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Synthesis and structure–activity relationship of cyclopentenone oximes as novel inhibitors of the production of tumor necrosis factor-α

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ABSTRACT

3-Alkyl-2-aryl-2-cyclopenten-1-one oxime derivatives (**1**) were studied as a novel class of inhibitors of tumor necrosis factor α (TNF-α) with regard to synthesis and in vitro SAR inhibition of TNF-α. The in vitro IC_{50} values of these compounds in rat and human peripheral blood mononuclear cells were at the sub-micromolar level.

Tumor necrosis factor-α (TNF-α), originally defined as an endotoxin-induced serum factor that induced necrosis of tumors,[1] is currently known as one of the most important cytokines in inflammation and immunology. Overexpression of TNF-α has been observed in a variety of immunological disorders including rheumatoid arthritis, ankylosing spondylitis, psoriasis, inflammatory bowel disease (IBD), sepsis, endotoxin shock, multiple sclerosis, insulin resistance, and chronic hepatitis.[2] Inhibition of TNF-α activity by TNF-α monoclonal antibodies or soluble receptors such as etanercept,[3] infliximab,[4] and adalimumab[5] has been effective in treating rheumatoid arthritis, ankylosing spondylitis, IBD, and psoriatic arthritis.

Despite their success in treating many disorders, their requirement of delivery via injections and associated high costs have limited their use to very few people. Small molecule inhibitors that inhibit either the action or production of TNF-α provide an alternative solution that carries low cost and allows oral or other non-injection modes of administration of the drug. Current research on small molecule TNF-α inhibitors (Fig. 1) has resulted in few successes due to weak clinical potencies, unwanted side effects, and narrow therapeutic margins. Therefore, an urgent need exists for new TNF-α inhibitors that can overcome these drawbacks.

We conducted an in vitro screen of in-house library compounds in our drug discovery program (COX-2) and selected cyclopentenone compounds that displayed TNF-α inhibiting activity at sub-micromolar concentrations. We identified a novel derivative, 2-cyclopenten-1-one oxime (**1**) (Fig. 2), with inhibitory activity against the production of TNF-α induced by LPS in rat peripheral blood mononuclear cells (PBMCs). Subsequently, we synthesized more 2-cyclopenten-1-one oxime compounds with different substituents and tested their TNF-α inhibitory activities.

Among alkyl–alkyl, aryl–aryl, alkyl–aryl, and aryl–alkyl combinations for R^1 and R^2, we found that alkyl–aryl substitutions resulted in the best inhibition of TNF-α in vitro. We further optimized these compounds by varying the length or size of acyclic or cyclic alkyl groups and phenyl ring substitutions (Fig. 3).

3-Alkyl-2-aryl-2-cyclopenten-1-one oxime derivatives (**1**) were prepared as outlined in Scheme 1. 3-Alkyl-2-cyclopenten-1-one (**2**) was synthesized from commercially available 2-cyclopenten-1-one or 3-alkoxy-2-cyclopenten-1-one. The addition of alkyl metal reagents (alkyllithium or alkylmagnesium chloride) to 2-cyclopenten-1-one and the oxidative rearrangement of the resulting allylic alcohol by PCC afforded **2**.[6] Alternatively, the addition of alkyl metal reagents to 3-alkoxy-2-cyclopenten-1-one followed by

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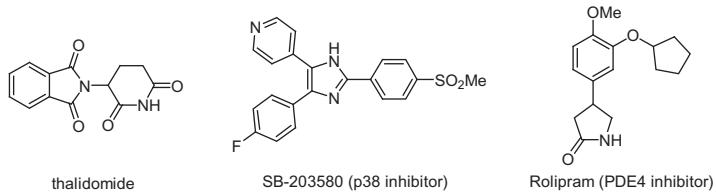


Figure 1. Examples of current small molecule TNF-α inhibitors.

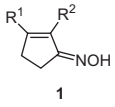


Figure 2. 2-Cyclopenten-1-one oxime (**1**), a novel class of TNF-α inhibitors.

