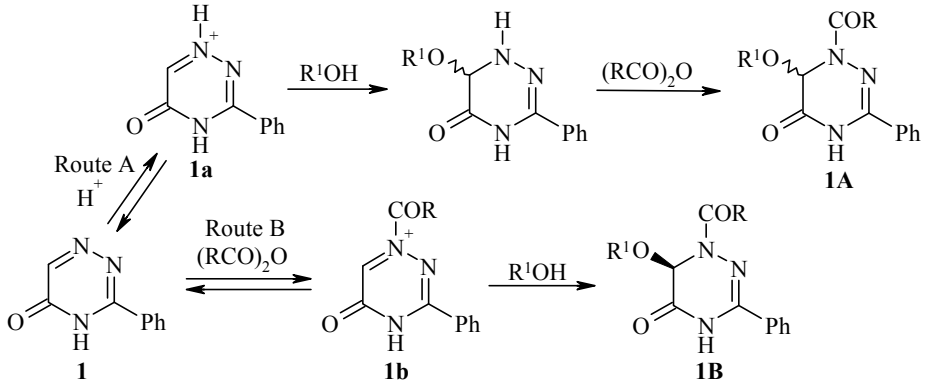
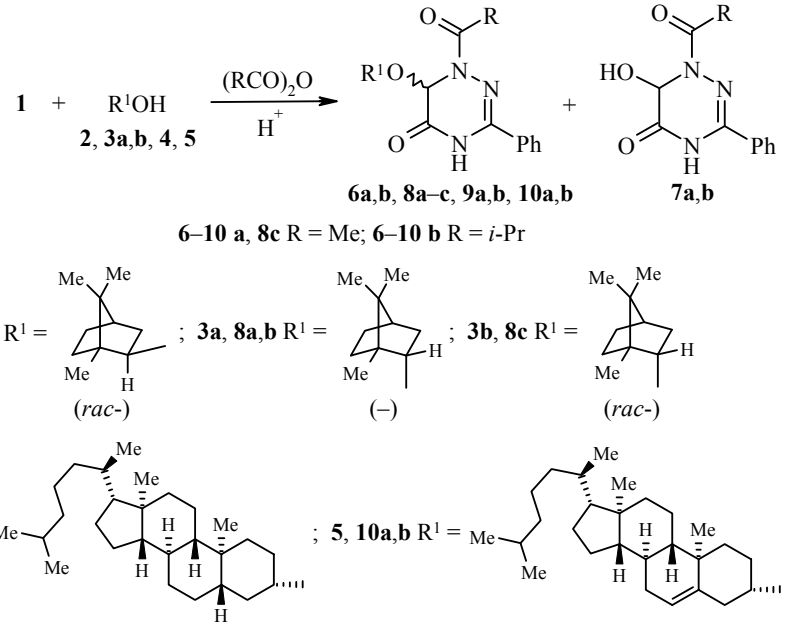
presumably exists either in the azinium form **1a** or the acylazinium salt **1b**, respectively. The use of a chiral nucleophile in the case of acid activation must lead to the mixture of diastereomers **1A** but when activated by acid anhydrides containing bulky substituents could give a diastereomerically enriched product **1B**.



In order to prepare diastereomerically enriched products, we have studied the possible use of different carboxylic acid anhydrides in the given reaction. A problem is in that, in the reaction of triazinone **1** with O-nucleophiles, the acid anhydride can interact both with the triazine substrate and with the O-nucleophile. It is known that a high activity of anhydride, like trifluoroacetic anhydride, can give a quantitative yield of borneol [14] or cholesterol [15] trifluoroacetates at room temperature. In order to minimize side reactions we have selected the low activity acetic, isobutyric, and pivalic anhydrides which differ only in their steric hindrance towards nucleophilic attack.

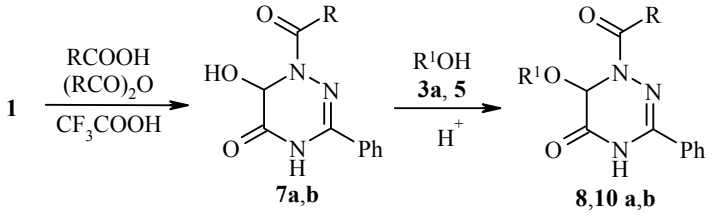
It was found that triazine **1** does not react at room temperature in pure acid anhydrides with the said O-nucleophiles, nor was a result obtained when the reactions were carried out in a mixture of the acid and its anhydride. Success was achieved by two routes. Firstly, we have found that the addition of trifluoroacetic acid to a suspension of the triazinone **1** in the anhydride leads to formation of the products of addition of the O-nucleophiles. Secondly, a preliminary reprecipitation of triazinone **1** when heating in the acid anhydride with subsequent addition of a nucleophile also gives the products of O-nucleophile addition.



