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Retro Diels Alder protocol for regioselective synthesis of novel [1,2,4]triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones†

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Reactions of diastereochemically varied norbornene-condensed 2-thioxopyrimidin-4-ones **6** and **10** with variously functionalized hydrazonoyl chlorides **2a–h** gave regioselectively angular norbornene-based [1,2,4]triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones **7a–h** and **11a,c–e**, respectively. Thermal retro Diels–Alder (RDA) reaction of **7a–h** and **11a,c–e** resulted in the target compounds **4a–h** as single products. On the other hand, reactions of thiouracil **1** and hydrozonoyl chlorides **2a–e** gave regioselectively [1,2,4]triazolo [4,3-*a*]pyrimidinone-5(1*H*)-ones **3a–e**. The opposite regioselectivity of thiouracil **1** and norbornene-condensed 2-thioxopyrimidin-4-ones **6** and **10** was attributed to electronic factors according to DFT calculations. The angular structure of norbornene based [1,2,4]triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones was confirmed by single crystal X-ray crystallography.

Introduction

Fused pyrimidines are important compounds, because of their wide spectrum of biological and pharmacological applications.[1–4] Compounds bearing the [1,2,4]triazolo[4,3-*a*]pyrimidinone ring system were reported to possess a wide range of pharmacological activities including antitumor,[5] antiallergic,[6] antimicrobial,[7] and 5α-reductase inhibitor properties.[8]

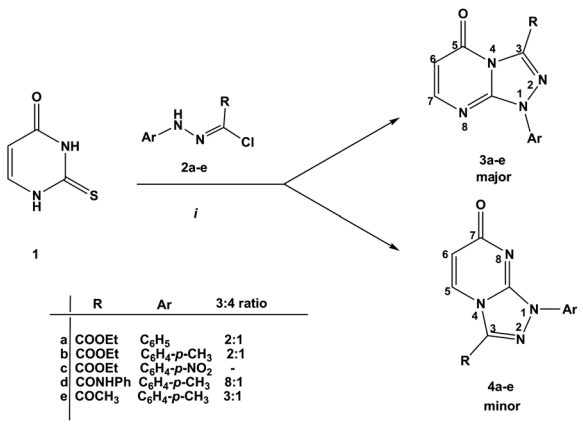
Hydrazonoyl halides, known since 1930, have attracted the interest of synthetic chemists in designing and synthesizing different heterocycles.[9] For example, [1,2,4]triazolo[4,3-*a*]pyrimidinones decorated with different functionalities can be incorporated into 2-thioxopyrimidin-4-ones by reacting the latter with the appropriate hydrazonoyl halide in the presence of a base.[10] To the best of our knowledge, the reported reactions of thiouracil derivatives with hydrazonoyl chlorides gave substituted [1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones in a regioselective manner.[11–15]

Recently, synthetic chemists have utilized RDA protocols for designing and synthesizing novel heterocyclic scaffolds. This method is highly efficient to build a double bond into the heterocyclic system.[16–23]

In the present work, we report the formation of novel [1,2,4]triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones **4a–h** by reacting norbornene-condensed 2-thioxopyrimidin-4-ones **6** and **10** with hydrazonyl chlorides **2a–h** with various functionalities followed by applying the RDA protocol. Note that **4a–h**, cann't accessible significantly from the reactions of thiouracil with hydrazonoyl chlorides.

Results and discussion

The reaction of thiouracil **1** with varied functionalized hydrazonoyl chlorides **2a–e** gave, as described earlier,[11–15] [1,2,4]



Scheme 1 Solvents and conditions: dioxane, TEA, reflux 4–6 h. The ratio of compounds **3** : **4** was calculated from the ^{1}H-NMR spectrum of the crude reaction mixture using the signals at around 6.1 ppm and 6.5 ppm for H-6 of regioisomers **3** and **4**, respectively. Separation of the regioisomers by column chromatography, eluent: EtOAc, R_f = **3**: 0.4; **4** : 0.05.

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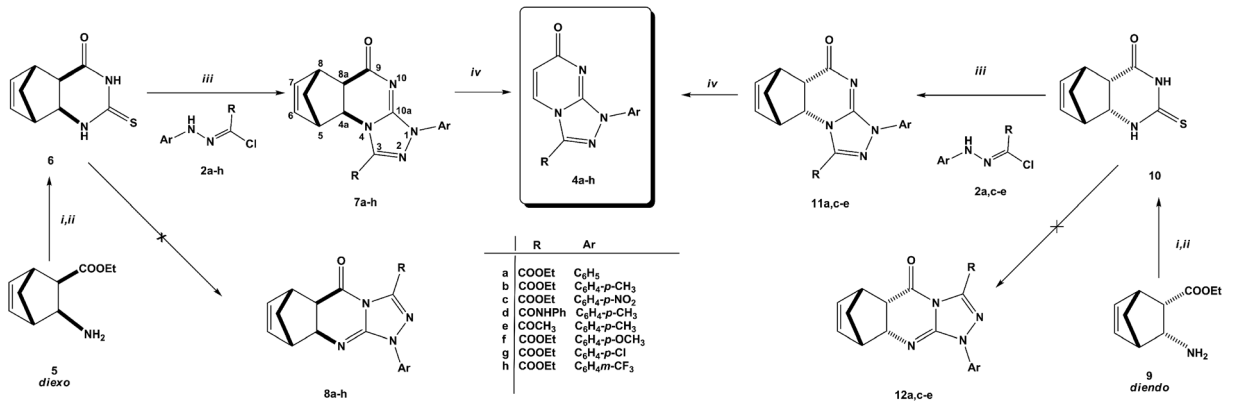


Scheme 2 Solvents and conditions: (i) $CSCl_2$, $NaHCO_3$, $CHCl_3$;[27] (ii) NH_3, MeOH;[27] (iii) dioxane, TEA, reflux, 4–6 h; (iv) MW: in 1,2-DCM, 200 °C, 30–120 min, 200 W.

