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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Novel tetrahydropyrimidine–adamantane hybrids as anti-inflammatory agents: synthesis, structure and biological evaluation

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Abstract A series of novel (3-((3*s*,5*s*,7*s*)-adamantan-1-yl)-1-alkyl/aralkyl/aryl-1,2,3,4-tetrahydroyrimidin-5-yl) (aryl)methanones (**5a–j**) has been synthesized by the reaction of 1-aryl-3-(alkyl/aralkyl/aryl)aminoprop-2-en-1-ones **3a–j**, 1-adamantanamine **4** and formaldehyde under thermal conditions. The structures of the products (**5a–j**) have been established with the help of spectral and analytical data. The stereochemistry of the products was established by X-ray crystallographic studies of a representative product (3-((3*s*,5*s*,7*s*)-adamantan-1-yl)-1-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)(4-chlorophenyl) methanone (**5g**) of the series. The target adamantane–tetrahydropyrimidine hybrids **5a–j** were evaluated for their anti-inflammatory activities as a result of which compounds **5e** (R=$C_6H_5CH_2$, Ar=C_6H_5), **5i** (R=CH_3, Ar=4-$CH_3C_6H_4$), **5j** (R=$C_6H_5CH_2$, Ar=4-$CH_3C_6H_4$) and **5g** (R=CH_3, Ar=4-ClC_6H_4) were found to exhibit excellent and promising anti-inflammatory activities.

Keywords Tetrahydropyrimidine · Adamantanamine · Anti-inflammatory · Enaminones · Formylated acetophenones

Introduction

Tetrahydropyrimidines and their analogues have attracted considerable attention because of their great pharmacological importance and biological activities such as antimicrobial (Elumalai *et al*., 2013; EL-Mahdy *et al*., 2013; El-Fattah *et al*., 2010; Baldev *et al*., 2012; Chauhan *et al*., 2012) and antimycobacterial activity (Elumalai *et al*., 2013), COX-2 inhibitor (Lokwani *et al*., 2012), anti-inflammatory (Dongarwar *et al*., 2011), antifungal (Gaffar *et al*., 2012), antioxidant (Mansouri *et al*., 2012) and anticancer (Desai *et al*., 2011). Keeping in view the biological properties of these molecules, we have reported the synthesis of novel 5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidines (Benzoyl-THP-1) (Karim *et al*., 2003), 5-benzoyl-1,2,3,4-tetrahydropyrimidines (Benzoyl-THP-2) (Chanda *et al*., 2004), bis-(5-benzoyl-1,2,3,4-tetrahydropyrimidines) (Benzoyl-THP-3) (Dutta *et al*., 2005), (1,2,3,4-tetrahydro-3-methyl-1-phenylpyrimidin-5-yl) (pyridin-4-yl)methanone (4-Isonicotinoyl-THP-4) (Vishwakarma *et al*., 2009) and [3,3′-(ethane-1,2-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis(pyridin-4-ylmethanone) (4-Isonicotinoyl-THP-5) with antibacterial property (Vishwakarma *et al*., 2009).

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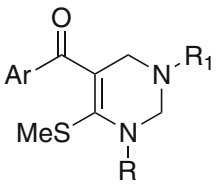
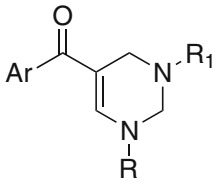


Benzoyl-THP-1



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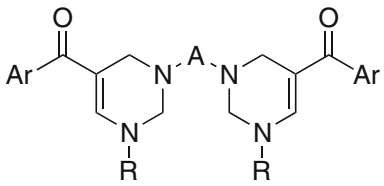
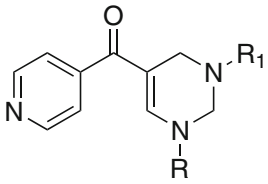
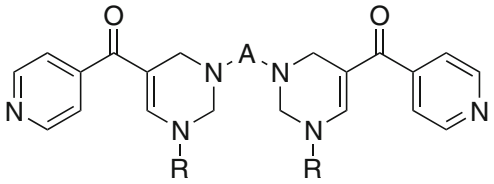


Benzoyl-THP-3



4-Isonicotinoyl-THP-4



4-Isonicotinoyl-THP-5

Recently, Kshirsagar and Shanmugasundaram have reported (2013) the synthesis of 1,2,3,4-tetrahydropyrimidine derivatives containing carbamates and carbamides with calcium channel blocking activity. However, to the best of our knowledge, tetrahydropyrimidine derivatives containing adamantane moiety are unknown in the literature, and hence, their biological properties remain unexplored. In light of these findings, it was thought worthwhile to synthesize molecular hybrids of 1,2,3,4-tetrahydropyrimidine derivatives by incorporating adamantane moiety and to evaluate their anti-inflammatory activities.

Inflammation is associated with many disease conditions such as cancer (O'Byrne and Dalgleish, 2001), heart failure (Gullestal *et al*., 2012), Parkinson's disease (Przedborski, 2010), Alzheimer's disease (Breitner, 1996) and other diseases. At present, non-steroidal anti-inflammatory drugs (NSAIDs) represent the most widely used drug in medicinal practice, and indeed, the use of this class of compounds has increased dramatically during the recent years among patients of all ages (Musu *et al*., 2011). In 1966, amantadine, a derivative of adamantane, was approved in the USA for use against A/H3N2 and subsequently for all influenza A infection (Hayden, 2006; Leng *et al*., 2007). New series of 5-(1-adamantyl)-1,3,4-thiadiazole derivatives were synthesized and tested for their antimicrobial and anti-inflammatory activities (Kadi *et al*., 2010). A series of new adamantyl triazoles and related derivatives was synthesized, the antimicrobial and anti-inflammatory activities of these compounds were determined, and these compounds show promising activities comparable to known antibacterial, antifungal and anti-inflammatory drugs (Al-Omar *et al*., 2010; Bredt and Snyder, 1994). Prompted by this, we herein report the synthesis, structure and anti-inflammatory activities of novel tetrahydropyrimidine–adamantane hybrids.

Results and discussion

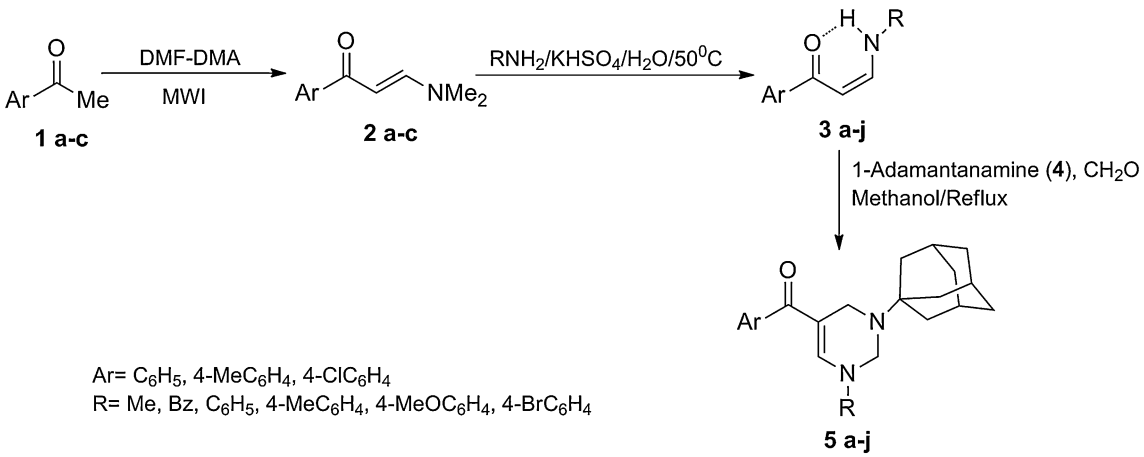
A series of novel hitherto unreported hybrids containing tetrahydropyrimidine and adamantane was synthesized. The anti-inflammatory activities of the compounds were evaluated, and their structures were elucidated by IR, NMR and MS. X-ray crystallographic study for a particular compound from the series was done for the final confirmation of the structures.