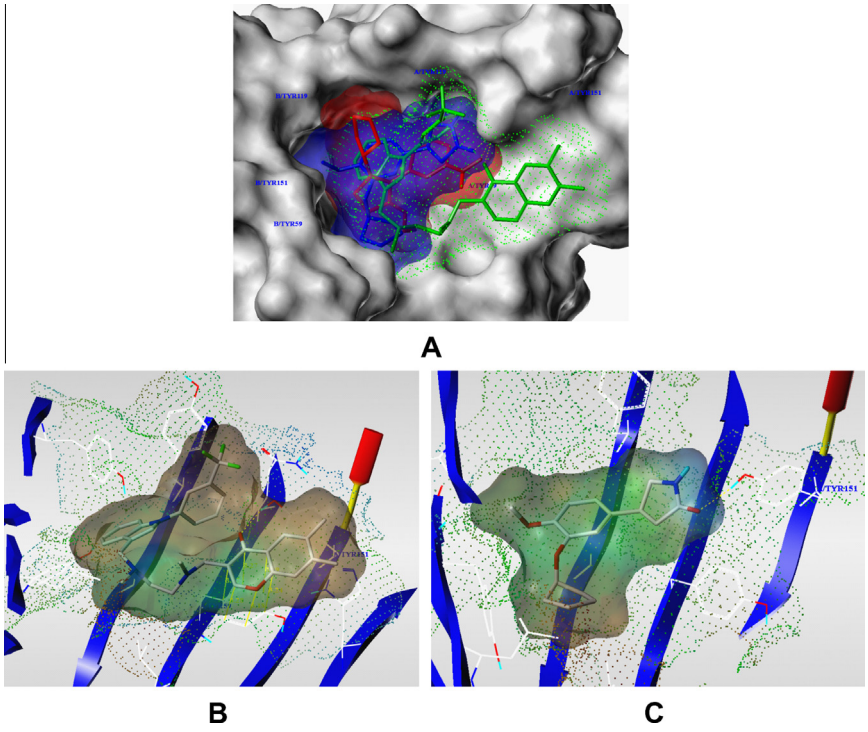
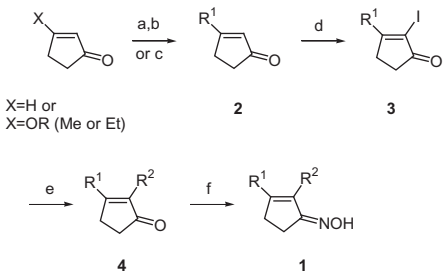


Figure 3. Binding mode between residues in the TNF-α binding pocket and result pose (A), rolipram (B), and **1ac** (C).

acidification also afforded **2**.[7] Iodination of **2** with iodine/pyridine/CCl_4[8] produced 2-iodo-2-cyclopenten-1-one (**3**). Suzuki coupling[9] of **3** with appropriate arylboronic acids afforded 3-alkyl-2-aryl-2-cyclopenten-1-one (**4**), which then condensed into the desired 3-alkyl-2-aryl-2-cyclopenten-1-one oximes (**1**)[10] by treatment with hydroxylamine hydrochloride in pyridine.



Scheme 1. Reagents and conditions: (a) R^1MgCl or R^1Li, THF, 1–2 h at 0 °C → room temp; (b) PCC/celite/CH_2Cl_2 for 2-cyclopenten-1-one; (c) R^1MgCl or R^1Li, THF, 1–2 h at 0 °C → room temp, and then aq HCl for 3-alkoxy-2-cyclopenten-1-one; (d) I_2, pyridine, CCl_4; (e) $R^2B(OH)_2$, $Pd(PPh_3)_4$, 2 N Na_2CO_3, toluene–EtOH, reflux; (f) $NH_2OH{\cdot}HCl$, pyridine.