Table 1 Energy difference (kJ mol^{-1}) between angular regioisomers **7**,**11** and their linear counterparts **8**,**12**. Isolated yields of angular regioisomers **7**,**11** were given

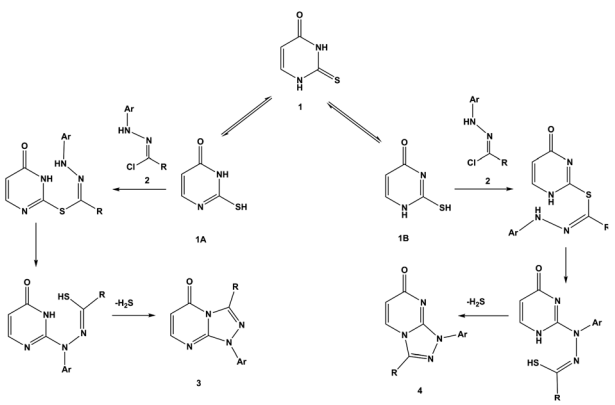
Entry	Energy difference ΔE^a kJ mol^{-1}	Yield[b] %	Entry	Energy difference ΔE^a kJ mol^{-1}	Yield[b] %
7a	50.75	66	**7g**	50.7	68
8a			**8g**		
7b	51.32	69	**7h**	47.75	67
8b			**8h**		
7c	47.48	60	**11a**	51.13	72
8c			**12a**		
7d	61.58	60	**11c**	46.07	75
8d			**12c**		
7e	38.84	45	**11d**	58.16	70
8e			**12d**		
7f	62.89	77	**11e**	44.58	50
8f			**12e**		

[a] Energy calculations were performed at the density functional theory (DFT) using the B3LYP functional. The 6-311G(d,p) basis sets were employed on all atoms. [b] The yield of isolated pure [1,2,4]triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones by column chromatography.

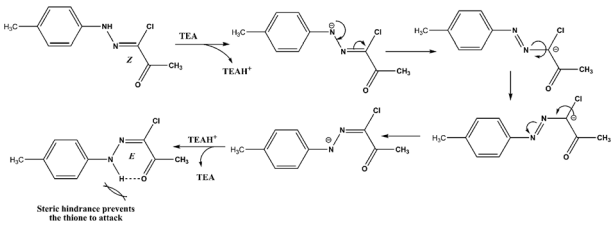
triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones **3a–e** as the major and [1,2,4]triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones **4a–e** as the minor products. The ratio of **3a–e** and **4a–e** was 8–2 : 1 (Scheme 1). The regioisomers could be easily separated by column chromatography *via* elution with EtOAc.

The challenge hence is how to have **4a–e** as major products. Since 2-thioxopyrimidin-4-one **6** condensed to norbornene can easily be converted to thiouracil **1** by the RDA strategy,[24] we used **6** instead of thiouracil **1** in the reaction with hydrazonoyl chlorides **2a–h** (Scheme 2). Strikingly, the regioselectivity of the reaction was inversed. Only angular regioisomers, [1,2,4]triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones **7a–h,** were formed and isolated in moderate yields (Table 1).

In a similar manner, the reaction of *diendo* norbornene-condensed 2-thioxopyrimidin-4-one **10** with functionalized hydrazonoyl chlorides **2a,c–e** was also found to be regioselective towards the formation of angular regioisomers, [1,2,4]triazolo [4,3-*a*]pyrimidin-7(1*H*)-ones **11a,c–e** (Scheme 2) (Table 1). The effect of norbornene on the stereochemical outcome was attributed to electronic, rather, than steric factors. Specifically, the C=C bond in thiouracil enforces the reaction towards the formation of [1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones **3a–e** because (i) the nitrogen located closer to the C=C double bond is more basic and (ii) tautomeric structure **1A** is thermodynamically more stable than **1B** (Scheme 3).



Scheme 3 Reaction pathways of thiouracil **1** and hydrazonoyl chlorides **2** to form regioisomers **3** and **4**.



Scheme 4 Isomerization of hydrazonoyl chlorides (**2e** as an example).

The lower yields of the reactions specially with hydrazonoyl chloride **2e** was ascribed to the tendency of hydrazonoyl chlorides, whose configuration is *Z*,[25] to isomerize to its *E* isomer under the reaction conditions as was deduced from the NMR spectra of the separated side product (ESI†). *E* isomer of hydrazonoyl chloride is more stable by hydrogen bonding and is hindered to be attacked by thione **6,10** to replace its chlorine atom (Scheme 4).

After heating in 1,2-dichlorobenzene (1,2-DCB) at 200 °C under microwave conditions, norbornene-fused triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones (**7a–h** and **11a,c–e**) underwent RDA reaction producing triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones **4a–h** in moderate yields in a short time (30–90 minutes, Scheme 2 and Table 2). The RDA reaction was monitored by TLC and could also be noticed by the odor of cyclopentadiene. RDA reactions of *diexo* isomers are easier than their *diendo* counterparts (entries 6–9) due to higher stability of *diendo* isomers as was confirmed from DFT calculations (ESI†).

Geometry optimization and total energies calculations were performed at the density functional theory (DFT) using Becke's three-parameter Lee–Yang–Parr (B3LYP) exchange functional with 6-311G(d,p) basis sets, using Gaussian-09 program.[26] Angular regioisomers **7a–h** and **11a,c–e** are thermodynamically more stable than their linear counterparts **8a–h** and **12a,c–e**, respectively (Table 1).