Chemistry

In order to synthesize the desired tetrahydropyrimidine–adamantane hybrids, enaminones of type **3** derived from acetophenone were required. Their synthesis could be achieved by first reacting acetophenone **1a–c** with DMF-DMA following a previously reported procedure (Kalita *et al*., 2014) to yield the formylated product **2a–c** and then converting **2a–c** into **3a–j** by a procedure (Kalita *et al*., 2014) developed in our laboratory (Scheme 1).

Synthesis of the desired tetrahydropyrimidine–adamantane hybrids was subsequently undertaken. Thus, when a mixture of enaminone **3a**, 1-adamantanamine and formaldehyde (1:1:2) in methanol (4 ml) was heated at reflux for 2.5 h, work up of the reaction mixture gave **5a** in 88 % yields, the structure of which was proposed to be (3-((3*s*,5*s*,7*s*)-adamantan-1-yl)-1-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl)methanone on the basis of spectral and analytical data. The reaction conditions could easily be extrapolated for the synthesis of **5b–j** in 85–96 % overall yields in 3–6 h (Scheme 1).

The structures of the products **5(a–j)** (Table 1) were established without any ambiguity. The infrared spectra of **5a–j** showed strong peaks in the region of 1,500 to



Scheme 1 Synthesis of tetrahydropyrimidine-adamantane hybrids **5(a–j)**

1,630 cm^{-1} due to extensively delocalized double bonds and carbonyl groups. The C–H stretching due to adamantane gave characteristic bands close to 2,900 and 2,840 cm^{-1}. In the ^{1}H NMR spectra of **5a–j**, the signals due to aromatic protons appear between 6.80 and 7.56 ppm. The C_6-H proton of the tetrahydropyrimidine ring resonated as singlet close to 6.99 ppm in **5a**, **5e**, **5f**, **5g** and **5i,** whereas it remains obscured by the aromatic protons in **5b**, **5c**, **5d**, **5h** and **5j**. The signals due to benzylic CH_2 protons in **5e** and **5j** appeared as singlet at 4.30 and 4.28 ppm, respectively. The CH_2 protons at C-2 of the tetrahydropyrimidine ring appeared between 3.94 and 4.65 ppm, while those at C-4 gave their signals in the range of 3.73–3.93 ppm. The three sets of protons of adamantyl group resonated as three distinct multiplets in ranges 1.64–1.73, 1.84–1.92 and 2.14–2.18 ppm. In the ^{13}C NMR spectra of the tetrahydropyrimidines, the most striking signal was due to carbonyl carbon (close to 190 ppm) and those due to adamantyl group carbon atoms appearing in the ranges of 29.43–29.62, 36.05–36.19, 43.17–43.41 and 53.28–53.80 ppm. The proposed cyclic structures for the tetrahydropyrimidines are further supported by the absence of NH ($\sim$12.00 ppm) and vinylic C–H ($\sim$6.00 ppm) proton signals of the starting enaminones in the spectra of **5a–j**. The mass spectra of the products were in conformity with the proposed structures.

Furthermore, the proposed structure of (3-((3*s*,5*s*,7*s*)-adamantan-1-yl)-1-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)(4-chlorophenyl) methanone (**5g**) was unequivocally confirmed by single-crystal X-ray crystallography (Fig. 1) with CCDC no. 976466. The crystals of **5g** suitable for X-ray analysis were obtained by crystallization from ethylacetate. The crystal belongs to monoclinic, space group P2(1)/c with $a = 14.1482$ (4) Å, $b = 15.0308$ (4) Å, $c = 9.1382$ (2) Å, $\beta = 92.645$ (1)°, $V = 1{,}941.25$ (9) $Å^3$ and $Z = 4$. The molecular graphic was performed using ORTEP-3, and displacement ellipsoids are drawn at 30 % probability level.

Biological activities

Anti-inflammatory activity

Inhibition of FCA-induced paw edema

Compounds (**5a–j**) were tested for their in vivo anti-inflammatory activities against FCA-induced paw edema in mice. The test was performed to examine the ability of the test compounds to reduce paw thickness after 24 h as compared to the untreated inflamed mice. The results are given in Table 2 which showed varying degrees of reduction in thickness. In general, **5g** and **5d** showed the highest reduction, followed by **5i** and **5e** in decreasing order.

Nitric oxide level in the paw exudates

The anti-inflammatory activities of compounds **5a–j** were also determined by studying the level of NO in paw exudates. The results of the NO level in paw exudates presented in Fig. 2 showed different levels of reduction in NO. Mice treated with compound **5a** showed highest reduction in NO level followed by **5b**, **5g** and **5i**.

Level of nitric oxide concentration in whole blood

Nitric oxide concentration in response to the test compounds was also determined in blood (Fig. 3). The results presented in Fig. 3 showed varying level of reduction in NO concentration. Compound **5h** showed highest reduction followed by **5j** and **5e**. Compounds **5b, 5c, 5f** and **5i**

Table 1 Synthesis of compounds **5a–j** by reaction of enaminones **3** with 1-adamantanamine **4**

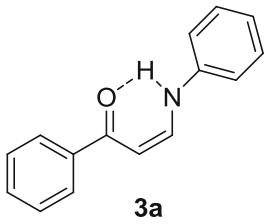
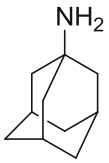
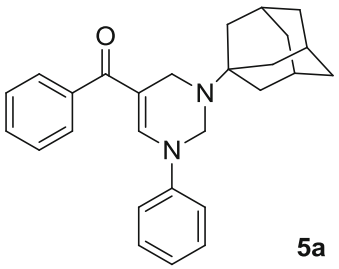
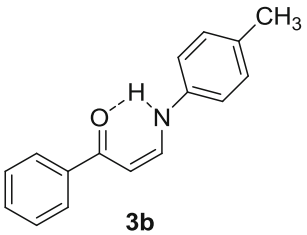
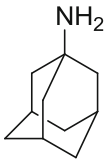
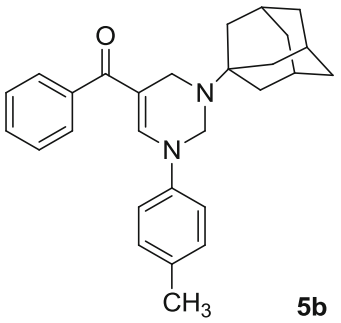
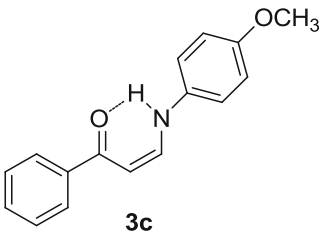
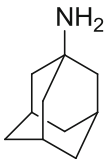
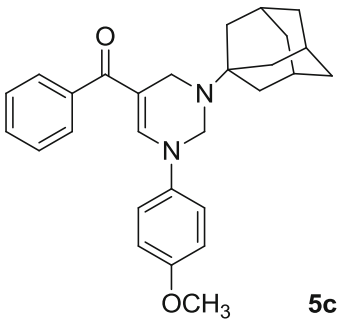
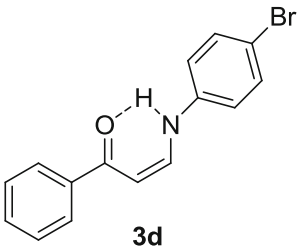
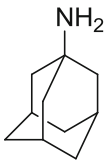
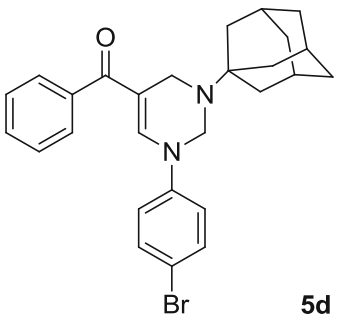
Entry	Enaminone	**4**	Product	% yield (time, h)
1	 **3a**		 **5a**	88 (2.5 h)
2	 **3b**		 **5b**	96 (4 h)
3	 **3c**		 **5c**	85 (4 h)
4	 **3d**		 **5d**	86 (5 h)