When R^1 was a bulky group such as cyclopentyl or cyclohexyl, the yield of the first step, that is, reaction of the alkyl metal reagent with 2-cyclopenten-1-one or 3-alkoxy-2-cyclopenten-1-one was very low. This problem was overcome by using TMSCl-assisted 1,4-addition.[11] For example, 1,4-addition of the cyclopentyl cuprate, which was generated with CuBr·MeS and cyclopentylmagnesium chloride, to 3-methoxy-2-cyclopenten-1-one was facilitated by trimethylsilyl chloride (TMSCl) in the presence of hexamethyl phosphoramide (HMPA), and the resulting TMS enol ether was converted to **2a** by simple treatment with aqueous hydrochloric acid as shown in Scheme 2.

These oxime compounds (**1**) were tested for inhibition of the TNF-α production stimulated by LPS in rat and human PBMCs using the protocols reported in the literature.[12] Table 1 summarizes these results in rat PBMCs along with TNF-α/PDE4 inhibitor rolipram as a positive control.

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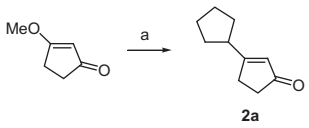

2a

Scheme 2. Reagents and conditions: (a) c-C_5H_9MgCl, CuBr·Me_2S, HMPA, TMSCl, THF, −78 °C → room temp, and then aq HCl.

Table 1
In vitro TNF-α inhibitory activities of cyclopentenone oxime derivatives (**1**) in rat peripheral blood mononuclear cells (rPBMCs)

Compds	R^1	R^2	TNF-α IC_{50}[a] (μM)
1aa	Cyclopentyl	4-Fluorophenyl	0.46
1ab	Cyclopentyl	3,4-Difluorophenyl	0.13
1ac	Cyclopentyl	3-Nitrophenyl	0.07
1ad	Cyclopentyl	3,4-Methylenedioxyphenyl	0.35
1ae	Cyclopentyl	3-Hydroxyphenyl	6.22
1af	Cyclopentyl	3-Trifluoromethyphenyl	3.07
1ba	Cyclohexyl	4-Fluorophenyl	1.24
1bb	Cyclohexyl	3,4-Difluorophenyl	0.34
1bc	Cyclohexyl	3-Chloro-4-fluorophenyl	0.42
1ca	*n*-Pentyl	4-Fluorophenyl	3.83
1cb	*n*-Pentyl	3,4-Difluorophenyl	3.65
1cc	*n*-Pentyl	3-Pyridinyl	14.12
1da	*n*-Butyl	4-Fluorophenyl	7.88
1db	*n*-Butyl	3,4-Methylenedioxyphenyl	2.52
1ea	*n*-Propyl	4-Fluorophenyl	2.66
1eb	*n*-Propyl	3,4-Difluorophenyl	0.72
1f	Ethyl	3,4-Difluorophenyl	4.56
1g	Methyl	3,4-Difluorophenyl	48.7
	Rolipram		0.27

[a] Values are the mean of at least two experiments.

Cyclopentyl as an R^1 alkyl group was the most potent inhibitor with an IC_{50} of 0.07 μM and 3-nitrophenyl as the R^2 group. The cyclohexyl group was less potent but was comparable to the *n*-propyl group, which showed the best effect among the linear alkyl chains. Inhibitory activity weakened as the chain length increased. Furthermore, inhibitory activity weakened with chain length shorter than that of *n*-propyl and with 3,4-difluorophenyl as the R^2 group, as seen in the IC_{50} values: *n*-pentyl < *n*-propyl > ethyl > > methyl (3.65, 0.72, 4.56, and 48.7 μM, respectively). Effects of various substituents on the phenyl ring of R^2 were also evaluated. With cyclopentyl as R^1, the strongest to weakest inhibition was as follows: 3-nitro > 3,4-difluoro > 4-fluoro ~ 3, 4-methylenedioxy > 3-CF_3 > 3-OH (IC_{50} 0.07, 0.13, 0.46, 0.35, 3.07, and 6.22 μM). The compounds **1ab** and **1ac** with 3,4-difluoro and 3-nitro substituents, respectively, showed the most potent activities with IC_{50} values of 0.13 and 0.07 μM, both of which are more potent than rolipram (IC_{50} 0.2 μM).

