



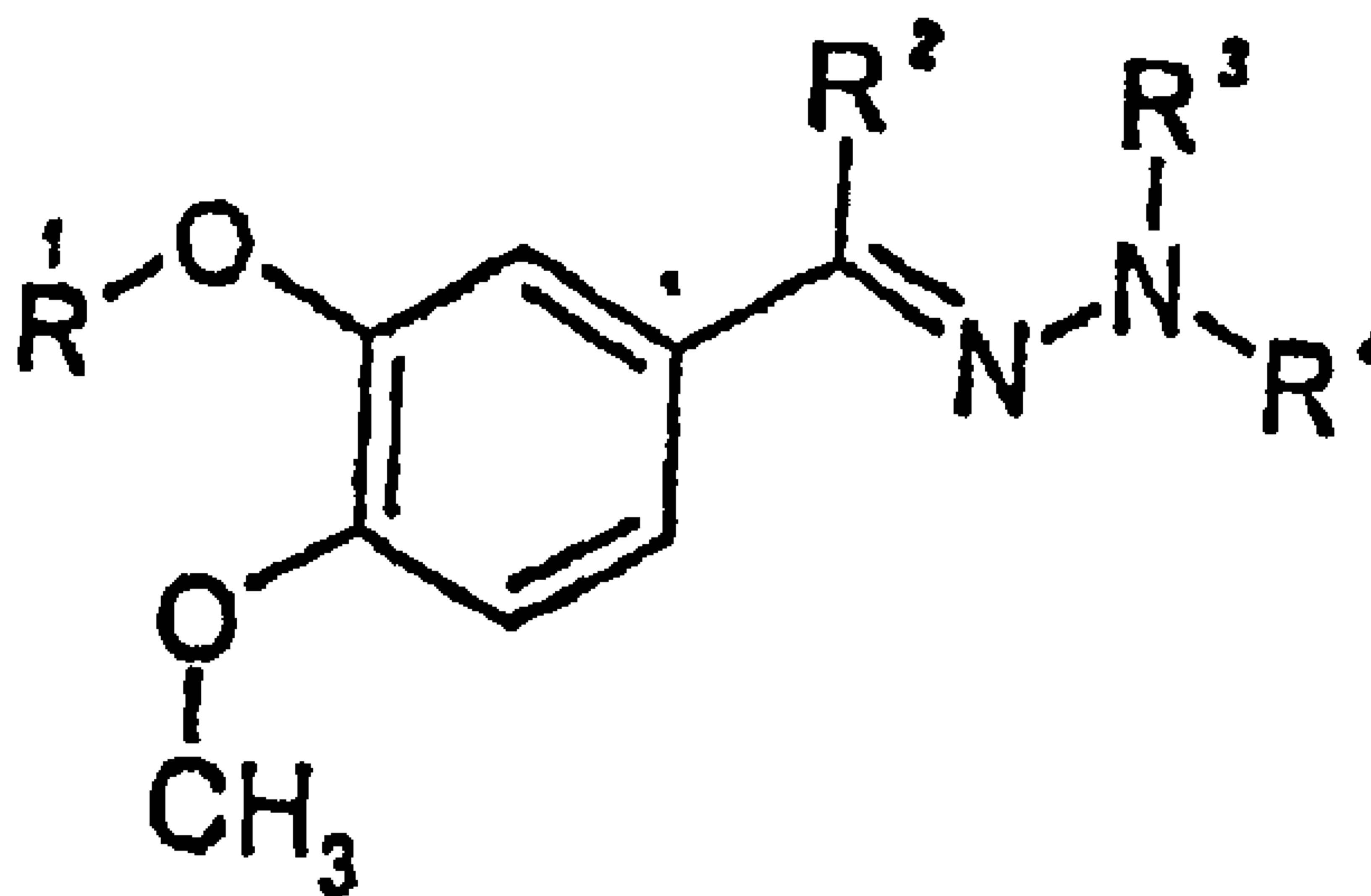
(86) Date de dépôt PCT/PCT Filing Date: 1999/05/28
(87) Date publication PCT/PCT Publication Date: 2000/12/07
(45) Date de délivrance/Issue Date: 2007/07/17
(85) Entrée phase nationale/National Entry: 2001/11/13
(86) N° demande PCT/PCT Application No.: KR 1999/000264
(87) N° publication PCT/PCT Publication No.: 2000/073280

(51) Cl.Int./Int.Cl. *C07C 251/86* (2006.01),
A61K 31/15 (2006.01), *A61K 31/16* (2006.01),
A61K 31/197 (2006.01), *A61K 31/395* (2006.01),
C07C 281/14 (2006.01), *C07C 281/18* (2006.01),
C07C 337/08 (2006.01), *C07D 211/98* (2006.01),
C07D 213/77 (2006.01), *C07D 213/86* (2006.01),
C07D 239/42 (2006.01), *C07D 295/30* (2006.01)

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(54) Titre : DERIVES DE CATHECOL-HYDRAZONE, PROCEDE DE PREPARATION CORRESPONDANT, ET
COMPOSITION PHARMACEUTIQUE RENFERMANT LESDITS DERIVES
(54) Title: CATHECOL HYDRAZONE DERIVATIVES, PROCESS FOR PREPARING THE SAME AND
PHARMACEUTICAL COMPOSITION CONTAINING THE SAME



(57) Abrégé/Abstract:

The present invention provides novel catechol hydrazone derivatives which inhibit the enzymatic activity of phosphodiesterase IV. The invention thus relates to catechol hydrazone derivatives of formula (I) or pharmaceutically acceptable salts thereof, wherein R¹ is C₁₋₇ alkyl or C₃₋₇ cycloalkyl; R² is hydrogen, hydroxyl, C₁₋₅ alkyl or -CH₂-CH₂C(=O)NH₂; R³ and R⁴ are independently hydrogen, C₁₋₇ alkyl, -C(=X)-R⁵, or 2-, 3- or 4-pyridyl, pyrimidyl or phenyl substituted with one or two selected from a group consisting of halogen, C₁₋₆ alkoxy, nitro, trifluoromethyl, C₁₋₆ alkyl and carboxyl, or R³ and R⁴ are directly bonded by C₃₋₄ containing oxygen, sulfur or nitrogen to form a heterocyclic ring, X is oxygen, sulfur or NH and R⁵ is C₁₋₇ alkyl, -NHR⁶, CONH₂ or 2-, 3- or 4-pyridyl, pyrimidyl or phenyl substituted with one selected from a group consisting of halogen, C₁₋₆ alkoxy, nitrile, trifluoromethyl, C₁₋₆ alkyl and carboxyl, and R⁶ is hydrogen, hydroxyl, NH₂, C₁₋₅ alkoxy, C₁₋₅ alkyl, pyridyl or phenyl.



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ABSTRACT

The present invention provides novel catechol hydrazone derivatives which inhibit the enzymatic activity of phosphodiesterase IV. The invention thus relates to catechol hydrazone derivatives of formula (I) or pharmaceutically acceptable salts thereof, wherein R^1 is C_{1-7} alkyl or C_{3-7} cycloalkyl; R^2 is hydrogen, hydroxyl, C_{1-5} alkyl or $-CH_2-CH_2C(=O)NH_2$; R^3 and R^4 are independently hydrogen, C_{1-7} alkyl, $-C(=X)-R^5$, or 2-, 3- or 4-pyridyl, pyrimidyl or phenyl substituted with one or two selected from a group consisting of halogen, C_{1-6} alkoxy, nitro, trifluoromethyl, C_{1-6} alkyl and carboxyl, or R^3 and R^4 are directly bonded by C_{3-4} containing oxygen, sulfur or nitrogen to form a heterocyclic ring, X is oxygen, sulfur or NH and R^5 is C_{1-7} alkyl, $-NHR^6$, $CONH_2$ or 2-, 3- or 4-pyridyl, pyrimidyl or phenyl substituted with one selected from a group consisting of halogen, C_{1-6} alkoxy, nitrile, trifluoromethyl, C_{1-6} alkyl and carboxyl, and R^6 is hydrogen, hydroxyl, NH_2 , C_{1-5} alkoxy, C_{1-5} alkyl, pyridyl or phenyl.

**CATHECOL HYDRAZONE DERIVATIVES,
PROCESS FOR PREPARING THE SAME AND
PHARMACEUTICAL COMPOSITION CONTAINING THE SAME**

5

FIELD OF THE INVENTION

The present invention relates to novel catechol hydrazone derivatives which inhibit the enzymatic activity of phosphodiesterase IV or tumor necrosis factor. These compounds may be useful in prevention or treatment of bronchial asthma, arthritis, bronchitis, chronic atretic airway, psoriasis, allergic rhinitis, dermatitis, AIDS, Crohn's disease, septicemia, septic shock, other inflammatory diseases such as cachexia, TNF related diseases, etc. Also, the present invention relates to a method for producing said compounds and a pharmaceutical composition containing said compound.

15

BACKGROUND OF THE INVENTION

Phosphodiesterase IV is an enzyme that specifically hydrolyzes cAMP (cyclic adenosine 3',5'-monophosphate) into inactive adenosine 3',5'-monophosphate. The cAMP has been shown to be a second messenger mediating the cellular responses to external stimuli and to act as relaxing or contradicting bronchial muscles.

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The inhibition of phosphodiesterase IV leads to the prevention of broncospasm by maintaining the concentration of cAMP and also induces an anti-inflammation. Therefore, compounds that inhibit phosphodiesterase IV should be effective in treating asthma and the like diseases.

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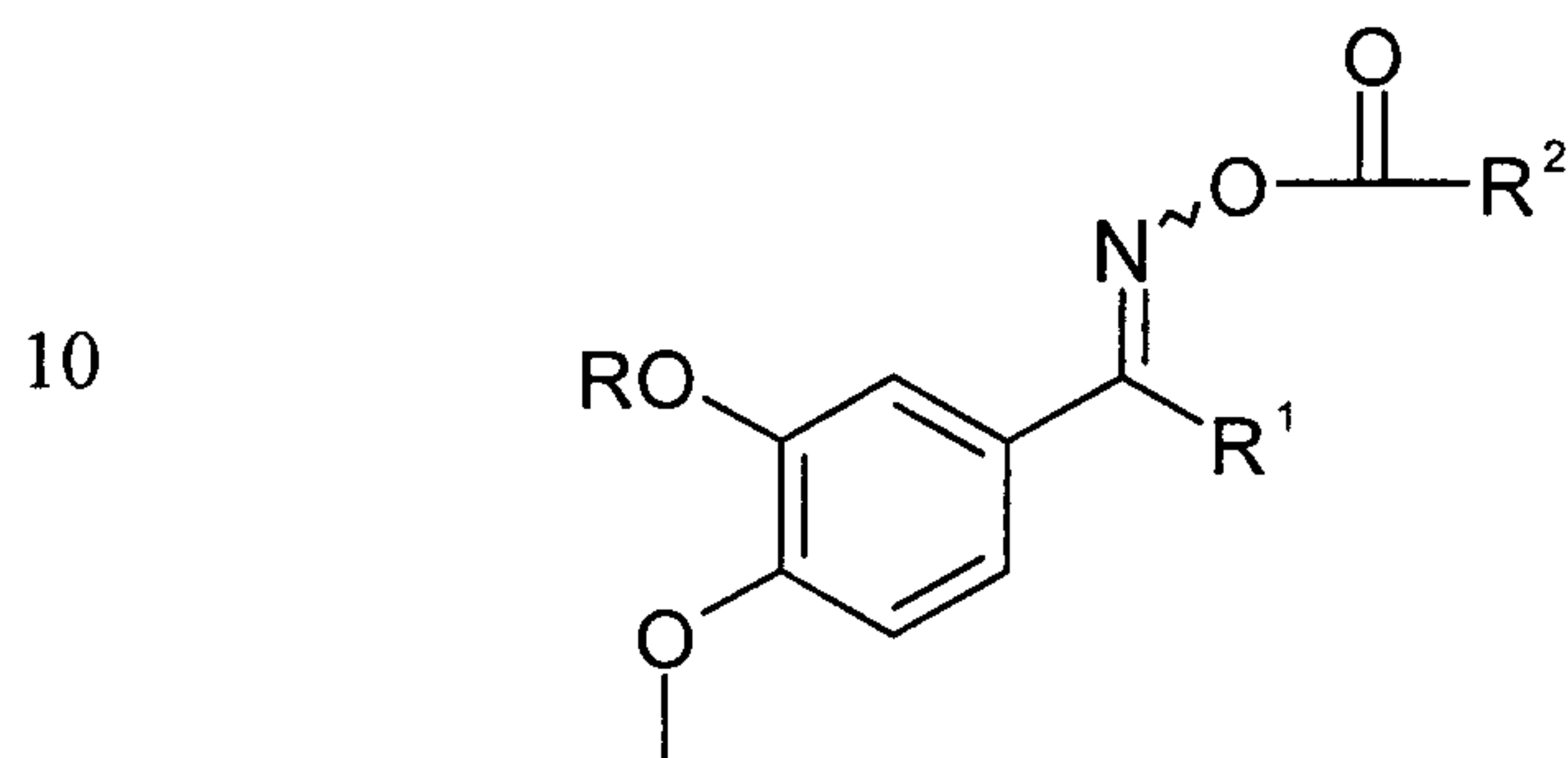
It is known that tumor necrosis factor (TNF) is implicated in infectious disease such as cachexia and autoimmune disease. Also, TNF appears to act as a primary mediator for inflammatory reaction such as septicemia and septic shock.