Table 1 continued

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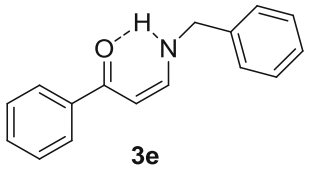
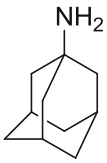
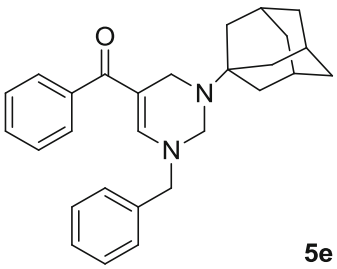
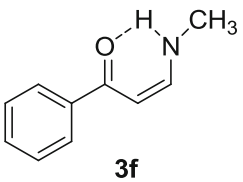
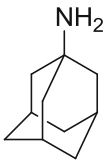
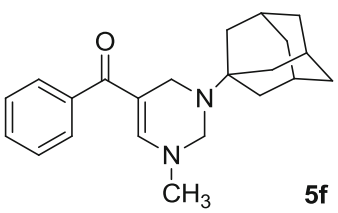
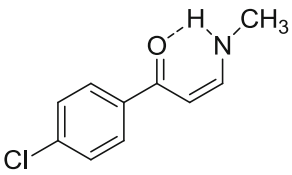
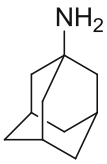
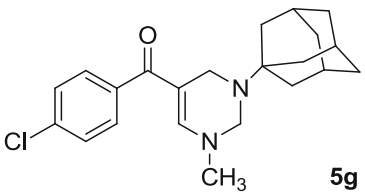
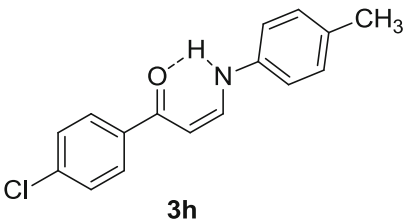
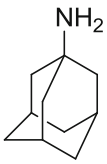
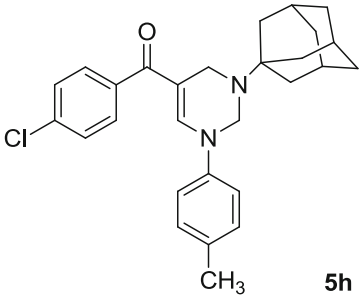
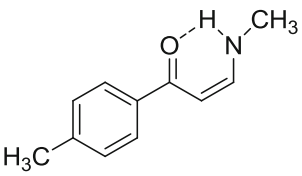
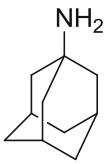
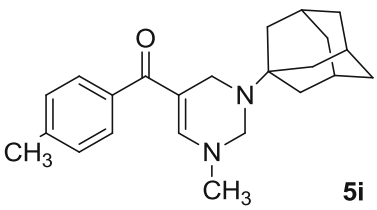
5	 **3e**		 **5e**	90 (5 h)
6	 **3f**		 **5f**	92 (5 h)
7	 **3g**		 **5g**	94 (3 h)
8	 **3h**		 **5h**	90 (6 h)
9	 **3i**		 **5i**	96 (5 h)

Table 1 continued

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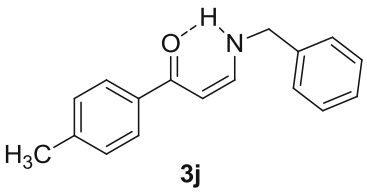
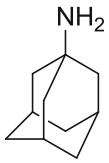
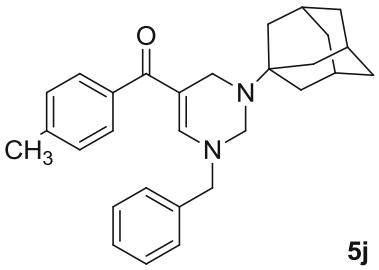
10	 **3j**		 **5j**	91 (4 h)

showed equal degrees of reduction, but compounds **5a**, **5d** and **5g** showed no reduction.

Differential leukocyte count in blood

Anti-inflammatory activities of the ten compounds were also studied by performing a differential leukocyte count in blood smear. Most of the compounds resulted in lower counts of both basophils and eosinophils or either basophils or eosinophils as compared to control mice as given in Fig. 4. The results reveal that blood from mice treated with compounds **5e** and **5j** have lowest levels of these cells.

In this investigation, paw thickness was taken as a physical parameter. From the results, it is clear that compounds **5d**, **5g**, **5i** and **5e** exhibited the highest ability to reduce paw edema after 24 h (Table 2), while the others showed no reduction in paw thickness. NO is an effective mediator of inflammation (Korhonen *et al*., 2005), and high levels of NO have been reported in many physiological processes including inflammatory response (Kang *et al*., 2008). Therefore, the inflammatory activities of compounds **5a–j** were also studied by determining the level of NO in paw exudates and whole blood. The results demonstrated varying degrees of reduction both in paw exudates and in whole blood. In paw exudates, compound **5a** showed the highest reduction followed by **5b**, **5g** and **5i**, whereas compound **5h** showed the highest reduction in NO in blood and is followed by **5j** and **5e**. Differential leukocytes count is another parameter which was studied in this investigation. Leukocytes such as eosinophils and basophils are present at the site of inflammatory response and are suggested to reduce inflammation caused by other leukocytes (Spuy *et al*., 2010). The anti-inflammatory activities of compounds **5a–j** were also studied by performing differential leukocytes count. As mentioned above, the results indicated that mice treated with compound **5e** and **5j** showed the lowest basophil and eosinophil counts (Fig. 4). While most of the tested compounds showed some anti-inflammatory properties, the above results led to the conclusion that compounds **5e**, **5i, 5j** and **5g** have the highest potential as anti-inflammatory agents.

Experimental

Chemistry

Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer (Perkin-Elmer). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECS 400 taking Me_4Si as the internal standard in $CDCl_3$. The X-ray diffraction data were collected at 296 K with Mo Kα radiation ($\lambda = 0.71073$ Å) using a Bruker Nonius SMART APEX II CCD diffractometer equipped with a graphite monochromator. The structures were solved by direct methods (SHELXS 97) and refined by full-matrix least-squares based on F square. All calculations were carried out using WinGX system version 1.80.05. All the non-H-atoms were refined in the anisotropic approximation: H-atoms were located at calculated positions. The electron spray mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap mass spectrometer. Elemental analysis was performed on a Vario-EL III instrument. Formylated acetophenones **2a–c** was synthesized by our previously reported procedure (Kalita *et al*., 2014).