As shown in Table 2, these compounds were also highly potent against human TNF-α, with an IC_{50} range of 0.24–4.59 μM, which was comparable to or better than that for the positive control, rolipram (IC_{50} 0.27 μM).

Table 2
In vitro TNF-α inhibitory activities of cyclopentenone oxime derivatives (**1**) in human peripheral blood mononuclear cells (hPBMCs)

Compounds	TNF-α, IC_{50}[a] (μM)
1ab	0.26
1ac	0.24
1ca	4.59
1db	2.92
Rolipram	0.27

[a] Values are the mean of at least two experiments.

Table 3
Docking score and polar interaction of the rolipram and 1ac with TNF-α active site

Compounds	Sufex-dock total score[a]	Polar interaction
Rolipram	7.3232	1.2018
1ac	6.3302	2.5228

[a] Represents the binding affinity expressed in units of $-\log K_d$.

To understand the interaction between **1ac** and TNF-α dimer, we performed molecular docking simulations between **1ac** and the TNF-α active site (X-ray crystal structure with protein databank [PDB] code 2az5)[13] with the Surflex-Dock v.2.7 SYBYL-X 2.1.1 software program (Tripos, L.P., St. Louis, MO, USA).

Using SYBYL, we extracted the ligand from the protein complex in the PDB file, and hydrogen atoms were added to the enzyme; staged minimization was performed using the Tripos Force Field. The partial atomic charges were calculated using the Gasteiger–Hückel method. The docked conformations with the highest docking scores were selected for binding mode analysis.

From the results of the analysis of the protein and the ligands rolipram and **1ac**, we observed that the ligand orientation in the binding site favored hydrophobic interaction. A partial H-bond observed in the interaction of the ligands with the active site residue tyr151 indicates a possible explanation for the strong inhibition.

The Surflex-Dock scores (total scores) are shown in Table 3. The total score of **1ac** (6.3302) was slightly lower than that of rolipram (7.3232); however, the 1ac had a superior polar interaction value of 2.5228 (rolipram, 1.2018). As a result of polar interaction, **1ac** showed stronger inhibitory activity (IC_{50} = 0.07) than rolipram (IC_{50} = 0.27). Therefore, the in vitro values were in good agreement with the results of docking simulations.

In summary, 2-cyclopenten-1-one oximes, a novel class of TNF-α inhibitors, has been successfully developed. Some of these compounds have more potent in vitro inhibitory activities than rolipram. Further investigations to develop these compounds as anti-inflammatory drugs are under way.

References and notes

1. Carswell, E. A.; Old, L. J.; Kassel, R. L.; Green, S.; Fiore, N.; Williamson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 3666.
2. Reviews: (a) Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **1999**, *42*, 2295; (b) Taylor, P. C.; Williams, R. O.; Feldmann, M. *Curr. Opin. Biotechnol.* **2004**, *15*, 557.
3. Enbrel™ (etanercept) Prescribing Information. Immunex Corporation. July 2005.
4. Remicade™ (infliximab) Prescribing Information. Centocor Inc., September 2005.
5. Humira™ (adalimumab) Prescribing Information. Abbott Lab. October 2005.
6. Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **1989**, *30*, 1033.
7. Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625.
8. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovi, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.
9. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
10. *Selected compounds were prepared as follows. 3-Cyclopentyl-2-cyclopenten-1-one (**2a**):* To a stirred suspension of 800 mg of copper bromide dimethylsulfide in 100 ml of THF equilibrated to −78 °C, were added in series 24 ml of 2.0 M cyclopentylmagnesium chloride in diethyl ether and 8 ml of HMPA under inert atmosphere. To the mixture was added a solution of 5.4 ml of TMSCl and 4.3 g of 3-methoxy-2-cyclopenten-1-one in 20 ml of THF. The reaction mixture was slowly warmed to room temperature and stirred for 3 h, to which was added 50 ml of 10% aqueous HCl. The resulting reaction mixture was stirred for another 10 min and subjected to extraction with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and filtered. Then the filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel, hexane/ethyl acetate = 3:1) to yield 4.5 g (78%) of 3-cyclopentyl-2-cyclopenten-1-one as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.94 (m, 1H), 2.82 (m, 1H), 2.61 (m, 2H), 2.41 (m, 2H), 1.96 (m, 2H), 1.77-1.5 (m, 6H); MS (EI): 150 (M^+).
*3-Cyclopentyl-2-iodo-2-cyclopenten-1-one (**3a**).* To a stirred solution of 4.35 g of 3-cyclopentyl-2-cyclopenten-1-one in 50 ml of carbon tetrachloride, were added 15 g of iodine and 2.4 ml of pyridine, and the reaction mixture was