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Therefore, it is expected that compounds with the inhibitory activity against

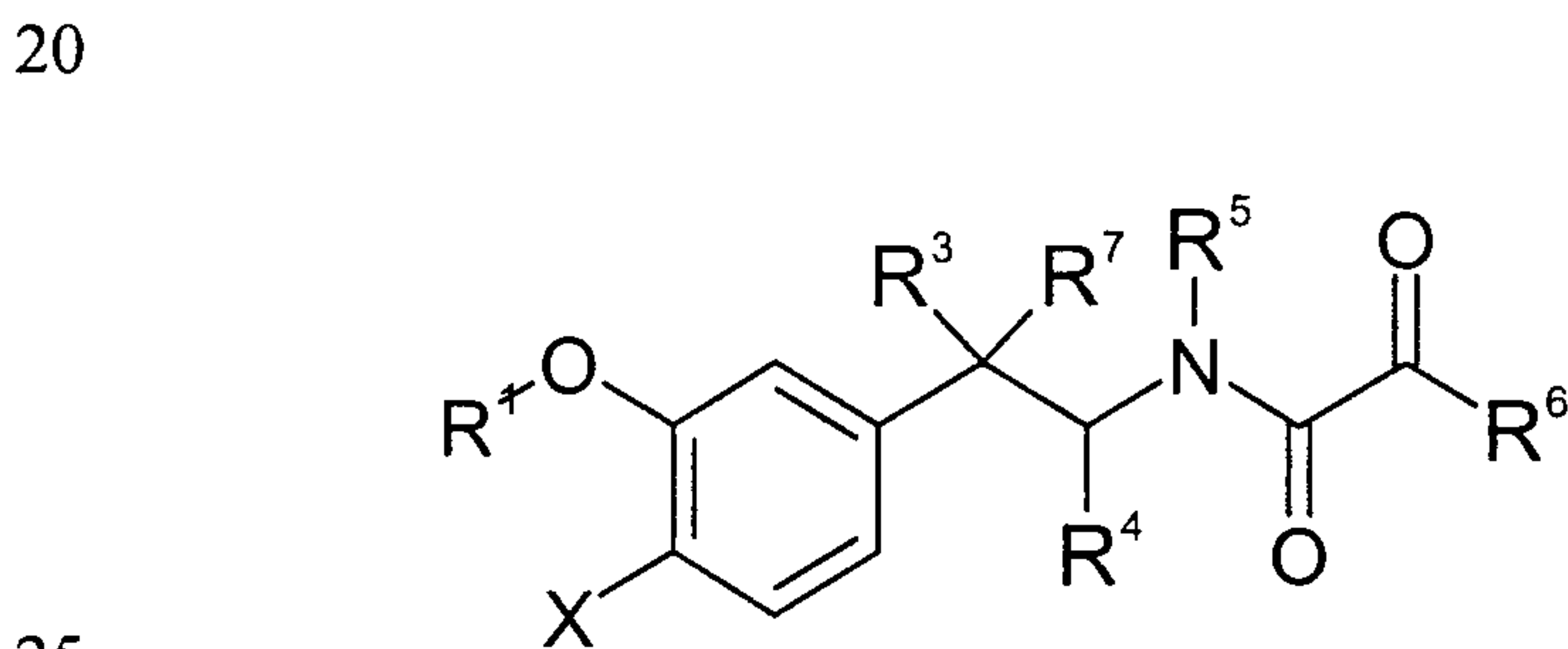
phosphodiesterase IV or TNF will be pharmaceutically valuable and there is always a need to develop new compounds which inhibit phosphodiesterase IV and TNF.

Many compounds have been suggested as inhibitors of phosphodiesterase IV and TNF. For example, EP 470,805 of American Home Product describes oximcarbamate and oximcarbonate of formula:



15 wherein R is C₃₋₇ alkyl or C₃₋₇ cycloalkyl, R¹ is halogen or lower alkyl, and R² is amino, lower alkylamino, arylamino, lower alkoxy or aryloxy.

US Patent No. 5,393,788 of SmithKline Beecham Corporation describes phenylalkyl oxamide compound of formula:

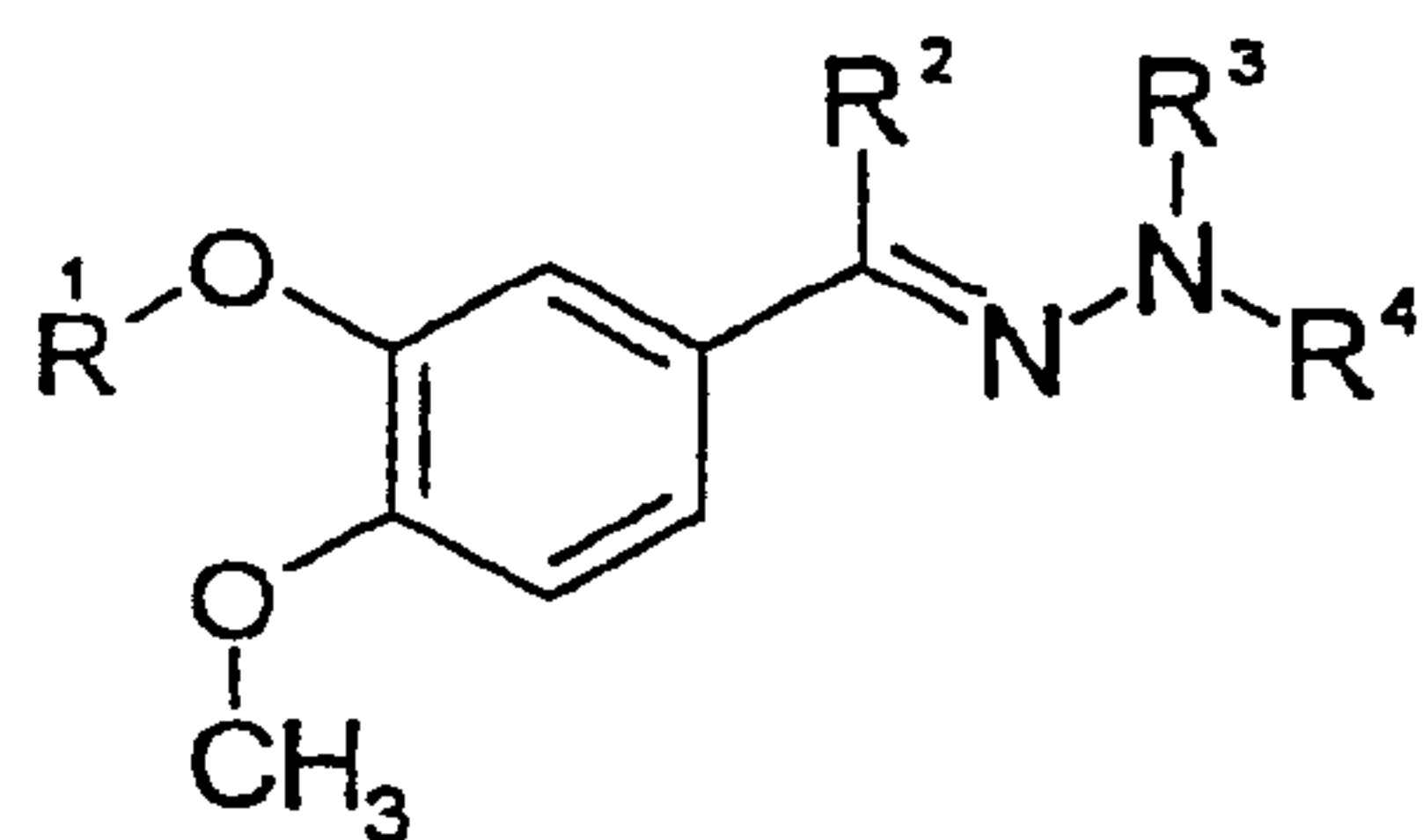


wherein R¹ is C₄₋₆ cycloalkyl, X is YR² halogen in which Y is oxygen or sulfur, or lower alkyl, R³ and R⁵ are independently OR⁷, R⁴ is hydrogen or C₁₋₂ alkyl, R⁶ is OR₇ or NR₇OR₇, and R⁷ is hydrogen or C₁₋₃ alkyl.

30

SUMMARY OF THE INVENTION

The present invention provides novel catechol hydrazone derivatives of formula I:



or pharmaceutically acceptable salts thereof, wherein

R^1 is C_{3-7} cycloalkyl;

R^2 is hydrogen, hydroxy, C_{1-3} alkyl or $-CH_2CH_2C(=O)NH_2$;

R^3 and R^4 are independently hydrogen, C_{1-7} alkyl, $-C(=X)-R^5$, or 2-, 3- or 4-pyridyl, pyrimidyl or phenyl substituted with one or two selected from a group consisting of halogen, C_{1-6} alkoxy, nitro, trifluoromethyl, C_{1-6} alkyl and carboxyl, or R^3 and R^4 are directly bonded by C_{3-4} containing oxygen, sulfur or nitrogen to form a heterocyclic ring, X is oxygen, sulfur or NH, and R^5 is C_{1-7} alkyl, $-NHR^6$, $CONH_2$ or 2-, 3- or 4-pyridyl, pyrimidyl or phenyl substituted with one radical selected from a group consisting of halogen, C_{1-6} alkoxy, nitrile, trifluoromethyl, C_{1-6} alkyl and carboxyl, and R^6 is hydrogen, hydroxy, NH_2 , C_{1-5} alkoxy, C_{1-5} alkyl, pyridyl or phenyl.

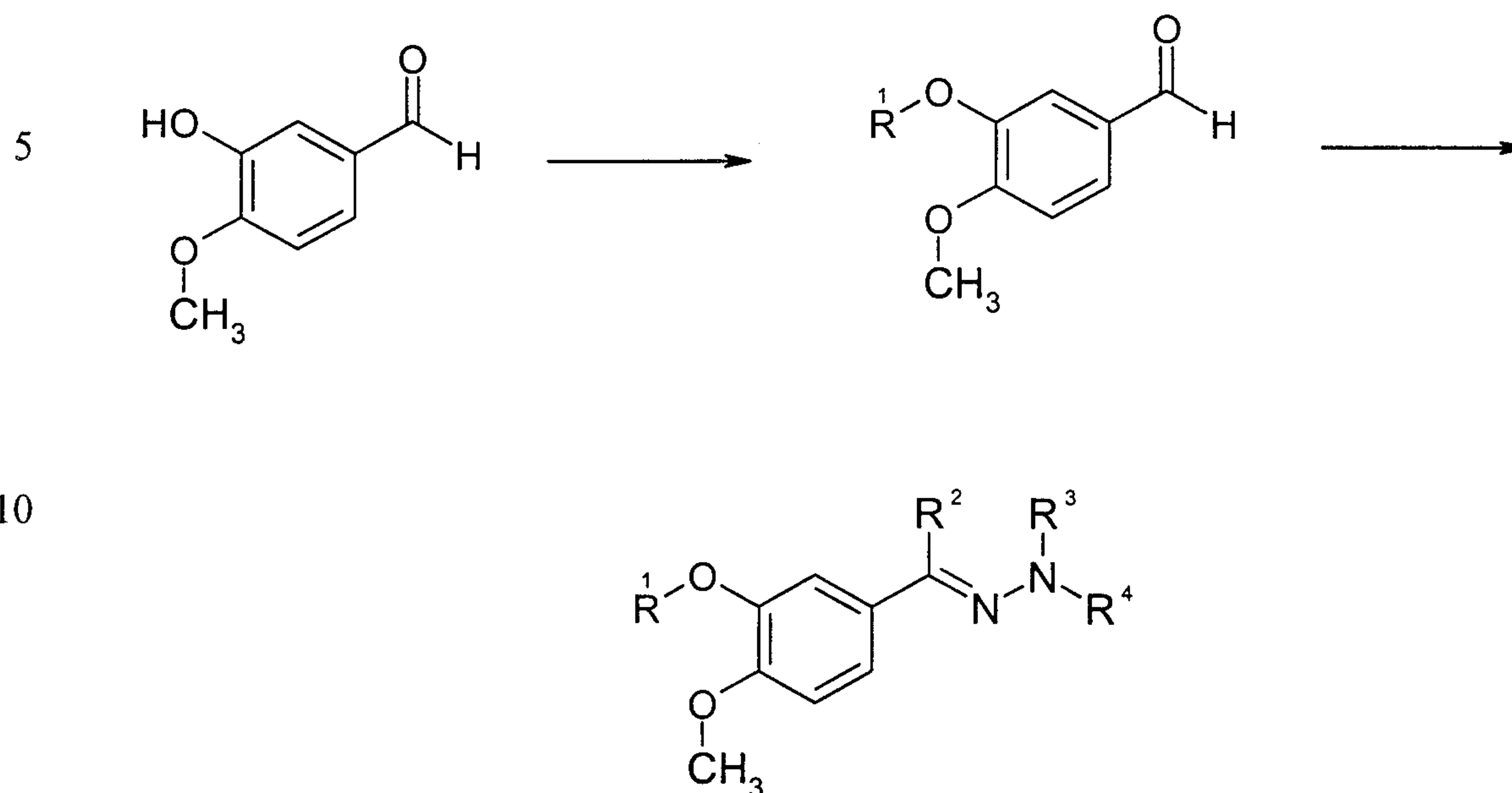
DETAILED DESCRIPTION OF THE INVENTION

The compound of formula I can be present as optical isomers or stereoisomers. Thus, the present invention includes such isomers and mixtures thereof.

The present invention provides a pharmaceutical composition for inhibiting phosphodiesterase IV or TNF which comprises a compound of formula I and a pharmaceutically acceptable carrier.

The compound of formula I can be prepared by the following reaction scheme

I:

Reaction Scheme I

wherein R^1 , R^2 , R^3 and R^4 are the same as defined above.

Some derivatives were synthesized by a known method (J. Med. Chem., 1994, 37, 1696). Hydrazone compounds were synthesized in yield of 60% to 90% in alcohol solvent using acid catalyst (Tetrahedron Lett. 1994, 35, 3711)

The invention will now be described with reference to the following illustrative Examples.

25 EXAMPLES

REFERENCE EXAMPLE 1

3-cyclopentyloxy-4-methoxybenzaldehyde

30 A solution of 100 g (0.66 mol) of isovanillin, 136.2 g (0.99 mol) of anhydrous potassium carbonate, and 3 g of potassium iodide in 650 ml of anhydrous dimethylformamide was stirred at 65°C. 127.3 g (0.85 mol) of cyclopentyl bromide was

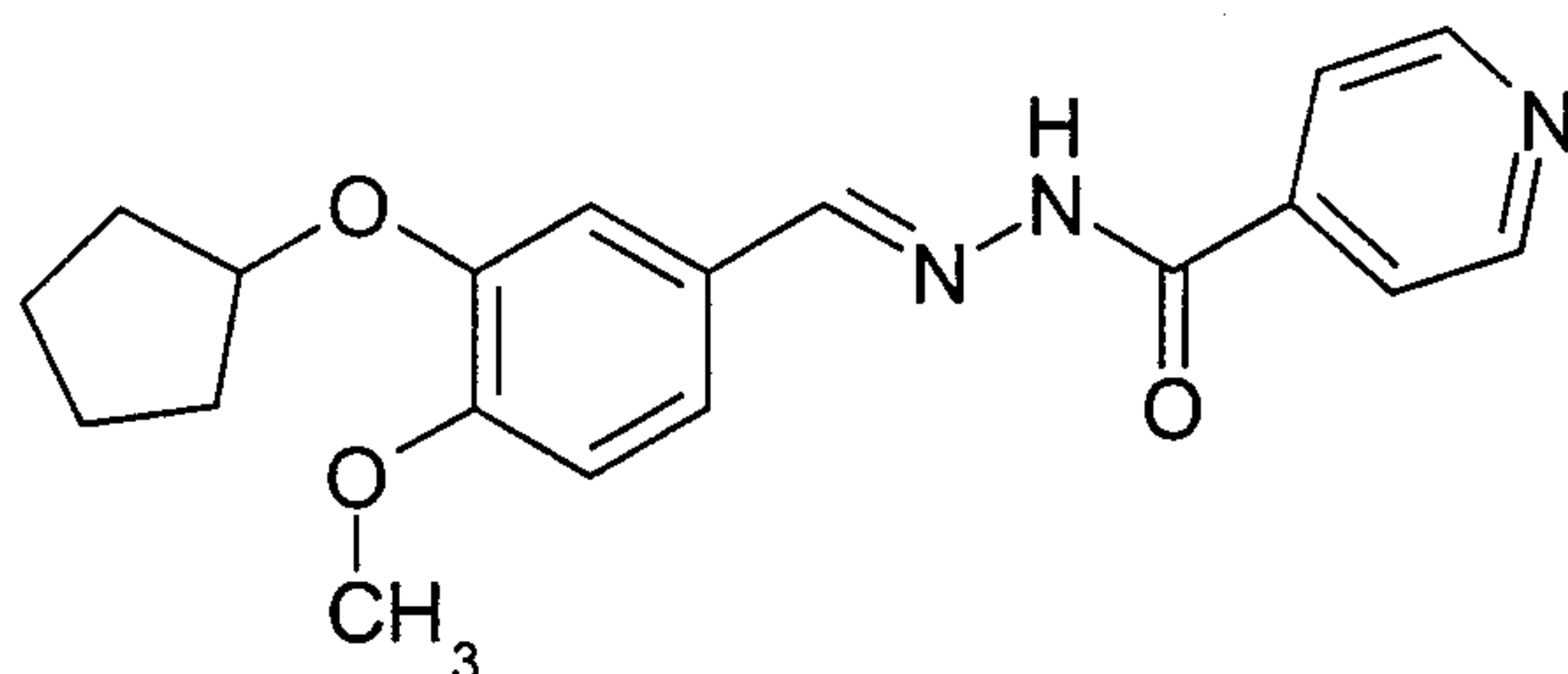
slowly added dropwise for 1 hour to the solution. This solution was stirred at 65°C for 1 day and, then, its temperature was lowered to a room temperature. It was diluted by 2.0 L of toluene and was washed with 1M sodium hydroxide (2 x 1.5 L). The aqueous layer was extracted with 0.5 L of toluene, and the organic layer was washed with distilled water (2 x 1.5 L). The organic layer was dried and concentrated to obtain 117 g of light brown oily title compound.