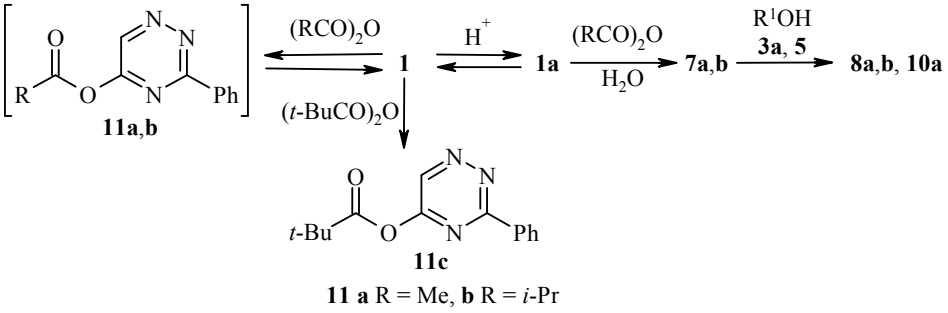
Hence a reaction of the 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) with a series of O-nucleophiles in acetic or isobutyric anhydride medium in the presence of CF_3COOH at room temperature gave the addition products **6-10**. It should be noted that no reaction was observed in a pivalic anhydride medium in the presence of CF_3COOH.

The ^1H and ^{13}C NMR spectra of the products obtained as a result of addition of the chiral nucleophiles **3a, 4, 5** to the C=N bond of the 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) showed a double set of signals corresponding in intensities to the formation of a 1:1 mixture of diastereomers. The HPLC analysis of the products **9-10a,b** also showed that they are formed as a 1:1 pair of diastereomers. It should be noted that the ^1H and ^{13}C NMR spectra of compound **6b** show a single set of signals even though the angle of rotation for this compound is zero. X-ray structural analysis shows that this compound also is an equimolar mixture of diastereomers (the molecular structure of one of the diastereomers is given in Fig. 1). The absence of stereoselectivity in the studied reaction series allows to assume that the 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) in this case enters the reaction as the protonated salt **1a**.

Besides the addition products of the alcohols to triazinone **1** and esters of the alcohols used in this work there were also compounds **7a,b** isolated in 10-15% yields as the products of water addition. Formation of these compounds can be explained by existence of the water traces in the air and in solvents in the process of the reaction products isolation [16]. To explain the formation of the products **7a,b**, we have carried out the same reaction but without addition of the O-nucleophiles. As a result, compounds **7a,b** were obtained in good yields. In order to test the assumption that the products **7a,b** can exchange the hydroxyl group for other O-nucleophiles we have studied their reactivity towards (-)-borneol and cholesterol. The products **8a,b** and **10a,b** were obtained as a result.



In the reaction between 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) with O-nucleophiles (first dissolving the triazinone **1** in the carboxylic acid anhydride with heating and then continuing the reaction at room temperature) the addition products **8a,b, 10a** were also formed. However, when the pivalic acid anhydride was used as a carboxylic acid anhydride the single reaction product was compound **11c** as a result of *O*-acylation. The structure of the compound obtained was proved by X-ray structural analysis (Fig. 2).



11 a R = Me, **b** R = *i*-Pr

It can be suggested that triazinone **1** in the carboxylic acid anhydride initially forms the product of *O*-acylation which, in the case of R =Me, *i*-Pr can dissociate to the starting triazine under the reaction conditions. Hence compounds **11a,b** are not observed under these conditions. When R = *t*-Bu, the position 6 of the triazine ring becomes non-reactive due to steric hindrance and only compound **11c** is formed.