Fig. 1 shows the electron distribution and relative stability of tautomers **A** and **B**. The C=C bond (such as in thiouracil) directs the tautomerism towards an excess of **A**. When it is absent (such as in **6,10**), the tautomeric equilibrium is shifted towards **B**. Tautomer **A** is responsible for the formation of linear triazolo[4,3-*a*]pyrimidin-5(1*H*)-one regioisomers, while tautomer **B** leads to the formation of angular triazolo[4,3-*a*]pyrimidin-7(1*H*)-one regioisomers.

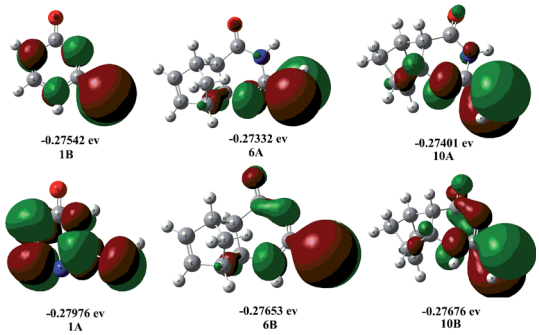


Fig. 1 Optimized geometric structure and HOMO energy levels of tautomers A and B of compounds 1, 6 and 10.

A conclusive evidence for the angular stereochemistry of the products of the reaction of norbornene-condensed 2-thioxopyrimidin-4-one **6,10** with hydrazonoyl chlorides **2a–h** was obtained by X-ray crystallographic analysis of compounds **7e** and **11d** (Fig. 2 and 3).

Experimental section

Materials and methods

NMR spectra were recorded at 500.20 MHz for ^{1}H-NMR and at 125.62 MHz for ^{13}C-NMR in $CDCl_3$ at room temperature, using a Bruker AV NEO Ascend 500 spectrometer (Bruker Biospin, Karlsruhe, Germany) with Double Resonance Broad Band Probe (BBO). Tetramethylsilane (TMS) was used as internal standard. Microwave-promoted reactions were performed using sealed reaction vials (10 mL) in a microwave (CEM, Discover, SP) cavity (CEM Corporation, Matthews, NC, USA). Reactions were monitored by thin layer chromatography (TLC) using aluminum sheets coated with silica gel (POLYGRAM®SIL G/UV254, Merck). TLC plates were inspected under UV light. Melting points were measured with a Hinotek-X4 micro melting point apparatus

Table 2 MW process for the synthesis of triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones **4a–h** under the optimized reaction conditions

Entry	Starting material	Product	Reaction time[a] (min)	Isolated yield[b] (%)
1	**7a** (*exo*)	**4a**	45	42
2	**11a** (*endo*)		60	52
3	**7b** (*exo*)	**4b**	60	54
4	**7c** (*exo*)	**4c**	90	41
5	**11c** (*endo*)		30	45
6	**7d** (*exo*)	**4d**	30	78
7	**11d** (*endo*)		30	67
8	**7e** (*exo*)	**4e**	120	90
9	**11e** (*endo*)		30	57
10	**7f** (*exo*)	**4f**	60	41
11	**7g** (*exo*)	**4g**	40	58
12	**7h** (*exo*)	**4h**	30	48

[a] $T = 200$ °C, $P_{max} = 200$ W, in 1,2-DCB. [b] After column chromatography.

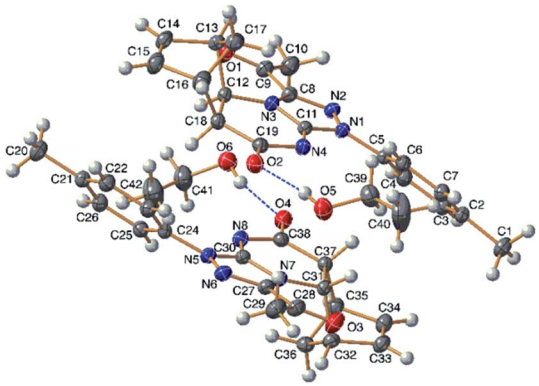


Fig. 2 TELP image of **7e** at 50% probability level. There are two independent molecules in the asymmetric unit.

(Hinotek, Ningbo, China) and are uncorrected. All theoretical calculations were performed using the Gaussian 09 package. The geometrical optimization was performed at the density functional theory (DFT) using the B3LYP. The 6-311G(d, p) basis sets were employed by all atoms.

Diexo **6** and *diendo* **10** norbornene-fused 2-thioxopyrimidin-4-ones were prepared from the corresponding norbornene amino ester **5** and **9**, respectively, according to the reported procedures.[27] Hydrazonoyl chlorides **2a–h** were synthesized according to the reported procedures.[28–30]

X-ray diffraction data of **7e** and **11d** were collected on a Rigaku Oxford Diffraction Supernova diffractometer using Mo Kα (**7e**) or Cu Kα (**11d**) radiation. The CrysAlisPro^{X} software package[31] was used for cell refinements and data reductions. The structures were solved by intrinsic phasing method using the SHELX^{X} software.[32] The data was corrected with empirical absorption correction based of equivalent reflections (**7e**) or analytical absorption correction (**11d**) CrysAlisPro^{X} structural refinements[31] were carried out using SHELXL^{X} software.[32] The NH hydrogen atoms were located from the difference Fourier map and refined isotropically. Other hydrogen atoms were positioned geometrically and constrained to ride on their parent atoms, with C–H = 0.95–1.00 Å and U_{iso} = 1.2–1.5U_{eq} (parent atom). The crystallographic details are summarized in Table S7.†

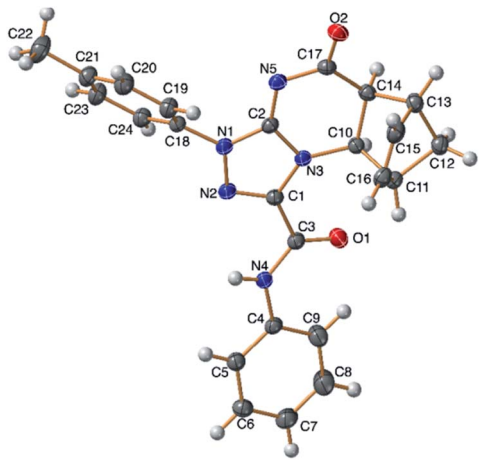


Fig. 3 TELP image of **11d** at 50% probability level.

