Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 15 (2007) 3912–3918
Bioorganic & Medicinal Chemistry

Synthesis and cytotoxic evaluation of new (4,5,6,7-tetrahydro-indol-1-yl)-3-*R*-propionic acids and propionic acid ethyl esters generated by molecular mimicry

Roberto Martínez,* Angel Clara-Sosa and Ma. Teresa Ramírez Apan

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad. Universitaria, Coyoacán 04510, México D.F., Mexico

Received 20 October 2006; revised 1 December 2006; accepted 11 December 2006
Available online 13 December 2006

Abstract—Indolones **4** and **5**, and indolyl-aminoacids **6a–e**, **7a–e**, and **8a** and **8b** were designed by structural modification of lead compound **3**. These compounds were tested on six tumor cell lines to determine the role of the azepinone ring and the *N*-phenyl substituent in the cytotoxicity of **3**. Our results show that **4** and **5** have dramatically reduced cytotoxicity, due to the loss of the azepinone moiety of lead compound **3**. In contrast, indolyl-aminoacids **6a**, **7a**, and **8a** (*N*-(L)-cysteine ethyl ester derivatives) inhibited the proliferation of almost all cancer cell lines tested, even though they lack the azepinone ring. In addition, derivative **6c** (*N*-(D)-alanine methyl ester group) was selectively cytotoxic to HCT-15 cells. Preliminary structure–activity relationship (SAR) studies with these compounds revealed the importance of the ethyl ester moiety on the amino acid moiety. Compounds **6a–e**, **7a–e**, and **8a** and **8b** were obtained in good yields by a catalytic Paal–Knorr reaction carried out under microwave irradiation using commercially available chiral amino esters or amino acids and 1,4-dicarbonyl compounds.

1. Introduction

Pharmacophore-based drug design begins with a comparison of active and inactive compounds. This provides an idea of how structural variations can change the biological activity of a compound and allows the development of a hypothesis about the interactions between the molecule and its receptor. This approach is known as molecular mimicry and is based on the determination of the structural elements necessary for activity of the lead compound.[1]

We have been interested in developing original heterocyclic compounds that inhibit the growth of cancer cells. Our approach has been to employ a molecular mimicry paradigm for the generation of new active leads.[2] In preliminary studies, we found that compounds with a pyrroloazepine group and two aromatic groups can be coupled with a ketene address element, generating products with activity and selectivity for some cancer cell lines (Fig. 1).[3] We have also shown that some of the best inhibitors contain *N*-(3-halogen)-phenyl and 2-nitrophenyl substituents.[4] These results suggest that there may be additional opportunities to find active constructs with various physicochemical properties.

Linkage of some amino acid esters to antitumor agents diminishes their toxicity and enhances their intestinal absorption and resistance to glycosidic bond metabolism.[5,6] Also, amino acid derivatives of 4′-dimethyl-4-deoxy-podophyllotoxin have better antitumor activity than the parent compound.[7]

In our previous investigations, we assumed that a pyrroloazepine group and two aromatic groups are required for activity. In the current study, we examined whether replacement of the azepinone moiety with an aliphatic cyclic ketone structure, which has different steric and hydrophobic properties, affects the anticancer activity of compounds **4** and **5**. Simultaneously, we explored whether a polar group as an amino acid motif is required in the active structure (series **6–8**, Fig. 2).

Pyrroles represent a very important class of heterocyclic ring. This structural motif is found in numerous natural

Keywords: Amino acids; Azepinones; Indolones; Cytotoxic activity; Paal–Knorr; Microwave.
* Corresponding author. Tel.: +52 56 22 44 41; fax: +52 56 16 22 03; e-mail: robmar@servidor.unam.mx