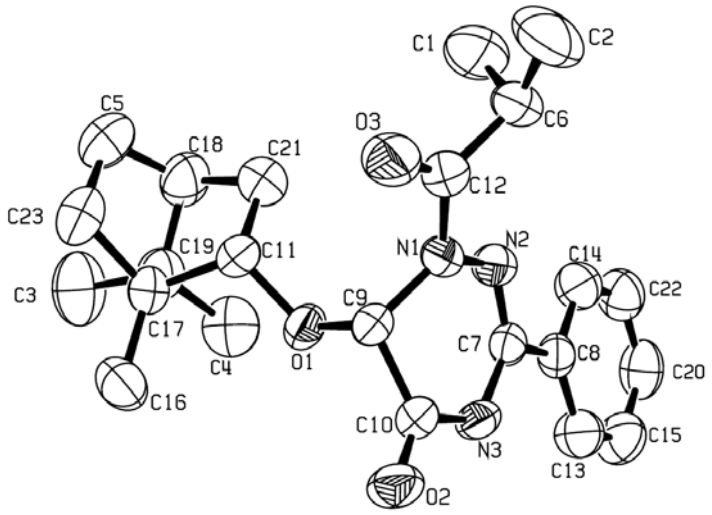


Fig. 1. Overall view of compound **6b** with 50% probability thermal ellipsoids.

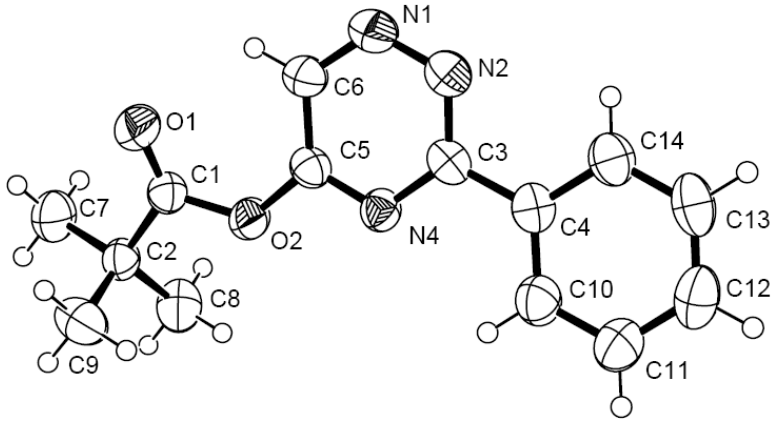


Fig. 2. Overall view of compound **11c** with 50% probability thermal ellipsoids.

There are two ways to explain the absence of stereoselectivity in the reactions yielding compounds **8-10a,b**. The first is proceeding of the reaction *via* the intermediate azinium salt **1a** which does not create sufficient steric hindrance upon reaction with the chiral nucleophiles **3-5**. The second is proceeding of the reaction *via* the intermediate formation of the racemic *N*(1)-acylated hydroxytriazines **7a,b**.

Hence we have, for the first time, obtained the products of addition of cholesterol, dihydrocholesterol, borneol, and isoborneol as O-nucleophiles to the azine ring. It was shown that addition of the said alcohols to 3-phenyl-1,2,4-triazin-5(4*H*)-one in acetic and isobutyric anhydrides occurs nondiastereoselectively.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 and 100 MHz respectively) with TMS as internal standard. UV spectra were recorded on a PerkinElmer Lambda 45 spectrometer using 2-propanol. Mass spectra were recorded on a Bruker Daltonics MicroTOF-Q II mass spectrometer with electrospray ionization. The optical rotation was measured on a PerkinElmer polarimeter.

TABLE 1. Basic Crystallographic Parameters for Compounds **6b** and **11c**

Parameters	Compound **6b**	Compound **11c**
Empirical formula	$C_{23}H_{31}N_3O_3$	$C_{14}H_{15}N_3O_2$
M	397.51	257.29
Crystal size, mm	0.45 × 0.36 × 0.21	0.25 × 0.20 × 0.15
Temperature, K	295(2)	295(2)
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
A,Å	16.575(3)	5.8524(7)
b, Å	6.5340(9)	18.848(3)
c, Å	21.338(5)	12.0716(15)
β, deg	109.579(18)	97.817(10)
V, Å^3	2177.3(7)	1319.2(3)
Z	4	4
ρ_{calc}, g·cm^{-3}	1.213	1.295
μ/mm^{-1}	0.081	0.089
θ/deg	2.71–26.38	2.75–26.37
Overall number of reflections measured /independent	9605 / 4436	5610 / 2780
R_{int}	0.0413	0.0208
Number of observed reflections with $I > 2\sigma(I)$	1696	1915
Completeness (for θ, deg)	99.6 % (26.38)	99.6 % (26.37)
R_1, $I > 2\sigma(I)$	0.0368	0.0382
wR_2, $I > 2\sigma(I)$	0.0464	0.0974
R_1, $I > 2\sigma(I)$	0.1100	0.0595
wR_2, $I > 2\sigma(I)$	0.0487	0.1037
Residual electron density/e Å^{-3}, ρ_{max}/ρ_{min}	0.125 / –0.159	0.206 / -0.148