General procedure for the synthesis of [1,2,4]triazolo-[4,3-*a*] pyrimidin-5(1*H*)-ones 3a–e and 5,8-methano[1,2,4]-triazolo [4,3-*a*]quinazolinones 7a–h and 11a,c–e

To a mixture of 0.5 mmol of 2-thioxopyrimidin-4-one (**1**,**6**,**10**) and 0.5 mmol of hydrazonyl chloride **2a–h** in dioxane (10 mL), 100 μL triethyl amine (TEA) were added. The mixture was heated under reflux conditions with stirring until completion of the reaction as confirmed by the disappearance of H_2S odor and TLC monitoring (*n*-hexane/EtOAC = 2 : 1 as the eluent). The solvent was evaporated under reduced pressure, the residue was dissolved in $CHCl_3$ (50 mL) and extracted with water (3 × 10 mL). Then the $CHCl_3$ layer was dried on Na_2SO_4, the solvent was evaporated, and the residue was dissolved in 5 mL EtOAc and purified by column chromatography on silica gel eluted by EtOAc. In the reaction of thiouracil **1** with hydrazonoyl chloride **2a–e**, the major **3a–e** and minor **4a–e** regioisomers were separated using TLC on silica gel (eluent EtOAc): **3a–e**, R_f 0.4, **4a–e** R_f 0.05. The products were crystallized from Et_2O to produce white or light yellow crystals.

Ethyl 5-oxo-1-phenyl-1,5-dihydro[1,2,4]triazolo[4,3-*a*] pyramidine-3-carboxylate (3a). Yield 45%, mp 116–120 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 7.6 Hz, 2H, Ar.), 8.06 (d, J = 6.5 Hz, 1H, H-7), 7.61–7.49 (m, 2H, Ar.), 7.42 (t, J = 7.5 Hz, 1H, Ar.), 6.14 (d, J = 6.6 Hz, 1H, H-6), 4.60 (q, J = 7.2 Hz, 2H, CH_2CH_3), 1.48 (t, J = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6(C=O), 155.9(CH), 155.3(C=O), 147.9(C), 136.2(C), 135.9(C), 129.5(CH), 128.1(CH), 121.1(CH), 103.2(CH), 64.1(CH_2), 13.9(CH_3).

Ethyl 5-oxo-1-(*p*-tolyl)-1,5-dihydro[1,2,4]triazolo[4,3-*a*] pyramidine-3-carboxylate (3b). Yield 43%, mp 175–176 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 6.5 Hz, 1H, H-7), 7.96 (d, J = 8.5 Hz, 2H, Ar.), 7.33 (d, J = 8.2 Hz, 2H, Ar.), 6.11 (d, J = 6.5 Hz, 1H, H-6), 4.59 (q, J = 7.2 Hz, 2H, CH_2CH_3), 2.42 (s, 3H, *p*-tolyl), 1.47 (t, J = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7(C=O), 155.9(CH), 155.4(C=O), 147.8(C), 138.3(C), 135.7(C), 133.7(C), 129.9(CH), 121.2(CH), 102.9(CH), 64.0(CH_2), 21.1(CH_3, *p*-tolyl), 13.9(CH_3).

Ethyl 1-(4-nitrophenyl)-5-oxo-1,5-dihydro[1,2,4]triazolo [4,3-*a*]pyrimidine-3-carboxylate (3c). Yield 48%, mp 165–168 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, J = 9.4 Hz, 2H, Ar.), 8.41 (d, J = 9.4 Hz, 2H, Ar.), 8.08 (d, J = 6.6 Hz, 1H, H-7), 6.22 (d, J = 6.6 Hz, 1H, H-6), 4.61 (q, J = 7.2 Hz, 2H, CH_2CH_3), 1.49 (t, J = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2(C=O), 155.4(CH), 154.9(C), 147.9(C), 146.1(C), 141.1(C), 136.7(C), 125.1(CH), 120.3(CH), 104.8(CH), 64.4(CH_2), 13.9(CH_3).

5-Oxo-*N*-phenyl-1-(*p*-tolyl)-1,5-dihydro[1,2,4]triazolo[4,3-*a*] pyramidine-3-carboxamide (3d). Yield 52%, mp 213–214 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.36 (s, 1H, NH), 8.16 (d, J = 6.2 Hz, 1H, H7), 8.04 (d, J = 8.5 Hz, 2H, Ar.), 7.82 (dd, J = 8.6, 1.0 Hz, 2H, Ar.), 7.42–7.37 (m, 2H, Ar.), 7.35 (d, J = 8.2 Hz, 2H, Ar.), 7.18 (t, J = 7.4 Hz, 1H, Ar.), 6.29 (d, J = 6.2 Hz, 1H, H-6), 2.43 (s, 3H, *p*-tolyl). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0(C=O), 156.8(CH), 150.8(C=O), 148.6(C), 139.7(C), 139.0(C), 137.6(C), 133.3(C),

129.9(CH), 129.1(CH), 125.2(CH), 122.0(CH), 120.4(CH), 102.8(CH), 21.2(CH_3, *p*-tolyl).