0968-0896/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2006.12.018

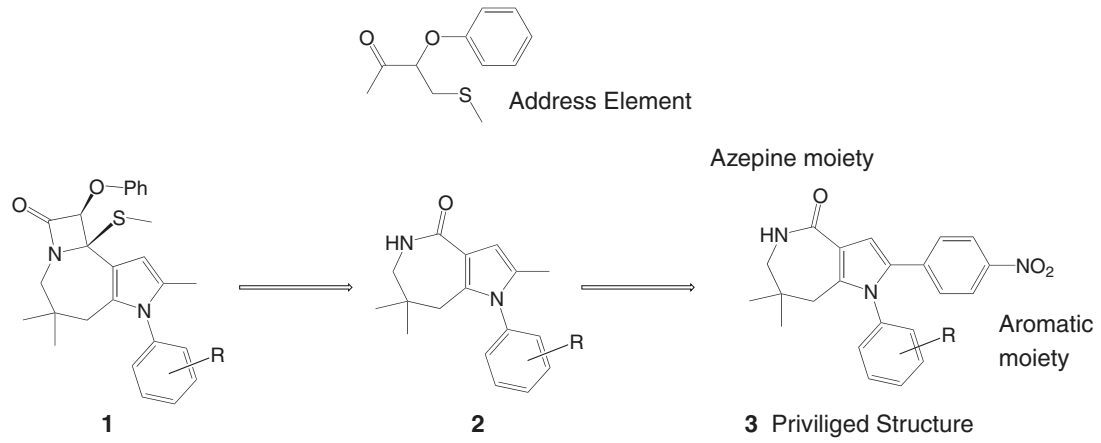


Figure 1. Generation of new active lead compounds from **1** via a molecular mimicry paradigm.

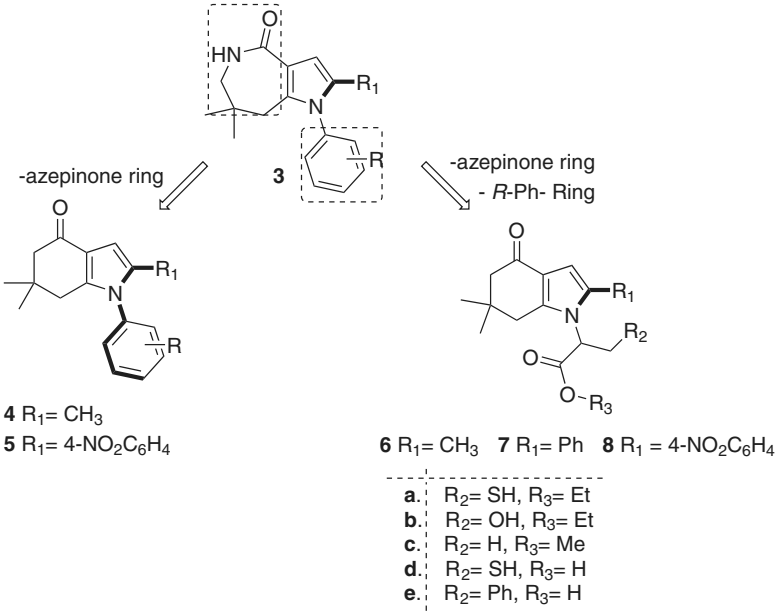


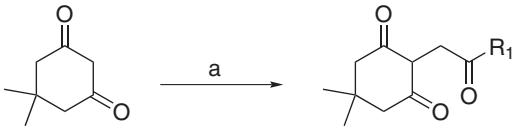
Figure 2. Structural modifications of lead compound **3**.

products with diverse biological properties,[8,9] synthetic drugs,[10] and optoelectronic or electrically conducting materials.[11,12] As a consequence, several synthetic methods have been developed for the construction of the pyrrole structure and its derivatives.[13–16] The Paal–Knorr synthesis is the best-known method for preparing the pyrrole ring. It typically employs amines and 1,4-dicarbonyl compounds as starting materials along with an acid as a catalyst.[17,18] Recently, several modifications of this method have been described, including the use of multicomponent processes,[19–21] acidic materials,[22] and microwave technology.[23–27]