Melting points were determined on a Boetius hot stage apparatus. The HPLC analysis of compounds **9-10a,b** was performed on a Knauer Smartline-1100 chromatograph with Reprosil 100 column (250×4.6 mm). TLC analysis was carried out using Merck silica gel 60 F254 and visualized by UV radiation. Column chromatography was performed using Merck silica gel 60 with EtOAc–CH_2Cl_2 (1:1) as eluent. Commercially available starting materials were used in the study, and the 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) was prepared by a known method [17].

X-ray structural analysis was performed on an Oxford Diffraction Xcalibur S CCD diffractometer using the software package CrysAlisPro [18]. The structures were solved by direct methods using the SHELXS-97 software package and refined in F^2 full-matrix least-squares analysis using SHELXL-97 [19]. The crystallographic data for compounds **6b** and **11c** is presented in Table 1 and has been deposited to the Cambridge Crystallographic Data Center as CCDC 768207 and 815379.

Synthesis of Compounds 6a,b, 8a-c, 9-10a,b (General Method). A. CF_3COOH (0.2 ml) was added to a suspension of the triazinone **1** (200 mg, 1.15 mmol) and the corresponding O-nucleophile **2-5** (1.73 mmol) in a mixture of Ac_2O (2 ml), AcOH (5 ml), and $CHCl_3$ (3 ml). The obtained mixture was stirred for 1 day at room temperature and evaporated to dryness. The residue was separated on a chromatographic column.

B. A suspension of the triazinone **1** (200 mg, 1.15 mmol) in the corresponding anhydride (3 ml) was heated to dissolution, and treated with the O-nucleophile (1.15 mmol) while cooling. The reaction mixture was stirred for 1 day at room temperature. The obtained solution was evaporated in a Petri dish to dryness and the residue was separated on a chromatographic column.

C. A suspension of triazinone **1** (200 mg, 1.15 mmol) and the corresponding O-nucleophile (1.15 mmol) in a mixture of the corresponding anhydride (2 ml) and CF_3COOH (0.2 ml) was stirred for 1 day at room temperature. The solution obtained was evaporated to dryness and the residue was separated on a chromatographic column.

D. CF_3COOH (0.2 ml) was added to a suspension of the triazinone **1** (200 mg, 1.15 mmol) and the corresponding O-nucleophile (1.73 mmol) in a mixture of Ac_2O (2 ml) and AcOH (5 ml). The solution obtained

was stirred for 1 day at room temperature. The precipitate formed was filtered off, recrystallized from ethanol, and purified on a chromatographic column if needed.

E. The O-nucleophile (0.7 mmol) and CF_3COOH (0.2 ml) were added to a suspension of compound **7a,b** (0.7 mmol) in AcOH (5 ml) and the mixture was stirred for 1 day at room temperature. The precipitate obtained was filtered off and recrystallized from alcohol (compounds **10a,b**). In the absence of a precipitate (compounds **8a,b**) the reaction mixture was evaporated and the residue was separated on a chromatographic column.