¹H NMR(CDCl₃,d): 9.84(s, 1H) 7.42(m, 2H) 6.95(d, 1H, J=9Hz) 4.87(m, 1H) 3.93(s, 3H) 2.1-1.6(m, 8H)

10 EXAMPLE 1

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde isonicotinic hydrazone

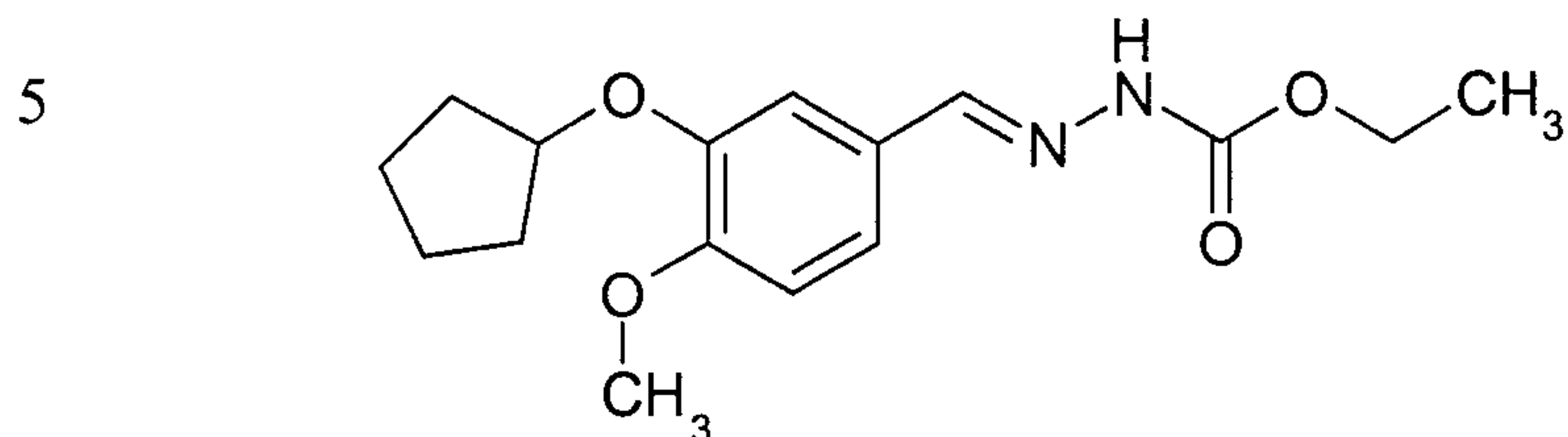
15



20 A catalytic amount of concentrated sulfuric acid was added to a solution of 0.44 g (2.0 mmole) of compound prepared by Reference Example 1 in 30 ml of ethanol and the mixture was stirred at room temperature for 10 minutes. 0.33 g of isonicotinic hydrazide was added to the reaction solution. The solution was stirred at 50°C for 4 hours and was concentrated under reduced pressure. The residue was dissolved in

25 dichloromethane and was washed twice with 50 ml of distilled water. The separated organic layer was dried over anhydrous magnesium sulfate and was distilled under reduced pressure. The resulting white crystal was recrystallized in dichloromethane to obtain 0.67 g (88.45%) of white title compound. m.p. 170 - 171°C

¹H NMR(DMSO-d₆): 1.60(2H, m) 1.75(4H, m) 1.92(2H, m) 3.81(3H, s) 4.85(1H, m) 7.04(1H, d J=8.4Hz) 7.24(1H, dd, J=8.4, 1.8Hz) 7.33(1H, d J=1.8Hz) 7.81(2H, dd, J=4.5, 1.6Hz) 8.39(1H, s) 8.78(2H, dd, J=4.5, 1.6Hz) 11.92(1H, s)

EXAMPLE 2**(E)-ethyl [(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinoformate**

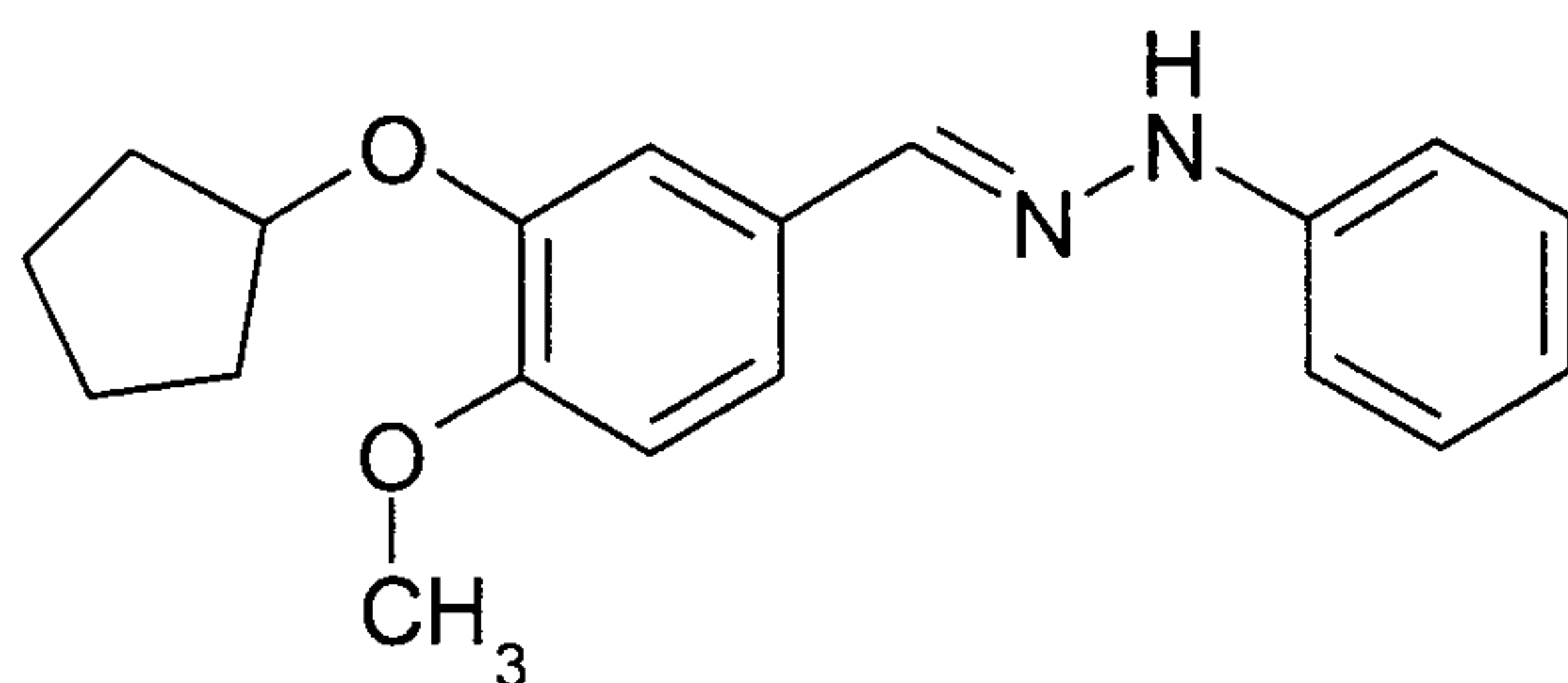
10 A catalytic amount of concentrated hydrochloric acid was added to a solution of 1.00 g (4.54 mmole) of compound prepared by Reference Example 1 in 80 ml of ethanol and the mixture was stirred at room temperature for 10 minutes. 0.73 g of ethyl carbazate was added to the reaction solution. The solution was stirred at 50°C for 4 hours and was concentrated under reduced pressure. The residue was dissolved in dichloromethane and

15 was washed twice with 50 ml of distilled water. The separated organic layer was dried over anhydrous magnesium sulfate and was distilled under reduced pressure. The resulting white crystal was recrystallized in dichloromethane to obtain 1.25 g (89.87%) of white title compound. m.p. 146 - 147°C

¹H NMR(DMSO-d₆): 1.23(3H, t, J=7.1Hz) 1.58(2H, m) 1.73(4H, m) 1.88(2H, m) 20 3.77(3H, s) 4.13(2H, q, J=7.1Hz) 4.80(1H, m) 6.98(1H, d J=8.4Hz) 7.07(1H, dd, J=8.4, 1.9Hz) 7.20(1H, d J=1.9Hz) 7.93(1H, s) 10.92(1H, s)

EXAMPLE 3**(E)-3-cyclopentyloxy-4-methoxybenzaldehyde phenylhydrazone**

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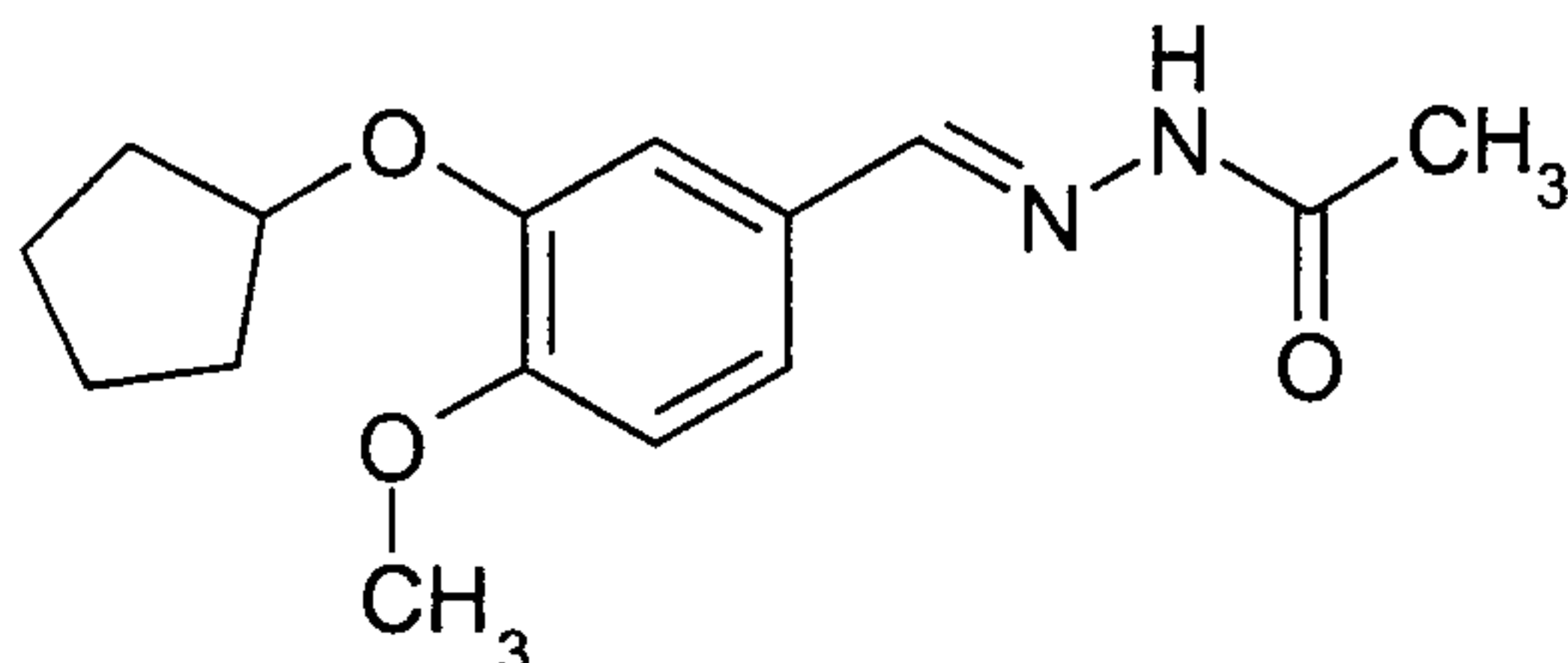
A catalytic amount of concentrated hydrochloric acid was added to a solution of

0.50 g (2.27 mmole) of compound prepared by Reference Example 1 in 60 ml of ethanol and the mixture was stirred at room temperature for 10 minutes. 0.34 ml of phenylhydrazine was added to the reaction solution. The solution was stirred at 50°C for 10 hours. The resulting precipitate was filtered and washed with 20 ml of ethanol to
 5 obtain 0.63 g (89.41%) of white title compound. m.p. 138 - 140°C ¹H NMR(DMSO-d₆): 1.60(2H, m) 1.75(4H, m) 1.92(2H, m) 3.77(3H, s) 4.85(1H, m) 6.72(1H, m) 6.95(1H, d J=8.2Hz) 7.03(2H, d, J=7.6Hz) 7.09(1H, dd, J=8.2, 1.8Hz) 7.20(2H, t) 7.26(1H, d J=1.8Hz) 7.78(1H, s) 10.12(1H, s)