stirred overnight. The mixture was first diluted with diethyl ether, washed in series with saturated aqueous sodium thiosulfate, aqueous sodium bicarbonate, and brine. The organic layer was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel, hexane/ethyl acetate = 6:1) to yield 4 g (50%) of 3-cyclopentyl-2-iodo-2-cyclopenten-1-one as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.23 (m, 1H), 2.74 (m, 2H), 2.57 (m, 2H), 1.98 (m, 2H), 1.78 (m, 4H), 1.55 (m, 2H) MS (EI): 176 (M^+).

*3-Cyclopentyl-2-(4-fluorophenyl)-2-cyclopenten-1-one (**4aa**):* A mixture of 65 mg of 3-cyclopentyl-2-iodo-2-cyclopenten-1-one, 40 mg of 4-fluorophenylboronic acid, 10 mg of tetrakis(triphenylphosphine)palladium, 4 ml of toluene, 2 ml of ethanol and 1.5 ml of 2 N aqueous sodium carbonate was stirred at 80 °C overnight. The reaction mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel, hexane/ethyl acetate = 4:1) to yield 52 mg (91%) of 3-cyclopentyl-2-(4-fluorophenyl)-2-cyclopenten-1-one as a solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.22 (m, 2H), 7.09 (m, 2H), 3.15 (m, 1H), 2.68 (m, 2H), 2.55 (m, 2H), 1.81 (m, 4H), 1.64 (m, 4H) MS (EI): 244 (M^+).

*3-Cyclopentyl-2-(4-fluorophenyl)-2-cyclopenten-1-one oxime (**1aa**):* A mixture of 50 mg of 3-cyclopentyl-2-(4-fluorophenyl)-2-cyclopenten-1-one and 20 mg of hydroxylamine hydrochloride in 5 ml of pyridine was stirred at room temperature overnight. Pyridine was removed under reduced pressure, and the resulting residue was subjected to extraction with ethyl acetate and 10% aqueous HCl. The organic layer was washed with aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, and filtered. Then the filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel, hexane/ethyl acetate = 4:1) to yield 40 mg (75%) of 3-cyclopentyl-2-(4-fluorophenyl)-2-cyclopenten-1-one oxime as a off-white solid. mp = 204–205 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24–7.19 (m, 2H), 7.11–7.04 (m, 2H), 6.73 (br s, 1H), 2.89 (m, 1H), 2.80 (m, 2H), 2.61 (m, 2H), 1.70 (m, 4H), 1.55 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 169.5, 163.3, 161.3, 161.2, 134.2, 131.2, 131.1, 130.1, 115.5, 115.3, 40.0, 32.1, 28.2, 26.2, 24.6; HRMS calcd for $C_{16}H_{18}FNO$ 259.1372 (M^+), found 259.1394.

*3-Cyclopentyl-2-(3,4-difluorophenyl)-2-cyclopenten-1-one oxime (**1ab**).*
^{1}H NMR ($CDCl_3$) δ 7.36 (br s, 1H), 7.16 (dt, J = 10.5 and 8.4 Hz, 1H), 7.07 (ddd, J = 2.1, 7.8 and 11.1 Hz, 1H), 6.96 (m, 1H), 2.88 (m, 1H), 2.77 (m, 2H), 2.61 (m, 2H), 1.70 (m, 4H), 1.55 (m, 4H); MS (EI): 277 (M^+).