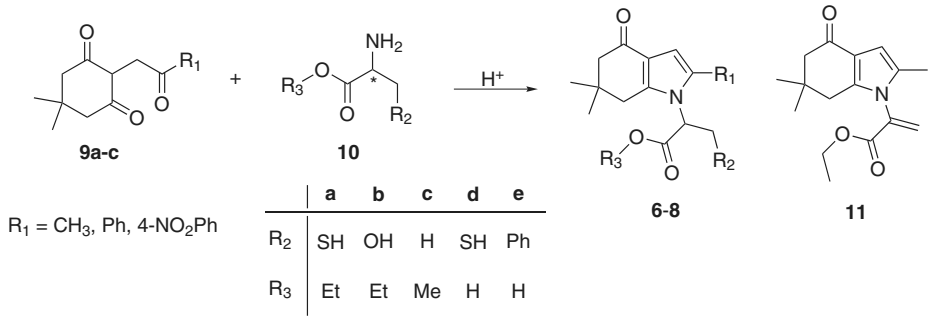
2. Results and discussion

2.1. Chemistry

The preparation of (4-oxo-4,5,6,7-tetrahydroindol-1-yl)-3-*R*-propionic acids and propionic acid ethyl esters **6a–e**, **7a–e**, and **8a** and **8b** involves a two-step procedure starting from commercially available 5,5-dimethyl-1,3-cyclohexanodione. The first step involves alkylation of 5,5-dimethyl-1,3-cyclohexanedione with the corresponding alkyl halide using K_2CO_3 or EtONa as a base (Scheme 1). The structures of these compounds were



Scheme 1. Synthesis of tricarbonyl compounds **9a–c**. Reagents: (a) (i) K_2CO_3, $CHCl_3$, and X–CH_2COR_1; or (ii) EtONa, EtOH, and X–CH_2COR_1.



Scheme 2. Synthesis of tetrahydroindolones by Paal–Knorr reaction.

verified by ^{1}H and ^{13}C NMR, IR, and MS spectral data.[28,29]

The second step involves ring closure in compounds **9** to indol-4-ones **6–8** under Paal–Knorr conditions using different amino acids as amines (Scheme 2). The initial experiment for ring closure of ketone **9a** with the amino ester **10b** (L-serine ethyl ester) was performed using acetic acid at reflux temperature; however, with these reaction conditions compound **11** was obtained due to the elimination of the hydroxyl group. To avoid the loss of chirality, we tried performing the condensation using **10a** (L-cysteine ethyl ester). It is well-known that the SH group would be a poorer leaving group than the OH group under the reaction conditions employed.[30] After several experiments, we were able to obtain the propionic acid ethyl ester **6a** using toluene as a solvent and 3 h of reflux.

In addition, **6a** was also obtained using microwave radiation for 45 min at an internal temperature of 110 °C. We used this microwave-assisted Paal–Knorr method to generate other 3-(tetrahydro-indo-yl)-3-*R*-propionic acid alkyl esters and propionic acids (Table 1).

As shown in Table 1, pyrrole ring closure is controlled by R_1 substituents in the 1,4-dicarbonyl compound **9**, indicating that the 2-methyl group is necessary for obtaining good yields and for reducing the reaction time (entries 1–5). Interestingly, similar tendencies were observed when the 2-methyl substituents were changed to 2-phenyl groups (entries 6–10). In contrast, replacement of the 2-methyl substituent of **9** with a 2-(4-nitrophenyl) moiety (entries 11–14) dramatically reduced the yield and increased the reaction time. HPLC analyses using a chiral column (Chiralcel OD) carried out to indolyl-aminoacids **7b** and **7c** showed the enantiomeric mixture with only 5% and 13% of ee, respectively.

2.2. Biological activity

Indolones **4** and **5**, and *N*-aminoacid-indolones **6–8** were evaluated in vitro for their ability to inhibit the growth of PC-3 prostate, U-251 central nervous system, K-562 leukemia, HCT-15 colon, MFC-7 breast, and SKUL lung cancer cells. The first cytotoxic evaluation was made using compounds **4** and **5**. These compounds did not inhibit the proliferation of the six cancer cell lines, indicating that the azepinone moiety is necessary for the cytotoxic activity of these series of compounds.