10 EXAMPLE 4

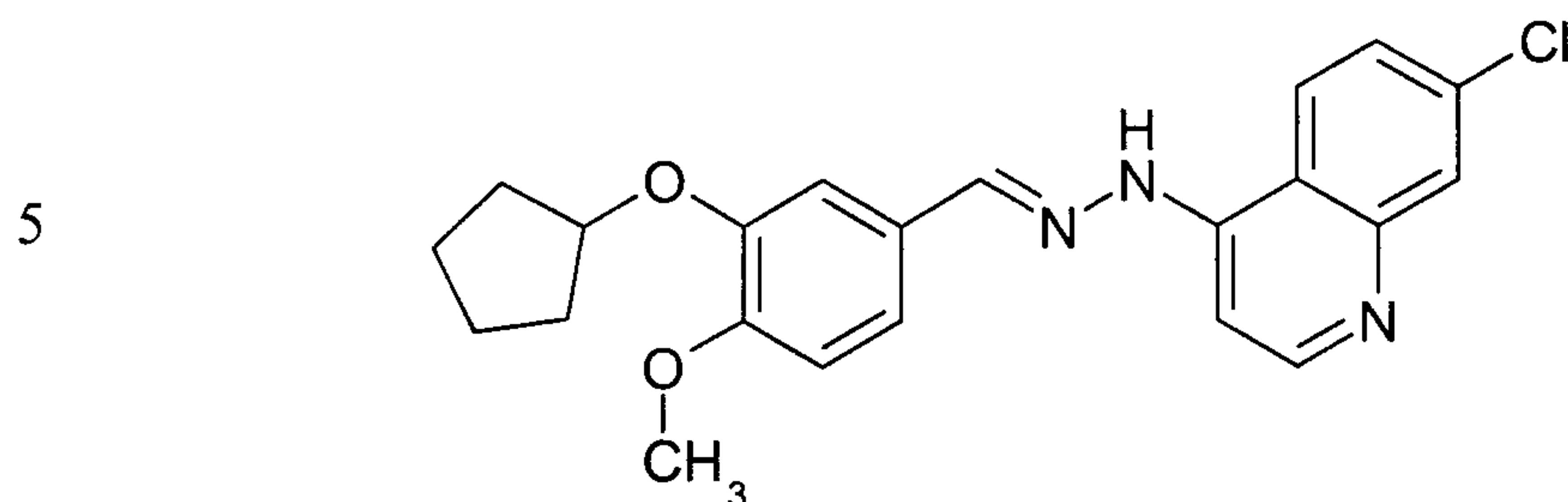
(E)-3-cyclopentyloxy-4-methoxybenzaldehyde acetic hydrazone

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A catalytic amount of concentrated hydrochloric acid was added to a solution of
 20 0.50 g (2.27 mmole) of compound prepared by Reference Example 1 in 60 ml of ethanol and the mixture was stirred at room temperature for 10 minutes. 0.26 g of acetic hydrazide was added to the reaction solution. The solution was stirred at 25°C for 10 hours and was concentrated under reduced pressure. The residue was dissolved in dichloromethane and was washed twice with 50 ml of distilled water. The separated
 25 organic layer was dried over anhydrous magnesium sulfate and was distilled under reduced pressure. The resulting white crystal was recrystallized in dichloromethane to obtain 0.59 g (94.06%) of white title compound. m.p. 155 - 156°C
¹H NMR(DMSO-d₆): 1.58(2H, m) 1.71(4H, m) 1.88(2H, m) 2.18(3H, s) 3.78(3H, s) 4.81(1H, m) 6.99(1H, d J=8.4Hz) 7.14(1H, dd, J=8.4, 1.8Hz) 7.24(1H, d J=1.8Hz)
 30 7.88(1H, s) 11.12(1H, s)

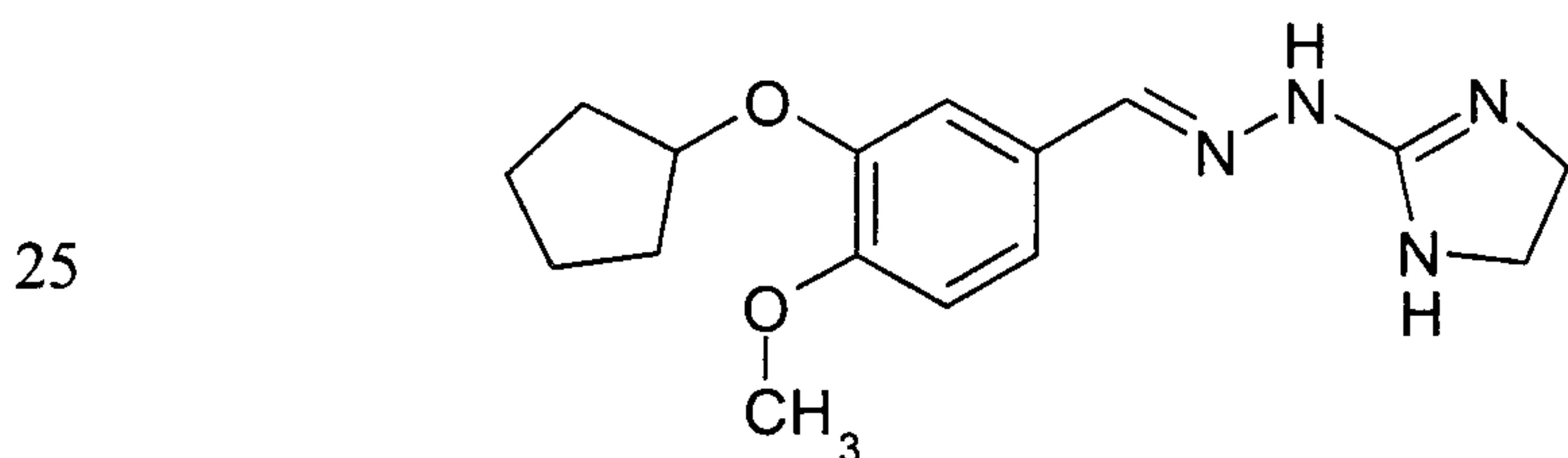
EXAMPLE 5

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde 7-chloroquinolone-4-ylhydrazone

10 A catalytic amount of concentrated hydrochloric acid was added to a solution of 0.50 g (2.27 mmole) of compound prepared by Reference Example 1 in 60 ml of ethanol and the mixture was stirred at room temperature for 10 minutes. 0.67 g of 7-chloro-4-hydrazinoquinoline was added to the reaction solution. The solution was stirred at 45°C for 10 hours. The resulting precipitate was filtered and washed with 20 ml of ethanol to

15 obtain 0.55 g (61.20%) of white title compound. m.p. 210 - 212°C

¹H NMR(DMSO-d₆): 1.61(2H, m) 1.78(4H, m) 1.94(2H, m) 3.81(3H, s) 4.89(1H, m) 7.04(1H, d J=8.3Hz) 7.28(1H, dd, J=8.3, 1.8Hz) 7.36(1H, d J=5.2Hz) 7.42(1H, d J=1.8Hz) 7.61(1H, d) 7.86(1H, s) 8.39(1H, s) 8.44(2H, d J=9.1Hz)

20 EXAMPLE 6**(E)-3-cyclopentyloxy-4-methoxybenzaldehyde 2-imidazolinohydrazone**

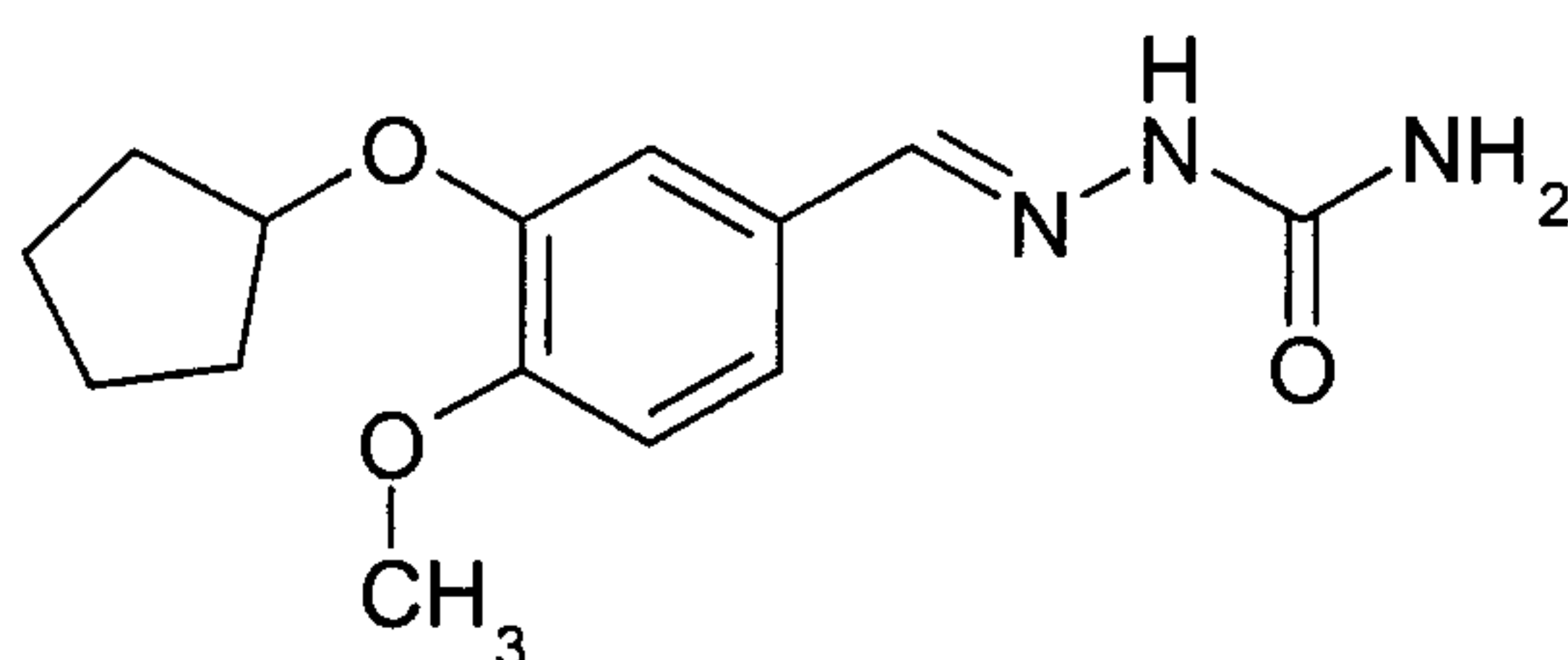
A catalytic amount of concentrated hydrochloric acid was added to a solution of 0.50 g (2.27 mmole) of compound prepared by Reference Example 1 in 50 ml of ethanol and the mixture was stirred at room temperature for 10 minutes. 0.63 g of hydrazino-2-imidazoline hydrobromide was added to the reaction solution. The solution was stirred

at 45°C for 8 hours and was concentrated under reduced pressure. The residue was dissolved in dichloromethane and was washed twice with 50 ml of distilled water. The separated organic layer was dried over anhydrous magnesium sulfate and was distilled under reduced pressure. The resulting light yellow oil was purified by a flash chromatography (silica gel, 7.5% methanol-dichloromethane as a developing solution) to obtain 0.45 g (65.56%) of white title compound. m.p. 87 - 90°C

¹H NMR(DMSO-d₆): 1.61(2H, m) 1.72(4H, m) 1.89(2H, m) 3.70(4H, s) 3.79(3H, s) 4.89(1H, m) 7.01(1H, d J=8.4Hz) 7.24(1H, dd, J=8.4, 1.8Hz) 7.44(1H, d J=1.8Hz) 8.06(1H, s)

EXAMPLE 7

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinecarboxamide



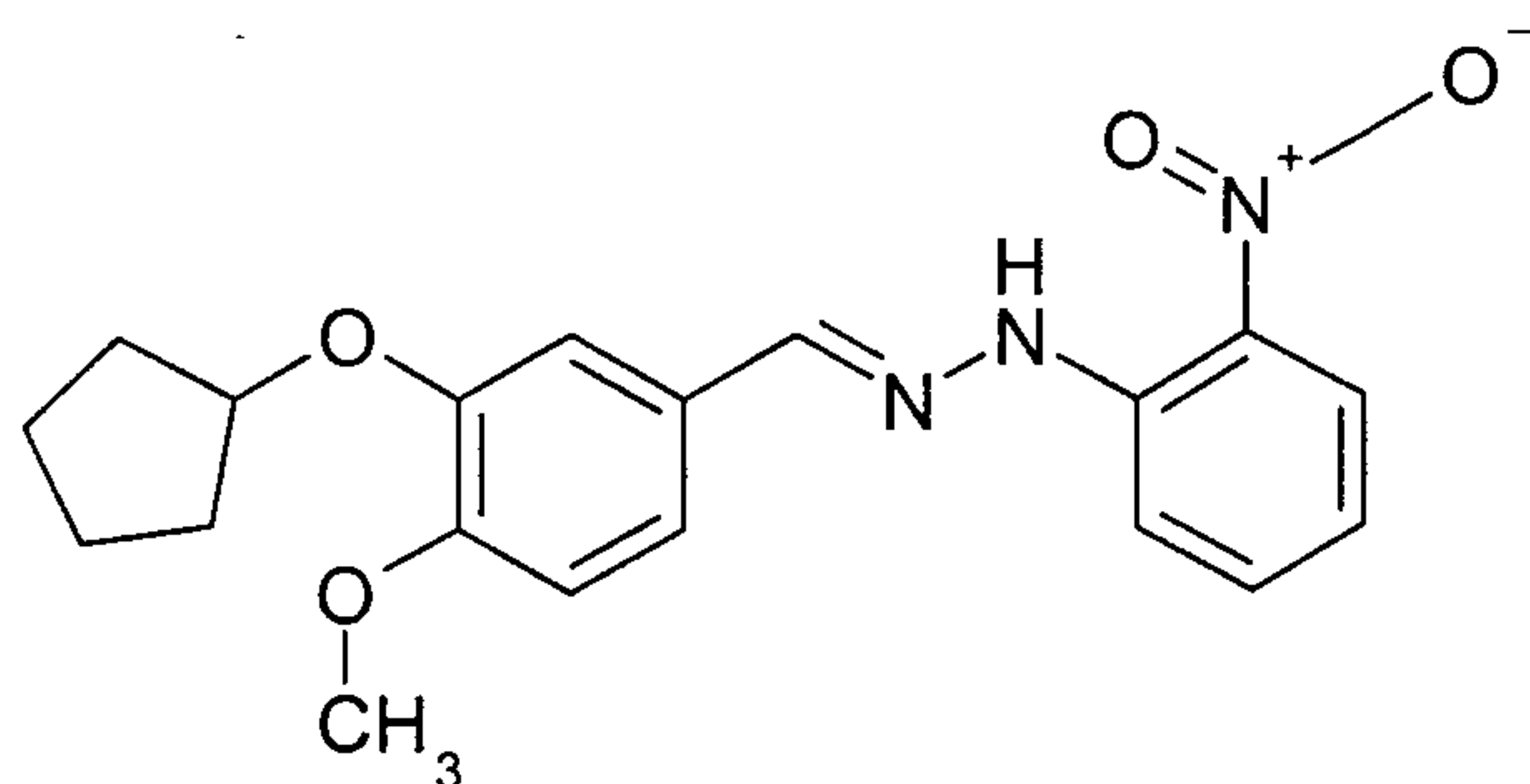
A reaction as in Example 6 was carried out using 0.50 g (2.27 mmole) of compound prepared in Reference Example 1 as a starting material to obtain 0.47 g (74.66%) of white title compound. m.p. 144 - 146°C