*General procedure for the synthesis of (3-((3s,5s,7s)-adamantan-1-yl)-1-alkyl/aralkyl/aryl-1,2,3,4-tetrahydropyrimidin-5-yl)(aryl)methanone (**5a–j**)*

A mixture of 1-adamantanamine (1 mmol) and formaldehyde (2 mmol) in 1 ml of methanol was stirred at room

Table 2 Paw thickness of mice bearing FCA-induced paw edema followed by intraperitoneal administration of 50 mg/kg bw of test compounds **5a–j** at different time intervals in comparison with untreated control

Treatment group	Time (h)	Paw edema (mm)		Increase in paw thickness from 0 h	Percentage increase/decrease in paw thickness
Control	0	3.08	±0.07	0	0.00
	1	3.27	±0.28	0.19	6.17
	3	3.42	±0.29	0.35	11.24
	24	3.69	±0.27	0.62	20.02
5a	0	3.83	±0.29	0	0.00
	1	3.83	±0.29	0	0.00
	3	3.07	±0.12	−0.77	−19.98
	24	3.83	±0.29	0.00	0.00
5b	0	3.67	±0.29	0	0.00
	1	3.17	±0.29	−0.5	−13.64
	3	3.53	±0.46	−0.13	−3.65
	24	4.00	±0.00	0.33	9.08
5c	0	3.87	±0.06	0	0.00
	1	3.77	±0.25	−0.10	−2.59
	3	3.57	±0.12	−0.3	−7.76
	24	3.87	±0.12	0.00	0.00
5d	0	3.87	±0.12	0	0.00
	1	3.43	±0.12	−0.43	−11.22
	3	3.23	±0.25	−0.63	−16.40
	24	3.47	±0.29	−0.40	−10.27
5e	0	3.77	±0.25	0	0.00
	1	3.47	±0.29	−0.3	−7.96
	3	3.13	±0.12	−0.64	−16.98
	24	3.53	±0.25	−0.24	−6.37
5f	0	3.87	±0.06	0	0.00
	1	3.87	±0.06	0	0.00
	3	3.13	±0.12	−0.73	−18.98
	24	3.93	±0.06	0.07	1.71
5g	0	3.90	±0.10	0	0.00
	1	3.50	±0.00	−0.4	−10.26
	3	3.13	±0.12	−0.77	−19.67
	24	3.33	±0.29	−0.57	−14.54
5h	0	3.97	±0.06	0	0.00
	1	3.77	±0.23	−0.20	−5.04
	3	3.00	±0.00	−0.97	−24.43
	24	3.87	±0.12	−0.10	−2.52
5i	0	3.70	±0.17	0	0.00
	1	3.77	±0.25	0.07	1.81
	3	3.17	±0.29	−3.53	−14.41
	24	3.43	±0.12	−0.27	−7.22
5j	0	4.00	±0.00	0	0.00
	1	3.77	±0.23	−0.23	−5.75
	3	3.27	±0.06	−0.73	−18.25
	24	3.93	±0.06	−0.07	−1.75

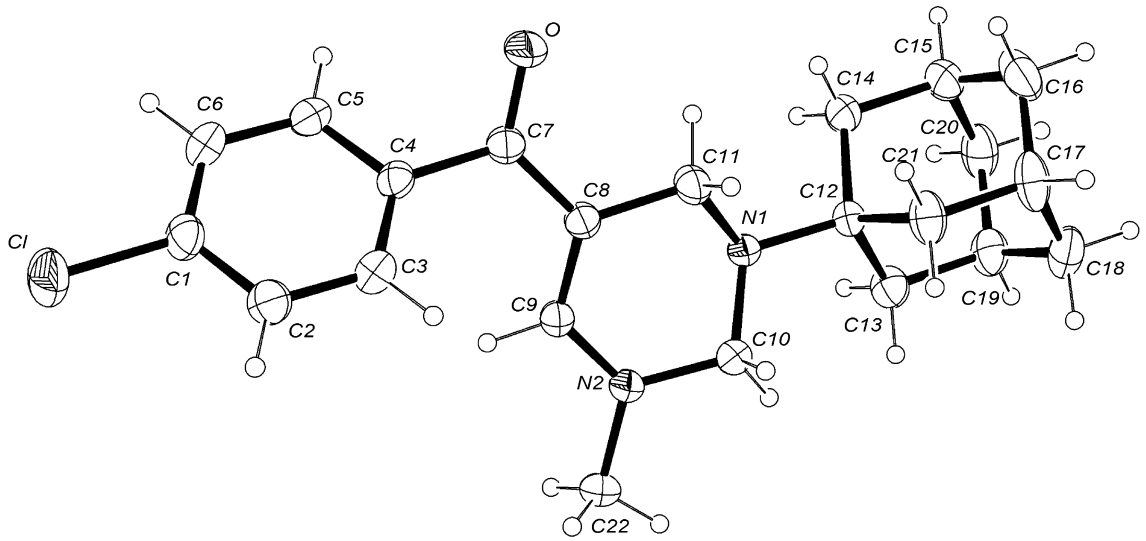
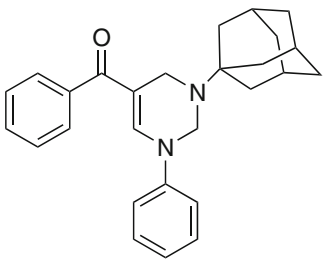


Fig. 1 Single-crystal X-ray structure of **5g**

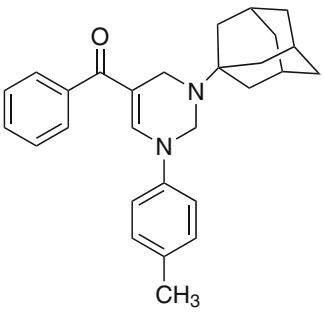
temperature for 5–10 min. To this was added a solution of the enaminone (1 mmol) in 4 ml of methanol and the resulting solution was refluxed for 2.5–6 h. On completion of the reaction (monitored by TLC), methanol was distilled off to give a gum. This gum, on trituration with hexane, gave a solid which was collected by filtration. The practically pure product thus obtained in 85–96 % overall yields were further purified by column chromatography (silica gel, 20 % EtOAc-Hexane).

(3-((3s,5s,7s)-adamantan-1-yl)-1-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl) methanone ***(5a)***



Yellow crystals from ethylacetate (88 %); m.p. 132–133 °C; IR (KBr) υ_{max} 2,900 (Adamantane), 2,846 (Adamantane), 1,598 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.58–1.67 (m, 6H, Adamantane), 1.80–1.81 (m, 6H, Adamantane), 2.09 (s, 3H, Adamantane), 3.94 (s, 2H, CH_2, tetrahydropyrimidine), 4.65 (s, 2H, CH_2, tetrahydropyrimidine), 6.94 (d, 2H, $J = 8.8$ Hz, phenyl), 7.07–7.1 (t, 1H, phenyl), 7.32 (d, 2H, $J = 8.8$ Hz, phenyl), 7.39–7.43 (m, 3H, phenyl), 7.48 (s, 1H, CH-C_6-tetrahydropyrimidine), 7.54–7.56 (m, 2H, phenyl); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 29.5 (3, CH, Adamantane), 36.4 (3, CH_2, Adamantane), 40.0 (3, CH_2, Adamantane), 41.3 (Cq, Adamantane), 54.7 (CH_2-tetrahydropyrimidine), 62.0 (CH_2-tetrahydropyrimidine), 113.7 (CH-phenyl), 118.1 (2, CH-phenyl), 123.8 (CH-phenyl), 128.1 (2, CH-phenyl), 128.3 (2, CH-phenyl), 129.6 (2, CH-phenyl), 130.0 (Cq), 139.9 (Cq), 143.8 (Cq), 146.5 (C_6-tetrahydropyrimidine), 193.3 (CO); Mass [ESI] m/z (%): 399 $[MH]^+$. Anal. Calcd. For $C_{27}H_{30}N_2O$ (398): C, 81.37; H, 7.59; N, 7.03. Found: C, 81.48; H, 7.53; N, 7.00 %.