Table 1. Paal–Knorr reaction between 1,4-dicarbonyl compounds **9** and amino acid ester[a] or amino acid **10**[b]

Entry	R_1	R_2	R_3	*t*	Yield (%)	Product
1	CH_3	HS	CH_3CH_2	45 min	93[c]	**6a**
2	CH_3	HO	CH_3CH_2	1 h 15 min	70	**6b**
3	CH_3	H	CH_3	1 h 30 min	74[d]	**6c**
4	CH_3	HS	H	1 h 40 min	94	**6d**
5	CH_3	Ph	H	2 h	77	**6e**
6	Ph	HS	CH_3CH_2	2 h	90	**7a**
7	Ph	HO	CH_3CH_2	4 h	71	**7b**
8	Ph	H	CH_3	4 h	50[d]	**7c**
9	Ph	HS	H	4 h	70	**7d**
10	Ph	Ph	H	4 h	70	**7e**
11	4-$NO_2C_6H_4$	HS	CH_3CH_2	4 h	12[e]	**8a**
12	4-$NO_2C_6H_4$	H	CH_3	6 h	26[e]	**8b**
13	4-$NO_2C_6H_4$	HS	CH_3CH_2	12 h	25[f]	**8a**
14	4-$NO_2C_6H_4$	H	CH_3	24 h	40[d,f]	**8b**

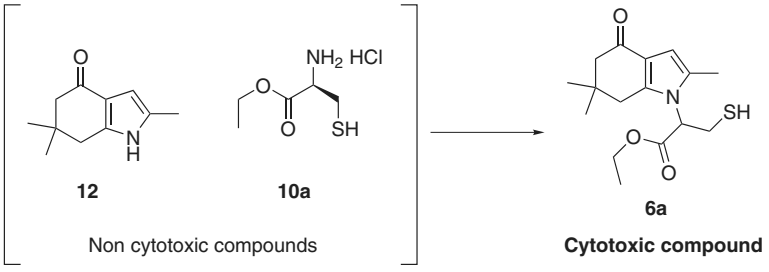
[a] The hydrochlorides of amino esters **10a–c** were used.
[b] All the experiments under microwave irradiation were carried out using a Discover System from CEM.
[c] AcOH is not necessary.
[d] D-Alanine methyl ester was employed.
[e] AcOH was used as a solvent.
[f] Traditional heating.

Table 2. IC_{50} values (μM) of compounds **6a–e**, **7a–e**, and **8a** for the growth of five cancer cell lines[a]

Compound	PC-3 (prostate)	U-251 (CNS)	K-562 (leukemia)	HCT-15 (colon)	MCF-7 (breast)	SKUL (lung)
6a	4.04 ± 1.0	3.36 ± 0.4	3.21 ± 1.1	1.45 ± 0.3	2.06 ± 0.1	2.07 ± 0.3
6b	>100	>100	51.65 ± 2.8	>100	>100	>100
6c	>100	>100	31.94 ± 2.7	1.73 ± 0.2	>100	>100
6d	>100	>100	>100	>100	>100	>100
6e	>100	>100	>100	>100	>100	>100
7a	2.74 ± 0.2	3.72 ± 0.5	2.5 ± 0.3	2.71 ± 0.2	2.46 ± 0.7	3.98 ± 0.3
7b	>100	>100	>100	17.92 ± 2.0	>100	>100
7c	>100	>100	>100	59.79 ± 5.9	54.41 ± 3.7	>100
7d	>100	>100	>100	>100	>100	>100
7e	>100	>100	>100	>100	>100	>100
8a	13.73 ± 0.7	8.5 ± 1.2	4.3 ± 0.2	5.96 ± 0.2	6.76 ± 0.4	10.05 ± 0.7
3[b]	6.3 ± 0.5	20.7 ± 0.9	13.7 ± 1.5	33.6 ± 4.5	11.8 ± 3.8	—

[a] The tumoral cell lines were supplied by the National Cancer Institute. The cytotoxic assay was carried out at 5000–7500 cells/mL using the sulforhamide B (SRB) protein assay to estimate cell growth. The percentage growth was evaluated spectrophotometrically in a Bio Kinetics reader spectrophotometer. Values are means of three experiments, (>100, not active).