1-Acetyl-3-phenyl-6-((1*S*/*R*,2*R*/*S*,4*R*/*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (6a). Yield 20% (method A). Colorless crystalline powder; mp 182-183ºC, R_f 0.8 (EtOAc–CH_2Cl_2, 1:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.65 (1.5H, s) and 0.74 (4.5H, s, $2CH_3$); 0.85 (1.5H, s) and 0.86 (1.5H, s, CH_3); 0.94-1.06 (2H, m, CH_2); 1.41-1.73 (4.5H, m) and 1.85-1.91 (0.5H, m, $2CH_2$, CH); 2.36 (1.5H, s) and 2.38 (1.5H, s, $COCH_3$); 3.49-3.51 (0.5H, m) and 3.57-3.60 (0.5H, m, H-2'); 5.85 (0.5H, s) and 5.86 (0.5H, s, H-6); 7.42-7.50 (3H, m, H Ph); 7.85-7.88 (2H, m, H Ph); 11.56 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 11.1; 11.4; 19.6; 19.8; 19.9; 21.0; 21.2; 33.6; 33.7; 37.9; 38.0; 44.3; 44.4; 46.2; 48.6; 48.8; 73.4; 74.9; 84.6; 86.1; 126.4; 126.5; 128.6; 130.3 (2C); 130.7 (2C); 141.0; 141.3; 161.4; 161.8; 172.7; 172.9. Found, *m/z*: 370.2110 $[M+H]^+$. $C_{21}H_{28}N_3O_3$. Calculated, *m/z*: 370.2125.

1-Isobutyryl-3-phenyl-6-((1*S*/*R*,2*R*/*S*,4*R*/*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (6b). Yield 25% (method C). Colorless crystalline powder; mp 204-205ºC, R_f 0.8 (EtOAc–CH_2Cl_2, 1:1). $[\alpha]_D^{20}$ = 0 (*c* = 0.5, MeOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.64-0.74 (6H, m, $2CH_3$); 0.85-0.91 (3H, m, CH_3); 0.93-1.06 (2H, m, CH_2); 1.12-1.14 (3H, m) and 1.19-1.25 (3H, m, $CH(C\underline{H}_3)_2$); 1.40-1.92 (5H, m, $2CH_2$, CH); 3.46-3.61 (2H, m, H-2', $C\underline{H}(CH_3)_2$); 5.84 (1H, s, H-6); 7.41-7.49 (3H, m, H Ph); 7.84-7.86 (2H, m, H Ph); 11.53 (1H, s, NH); ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 12.0; 18.8; 19.3; 20.1; 20.4; 27.1; 30.6; 34.1; 38.8; 44.9; 46.7; 49.4; 75.7; 86.8; 126.9; 129.2; 130.9; 131.3; 141.7; 162.0; 179.1. Found, *m/z*: 398.2414 $[M+H]^+$. $C_{23}H_{32}N_3O_3$. Calculated, *m/z*: 398.2438.

1-Acetyl-3-phenyl-6-((1*S*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (8a). Yield 53% (method A), 31% (method B), 17% (method E). Colorless crystalline powder; mp 183-184ºC, R_f 0.65 (EtOAc–CH_2Cl_2, 1:1). $[\alpha]_D^{20}$ = -18.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.71 (1.5H, s), 0.80-0.83 (6H, s), and 0.89 (1.5H, s, $3CH_3$); 0.97-1.01 (0.5H, m), 1.05-1.22 (2.5H, m, CH_2); 1.57-1.67 (2H, m, CH_2); 1.74-1.82 (1H, m); 2.06-2.15 (0.5H, m) and 2.21-2.29 (0.5H, m, CH); 2.46 (1.5H, s) and 2.47 (1.5H, s, $COCH_3$); 4.06 (0.5H, ddd, *J* = 9.6, *J* = 3.2, *J* = 1.9) and 3.98 (0.5H, ddd, *J* = 9.5, *J* = 3.2, *J* =1.9, H-2'); 6.21 (1H, s, H-6); 7.48-7.56 (3H, m, H Ph); 7.81-7.86 (2H, m, H Ph); 9.08 (0.5H, s) and 9.13 (0.5H, s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.3; 13.5; 18.9 (2C); 19.6; 19.7; 21.5; 21.7; 26.3; 28.0; 36.0; 36.1; 44.9; 45.0; 47.5; 47.7; 49.3; 49.6; 74.9; 76.1; 84.5; 86.5; 125.9; 129.0; 130.2; 131.1; 139.6; 139.7; 162.8; 163.1; 173.7; 173.9. Found, *m/z*: 370.2115 $[M+H]^+$ $C_{21}H_{28}N_3O_3$. Calculated, *m/z*: 370.2125.