3-Acetyl-1-(*p*-tolyl)-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (3e). Yield 42%, mp 120–125 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 6.5 Hz, 1H, H-7), 7.98 (d, J = 8.6 Hz, 2H, Ar.), 7.35 (d, J = 8.2 Hz, 2H, Ar.), 6.16 (d, J = 10.5 Hz, 1H, H-6), 2.82 (s, 3H, COCH_3), 2.43 (s, 3H, *p*-tolyl). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.3(C=O), 155.6(C=O), 155.5(CH), 148.4(C), 141.4(C), 138.5(C), 133.6(C), 130.0(CH), 121.3(CH), 103.5(CH), 29.8(COCH_3), 21.1(CH_3, *p*-tolyl).

Ethyl (4a*S,5*S**,8*R**,8a*R**)-1-phenyl-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo[4,3-*a*]quinazoline-3-carboxylate (7a).** Yield 66%, mp 190–192 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 7.8 Hz, 2H, Ar.), 7.46 (t, J = 7.9 Hz, 2H, Ar.), 7.36 (t, J = 7.4 Hz, 1H, Ar.), 6.48 (dd, J = 5.5, 2.9 Hz, 1H), 6.28 (dd, J = 5.3, 3.1 Hz, 1H), 4.56 (m, 3H), 3.58 (s, 1H), 3.30 (s, 1H), 2.70 (d, J = 9.0 Hz, 1H), 1.54 (s, 2H), 1.50 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8(C=O), 156.3(C=O), 154.1(C), 140.3(CH), 137.7(C), 136.1(C), 134.3(CH), 129.1(CH), 128.2(CH), 122.2(CH), 63.3(CH_2), 57.3(CH), 52.8(CH), 49.7(CH), 43.9(CH_2), 40.5(CH), 14.2(CH_3).

Ethyl (4a*S,5*S**,8*R**,8a*R**)-1-(*p*-tolyl)-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo[4,3-*a*]quinazoline-3-carboxylate (7b).** Yield 69%, mp 191–193 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.1 Hz, 2H, Ar.), 7.25 (d, J = 8.1 Hz, 2H, Ar.), 6.47 (s, 1H), 6.27 (s, 1H), 4.53–4.57 (m, 3H), 3.58 (s, 1H), 3.29 (s, 1H), 2.69 (d, J = 9.0 Hz, 1H), 2.38 (s, 3H, *p*-tolyl), 1.53 (s, 2H), 1.49 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7(C=O), 156.4(C=O), 153.9(C), 140.5(CH), 138.1(C), 137.5(C), 134.3(CH), 133.7(C), 130.1(CH), 122.2(CH), 63.5(CH_2), 57.3(CH), 52.9(CH), 49.5(CH), 43.7(CH_2), 40.5(CH), 21.0(CH_3, *p*-tolyl), 14.0(CH_3).

Ethyl (4a*S,5*S**,8*R**,8a*R**)-1-(4-nitrophenyl)-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo[4,3-*a*]quinazoline-3-carboxylate (7c).** Yield 60%, mp 238–240 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, J = 9.2 Hz, 2H, Ar.), 8.32 (d, J = 9.2 Hz, 2H, Ar.), 6.49 (dd, J = 5.5, 2.9 Hz, 1H), 6.29 (dd, J = 5.3, 3.1 Hz, 1H), 4.6–4.55 (m, 3H), 3.59 (s, 1H), 3.30 (s, 1H), 2.72 (d, J = 9.0 Hz, 1H), 1.58–1.5 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6(C=O), 156.0(C=O), 154.4(C), 146.1(C), 141.2(C), 140.2(CH), 138.5(C), 134.4(CH), 124.7(CH), 121.6(CH), 63.8(CH_2), 57.4(CH), 53.0(CH), 49.8(CH), 44.1(CH_2), 40.6(CH), 14.2(CH_3).

(4a*S,5*S**,8*R**,8a*R**)-*N*-Phenyl-1-(*p*-tolyl)-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo[4,3-*a*]quinazoline-3-carboxamide (7d).** Yield 60%, mp 224–226 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H, NH), 7.92 (d, J = 8.1 Hz, 2H, Ar.), 7.69 (d, J = 7.9 Hz, 2H, Ar.), 7.43 (t, J = 7.7 Hz, 2H, Ar.), 7.31–7.20 (m, 3H, Ar.), 6.51–6.39 (m, 1H), 6.37–6.27 (m, 1H), 4.61 (d, J = 9.0 Hz, 1H), 3.55 (s, 1H), 3.44 (s, 1H), 2.68 (d, J = 8.9 Hz, 1H), 2.37 (s, 3H, *p*-tolyl), 1.52 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8(C=O), 154.0(C=O), 153.0(C=O), 139.9(CH), 139.4(C), 138.3(C), 136.1(C), 134.8(CH), 133.5(C), 129.7(CH), 129.4(CH), 125.7(CH), 122.0(CH), 120.4(CH), 57.4(CH), 52.9(CH), 49.8(CH), 43.9(CH_2), 40.5(CH), 21.1(CH_3).