[b] R=3-Cl.



Scheme 3.

Replacement of the *N*-(*R*-phenyl) substituent of series **4** and **5** with an *N*-aminoacid moiety (series 6–8) improved their cytotoxic potency in all or at least in some of the cell lines.

Notably, in all of the cancer cell lines except for PC-3 prostate cancer cells, the *N*-(L)-cysteine ethyl ester derivatives **6a**, **7a**, and **8a** were more cytotoxic than lead compound **3** (Table 2). Also, compound **6c** (*N*-(D)-alanine methyl ester group; IC_{50} = 1.73 μM) was 15-fold more cytotoxic than **3** (IC_{50} = 33.6 μM) against the HCT-15 cancer cell line; however, it was 2-fold less active than **3** against the K-562 cancer cells (IC_{50} = 31.94 vs 13.7 μM). Similarly, the *N*-(D)-alanine derivative **7c** was significantly less potent than **3** at killing leukemia and breast cancer lines.

Likewise, incorporation of an (L)-serine ethyl ester residue into the indolone ring for analog **6b** also led to 4-fold decrease in potency compared to **3** in K-562 cells. In contrast, replacing the 2-methyl substituent of **6b** with a 2-(4-nitrophenyl) moiety (compound **7b**) improved its potency and selectivity for the HCT-15 cancer cells (IC_{50} = 17.92 vs 33.7 μM). The replacement of the *N*-(L)-cysteine ethyl ester (compounds **6a** and **7a**) with *N*-(L)-cysteine generated compounds **6d** and **7d**, which have a free carboxylic amino acid moiety. Unfortunately, these compounds did not inhibit the proliferation of the six cancer cell lines. Similarly, the *N*-(L)-phenylalanine derivatives **6e** and **7e** did not show activity against the six cancer cell lines, indicating that the ethyl ester moiety is essential for the cytotoxic activity of these series of compounds.

Because an *N*-amino acid residue was considered optimal for this template, we removed it, producing compound **12**, and examined its effect. Unfortunately, this compound was inactive against all of the cancer cell lines tested. In addition, the cytotoxic activity of the L-cysteine ethyl ester amino acid **10a** was lost. These results support the idea that the *N*-amino acid portion is important for activity (Scheme 3).

3. Conclusion

We synthesized new indolones containing an amino acid or amino ester residue in good yields using a catalytic Paal–Knorr reaction with commercially available chiral amino esters or amino acids and 1,4-dicarbonyl compounds coupled with microwave irradiation. Three new indolones containing *N*-(L)-cysteine ethyl esters were found to be growth inhibitors of PC-3 prostate, U-251 central nervous system, K-562 leukemia, HCT-15 colon, MFC-7 breast, and SKUL lung cancer cells. Also, substitution of the *N*-phenyl substituent of indolones **4** with an *N*-(D)-alanine methyl ester group resulted in compound **6c**, which had enhanced cytotoxic activity against the HCT-15 cancer cell line. Furthermore, substitution of the ethyl ester moiety on **6a** and **7a** with a hydroxyl motif resulted in a loss of cytotoxicity.

Due to the good ability to inhibit the growth of all or some cancer cell lines tested that was given for a enantiomeric mixture of the compounds **6–8** (see Table 2), the synthesis and cytotoxic evaluation of enantiopure compounds is now matter of great importance.

4. Experimental

4.1. General

Melting points were determined on a Melt-Tem II melting point apparatus and are uncorrected. The IR spectra were determined in a Nicolet FT Magna-IR 750 spectrometer. The ^{1}H and ^{13}C NMR were determined in Varian Gemini 200 MHz, Eclipse 300 MHz Jeol, and Bruker Avance 300 MHz spectrometers in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with Jeol AX505-HA and SX-100 Jeol mass spectrometers. Reaction mixtures and chromatography fractions were concentrated by using a rotary evaporator (ca. 20 °C/20 Torr). Chiral HPLC analyses were performed on a Chiralcel OD column 254 nm UV detector, diameter 0.46 cm, length 25 cm. For column chromatography, the Merck silica gel 60 F-254 was employed. Commercial grade reagents were used without further purification except when indicated.