¹H NMR(DMSO-d₆): 1.58(2H, m) 1.71(4H, m) 1.89(2H, m) 3.76(3H, s) 4.92(1H, m) 6.44(2H, brs) 6.93(1H, d J=8.3Hz) 7.09(1H, dd, J=8.3, 1.9Hz) 7.36(1H, d J=1.9Hz) 7.75(1H, s) 10.08(1H, s)

EXAMPLE 8

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde 2-nitrophenylhydrazone

5



10 A reaction as in Example 3 was carried out using 0.50 g (2.27 mmole) of compound prepared in Reference Example 1 as a starting material to obtain 0.63 g (78.09%) of red yellow title compound. m.p. 135°C (decomposed)

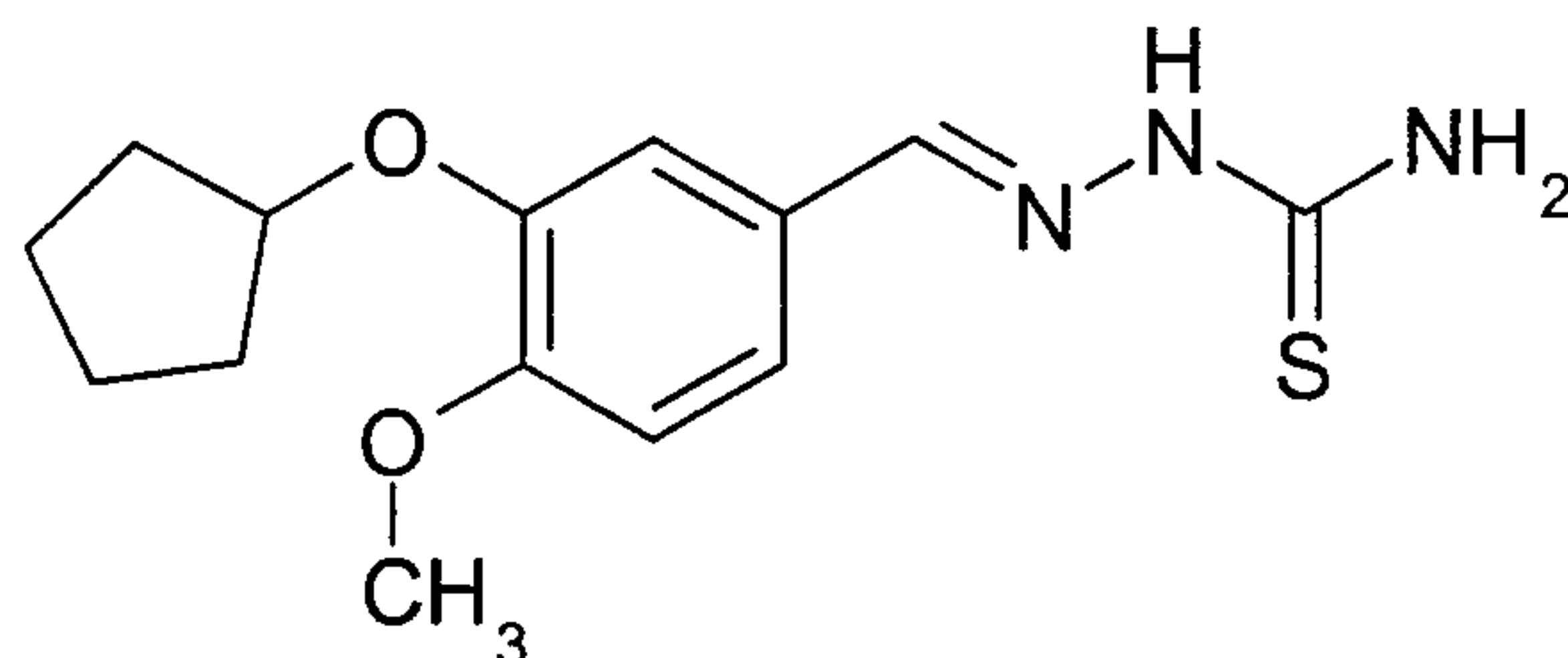
¹H NMR(DMSO-d₆): 1.61(2H, m) 1.77(4H, m) 1.94(2H, m) 3.80(3H, s) 4.88(1H, m) 6.89(1H, m) 7.03(1H, d J=8.4Hz) 7.22(1H, dd, J=8.4, 1.9Hz) 7.35(1H, d J=1.9Hz) 7.66(1H, t J=1.6Hz) 7.95(1H, d J=8.7Hz) 8.11(1H, dd J=8.5, 1.4Hz) 8.39(1H, s) 11.15(1H, s)

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EXAMPLE 9

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinecarbothioamide

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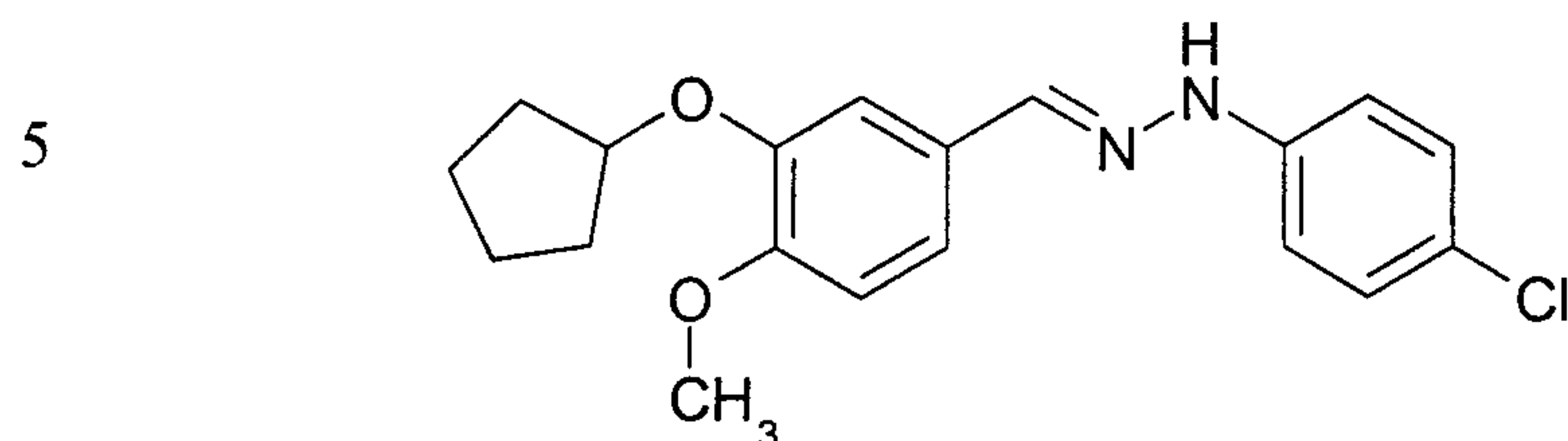


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A reaction as in Example 6 was carried out using 1.00 g (4.54 mmole) of compound prepared in Reference Example 1 as a strating material to obtain 0.94 g (70.57%) of white title compound. m.p. 112 - 114°C

¹H NMR(DMSO-d₆): 1.57(2H, m) 1.71(4H, m) 1.88(2H, m) 3.76(3H, s) 4.91(1H, m) 6.44(2H, brs) 6.93(1H, d J=8.4Hz) 7.09(1H, dd, J=8.4, 1.9Hz) 7.36(1H, d J=1.9Hz) 7.74(1H, s) 10.06(1H, s)

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EXAMPLE 10**(E)-3-cyclopentyloxy-4-methoxybenzaldehyde 4-chlorophenylhydrazone**

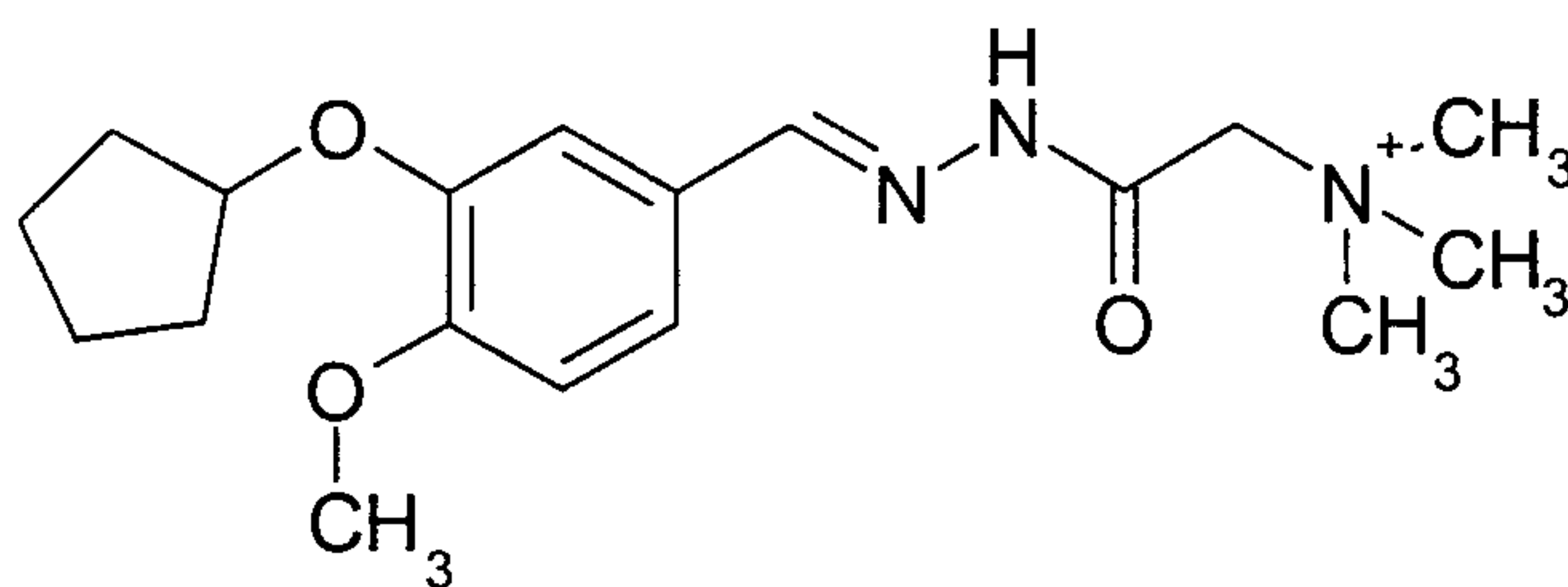
10 A reaction as in Example 6 was carried out using 1.50 g (6.81 mmole) of compound prepared in Reference Example 1 as a starting material to obtain 1.65 g (70.26%) of white title compound. m.p. 133 - 135°C

¹H NMR(DMSO-d₆): 1.60(2H, m) 1.76(4H, m) 1.91(2H, m) 3.78(3H, s) 4.86(1H, m) 6.97(1H, d J=8.4Hz) 7.04(2H, dd J=6.8, 2.1Hz) 7.12(1H, dd, J=8.4, 1.9Hz) 7.24(2H, dd J=6.8, 2.1Hz) 7.27(1H, d J=1.9Hz) 7.87(1H, s) 10.27(1H, s)

15

EXAMPLE 11**(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinecarbonylmethyl (trimethyl) ammonium chloride**

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25

A reaction as in Example 6 was carried out using 1.50 g (6.81 mmole) of compound prepared in Reference Example 1 and 1.03 g of (carboxymethyl)trimethylammonium chloride hydrazide as starting materials to obtain 1.73 g (68.68%) of white title compound. m.p. 178 - 179°C

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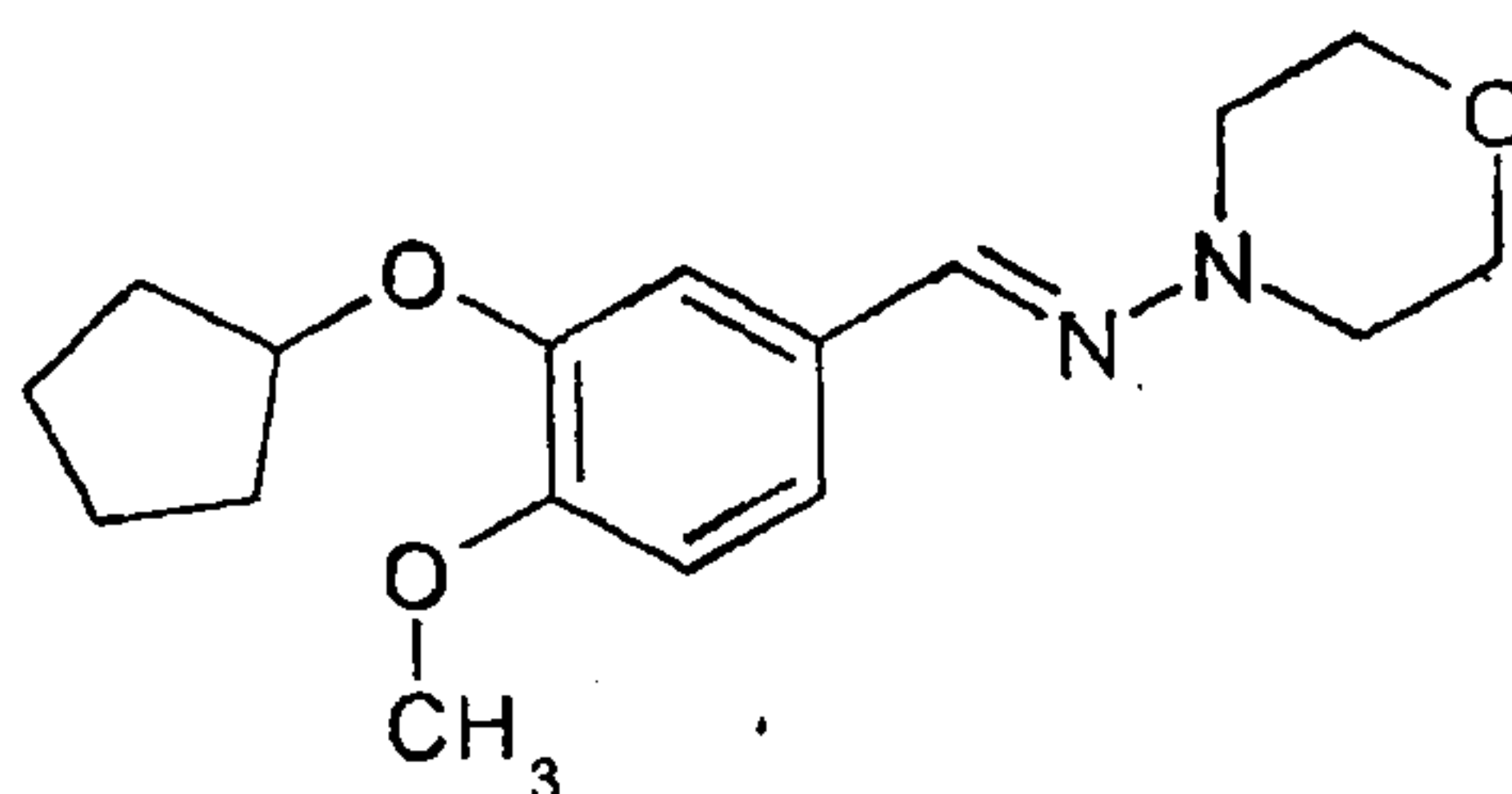
¹H NMR(DMSO-d₆): 1.60(2H, m) 1.73(4H, m) 1.90(2H, m) 3.30(9H, s) 3.79(3H, s) 4.33(2Ha, s) 4.79(2Ha, s) 4.84(1H, m) 7.03(1H, d J=8.4Hz) 7.23(1H, dd, J=8.4, 1.8Hz)