*3-Cyclopentyl-2-(3-nitrophenyl)-2-cyclopenten-1-one oxime (**1ac**)*
^{1}H NMR ($CDCl_3$) δ 8.19–8.14 (m, 2H), 7.62–7.53 (m, 2H), 6.78 (s, 1H), 2.84 (m, 3H), 2.66 (m, 2H), 1.74 (m, 4H), 1.56 (m, 4H); MS (EI): 286 (M^+).

*3-Cyclopentyl-2-(3,4-methylenedioxyphenyl)-2-cyclopenten-1-one oxime (**1ad**).*
^{1}H NMR ($CDCl_3$) δ 6.83 (d, J = 7.8 Hz, 1H), 6.43–6.68 (m, 2H), 5.96 (s, 2H), 2.92 (m, 1H), 2.60 (m, 2H), 2.77 (m, 2H), 1.70 (m, 4H), 1.54 (m, 4H); MS (EI): 285 (M^+).

*3-Cyclopentyl-2-(3-hydroxyphenyl)-2-cyclopenten-1-one oxime (**1ae**).*
^{1}H NMR ($CDCl_3$) δ 7.26–7.21 (m, 2H), 6.79–6.70 (m, 3H), 2.93 (m, 1H), 2.80 (m, 2H), 2.61 (m, 2H), 1.70 (m, 4H), 1.54 (m, 4H); MS (EI): 257 (M^+).

*3-Cyclopentyl-2-(4-trifluoromethylphenyl)-2-cyclopenten-1-one oxime (**1af**).*
^{1}H NMR ($CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.26 (m, 1H), 2.77 (m, 2H), 2.59 (m, 2H), 2.47 (m, 1H), 1.75–1.16 (m, 10H); MS (EI): 309 (M^+).

*3-Cyclohexyl-2-(4-fluorophenyl)-2-cyclopenten-1-one oxime (**1ba**).*
^{1}H NMR ($CDCl_3$) δ 7.20 (m, 2H), 7.08 (m, 2H), 6.78 (br s, 1H), 2.77 (m, 2H), 2.59 (m, 2H), 2.47 (m, 1H), 1.75–1.16 (m, 10H); MS (EI): 273 (M^+).

*3-Cyclohexyl-2-(3,4-difluorophenyl)-2-cyclopenten-1-one oxime (**1bb**).*
^{1}H NMR ($CDCl_3$) δ 7.19 (dt, J = 10.2 and 8.4 Hz, 1H), 7.06 (ddd, J = 2.1, 7.5 and 11.1 Hz, 1H), 6.97–6.91 (m, 2H), 2.77 (m, 2H), 2.58 (m, 2H), 2.46 (m, 1H), 1.76–1.16 (m, 10H); MS (EI): 291 (M^+).

*3-Cyclohexyl-2-(3-chloro-4-fluorophenyl)-2-cyclopenten-1-one oxime (**1bc**).*
^{1}H NMR ($CDCl_3$) δ 7.28 (dd, J = 2.1 and 6.9 Hz, 1H), 7.16 (t, J = 8.7 Hz, 1H), 7.08 (ddd, J = 2.1, 4.8 and 8.7 Hz, 1H), 6.93 (br s, 1H), 2.77 (m, 2H), 2.59 (m, 2H), 2.45 (m, 1H), 1.75–1.16 (m, 10H); MS (EI): 307 (M^+).

*3-Pentyl-2-(4-fluorophenyl)-2-cyclopenten-1-one oxime (**1ca**).*
7.41–7.36 (m, 2H), 7.32–7.22 (m, 3H), 6.85 (br s, 1H), 2.81 (m, 2H), 2.60 (m, 2H), 2.28 (t, J = 7.8 Hz, 2H), 1.47 (m, 2H), 1.24 (m, 4H), 0.85 (t, J = 6.8 Hz, 3H); MS (EI): 261 (M^+).