1-Isobutyryl-3-phenyl-6-(1*S*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (8b). Yield 8% (method B), 17% (method C), 13% (method E). Colorless crystalline powder; mp 158ºC, R_f 0.8 (EtOAc–CH_2Cl_2, 1:1). $[\alpha]_D^{20}$ = -14.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.69-1.31 (17H, m, $3CH_3$, CH_2, $CH(C\underline{H}_3)_2$); 1.55-1.67 (2H, m, CH_2); 1.75-1.82 (2H, m, CH_2); 2.04-2.13 (0.5H, m, CH); 2.20-2.28 (0.5H, m, CH); 3.60-3.69 (1H, m, $C\underline{H}(CH_3)_2$); 3.92-3.96 (0.5H, m) and 4.07-4.10 (0.5H, m, H-2'); 6.19 (0.5H, s) and 6.22 (0.5H, s, H-6); 7.48-7.55 (3H, m, H Ph); 7.87-7.91 (2H, m, H Ph); 9.93 (0.5H, s) and 9.99 (0.5H, s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.3; 13.5; 18.5; 18.8 (2C); 18.9; 19.1; 19.6; 26.2; 28.0 (2C); 30.9; 31.0; 35.7; 36.3; 44.9; 45.0; 47.5; 47.6; 49.1; 49.6; 74.8; 76.4; 77.0; 77.3; 83.7; 86.6; 125.8; 129.0; 130.4; 131.0; 139.1; 139.4; 162.4; 162.8; 179.8; 180.2. Found, *m/z*: 398.2434 $[M+H]^+$. $C_{23}H_{31}N_3O_3$. Calculated, *m/z*: 398.2438.

1-Acetyl-3-phenyl-6-((1S/*R*,2S/*R*,4*R*/*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (8c). Yield 12% (method A), 20% (method C). Colorless crystalline powder; mp 189-190ºC, R_f 0.65 (EtOAc–CH_2Cl_2, 1:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.67 (1.5H, s), 0.80-0.83 (6H, s) and 0.87 (1.5H, s, $3CH_3$); 0.91-0.95 (0.5H, m), 1.00-1.20 (2.5H, m), 1.56-1.67 (2H, m) and

1.72-1.79 (1H, m, $3CH_2$); 2.00-2.08 (0.5H, m) and 2.16-2.24 (0.5H, m, CH); 2.36 (1.5H, s) and 2.37 (1.5H, s, $COCH_3$); 3.84-3.88 (0.5H, m) and 3.93-3.97 (0.5H, m, H-2'); 5.87 (1H, s, H-6); 7.42-7.50 (3H, m, H Ph); 7.88-7.91 (2H, m, H Ph); 11.61 (1H, s, NH). ^{13}C NMR spectrum ($DMSO-d_6$), δ, ppm: 13.0; 13.3; 18.4; 19.3; 19.4; 21.0; 21.2; 25.7; 25.8; 27.7; 35.6; 44.1; 44.2; 46.9; 47.2; 48.7; 49.0; 74.3; 75.4; 82.5; 84.4; 126.5; 128.6; 130.2; 130.3; 130.8; 140.7; 141.0; 161.5; 161.7; 172.7; 173.0. Found, *m/z*: 370.2113 $[M+H]^+$. $C_{21}H_{28}N_3O_3$. Calculated, *m/z*: 370.2125.

1-Acetyl-6-[(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yloxy]-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (9a). Yield 51% (method D). Colorless crystalline powder; mp 199-200ºC, R_f 0.9 (EtOAc–CH_2Cl_2, 1:1). $[\alpha]_D^{20}$ = +13.7 (*c* = 1.0, $CHCl_3$). UV spectrum, λ_{max}, nm: 228, 292. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.57-0.64 (4H, m); 0.74 (3H, s, CH_3); 0.84-0.87 (10H, m); 0.95-2.03 (20H, m); 1.42-2.03 (9H, m); 2.37 (3H, s, $COCH_3$); 3.49-3.59 (1H, m, H-3'); 5.92 (1H, s, H-6); 7.40-7.49 (3H, m, H Ph); 7.89-7.90 (2H, m, H Ph); 11.58 (1H, s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 12.1; 12.2; 18.7; 21.2; 21.6; 22.6; 22.8; 23.8; 24.2; 28.0; 28.1; 28.3; 28.5; 28.7; 28.8; 32.0; 34.6; 35.0; 35.5 (2C); 35.8; 36.2; 36.9; 37.0; 39.5; 40.0; 42.6; 44.6; 44.9; 54.3; 56.2; 56.4; 73.5; 73.7; 77.2; 79.2; 79.4; 125.9; 129.0; 130.1; 131.1; 139.4; 139.5; 163.1 (2C); 173.7. Found, *m/z*: 610.4523 $[M+Li]^+$. $C_{38}H_{57}N_3O_3Li$. Calculated *m/z*: 610.4555.