7.29(1H, d J=1.8Hz) 8.01(1Ha',s) 8.26(1Ha', s) 12.05(1H, brs)

EXAMPLE 12

5 (E)-N-(1,4-oxazine-4-yl)-3-cyclopentyloxy-4-methoxyphenylmethaneimine

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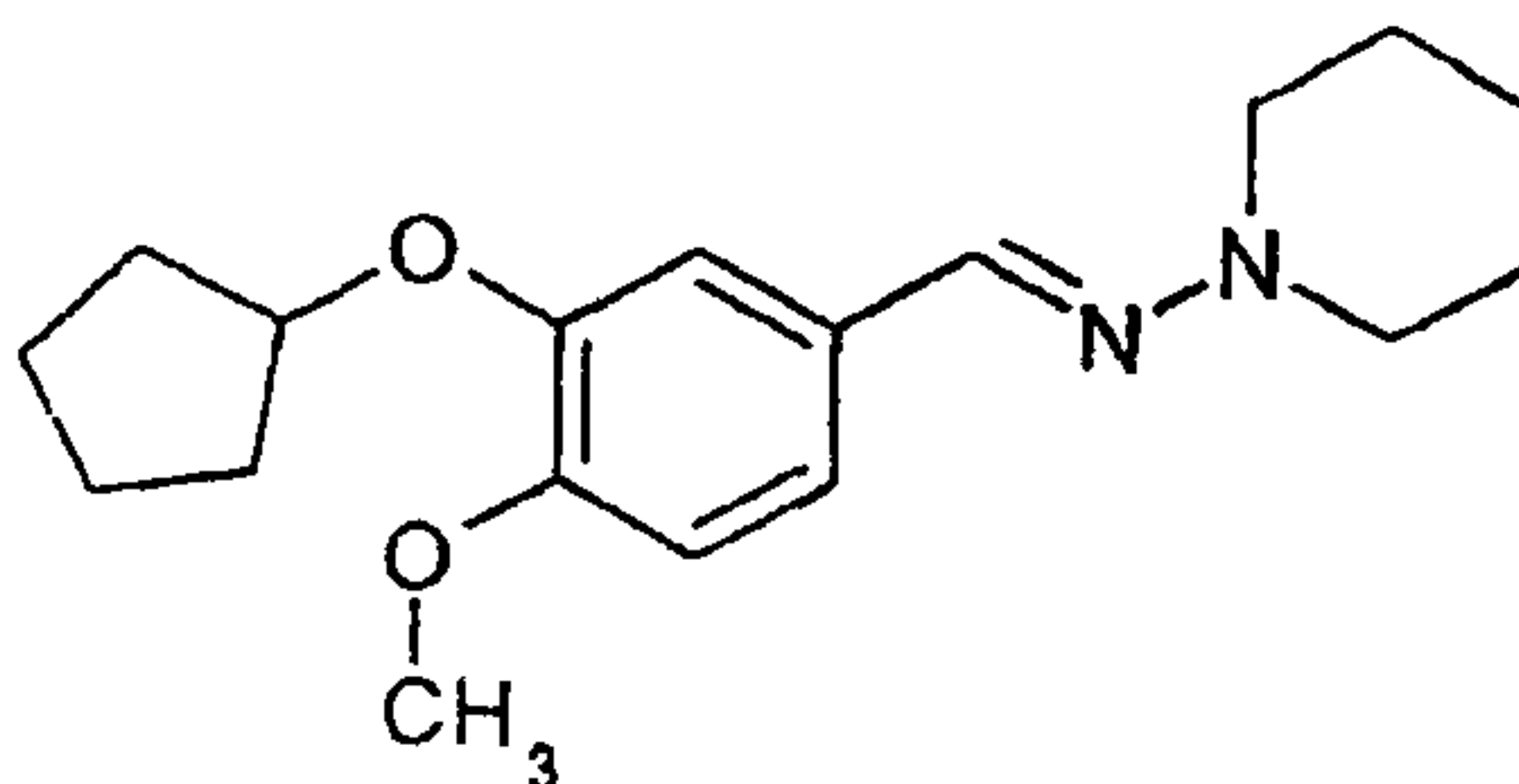


15 5.0 g (22.7 mmole) of compound prepared by Reference Example 1 was dissolved in 60 ml of ethanol and the resulting solution was stirred at room temperature for 10 minutes. 2.91 ml of N-aminomorpholine was added to the reaction solution. The solution was stirred at 5°C for 14 hours. The resulting precipitate was filtered and washed with 20 ml of ethanol to obtain a white solid. This solid was recrystallized in isopropylether to obtain 6.37 g (92.19%) of title compound. m.p. 108 - 109°C
 20 ¹H NMR(DMSO-d₆): 1.56(m, 2H) 1.70(m, 4H) 1.88(m, 2H) 3.03(m, 4H) 3.67(m, 7H) 4.77(m, 1H) 6.88(d, 1H) 7.04(dd, 1H) 7.18(d, 1H) 7.62(s, 1H)

EXAMPLE 13

(E)-N-piperidino-3-cyclopentyloxy-4-methoxyphenylmethaneimine

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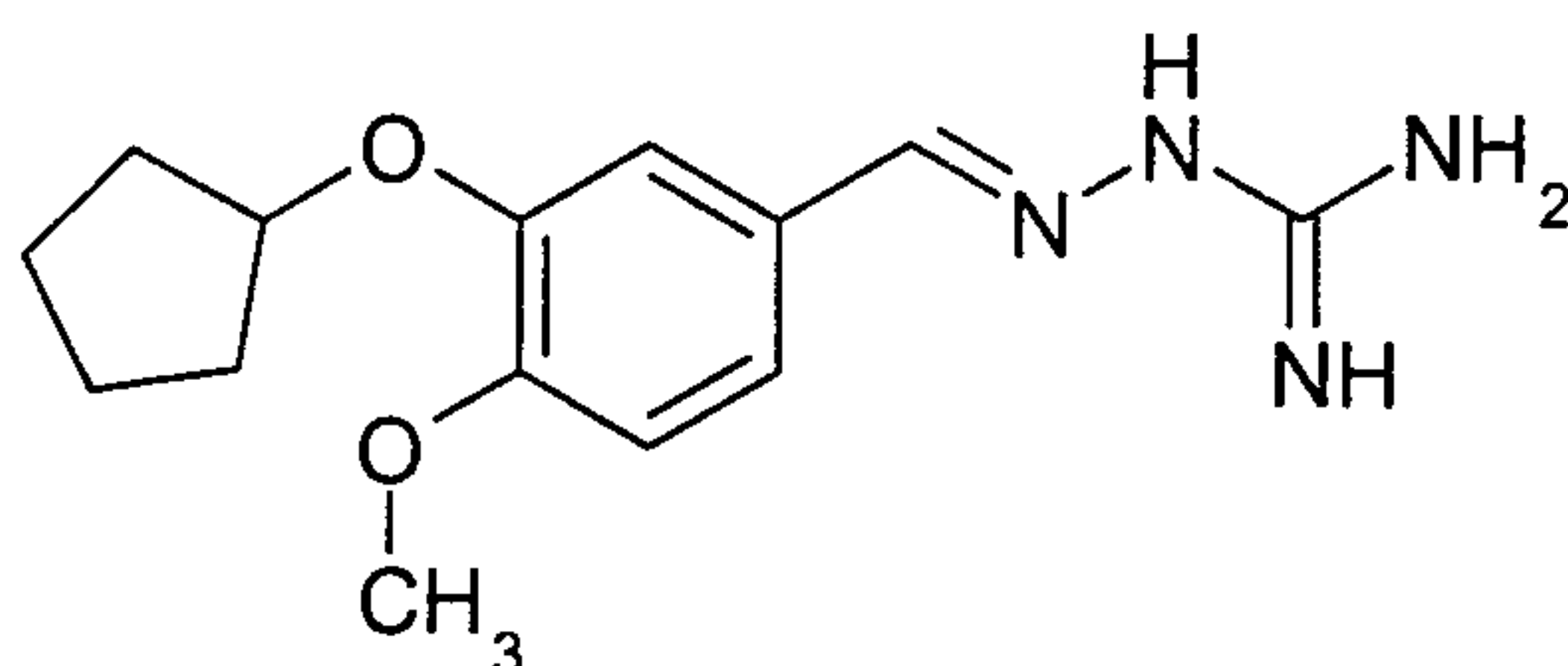
A reaction as in Example 12 was carried out using 0.50 g (2.27 mmole) of compound prepared in Reference Example 1 and 0.31 ml of N-aminopiperidine as

starting materials to obtain 0.65 g (94.68%) of white title compound. m.p. 81 - 82°C
¹H NMR(DMSO-d₆): 1.52(m, 4H) 1.67(m, 8H) 1.90(m, 2H) 3.04(m, 4H) 3.70(s, 3H)
 4.76(m, 1H) 6.89(d, 1H) 7.04(dd, 1H) 7.18(d, 1H) 7.57(s, 1H)

5 EXAMPLE 14

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinecarboximidamide

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A reaction as in Example 6 was carried out using 1.50 g (6.81 mmole) of compound prepared in Reference Example 1 and 0.73 g of aminoguanidine hydrochloride as starting materials to obtain 1.60 g (85.02%) of white title compound. m.p. 100 - 103°C

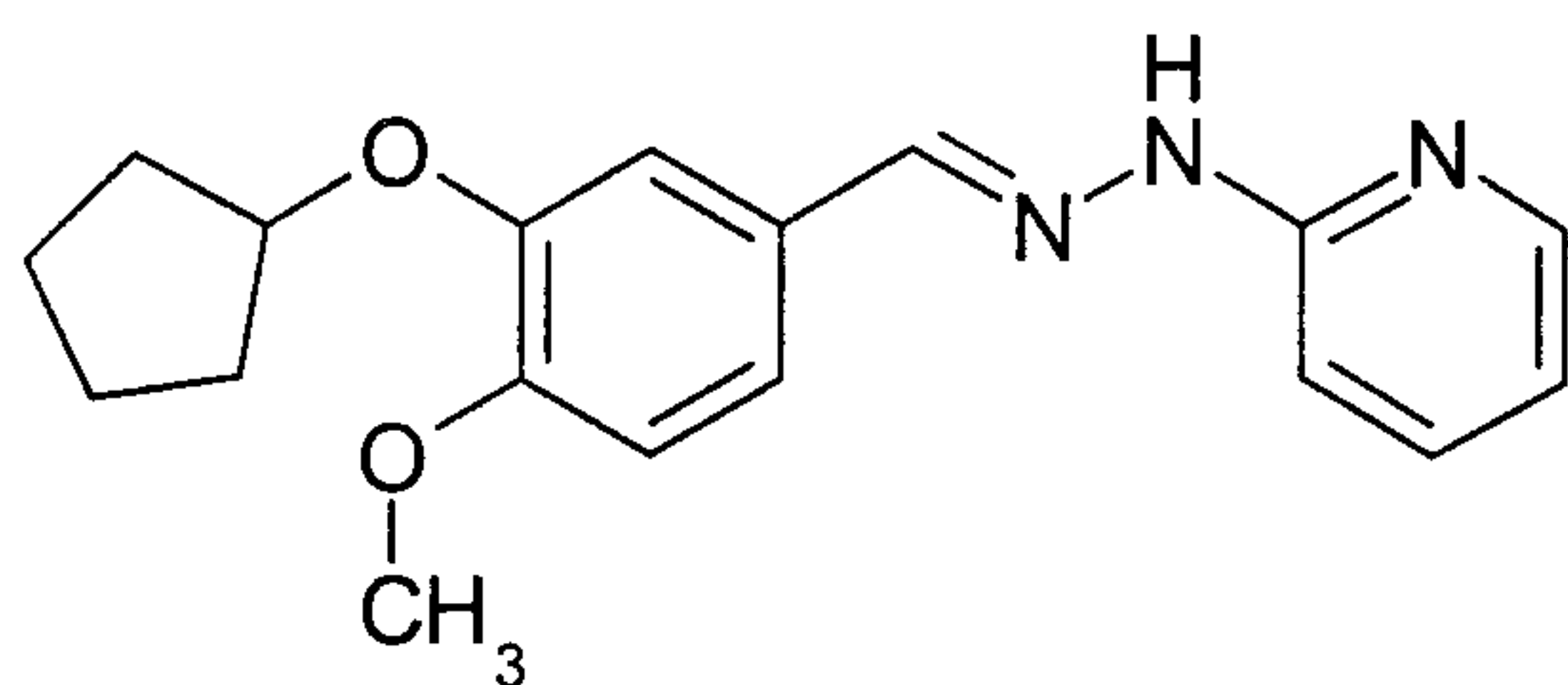
¹H NMR(DMSO-d₆): 1.62~1.64(2H, m) 1.74~1.78(4H, m) 1.94~1.97(2H, m) 3.84(3H, s) 4.95~4.98(1H, m) 7.05(1H, d J=8.4Hz) 7.33(1H, dd, J=8.4, 2.0Hz) 7.54(1H, d J=1.9Hz) 7.7(1H, brs) 8.36(1H, s) 11.69(1H, s)