(4a*S,5*S**,8*R**,8a*R**)-3-Acetyl-1-(*p*-tolyl)-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo[4,3-*a*]quinazoline (7e).** Yield 45%, mp 118–120 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.5 Hz, 2H, Ar.), 7.27 (d, J = 8.1 Hz, 2H, Ar.), 6.45 (dd, J = 5.4, 2.9 Hz, 1H), 6.30 (dd, J = 5.3, 3.1 Hz, 1H), 4.51 (d, J = 8.9 Hz, 1H), 3.55 (s, 1H), 3.18 (s, 1H), 2.72 (s, 3H, COCH_3), 2.65 (d, J = 9.0 Hz, 1H), 2.39 (s, 3H, *p*-tolyl), 1.57–1.42 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.7(C=O), 176.7(C=O), 154.1(C), 142.1(C), 140.0(CH), 138.1(C), 134.7(CH), 133.8(C), 129.7(CH), 122.1(CH), 57.4(CH), 52.7(CH), 49.8(CH), 44.4(CH_2), 40.6(CH), 26.5(COCH_3), 21.1(CH_3, *p*-tolyl).

Ethyl (4a*S,5*S**,8*R**,8a*R**)-1-(4-methoxyphenyl)-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo-[4,3-*a*]quinazoline-3-carboxylate (7f).** Yield 77%, mp 185–187 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 2H, Ar.), 6.95 (d, J = 9.0 Hz, 2H, Ar.), 6.47 (dd, J = 5.4, 2.8 Hz, 1H), 6.27 (dd, J = 5.2, 3.1 Hz, 1H), 4.60–4.46 (m, 3H), 3.83 (s, 3H, OCH_3), 3.57 (s, 1H), 3.29 (s, 1H), 2.68 (d, J = 9.0 Hz, 1H), 1.53 (s, 2H), 1.49 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8(C=O), 159.0(C=O), 156.3(C), 153.7(C), 140.4(CH), 137.4(C), 134.3(CH), 129.1(C), 123.9(CH), 114.2(CH), 63.3(CH_2), 57.3(CH), 55.5(CH), 52.8(CH), 49.7(CH), 43.9(CH_2), 40.5(OCH_3), 14.1(CH_3).

Ethyl (4a*S,5*S**,8*R**,8a*R**)-1-(4-chlorophenyl)-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo-[4,3-*a*]quinazoline-3-carboxylate (7g).** Yield 68%, mp 218–224 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.9 Hz, 2H, Ar.), 7.43 (d, J = 8.9 Hz, 2H, Ar.), 6.48 (dd, J = 5.5, 2.9 Hz, 1H), 6.28 (dd, J = 5.4, 3.1 Hz, 1H), 4.59–4.50 (m, 3H), 3.58 (s, 1H), 3.29 (s, 1H), 2.70 (d, J = 9.0 Hz, 1H), 1.53 (d, J = 7.9 Hz, 2H), 1.50 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6(C=O), 156.1(C=O), 154.0(C), 140.3(CH), 137.8(C), 134.8(C), 134.3(CH), 133.6(C), 129.2(CH), 123.1(CH), 63.5(OCH_2), 57.3(CH), 52.8(CH), 49.7(CH), 43.9(CH_2), 40.4(CH), 14.1(CH_3).

Ethyl (4a*S,5*S**,8*R**,8a*R**)-1-(3-(trifluoromethyl)phenyl)-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo-[4,3-*a*]quinazoline-3-carboxylate (7h).** Yield 67%, mp 160–162 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61–8.48 (m, 1H, Ar.), 8.25 (s, 1H, Ar.), 7.64–7.57 (m, 2H, Ar.), 6.49 (dd, J = 5.5, 2.9 Hz, 1H), 6.29 (dd, J = 5.4, 3.1 Hz, 1H), 4.61–4.56 (m, 3H), 3.58 (s, 1H), 3.30 (s, 1H), 2.71 (d, J = 9.0 Hz, 1H), 1.58–1.48 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6(C=O), 156.1(C=O), 154.3(C), 140.4(CH), 138.1(C), 136.7(C), 134.5(CH), 131.8(C), 131.7(C), 130.0(CH), 125.4(CH), 124.5(CH), 118.6(CH), 63.7(CH_2), 57.3(CH), 53.0(CH), 49.8(CH), 44.0(CH_2), 40.3(CH), 14.2(CH_3).

Ethyl (4a*R,5*S**,8*R**,8a*S**)-1-phenyl-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo[4,3-*a*]quinazoline-3-carboxylate (11a).** Yield 72%, mp 191–193 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 7.8 Hz, 2H, Ar.), 7.44 (t, J = 7.9 Hz, 2H, Ar.), 7.33 (t, J = 7.4 Hz, 1H, Ar.), 6.42 (dd, J = 5.5, 2.7 Hz, 1H), 5.94 (dd, J = 5.5, 2.7 Hz, 1H), 5.14 (dd, J = 10.0, 3.5 Hz, 1H), 4.55 (q, J = 7.1 Hz, 2H, CH_2CH_3), 3.71 (s, 1H), 3.68 (s, 1H), 3.27 (dd, J = 10.0, 3.9 Hz, 1H), 1.58 (dd, J = 27.1, 9.3 Hz, 2H), 1.50 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8(C=O), 156.3(C=O), 154.1(C), 140.3(CH), 137.8(C), 136.1(C), 132.1(CH), 129.1(CH), 127.9(CH), 122.2(CH), 63.4(CH_2), 57.1(CH), 49.5(CH), 49.4(CH), 46.4(CH_2), 41.2(CH), 14.1(CH_3).

Ethyl (4a*R,5*S**,8*R**,8a*S**)-1-(4-nitrophenyl)-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazol[4,3-*a*]quinazoline-3-carboxylate (11c).** Yield 75%, mp 190–192 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 9.2 Hz, 2H, Ar.), 8.30 (d, J =

9.2 Hz, 2H, Ar.), 6.42 (dd, J = 5.4, 2.6 Hz, 1H), 5.97 (dd, J = 5.4, 2.6 Hz, 1H), 5.15 (dd, J = 10.0, 3.4 Hz, 1H), 4.58 (q, J = 7.1 Hz, 2H, CH_2CH_3), 3.71 (s(broad), 2H), 3.30 (dd, J = 10.0, 3.8 Hz, 1H), 1.60 (dd, J = 32.6, 9.4 Hz, 2H), 1.52 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7(C=O), 156.0(C=O), 154.5(C), 146.0(C), 141.2(C), 140.4(CH), 138.5(C), 132.2(CH), 124.6(CH), 121.6(CH), 63.8(CH_2), 57.2(CH), 49.6(CH), 49.4(CH), 46.5(CH_2), 41.2(CH), 14.2(CH_3).