6-[(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yloxy]-1-isobutyryl-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (9b). Yield 6% (method C). Colorless crystalline powder; mp 191-192ºC, R_f 0.9 (EtOAc–CH_2Cl_2, 1:1). $[\alpha]_D^{20}$ = +15.4 (*c* = 0.5, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.56-0.63 (4H, m); 0.74 (3H, s); 0.85-1.84 (43.5H, m); 1.92-1.97 (1H, m); 2.01-2.09 (0.5H, m); 3.59-3.74 (2H, m, C<u>H</u>$(CH_3)_2$, H-3'); 6.27 (0.5H, s) and 6.28 (0.5H, s, H-6); 7.47-7.54 (3H, m, H Ph); 7.81-7.83 (2H, m, H Ph); 8.95 (1H, s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 12.1; 12.2; 18.6; 18.7; 19.1 (2C); 21.2; 22.6; 22.8 (2C); 24.2; 28.0; 28.2; 28.6; 28.7; 28.8; 31.0; 32.0; 34.7; 35.2; 35.5; 35.8; 36.2; 36.9; 37.0; 39.5; 40.0; 42.6; 44.7; 44.9; 54.3; 56.3; 56.5; 74.0; 74.1; 79.3; 79.5; 125.9; 129.0; 130.3; 131.0; 139.1; 163.1; 180.0 (2C). Found, *m/z*: 632.4743 $[M+H]^+$. $C_{40}H_{62}N_3O_3$. Calculated, *m/z*: 632.4786.

1-Acetyl-6-[(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yloxy]-3-phenyl-1,6-dihyd-ro-1,2,4-triazin-5(4*H*)-one (10a). Yield 8% (method B); 35% (method C), 50% (method D), 44% (method E). Colorless crystalline powder; mp 182-183ºC, R_f 0.9 (EtOAc–CH_2Cl_2, 1:1). $[\alpha]_D^{20}$ = -6.5 (*c* = 1.0, $CHCl_3$). UV spectrum, λ_{max}, nm: 229, 292. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.66 (3H, s, CH_3); 0.85-1.61 (34H, m); 1.78-2.03 (4.5H, m); 2.08-2.36 (2H, m); 2.48 (1.5H, s) and 2.49 (1.5H, s, $COCH_3$); 2.53-2.58 (0.5H, m); 3.60-3.71 (1H, m, H-3'); 5.31-5.33 (0.5H, m) and 5.38-5.40 (0.5H, m, =CH); 6.28 (0.5H, s) and 6.29 (0.5H, s, H-6); 7.47-7.54 (3H, m, H Ph); 7.83-7.85 (2H, m, H Ph); 9.31 (0.5H, s) and 9.38 (0.5H, s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 11.9; 18.7; 19.3; 21.1; 21.6; 22.6; 22.9; 23.8; 24.3; 28.0; 28.3; 28.7; 31.9 (2C); 32.0; 35.8; 36.2; 36.6; 37.0; 37.1; 39.0; 39.2; 39.5; 39.8; 42.3; 50.0; 50.1; 56.1; 56.7; 73.4; 73.7; 79.3; 79.6; 122.1; 122.4; 126.0; 129.0; 130.1; 131.2; 139.4; 140.1; 140.3; 163.1; 163.2; 173.7 (2C). Found, *m/z*: 602.4296 $[M+H]^+$. $C_{38}H_{56}N_3O_3$. Calculated, *m/z*: 602.4316.