*3-Pentyl-2-(3,5-difluorophenyl)-2-cyclopenten-1-one oxime (**1cb**).*
^{1}H NMR ($CDCl_3$) δ 7.71 (br s, 1H), 6.77 (m, 3H), 2.79 (m, 2H), 2.60 (m, 2H), 2.28 (t, J = 7.8 Hz, 2H), 1.47 (m, 2H), 1.23 (m, 4H), 0.86 (t, J = 6.6 Hz, 3H); MS (EI): 279 (M^+).

*3-Pentyl-2-(3-pyridinyl)-2-cyclopenten-1-one oxime (**1cc**).*
^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1H), 8.68–8.51 (m, 2H), 7.61 (m, 1H), 7.30 (m, 1H), 2.83 (m, 2H), 2.63 (m, 2H), 2.30 (t, J = 7.8 Hz, 2H), 1.49 (m, 2H), 1.25 (m, 4H), 0.85 (t, J = 6.6 Hz, 3H); MS (EI): 244 (M^+).

*3-Butyl-2-(4-fluorophenyl)-2-cyclopenten-1-one oxime (**1da**).*
^{1}H NMR ($CDCl_3$) δ 7.20 (m, 2H), 7.07 (m, 2H), 2.79 (m, 2H), 2.59 (m, 2H), 2.26 (t, J = 7.8 Hz, 2H), 1.45 (m, 2H), 1.26 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H); MS (EI): 247 (M^+).

*3-Butyl-2-(3,4-fluorophenyl)-2-cyclopenten-1-one oxime (**1db**).*
^{1}H NMR ($CDCl_3$) δ 6.95 (br s, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.43 – 6.68 (m, 2H), 5.96 (s, 2H), 2.78 (m, 2H), 2.60 (m, 2H), 2.27 (t, J = 7.7 Hz, 2H), 1.45 (m, 2H), 1.27 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); MS (EI): 265 (M^+).

*2-(4-Fluorophenyl)-3-propyl-2-cyclopenten-1-one oxime (**1ea**).*
^{1}H NMR ($CDCl_3$) δ 7.24–7.17 (m, 3H), 7.10–7.03 (m, 2H), 2.79 (m, 2H), 2.59 (m, 2H), 2.25 (t, J = 7.7 Hz, 2H), 1.50 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); MS (EI): 233 (M^+).

*2-(3,4-Difluorophenyl)-3-propyl-2-cyclopenten-1-one oxime (**1eb**)*
^{1}H NMR ($CDCl_3$) δ 7.83 (br s, 1H), 7.17 (dt, J = 10.5 and 8.4 Hz, 1H), 7.07 (ddd, J = 2.1, 7.8 and 11.1 Hz, 1H), 6.96 (m, 1H), 2.78 (m, 2H), 2.58 (m, 2H), 2.25 (t, J = 7.8 Hz, 2H), 1.50 (m, 2H), 0.87 (t, J = 7.5 Hz, 3H); MS (EI): 251 (M^+).

*3-Ethyl-2-(3.4-difluorophenyl)-2-cyclopenten-1-one oxime (**1f**).*
^{1}H NMR ($CDCl_3$) δ 7.24 (m, 2H), 7.08 (m, 1H), 6.89 (s, 1H), 2.81 (m, 2H), 2.61 (m, 2H), 2.30 (q, J = 7.8 Hz, 2H), 1.08 (t, J = 7.7 Hz, 3H); MS (EI): 237 (M^+).

*2-(3,4-Difluorophenyl)-3-methyl-2-cyclopenten-1-one oxime (**1g**).*
^{1}H NMR ($CDCl_3$) δ 7.19–7.10 (m, 2H), 7.04 (m, 1H), 6.75 (s, 1H), 2.81 (m, 2H), 2.60 (m, 2H), 1.94 (m, 3H); MS (EI): 223 (M^+).

11. Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.
12. Gabriel, P.; Cakman, I.; Rink, L. *Exp. Gerontol.* **2002**, *37*, 235.
13. Badger, A. M.; Bradbeer, J. N.; Votta, B.; Lee, J. C.; Adams, J. L.; Griswold, D. E. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 1453.