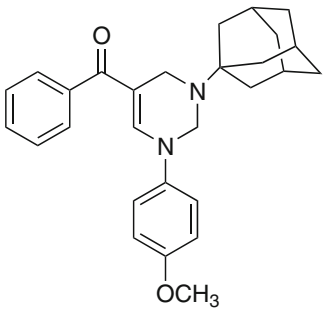
(3-((3s,5s,7s)-adamantan-1-yl)-1-(p-tolyl)-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl)methanone ***(5b)***



Yellow crystals from ethylacetate (96 %); m.p. 143–144 °C; IR (KBr) υ_{max} 2,904 (Adamantane), 2,853 (Adamantane), 1,581 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.58–1.67 (m, 6H, Adamantane), 1.80–1.81 (m, 6H, Adamantane), 2.09 (s, 3H, Adamantane), 2.30 (s, 3H, CH_3, phenyl), 3.93 (s, 2H, CH_2, tetrahydropyrimidine), 4.61 (s, 2H, CH_2, tetrahydropyrimidine), 6.84 (d, 2H, J = 8.8 Hz, phenyl), 7.12 (d, 2H, J = 8.8 Hz, phenyl), 7.36–7.44 (m, 4H, 3H-phenyl, 1H-C_6-tetrahydropyrimidine), 7.54 (d, 2H, $J = 8$ Hz, phenyl); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 20.7 (CH_3-phenyl), 29.6 (3, CH, Adaman-tane), 36.5 (3, CH_2, Adamantane), 40.0 (3, CH_2, Adamantane), 41.2 (Cq, Adamantane), 54.6 (CH_2-tetrahydropyrimidine), 62.2 (CH_2-tetrahydropyrimidine), 113.1 (CH-phenyl), 118.1 (2, CH-phenyl), 128.0 (2,

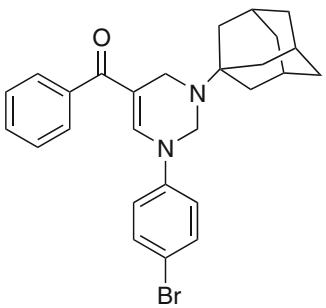
CH-phenyl), 128.3 (2, CH-phenyl), 129.8 (2, CH-phenyl), 130.1 (Cq), 133.7 (Cq), 140.0 (Cq), 141.5 (Cq), 146.9 (C_6-tetrahydropyrimidine), 193.1 (CO); Mass [ESI] m/z (%): 413 $[MH]^+$. Anal. Calcd. For $C_{28}H_{32}N_2O$ (412): C, 81.51; H, 7.82; N, 6.79. Found: C, 81.45; H, 7.76; N, 6.75 %.

(3-((3s,5s,7s)-adamantan-1-yl)-1-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl) methanone ***(5c)***



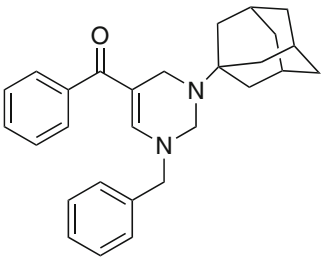
Yellow crystals from ethylacetate (85 %); m.p. 105–106 °C; IR (KBr) υ_{max} 2,906 (Adamantane), 2,846 (Adamantane), 1,627 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.58–1.67 (m, 6H, Adamantane), 1.81–1.82 (m, 6H, Adamantane), 2.09 (s, 3H, Adamantane), 3.77 (s, 3H, OCH_3, phenyl), 3.93 (s, 2H, CH_2, tetrahydropyrimidine), 4.58 (s, 2H, CH_2, tetrahydropyrimidine), 6.84–6.92 (m, 4H, 3H-phenyl, 1H-C_6-tetrahydopyrimidine), 7.36–7.42 (m, 4H, phenyl), 7.52–7.54 (m, 2H, phenyl); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 29.6 (3, CH, Adamantane), 36.5 (3, CH_2, Adamantane), 40.0 (3, CH_2, Adamantane), 41.2 (Cq, Adamantane), 54.6 (CH_2-tetrahydropyrimidine), 55.5 (OCH_3-phenyl), 62.7 (CH_2-tetrahydropyrimidine), 112.6 (Cq), 114.7 (2, CH-phenyl), 120.4 (2, CH-phenyl), 128.0 (2, CH-phenyl), 128.2 (2, CH-phenyl), 129.8 (CH-phenyl), 137.6 (Cq), 140.1 (Cq), 147.3 (Cq), 156.5 (C_6-tetrahydropyrimidine), 192.9 (CO); Mass [ESI] m/z (%): 429 $[MH]^+$. Anal. Calcd. For $C_{28}H_{32}N_2O_2$ (428): C, 78.47; H, 7.53; N, 6.54. Found: C, 78.55; H, 7.49; N, 6.51 %.

(3-((3s,5s,7s)-adamantan-1-yl)-1-(4-bromophenyl)-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl) methanone ***(5d)***



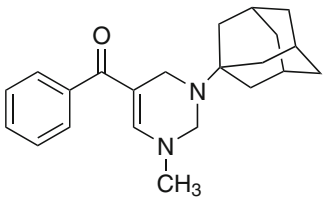
Yellow crystals from ethylacetate (86 %); m.p. 163–165 °C; IR (KBr) υ_{max} 2,908 (Adamantane), 2,847 (Adamantane), 1,636 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.60–1.64 (m, 6H, Adamantane), 1.78–1.79 (m, 6H, Adamantane), 2.09 (s, 3H, Adamantane), 3.92 (s, 2H, CH_2, tetrahydropyrimidine), 4.61 (s, 2H, CH_2, tetrahydropyrimidine), 6.80 (d, 2H, $J = 8.8$ Hz, phenyl), 7.41–7.43 (m, 6H, 5H- phenyl, 1H-C_6-tetahydropyimidine), 7.54 (d, 2H, J = 8.8 Hz, phenyl); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 29.5 (3, CH, Adamantane), 36.4 (3, CH_2, Adamantane), 40.0 (3, CH_2, Adamantane), 41.2 (Cq, Adamantane), 54.7 (CH_2-tetrahydropyrimidine), 61.9 (CH_2-tetrahydropyrimidine), 114.5 (Cq), 116.5 (Cq), 119.4 (2, CH-phenyl), 128.1 (2, CH-phenyl), 128.3 (2, CH-phenyl), 130.2 (CH-phenyl), 132.5 (2, CH-phenyl), 139.7 (Cq), 142.8 (Cq), 145.6 (C_6-tetrahydropyrimidine), 193.3 (CO); Mass [ESI] m/z (%): 477 $[MH]^+$. Anal. Calcd. For $C_{27}H_{29}BrN_2O$ (476): C, 67.92; H, 6.12; N, 5.87. Found: C, 68.06; H, 6.09; N, 5.90 %.

(3-((3s,5s,7s)-adamantan-1-yl)-1-benzyl-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl) methanone ***(5e)***



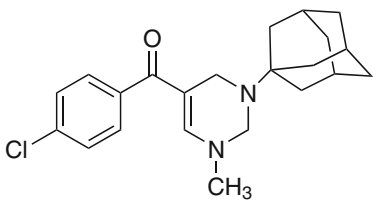
Yellow crystals from ethylacetate (90 %); m.p. 153 °C; IR (KBr) υ_{max} 2,904 (Adamantane), 2,853 (Adamantane), 1,562 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.59–1.62 (m, 6H, Adamantane), 1.66–1.73 (m, 6H, Adamantane), 2.06 (s, 3H, Adamantane), 3.78 (s, 2H, CH_2, benzyl), 3.99 (s, 2H, CH_2, tetrahydropyrimidine), 4.30 (s, 2H, CH_2, tetrahydropyrimidine), 7.17 (s, 1H, CH-C_6-tetrahydropyrimidine), 7.22 (d, 2H, $J = 8.8$ Hz, phenyl), 7.30–7.40 (m, 6H, phenyl), 7.48–7.50 (m, 2H, phenyl); ^{13}C NMR (400 MHz, $CDCl_3$) δ 29.5 (3, CH, Adamantane), 36.5 (3, CH_2, Adamantane), 39.3 (3, CH_2, Adamantane), 40.7 (Cq, Adamantane), 54.2 (CH_2-benzyl), 58.0 (CH_2-tetrahydropyrimidine), 61.0 (CH_2-tetrahydropyrimidine), 109.4 (CH-phenyl), 127.4 (2, CH-phenyl), 127.9 (2, CH-phenyl), 128.0 (2, CH-phenyl), 128.1 (2, CH-phenyl), 128.9 (CH-phenyl), 129.4 (Cq), 135.8 (Cq), 140.1 (Cq), 151.4 (C_6-tetrahydropyrimidine), 192.0 (CO); Mass [ESI] m/z (%): 413$[MH]^+$. Anal. Calcd. For $C_{28}H_{32}N_2O$ (412): C, 81.51; H, 7.82; N, 6.79. Found: C, 81.60; H, 7.76; N, 6.77 %.