1-Isobutyryl-6-[(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yloxy]-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (10b). Yield 28% (method C), 60% (method E). Colorless crystalline powder; mp 209-210ºC, R_f 0.85 (EtOAc–CH_2Cl_2, 1:1). $[\alpha]_D^{20}$ = -4.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.68 (3H, s, CH_3); 0.88-1.70 (39H, m); 1.80-2.04 (4.5H, m); 2.04-2.28 (2H, m); 2.50-2.55 (0.5H, m); 3.62-3.74 (2H, m, C<u>H</u>$(CH_3)_2$, H-3'); 5.31-5.33 (0.5H, m) and 5.40-5.41 (0.5H, m, =CH); 6.29 (0.5H, s) and 6.31 (0.5H, s, H-6); 7.49-7.56 (3H, m, H Ph); 7.89-7.92 (2H, m, H Ph); 9.85 (0.5H, s) and 9.92 (0.5H, s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 11.8; 18.5; 18.6; 18.7; 19.1 (2C); 19.3; 21.0; 22.6; 22.8; 23.8; 24.3; 28.0; 28.2; 28.3; 28.8; 31.0 (2C); 31.8; 31.9 (2C); 35.8; 36.2; 36.6; 37.0; 37.1; 39.1; 39.3; 39.5; 39.7; 42.3; 49.9; 50.0; 56.1; 56.7; 73.9; 74.1; 77.2; 79.5; 79.8; 122.0; 122.3; 125.9; 129.0; 130.2; 131.0; 139.1; 139.2; 140.1; 140.3; 163.1; 179.9 (2C). Found, *m/z*: 630.4632 $[M+H]^+$. $C_{40}H_{60}N_3O_3$. Calculated, %: *m/z* 630.4629.

1-Acetyl-6-hydroxy-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (7a). A suspension of the 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) (1.0 g, 5.77 mmol) in a mixture of AcOH (10 ml), Ac_2O (3 ml), and CF_3COOH (0.5 ml) was stirred for 1 day at room temperature. The triazine **1** was gradually dissolved and after some time a precipitate was formed. The precipitate was filtered off, washed with a small amount of AcOH and ether, and dried. The product was quite pure, but could be separated on a chromatographic column if needed. Yield 0.93 g (69%). Colorless crystalline powder; mp 185-186ºC, R_f 0.4 (EtOAc–CH_2Cl_2, 1:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.36 (3H, s, $COCH_3$); 5.92 (1H, d, *J* = 6.3, H-6); 7.20 (1H, d, *J* = 6.3, OH); 7.39-7.48 (3H, m, H Ph); 7.89-7.92 (2H, m, H Ph); 11.43 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.2; 69.2; 126.4; 128.5; 130.4; 130.6; 140.1; 163.5; 172.3. Found, *m/z*: 232.0710 $[M-H]^-$. $C_{11}H_{10}N_3O_3$. Calculated, *m/z*: 232.0728.

6-Hydroxy-1-isobutyryl-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one (7b). A suspension of 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) (200 mg, 1.15 mmol) in a mixture of isobutyric acid (3 ml), isobutyric anhydride (1 ml), and CF_3COOH (0.2 ml) was stirred for 1 day at room temperature. The solution obtained was evaporated in a Petri dish and the residue was separated on a chromatographic column. Yield 195 mg (65%). Yellow crystalline powder; mp 225-226ºC, R_f 0.4 (EtOAc–CH_2Cl_2, 1:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.17 (6H, dd, *J* = 21.9, *J* = 6.9, $CH(C\underline{H}_3)_2$); 3.52-3.62 (1H, m, *J* = 7.0, $C\underline{H}(CH_3)_2$); 5.91 (1H, d, *J* = 6.3, H-6); 7.20 (1H, d, *J* = 6.3, OH); 7.38-7.50 (3H, m, H Ph); 7.89-7.92 (2H, m, H Ph); 11.44 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 18.2; 19.0; 30.0; 69.4; 126.4; 128.6; 130.5; 130.6; 140.0; 163.6; 178.2. Found, *m/z*: 260.1026 $[M-H]^-$. $C_{13}H_{15}N_3O_3$. Calculated, *m/z*: 260.1041.

3-Phenyl-1,2,4-triazin-5-ylpivalate (11c). A suspension of the 3-phenyl-1,2,4-triazin-5(4*H*)-one (**1**) (150 mg, 0.87 mmol) was heated in pivalic anhydride (3 ml) to dissolution and then stirred for 1 day at room temperature. The reaction mixture was separated on a chromatographic column. Yield 46%. Colorless crystalline powder; mp 77-78ºC, R_f 0.6 (EtOAc–CH_2Cl_2, 1:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.44 (9H, s, $3CH_3$); 7.51-7.59 (3H, m, H Ph); 8.51-8.54 (2H, m, H Ph); 9.13 (1H, s, H-6). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 26.8; 39.7; 128.6; 128.8; 132.1; 133.9; 142.2; 159.1; 164.3; 174.7.

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