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EXAMPLE 15

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde 2-pyridinylhydrazone

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30

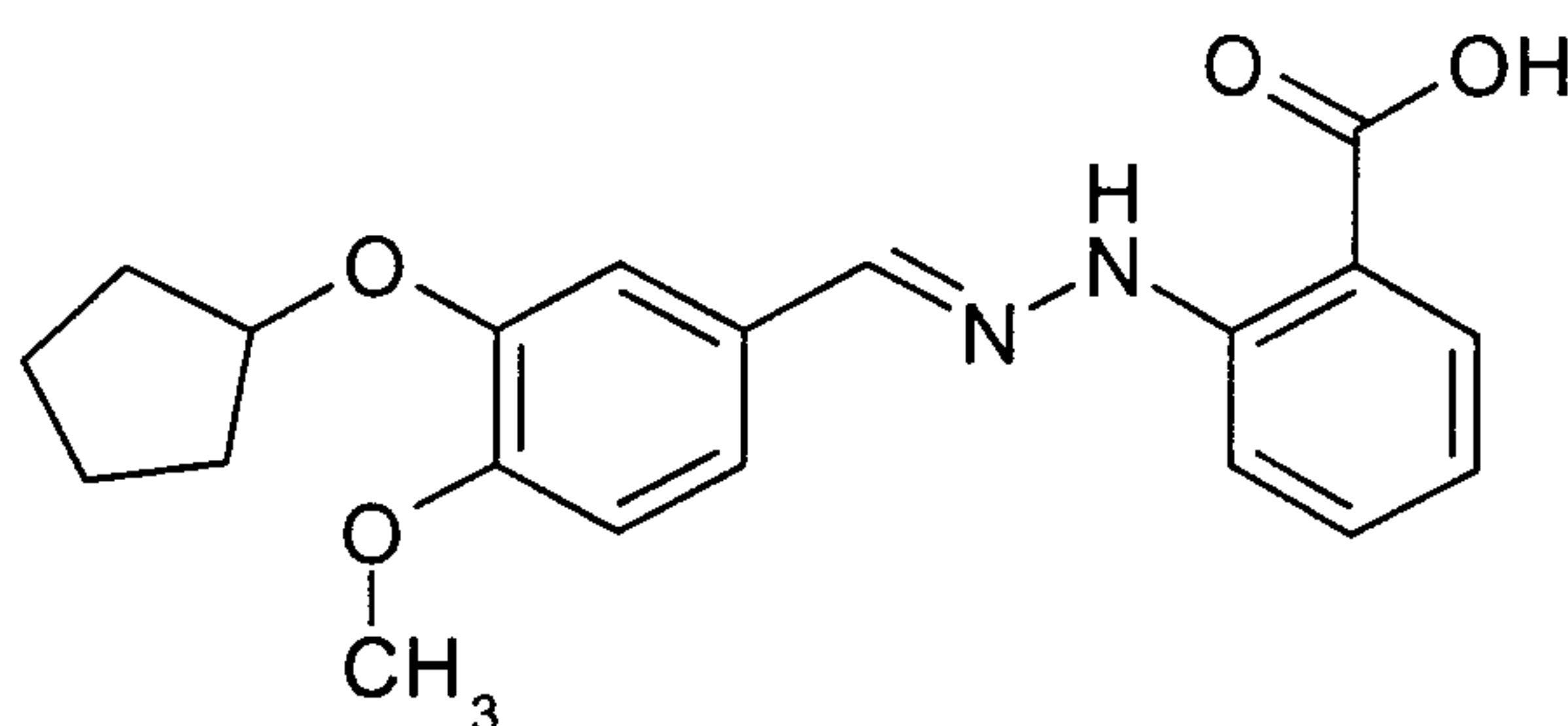
A reaction as in Example 6 was carried out using 0.80 g (3.63 mmole) of compound prepared in Reference Example 1 and 0.39 g of 2-hydrazinopyrimidine as starting materials to obtain 0.96 g (84.89%) of white title compound. m.p. 142 - 143°C

¹H NMR(DMSO-d₆): 1.58~1.61(2H, m) 1.71~1.76(4H, m) 1.89~1.94(2H, m) 3.77(3H, s) 4.84~4.87(1H, m) 6.73~6.74(1H, m) 6.97(1H, d J=8.3Hz) 7.10(1H, dd, J=8.3, 1.8Hz) 7.20(1H, d J=8.4Hz) 7.27(1H, d J=1.8Hz) 7.62~7.63(1H, m) 7.94(1H, s) 8.09(1H, dd J=4.9, 1.0Hz) 10.67(1H, s)

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EXAMPLE 16**(E)-3-cyclopentyloxy-4-methoxybenzaldehyde 2-carboxyphenylhydrazone**

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A reaction as in Example 6 was carried out using 0.80 g (3.63 mmole) of compound prepared in Reference Example 1 and 0.66 g of 2-hydrazinobenzoic hydrochloride as starting materials to obtain 1.05 g (81.57%) of white title compound. m.p. 174 - 176°C

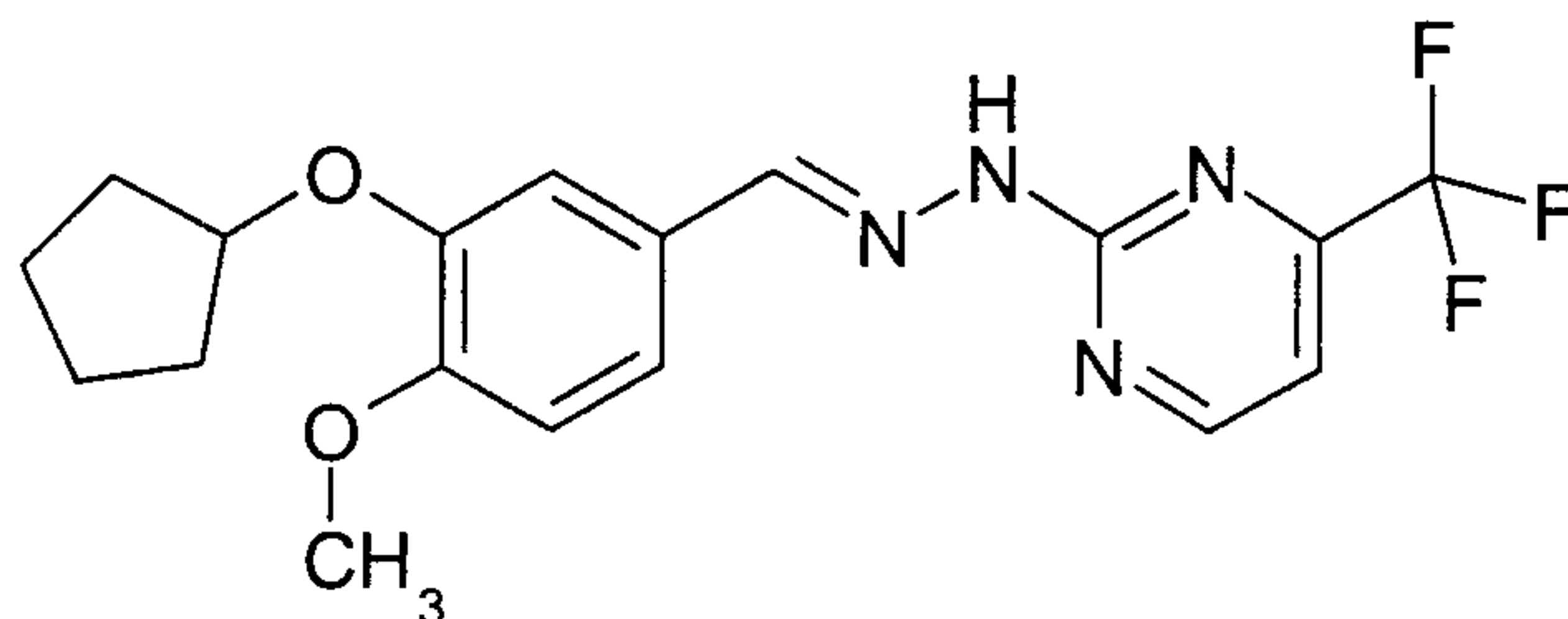
¹H NMR(DMSO-d₆): 1.59~1.60(2H, m) 1.71~1.76(4H, m) 1.92~1.93(2H, m) 3.78(3H, s) 4.85(1H, m) 6.78(1H, dd J=7.0, 1.0Hz) 6.99(1H, d J=8.4Hz) 7.20(1H, dd, J=8.4, 1.9Hz) 7.32(1H, d J=1.9Hz) 7.50(1H, dd J=7.0, 1.6Hz) 7.68(1H, dd J=8.5, 0.8Hz) 7.84(1H, dd J=8.0, 1.4Hz) 8.05(1H, s) 8.79(1H, d J=4.9Hz) 11.17(1H, s)

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EXAMPLE 17**(E)-3-cyclopentyloxy-4-methoxybenzaldehyde 4-trifluoromethylpyrimidin-2-ylhydrazone**

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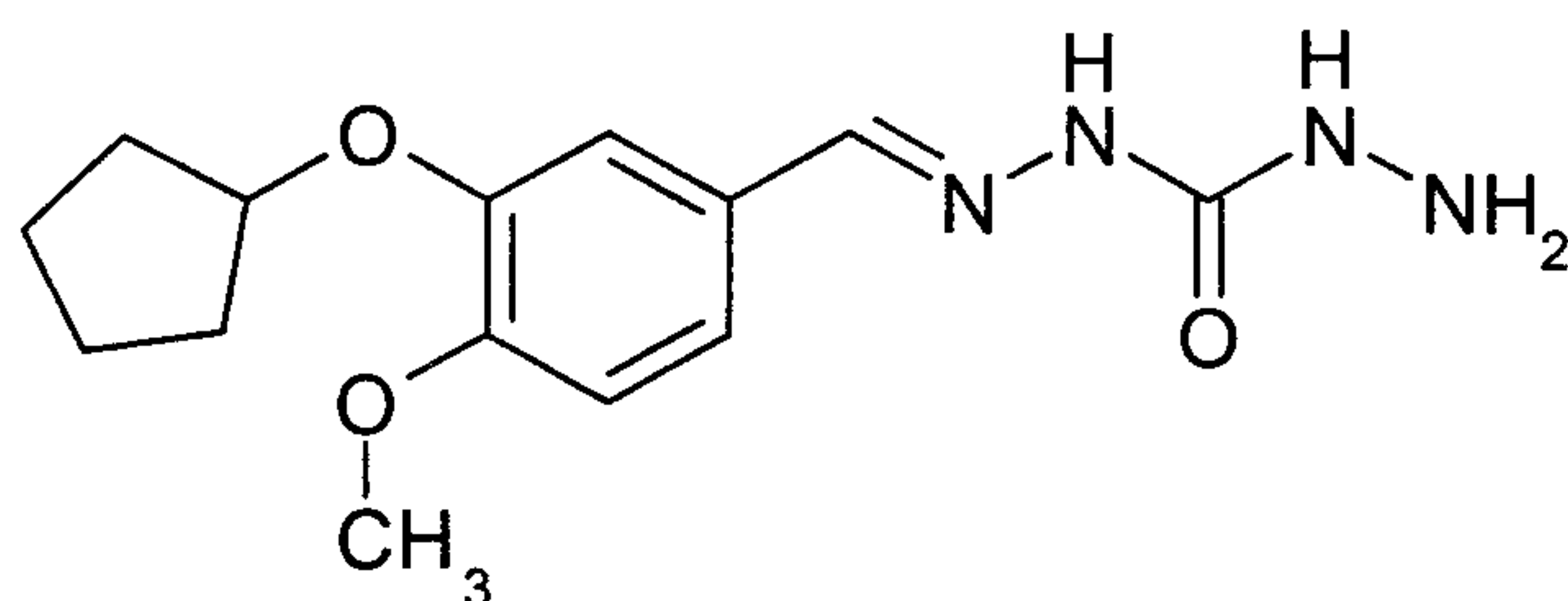


A reaction as in Example 6 was carried out using 0.80 g (3.63 mmole) of compound prepared in Reference Example 1 and 0.63 g of 2-hydrazino-4-(trifluoromethyl)pyrimidine as starting materials to obtain 1.10 g (79.62%) of white title compound. m.p. 73 - 75°C

¹H NMR(DMSO-d₆): 1.58~1.59(2H, m) 1.72~1.76(4H, m) 1.89(2H, m) 3.79(3H, s) 4.81~4.84(1H, m) 7.01(1H, d J=8.4Hz) 7.19(1H, dd, J=8.4, 2.0Hz) 7.21(1H, d J=4.9Hz) 7.27(1H, d J=2.0Hz) 8.11(1H, s) 8.79(1H, d J=4.9Hz) 1.67(1H, s)

EXAMPLE 18

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinecarbohydrazine



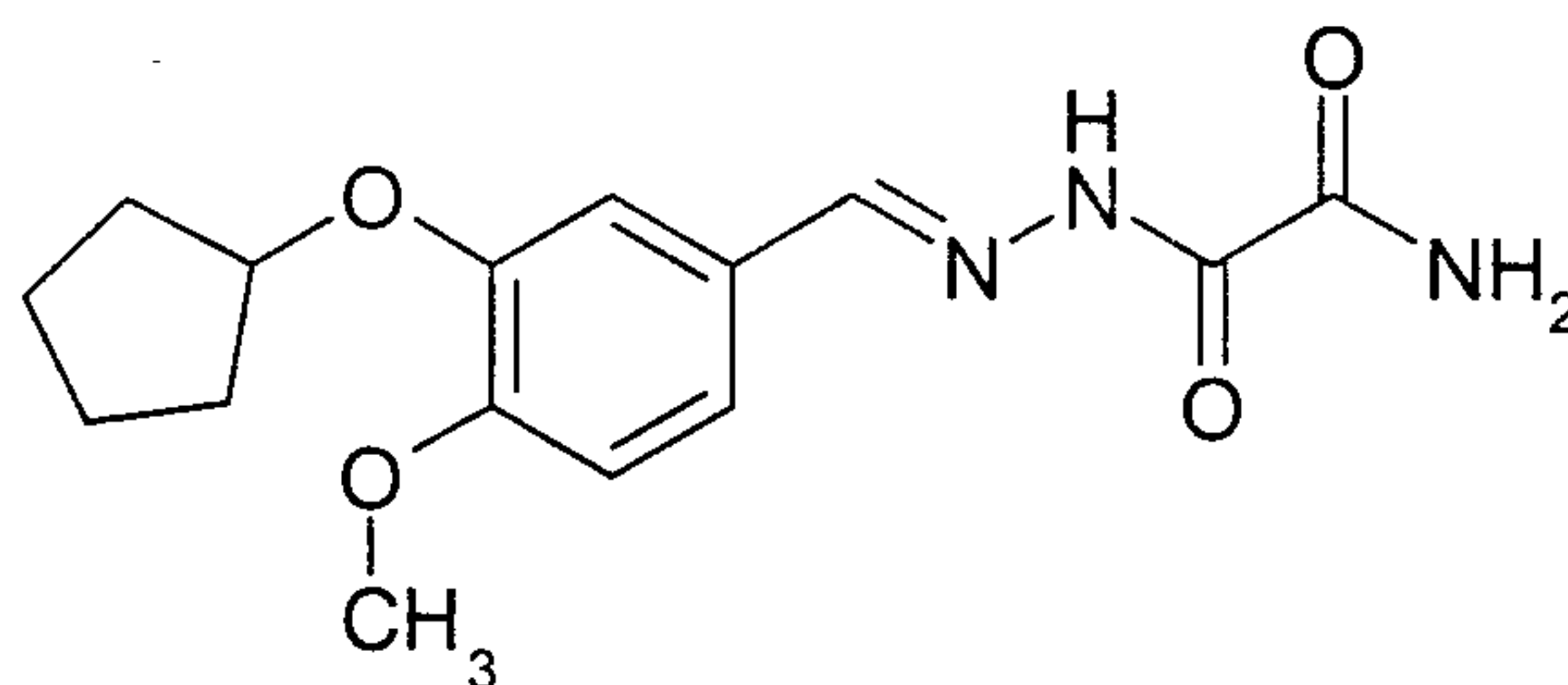
A catalytic amount of glacial acetic acid was added to a solution of 1.0 g (4.54 mmol) of compound prepared in Reference Example 1 in 50 ml of methanol and the mixture was stirred at room temperature for 10 minutes and added dropwise over 20 minutes to a solution of 1.0 g of carbohydrazine in 50 ml of distilled water. The reaction mixture was stirred at room temperature for 1 hour and the precipitated solids were filtered to obtain 0.89 g (67.06%) of white title compound. m.p. 179-181°C