(3-((3s,5s,7s)-adamantan-1-yl)-1-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl) methanone ***(5f)***



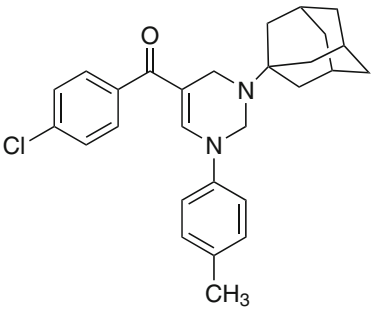
Yellow crystals from ethylacetate (92 %); m.p. 125–126 °C; IR (KBr) υ_{max} 2,899 (Adamantane), 2,839 (Adamantane), 1,626 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.62–1.71 (m, 6H, Adamantane), 1.83–1.84 (m, 6H, Adamantane), 2.13 (s, 3H, Adamantane), 2.92 (s, 3H, CH_3, tetahydropyrimidine), 3.76 (s, 2H, CH_2, tetrahydropyrimidine), 4.02 (s, 2H, CH_2, tetrahydropyrimidine), 6.96 (s, 1H, CH-C_6-tetrahydropyrimidine), 7.35–7.40 (m, 3H, phenyl), 7.47 (d, 2H, J = 8.8 Hz, phenyl); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 29.6 (3, CH, Adamantane), 36.6 (3, CH_2, Adamantane), 39.4 (3, CH_2, Adamantane), 40.3 (CH_3, tetahydropyrimidine), 40.5 (Cq, Adamantane), 54.3 (CH_2, tetrahydropyrimidine), 62.5 (CH_2-tetrahydropyrimidine), 108.9 (Cq), 127.9 (2, CH-phenyl), 128.0 (2, CH-phenyl), 129.3 (CH-phenyl), 140.6 (Cq), 151.7 (C_6-tetrahydropyrimidine), 191.7 (CO); Mass [ESI] m/z (%): 337 $[MH]^+$. Anal. Calcd. For $C_{22}H_{28}N_2O$ (336): C, 78.53; H, 8.39; N, 8.33. Found: C, 78.59; H, 8.35; N, 8.30 %.

(3-((3s,5s,7s)-adamantan-1-yl)-1-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)(4-chlorophenyl) methanone ***(5g)***



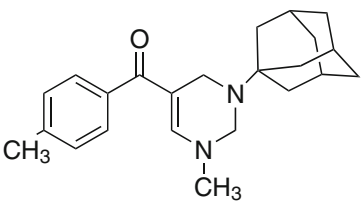
Yellow crystals from ethylacetate (94 %); m.p. 163 °C; IR (KBr) υ_{max} 2,914 (Adamantane), 2,862 (Adamantane), 1,633 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.61–1.71 (m, 6H, Adamantane), 1.80–1.83 (m, 6H, Adamantane), 2.13 (s, 3H, Adamantane), 2.94 (s, 3H, CH_3, tetahydropyrimidine), 3.73 (s, 2H, CH_2, tetrahydropyrimidine), 4.03 (s, 2H, CH_2, tetrahydropyrimidine), 6.93 (s, 1H, CH-C_6-tetrahydropyrimidine), 7.34 (d, 2H, J = 8.8 Hz, phenyl), 7.41 (d, 2H, J = 8.8 Hz, phenyl); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 29.5 (3, CH, Adamantane), 36.5 (3, CH_2, Adamantane), 39.4 (3, CH_2, Adamantane), 40.2 (CH_3, tetahydropyrimidine), 40.7 (Cq, Adamantane), 54.3 (CH_2, tetrahydropyrimidine), 62.5 (CH_2-tetrahydropyrimidine), 108.8 (Cq), 128.2 (2, CH-phenyl), 129.5 (2, CH-phenyl), 135.2 (Cq), 138.9 (Cq), 151.6 (C_6-tetrahydropyrimidine), 190.2 (CO); Mass [ESI] m/z (%): 371 $[MH]^+$. Anal. Calcd. For $C_{22}H_{27}ClN_2O$ (370): C, 71.24; H, 7.34; N, 7.55. Found: C, 71.37; H, 7.29; N, 7.58 %.

(3-((3s,5s,7s)-adamantan-1-yl)-1-(p-tolyl)-1,2,3,4-tetrahydropyrimidin-5-yl)(4-chlorophenyl) methanone ***(5h)***



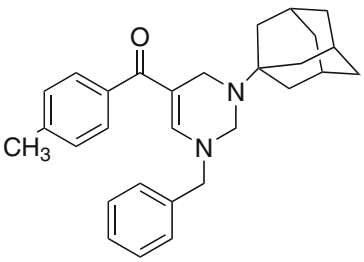
Yellow crystals from ethylacetate (90 %); m.p. 155–156 °C; IR (KBr) υ_{max} 2,904 (Adamantane), 2,832 (Adamantane), 1,572 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.58–1.71 (m, 6H, Adamantane), 1.79–1.80 (m, 6H, Adamantane), 2.09 (s, 3H, Adamantane), 2.31 (s, 3H, CH_3, phenyl), 3.91 (s, 2H, CH_2, tetrahydropyrimidine), 4.62 (s, 2H, CH_2, tetrahydropyrimidine), 6.84 (d, 2H, J = 8.8 Hz, phenyl), 7.12 (d, 2H, J = 8.8 Hz, phenyl), 7.35–7.39 (m, 3H, 2H- phenyl, 1H-C_6-tetahydopyrimidine), 7.48 (d, 2H, J = 8.8 Hz, phenyl); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 20.7 (CH_3-phenyl), 29.6 (3, CH, Adamantane), 36.5 (3, CH_2, Adamantane), 40.1 (3, CH_2, Adamantane), 41.2 (Cq, Adamantane), 54.7 (CH_2-tetrahydropyrimidine), 62.3 (CH_2-tetrahydropyrimidine), 113.0 (Cq), 118.5 (2, CH-phenyl), 128.3 (2, CH-phenyl), 129.7 (2, CH-phenyl), 130.2 (2, CH-phenyl), 134.0 (Cq), 135.9 (Cq), 138.4 (Cq), 141.5 (Cq), 146.8 (C_6-tetrahydropyrimidine), 191.5 (CO); Mass [ESI] m/z (%): 447 $[MH]^+$. Anal. Calcd. For $C_{28}H_{31}ClN_2O$ (446): C, 75.23; H, 6.99; N, 6.27. Found: C, 75.33; H, 6.95; N, 6.25 %.