(4a*R,5*S**,8*R**,8a*S**)-*N*-Phenyl-1-(*p*-tolyl)-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo[4,3-*a*]quinazoline-3-carboxamide (11d).** Yield 70%, mp 236–238 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.85 (d, J = 8.3 Hz, 2H, Ar.), 7.71 (d, J = 7.9 Hz, 2H, Ar.), 7.43 (t, J = 7.8 Hz, 2H, Ar.), 7.25 (dd, J = 16.3, 6.2 Hz, 3H, Ar.), 6.38 (d, J = 5.2 Hz, 1H), 5.95 (d, J = 5.1 Hz, 1H), 5.22–5.12 (m, 1H), 3.86 (s, 1H), 3.65 (s, 1H), 3.30–3.18 (m, 1H), 2.37 (s, 3H, *p*-tolyl), 1.56 (dd, J = 22.5, 9.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8(C=O), 154.0(C), 153.0(C), 140.1(CH), 139.6(C), 138.1(C), 136.3(C), 133.6(C), 132.4(CH), 129.6(CH), 129.3(CH), 125.7(CH), 121.9(CH), 120.2(CH), 57.2(CH), 49.6(CH), 49.5(CH), 46.4(CH_2), 41.2(CH), 21.1(CH_3).

(4a*R,5*S**,8*R**,8a*S**)-3-Acetyl-1-(*p*-tolyl)-9-oxo-1,4a,5,8,8a,9-hexahydro-5,8-methano[1,2,4]triazolo[4,3-*a*]quinazoline (11e).** Yield 50%, mp 210–212 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H, Ar.), 7.25 (d, J = 8.3 Hz, 2H, Ar.), 6.39 (s, 1H), 5.90 (s, 1H), 5.10 (d, J = 10.0 Hz, 1H), 3.66 (s, 2H), 3.25 (d, J = 13.4 Hz, 1H), 2.72 (s, 3H), 2.38 (s, 3H), 1.57 (dd, J = 20.6, 9.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.6(C=O), 177.0(C=O), 154.1(C), 142.3(C), 140.2(CH), 138.1(C), 133.7(C), 132.2(CH), 129.7(CH), 121.9(CH), 57.1(CH), 49.5(CH), 49.3(CH), 46.3(CH_2), 41.2(CH), 26.6($CO\mathit{CH_3}$), 21.1(CH_3, *p*-tolyl).

RDA protocol for the synthesis of [1,2,4]triazolo[4,3-*a*] pyrimidines 4a–h

Norbornene-fused [1,2,4]triazolo[4,3-*a*]pyrimidinones **7a–h** or **11a,c–e** (0.1 mmol) was dissolved in 1,2-DCM (2 mL) in a 10 mL sealed reaction vial. The solution was stirred at 200 °C for 30–120 min. at max. 200 W microwave irradiation. After completing the reaction, monitored by TLC, the solvent was evaporated, the residue was dissolved in EtOAc and purified by column chromatography on silica gel eluting with EtOAc.

Ethyl 7-oxo-1-phenyl-1,7-dihydro[1,2,4]triazolo-[4,3-*a*] pyrimidine-3-carboxylate (4a). Yield 42% from **7a**, 52% from **11a**, mp 215–218 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, J = 7.9 Hz, 1H, H-5), 8.19 (d, J = 7.9 Hz, 2H, Ar.), 7.51 (d, J = 7.9 Hz, 2H, Ar.), 7.39 (t, J = 7.4 Hz, 1H, Ar.), 6.50 (d, J = 7.8 Hz, 1H, H-6), 4.59 (q, J = 7.2 Hz, 2H, CH_2CH_3), 1.51 (t, J = 7.1 Hz, 3H, CH_2CH_3).^{13}C NMR (125 MHz, $CDCl_3$) 168.5(C=O), 156.2(C=O), 149.2(C), 135.9(C), 132.4(C), 130.6(CH), 129.4(CH), 128.2(CH), 121.4(CH), 114.9(CH), 63.9(OCH_2), 14.2(CH_3).

Ethyl 7-oxo-1-(*p*-tolyl)-1,7-dihydro[1,2,4]triazolo[4,3-*a*] pyramidine-3-carboxylate (4b). Yield 54%, mp 193–195 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, J = 7.7 Hz, 1H, H-5), 8.05 (d, J = 8.6 Hz, 2H, Ar.), 7.29 (d, J = 7.9 Hz, 2H, Ar.), 6.49 (d, J = 7.8 Hz, 1H, H-6), 4.58 (q, J = 7.2 Hz, 2H, CH_2CH_3), 2.40 (s, 3H, *p*-tolyl), 1.50 (t, J = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5(C=O), 156.2(C=O), 149.1(C), 138.3(C), 133.4(C), 132.2(C), 130.5(CH), 129.8(CH), 121.3(CH), 114.9(CH), 63.8(OCH_2), 21.1(CH_3), 14.1(CH_3).