¹H NMR(DMSO-d₆): 1.61(2H, m) 1.72(4H, m) 1.89(2H, m) 3.76(3H, s) 4.05(2H, brs) 4.94(1H, m) 6.92(1H, d J=8.3Hz) 7.07(1H, dd, J=8.3, 1.7Hz) 7.42(1H, d J=1.6Hz) 7.74(1H, s) 8.03(1H, s) 10.23(1H, s)

EXAMPLE 19

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinedicarboxamide

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A catalytic amount of glacial acetic acid was added to a solution of 1.0 g (4.54 mmol) of compound prepared in Reference Example 1 in 50 ml of methanol and the mixture was stirred at room temperature for 10 minutes and added dropwise over 30 minutes to a solution of 1.17 g of oxamic hydrazide in 60 ml of distilled water. The reaction mixture was stirred at room temperature for 2 hours and the precipitated solids were filtered to obtain 1.12 g (80.80%) of white title compound. m.p. 233-235°C

15

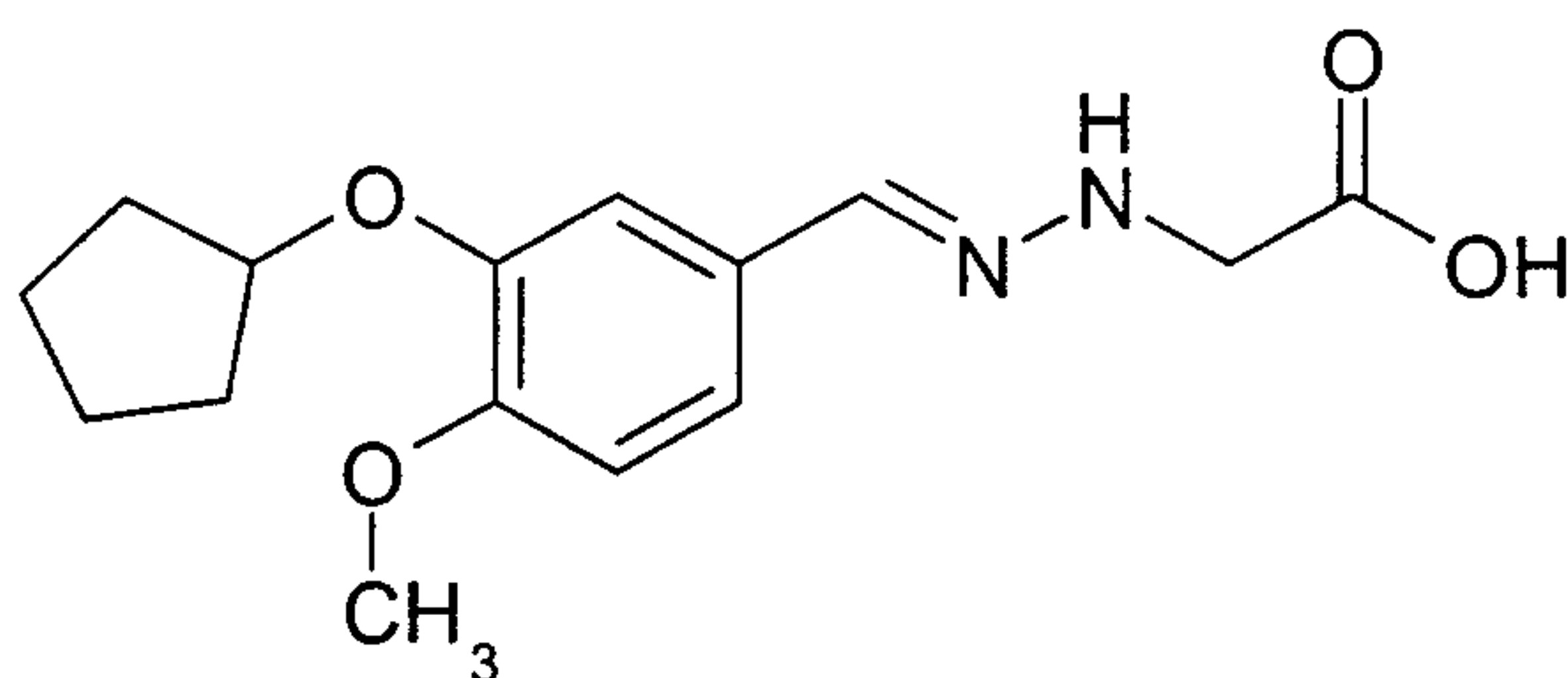
¹H NMR(DMSO-d₆): 1.57(2H, m) 1.71(4H, m) 1.87(2H, m) 3.76(3H, s) 4.11(2H, brs) 4.95(1H, m) 6.91(1H, d J=8.5Hz) 7.28(1H, dd, J=8.5, 2.2Hz) 7.42(1H, d J=2.1Hz) 7.83(1H, s) 9.32(1H, s)

EXAMPLE 20

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(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinoacetic acid

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A reaction as in Example 6 was carried out using 0.80 g (3.63 mmole) of compound prepared in Reference Example 1 and 0.63 g of ethylhydrazinoacetate as starting materials to obtain 0.98 g of white ethyl (E)-2-[3-cyclopentyloxy-4-methoxyphenylmethylene]hydrazinoacetate. The prepared ester compound was

hydrolysed in the mixture of methanol and 1.0 N aqueous sodium hydroxide solution to afford 0.75 g (70.77%) of white title solid. m.p. 165°C (decomposed)

¹H NMR(DMSO-d₆): 1.59(2H, m) 1.71(4H, m) 1.87(2H, m) 3.74(3H, s) 3.83(2H, brs) 4.77(1H, m)

5 6.90(1H, d J=8.5Hz) 6.96(1H, dd, J=8.3, 1.7Hz) 7.09(1H, d J=1.7Hz) 7.57(1H, s)

EXPERIMENTAL EXAMPLE

Inhibition of Phosphodiesterase IV Activity

10 Compounds prepared by Examples 1 through 16 and Rolipram as control were tested on the inhibition of phosphodiesterase IV.

Phosphodiesterase IV partially purified from human U937 cells, test compound and 1.0 uM cAMP including 0.01 uM [³H]cAMP were incubated at 30°C for 20 minutes. 15 The PDE reaction to convert cAMP into AMP was completed by boiling the reaction solution for 2 minutes. AMP was converted into adenosine by adding snake venom nucleotidase and incubating the reaction solution at 30°C for 10 minutes. While unhydrolyzed cAMPs were bonded to AG1-X2 resin, the [³H]adenosine in the aqueous solution was quantified by scintillation counting. The results are shown in Table I below, 20 in which the values indicate inhibition (%) of the PDE IV by each test compound.

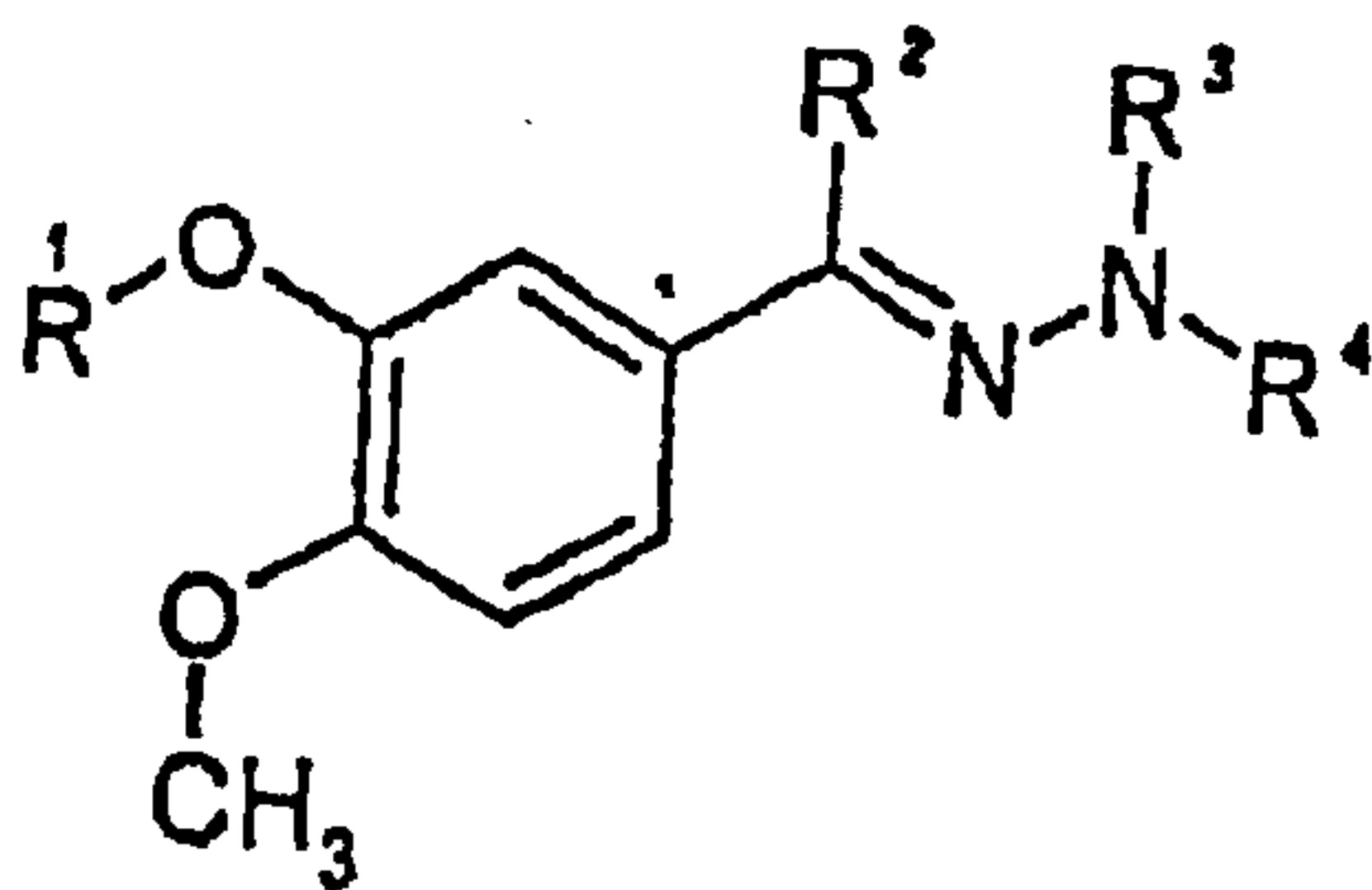
Table I

Test Compounds	Concentration (uM)	Inhibition (%)
25 Rolipram (Control)	20	70.1
	2	62.5
EXAMPLE 1	20	66.7
	2	38.4
EXAMPLE 2	20	63.7
	2	46.7
30 EXAMPLE 3	20	80.4
	2	46.6

5	EXAMPLE 4	20	72.1
		2	51.7
10	EXAMPLE 5	20	64.9
		2	37.9
15	EXAMPLE 6	20	58.3
		2	31.7
20	EXAMPLE 7	20	89.7
		2	66.2
25	EXAMPLE 9	20	81.0
		2	69.0
30	EXAMPLE 10	20	70.7
		2	39.3
	EXAMPLE 11	20	45.1
		2	43.3
	EXAMPLE 12	20	79.4
		2	62.9
	EXAMPLE 13	20	73.3
		2	31.4
	EXAMPLE 14	20	57.7
		2	14.7
	EXAMPLE 15	20	63.6
		2	49.4
	EXAMPLE 16	20	76.6
		2	42.3

CLAIMS

1. A compound of formula 1:



or pharmaceutically acceptable salts thereof, wherein

R¹ is C₃₋₇cycloalkyl;

10 R² is hydrogen, hydroxyl, C₁₋₅ alkyl or -CH₂CH₂C(=O)NH₂;

R³ and R⁴ are independently hydrogen, C₁₋₇ alkyl, -C(=X)-R⁵, or 2-, 3- or 4-pyridyl, pyrimidyl or phenyl substituted with one or two radicals selected from a group consisting of halogen, C₁₋₆ alkoxy, nitro, trifluoromethyl, C₁₋₆ alkyl and carboxyl, or R³ and R⁴ together with the nitrogen atom to which they are attached, represent piperidine or morpholine,

X is oxygen, sulfur or NH, and R⁵ is C₁₋₇ alkyl, -NHR⁶, CONH₂ or 2-, 3- or 4-pyridyl, pyrimidyl or phenyl substituted with one radical selected from a group consisting of halogen, C₁₋₆-alkoxy, nitrile, trifluoromethyl, C₁₋₆ alkyl and carboxyl, and R⁶ is hydrogen, hydroxyl, NH₂, C₁₋₅ alkoxy, C₁₋₅ alkyl, pyridyl or phenyl.

20

2. The compound according to claim 1, wherein R¹ is cyclopentyl, R² is hydrogen, R³ and R⁴ are independently C₁₋₅ alkyl, -C(=X)-R⁵, or 2-, 3- or 4-pyridyl, pyrimidyl or phenyl substituted with one radical selected from a group consisting of halogen, nitro, trifluoromethyl and carboxyl, or R³ and R⁴ together with the nitrogen atom to which they are attached, represent piperidine or morpholine, X is oxygen, sulfur or NH, and R⁵ is -NHR⁶ or 4-pyridyl and R⁶ is hydrogen, hydroxy or 4-pyridyl.

3. The compound according to claim 1, being selected from a group consisting of

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde isonicotinic hydrazone,

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde phenylhydrazone,

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde acetic hydrazone,

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazine carboxamide,

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde 2-nitrophenylhydrazone,

10

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinecarbothioamide,

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde-4-chlorophenylhydrazone,

(E)-N-(1,4-oxazine-4-yl)-3-cyclopentyloxy-4-methoxyphenylmethaneimine,

(E)-N-piperidino-3-cyclopentyloxy-4-methoxyphenylmethaneimine,

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinecarboximidamide,

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde-2-pyridinylhydrazone,

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde 2-carboxyphenylhydrazone,

(E)-3-cyclopentyloxy-4-methoxybenzaldehyde 4-trifluoromethylpyrimidin-2-ylhydrazone,

20

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinecarbohydrazine,

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinedicarboxamide, and

(E)-2-[(3-cyclopentyloxy-4-methoxyphenyl)methylene]hydrazinoacetic acid.

4. A pharmaceutical composition for inhibiting phosphodiesterase IV or TNF which comprises a pharmaceutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