(3-((3s,5s,7s)-adamantan-1-yl)-1-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)(p-tolyl) methanone ***(5i)***



Yellow crystals from ethylacetate (96 %); m.p. 115 °C; IR (KBr) υ_{max} 2,908 (Adamantane), 2,847 (Adamantane), 1,633 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.61–1.70 (m, 6H, Adamantane), 1.83–1.84 (m, 6H, Adamantane), 2.12 (s, 3H, Adamantane), 2.37 (s, 3H, CH_3, phenyl) 2.92 (s, 3H, CH_3, tetahydropyrimidine), 3.75 (s, 2H, CH_2, tetrahydropyrimidine), 4.01 (s, 2H, CH_2, tetrahydropyrimidine), 6.99 (s, 1H, CH-C_6-tetrahydropyrimidine), 7.17 (d, 2H, $J = 8.8$ Hz, phenyl), 7.38 (d, 2H, $J = 8.8$ Hz, phenyl); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 21.3 (CH_3, phenyl), 29.6 (3, CH, Adamantane), 36.6 (3, CH_2, Adamantane), 39.4 (3, CH_2, Adamantane), 40.3 (CH_3, tetahydropyrimidine), 40.5 (Cq, Adamantane), 54.3 (CH_2, tetrahydropyrimidine), 62.5 (CH_2-tetrahydropyrimidine), 109.0 (Cq), 128.2 (2, CH-phenyl), 128.6 (2, CH-phenyl), 137.8 (Cq), 139.4 (Cq), 151.4 (C_6-tetrahydropyrimidine), 191.7 (CO); Mass [ESI] m/z (%): 351 $[MH]^+$. Anal. Calcd. For $C_{23}H_{30}N_2O$ (350): C, 78.82; H, 8.63; N, 7.99. Found: C, 78.85; H, 8.57; N, 8.00 %.

(3-((3s,5s,7s)-adamantan-1-yl)-1-benzyl-1,2,3,4-tetrahydropyrimidin-5-yl)(p-tolyl)methanone ***(5j)***



White crystals from ethylacetate (91 %); m.p. 131–132 °C; IR (KBr) υ_{max} 2,904 (Adamantane), 2,832 (Adamantane), 1,561 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.58–1.62 (m, 6H, Adamantane), 1.65–1.73 (m, 6H, Adamantane), 2.05 (s, 3H, Adamantane), 2.37 (s, 2H, CH_3, phenyl), 3.77 (s, 2H, CH_2, benzyl), 3.98 (s, 2H, CH_2, tetrahydropyrimidine), 4.28 (s, 2H, CH_2, tetrahydropyrimidine), 7.18–7.19 (m, 5H, phenyl), 7.39–7.41 (m, 5H, 4H-phenyl, 1H-C_6-tetrahydropyrimidine); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 21.3 (CH_3, phenyl), 29.6 (3, CH, Adamantane), 36.5 (3, CH_2, Adamantane), 39.4 (3, CH_2, Adamantane), 40.8 (Cq, Adamantane), 54.2 (CH_2, benzyl), 58.0 (CH_2-tetrahydropyrimidine), 61.0 (CH_2-tetrahydropyrimidine), 109.4 (CH-phenyl), 127.4 (Cq), 128.0 (2, CH-phenyl), 128.3 (2, CH-phenyl), 128.6 (2, CH-phenyl), 128.8 (2, CH-phenyl), 136.0 (Cq), 138.7 (Cq), 139.5 (Cq), 151.4 (C_6-tetrahydropyrimidine), 192.0 (CO); Mass [ESI] m/z (%): 427 $[MH]^+$. Anal. Calcd. For $C_{29}H_{34}N_2O$ (426): C, 81.65; H, 8.03; N, 6.57. Found: C, 81.69; H, 7.98; N, 6.54 %.

Biology

Anti-inflammatory activity

Griess reagent system was purchased from Promega (USA). Wright stain, anhydrous potassium dihydrogen phosphate, potassium chloride, disodium hydrogen phosphate, sodium-EDTA and dimethyl sulfoxide were procured from HiMEDIA. Methanol used in our experiments was purchased from Merck, and Fruend's complete adjuvant (FCA) was procured from Genei.

Methodology

Anti-inflammatory activities of the test compounds were studied by measuring paw diameter, assay of NO concentration in blood and in paw exudates and by performing a differential WBC count in mice carrying FCA-induced paw edema and subsequently treating with test compounds.

Induction of paw edema The anti-inflammatory activities of the test compounds were determined by following the method of (Lai *et al*., 2009) with some modification. Swiss Albino mice aged between 8 and 10 weeks of either sex (three per group) maintained at controlled temperature with 12-h light/12-h dark conditions, provided with standard mice feed and common tap drinking water were used in all experiments. About 50 µl of the Fruend's complete adjuvant (FCA) was injected into the plantar side of left hind paws of the mice (Winter *et al.,* 1962). Paw diameter of the FCA-induced edema of mice was measured at 0-, 1, 3 and 24 h after administration of the FCA by using a caliper. Test compounds (dissolved in 10 % DMSO) at a dose of 50 mg/kg body weight were administered 1 h after FCA injection. The percentage increase/decrease in the paw edema is calculated by the formula $\frac{b-a}{a} \times 100$ where '*a*' is the paw diameter at 0 h, and '*b*' is the paw diameter at different time intervals. After 24 h, blood was collected by retro-orbital bleeding and used for estimating NO and preparing blood smear. Mice were then killed by cervical dislocation. The left hind paw tissue was excised, rinsed with ice-cold normal saline and homogenized in 1 ml of cold normal saline. The homogenate was then centrifuged at 12,000 rpm for 5 min, and the supernatant thus obtained was used for NO assay.

NO assay NO^{2-} was measured by using the Griess reaction. Three columns in the 96-well plates were designated for the nitrite standard reference curve. Six serial twofold dilution of 100 µM nitrite solution (50 µl/well) in

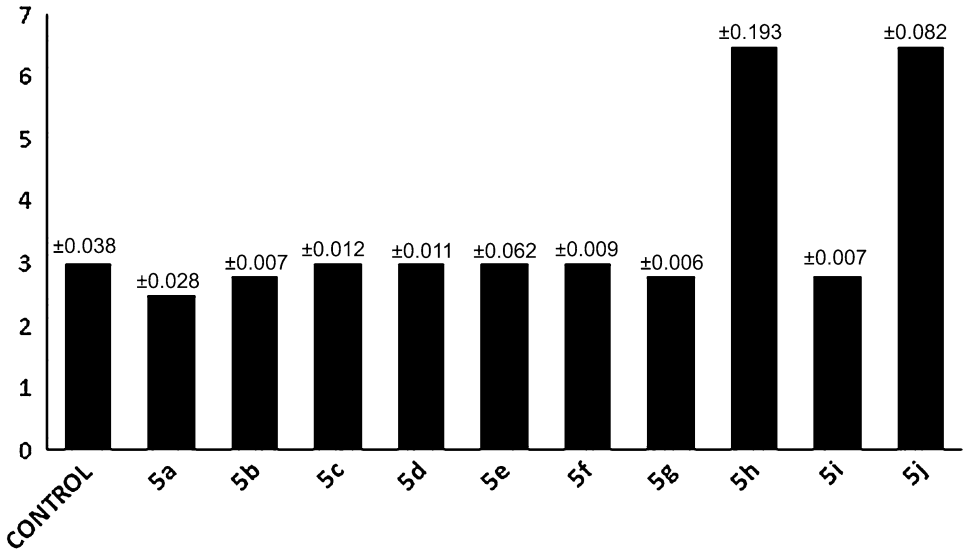


Fig. 2 Concentration of the NO (in μM) in the paw exudates of different treatment groups. Mice were injected with 50 μl of FCA in plantar side of hind paw followed by intraperitoneal administration of test compounds **5a**–**j** (50 mg/kg bw) 1 h later. Mice were killed after 24 h following FCA injection, and the hind paw was excised and homogenized in 1 ml normal saline. NO level was measured by using the Griess reaction with standard nitrite reference curve. Each group represents the mean ± S.E.M ($n = 3$). *$P < 0.05$ statistical significance compared with control (unpaired Student's t test)