Ethyl 1-(4-nitrophenyl)-7-oxo-1,7-dihydro[1,2,4]triazolo-[4,3-*a*]pyrimidine-3-carboxylate (4c). Yield 41% from **7c**, 45% from **11c**, mp 205–207 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 7.6 Hz, 1H, H-5), 8.59 (d, J = 9.7 Hz, 2H, Ar.),8.37 (d, J = 9.2 Hz, 2H, Ar.), 6.53 (d, J = 7.6 Hz, 1H, H-6), 4.61 (q, J = 7.2 Hz, 2H, CH_2CH_3),1.53 (t, J = 7.3 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0(C=O), 155.8(C=O), 149.3(C), 146.3(C), 140.7(C), 133.2(C), 130.8(CH), 125.0(CH), 120.9(CH), 114.9(CH), 64.2(OCH_2), 14.1(CH_3).

7-Oxo-*N*-phenyl-1-(*p*-tolyl)-1,7-dihydro[1,2,4]triazolo[4,3-*a*] pyrimidine-3-carboxamide (4d). Yield 78% from **7d**, 67% from **11d**, mp 253–255 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (d, J = 7.9 Hz, 1H, H-5), 8.77 (br, 1H, NH), 8.01 (d, 2H, J = 8.2 Hz, Ar.), 7.69 (d, J = 8.0 Hz, 2H, Ar.), 7.40–7.48 (m, 3H, Ar.), 7.27–7.33 (m, 2H, Ar.), 6.49 (d, J = 7.9 Hz, 1H, H-6), 2.41 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6(C=O), 152.9(C=O), 138.4(C), 135.8(C), 134.0(C), 133.3(C), 131.1(CH), 130.5(CH), 129.9(CH), 129.4(CH), 127.7(CH), 126.0(CH), 121.1(CH), 120.4(CH), 114.7(CH), 21.1(CH_3).

3-Acetyl-1-(*p*-tolyl)-[1,2,4]triazolo[4,3-*a*]pyrimidin-7(1*H*)-one (4e). Yield 90% from **7e**, 57% from **11e**, mp 216–217 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 7.8 Hz, 1H, H-5), 8.05 (d, J = 8.4 Hz, 2H, Ar.), 7.31 (d, J = 8.7 Hz, 2H, Ar.), 6.46 (d, J = 7.8 Hz, 1H, H-6), 2.77 (s, 3H, $CO\mathit{CH_3}$), 2.41 (s, 3H, *p*-tolyl). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.8(C=O), 168.5(C=O), 149.1(C), 138.5(C), 136.8(C), 133.5(C), 131.1(CH), 129.9(CH), 121.1(CH), 114.9(CH), 26.4(CH_3), 21.1(CH_3).

Ethyl 1-(4-methoxyphenyl)-7-oxo-1,7-dihydro[1,2,4]triazolo-[4,3-*a*]pyrimidine-3-carboxylate (4f). Yield 41%, mp 171–175 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, J = 7.7 Hz, 1H, H-5), 8.04 (d, J = 9.2 Hz, 2H, Ar.), 7.00 (d, J = 9.1 Hz, 2H, Ar.), 6.49 (d, J = 7.7 Hz, 1H, H-6), 4.58 (q, J = 7.2 Hz, 2H, CH_2CH_3), 3.85 (s, 3H, OCH_3), 1.50 (t, J = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5(C=O), 159.3(C=O), 156.2(C), 149.0(C), 132.1(C), 130.5(CH), 128.8(C), 123.2(CH), 114.9(CH), 114.4(CH), 63.7(OCH_2), 55.6(OCH_3), 14.1(CH_3).

Ethyl 1-(4-chlorophenyl)-7-oxo-1,7-dihydro[1,2,4]triazolo-[4,3-*a*]pyrimidine-3-carboxylate (4g). Yield 58%, mp 178–180 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 7.7 Hz, 1H, H-5), 8.22 (d, J = 8.8 Hz, 2H, Ar.), 7.48 (d, J = 9.1 Hz, 2H, Ar.), 6.55 (d, J = 7.5 Hz, 1H, H-6), 4.59 (q, J = 7.3 Hz, 2H, CH_2CH_3), 1.51 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3(C=O), 156.1(C=O), 149.1(C), 134.5(C), 133.9(C), 132.5(C), 130.6(CH), 129.5(CH), 122.3(CH), 115.0(CH), 64.0(OCH_2), 14.1(CH_3).

Ethyl 7-oxo-1-(3-(trifluoromethyl)phenyl)-1,7-dihydro[1,2,4] triazolo[4,3-*a*]pyrimidine-3-carboxylate (4h). Yield 48%, mp 193–195 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70–8.72 (m, 2H, Ar, H-5), 8.30 (brs, 1H, Ar.), 7.64–7.69 (m, 2H, Ar.), 6.53 (d, J = 7.8 Hz, 1H, H-6), 4.60 (q, J = 7.1 Hz, 2H, CH_2CH_3), 1.53 (t, J = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2(C=O), 156.0(C=O), 149.2(C), 136.4(C), 132.8(C), 130.2(C), 124.7(CH), 124.7(CH), 124.5(CH), 117.8(CH), 117.8(CH), 115.0(CH), 64.1(CH_2), 14.1(CH_3).

Conclusions

In the present work, we prepared triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones **4a–h**. These compounds cannot be prepared by the reactions of thiouracil **1** and hydrazonoyl chloride **2a–h**, because these reactions are regioselective towards [1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones **3a–d**. For overcoming this obstacle, we used *diexo* **6** or *diendo* **10** norbornene-condensed 2-thioxopyrimidin-4-ones characterized by two structural features: (i) the absence of the C=C bond in the pyrimidinone moiety that ensures the direction of the regioselectivity towards triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones and (ii) the easy removal of cyclopentadiene by the RDA reaction and the concomitant rebuilding the C=C bond in the pyrimidinone moiety to obtain triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones **4a–h** as the final products.

Conflicts of interest

There are no conflicts to declare.

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