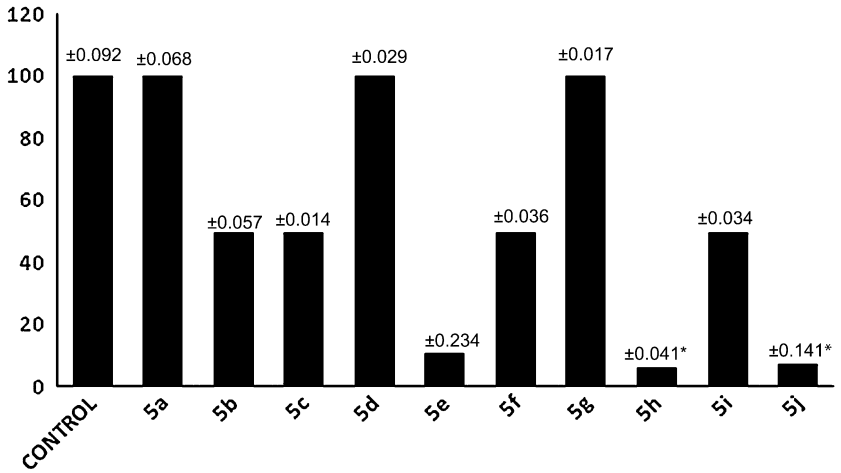


Fig. 3 Concentration of the NO in whole blood of the different treatment groups. Paw edema was induced by injecting FCA in all groups of mice. Mice were then given intraperitoneal injections of test compounds **5a**–**j** (50 mg/kg bw). Blood was collected by retro-orbital bleeding, and the whole blood was used to measure the level of NO by using the Griess reaction with standard nitrite reference curve. Each group represents the mean ± S.E.M ($n = 3$) *$P < 0.05$ statistical significance compared with control (unpaired Student's t test)

triplicate was performed to generate the nitrite standard reference curve. Fifty microliters of experimental sample was taken in triplicate in test wells. To all wells, 50 μl of sulfanilamide solution was added and incubated for 5–10 min at room temperature protected from light. Thereafter, 50 μl of the N-(1-napthyl)ethylenediamine dihydrochloride (NED) solution was dispensed to all wells. The plate was incubated at room temperature for 5–10 min, protected from light. A purple/magenta color begins to form immediately. The absorbance was measured within 30 min at 520 nm.

The concentration of NO in experimental samples was calculated from the standard curve obtained from above.

Differential WBC count The differential WBC count was performed according to the method described by (Houwen, 2000). Blood film was prepared on glass slides by wedge method and air-dried. The blood films were fixed for 30 s

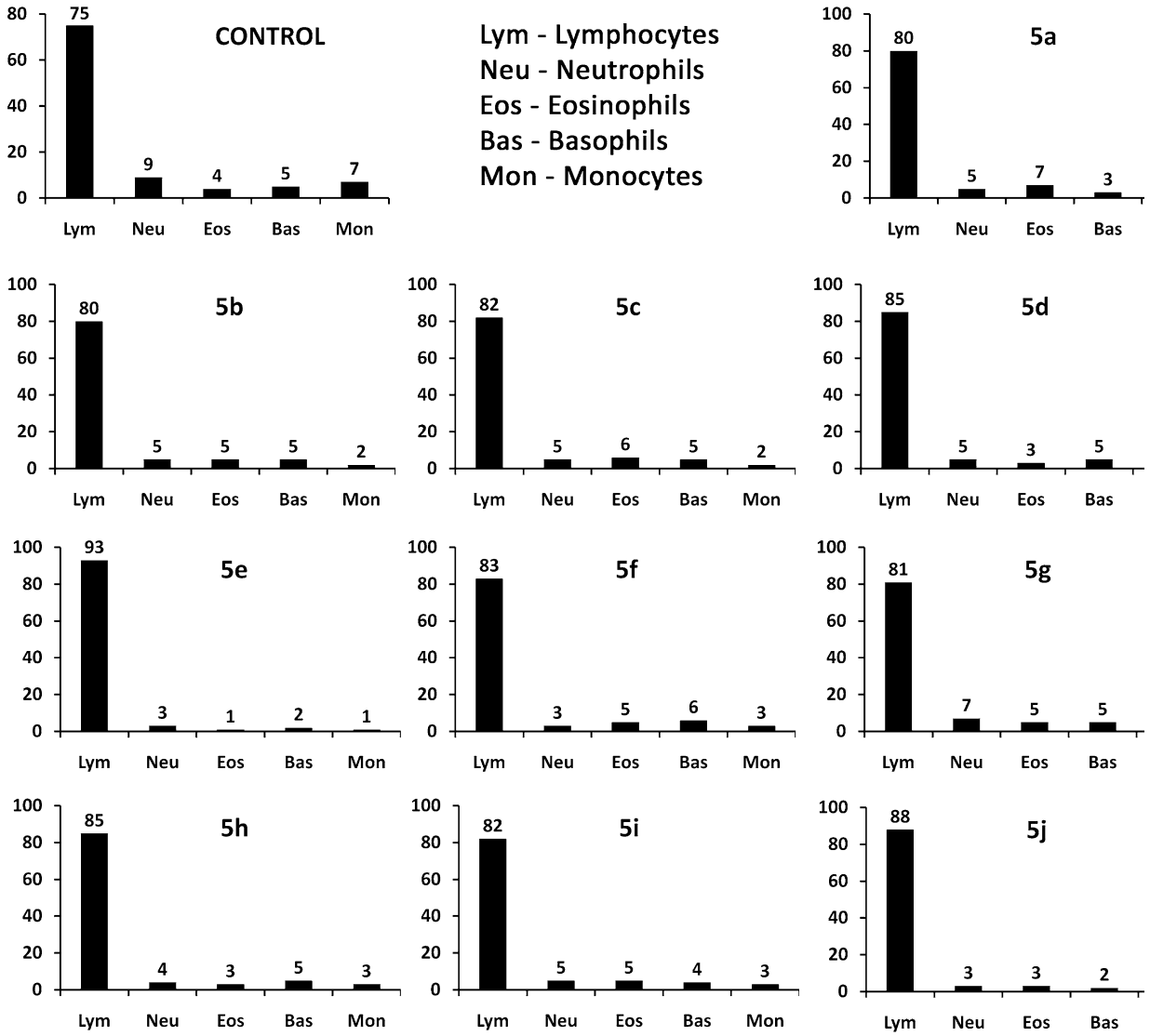


Fig. 4 Percentage counts of different types of leukocytes in mice treated with test compound in comparison with untreated control. Mice were killed 24 h after FCA injection. Blood smear was prepared, the slides were stained with Wright's stain, and cells were counted under a microscope

in absolute methanol. Slides were stained for 2 min with Wright's stain, and an aliquot of Sorensen's buffer was added and allowed to stand for 3 min. Slides were rinsed with distilled water and air-dried. The prepared slides were viewed under a microscope with 40X objective, and WBCs were counted.

Conclusion

The present paper describes an efficient strategy for the synthesis of hitherto unreported 1,2,3,4-tetrahydropyrimidines containing adamantane moiety from easily accessible starting materials in good to excellent yields. The structures of these molecular hybrids have been unambiguously established with help of IR, PMR, CMR, MS and X-ray crystallography. These products **5a–j** were tested for their anti-inflammatory activities, and overall data of all parameters reveal that compounds **5e**, **5i, 5j** and **5g** possess excellent anti-inflammatory properties. It is noteworthy that compounds **5e**, **5i, 5j** and **5g** have either bynzyl or methyl group in position 1 of the tetrahydropyrimidine ring, while the rest of the products bearing phenyl group in position 1 of the ring exhibited poor anti-inflammatory properties. Further studies on this class of molecules correlating substituents in tetrahydropyrimidine ring

and anti-inflammatory activities, with a view to improving the biological properties, are currently in progress.

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