4.2. Synthesis

4.2.1. General procedure for the synthesis of chiral (4,5,6,7-tetrahydro-indol-1-yl)-3-R_2-propionic acids and propionic acid ethyl esters (6–8). A solution of 0.1 g of ketones **9a–c** (1 equiv) and the amino acid esters **10a–c** or amino acids **10d** and **10e** (1.2 equiv) in toluene (5 mL) and acetic acid (0.1–0.5 mL) was prepared in a 10-mL round-bottomed flask, equipped with a stirrer bar and a reflux condenser. The solution was inserted into the cavity of a Discovery Microwave System apparatus (from CEM) and heated at 300 W (internal temperature 110 °C) until the disappearance of starting material. The solvent and acetic acid were evaporated and the required compounds (**6–8**) were purified by flash chromatography.

4.2.1.1. 2-(2,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-3-mercapto-propionic acid ethyl ester (6a). Yield: 93%; IR (film, cm^{-1}) 3109, 2959, 2871, 1739, 1652. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.07 (s, 3H), 1.13 (s, 3H), 1.25 (t, 3H), 1.32 (dd, 1H, ^{3}J = 6.6, ^{3}J = 6.9 Hz, SH), 2.22 (s, 3H), 2.28 (d, 1H, ^{2}J = 16.0 Hz), 2.36 (d, 1H, ^{2}J = 16.0 Hz), 2.58 (s, 2H), 3.14 (m 1H), 3.32 (m, 1H), 4.24 (m, 2H), 4.83 (dd, 1H, ^{3}J = 5.74, 9.9 Hz), 6.3 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.8, 13.8, 25.4, 27.6, 29.0, 35.5, 36.7, 51.4, 60.0, 62.1, 104.3, 119.2, 130.8, 142.3, 168.2, 193.0. FABHRMS *m*/*z*: observed, 310.1476; estimated, 310.1477.

4.2.1.2. 2-(2,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-3-hydroxy-propionic acid ethyl ester (6b). Yield: 70%; IR (film, cm^{-1}) 3376, 2958, 2932, 1739, 1635. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.02 (s, 3H), 1.08 (s, 3H), 1.25 (t, 3H), 2.18 (s, 2H), 2.19 (s, 3H), 2.46 (d, 1H, ^{2}J = 15.9 Hz), 2.57 (d, 1H, ^{2}J = 15.9 Hz), 3.97 (dd, 1H, ^{3}J = 7.8 Hz, ^{2}J = 12 Hz), 4.25 (m, 3H), 4.86 (dd, 1H ^{3}J = 6.3, 6.0 Hz), 6.2 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.8, 13.9, 27.8, 29.0, 35.52, 36.82, 51.18, 59.4, 61.4, 62.1, 104.3, 119.0, 131.2, 143.6, 168.9, 193.9. FABHRMS *m*/*z*: observed, 294.1705; estimated, 294.1705.

4.2.1.3. 2-(2,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-propionic acid methyl ester (6c). Yield: 74%; IR (film, cm^{-1}) 2955, 2871, 1745, 1653, ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.06 (s, 3H), 1.12 (s, 3H), 1.67 (d, 3H, ^{3}J = 7.3 Hz), 2.20 (s, 3H), 2.26 (d, 1H, ^{2}J = 16.4 Hz), 2.34 (d, 1H, ^{2}J = 16.4 Hz), 2.46 (d, 1H, ^{2}J = 16.0 Hz), 2.61 (d, 1H, ^{2}J = 16.0 Hz), 3.76 (s, 3H), 4.86 (c, 1H, ^{3}J = 7.3 Hz), 6.26 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.6, 17.2, 27.7, 29.0, 35.6, 36.9, 51.5, 52.6, 52.7, 103.9, 119.1, 130.2, 142.1, 170.6, 193.1. MS (EI) *m*/*z*: 263.

4.2.1.4. 2-(2,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-3-mercapto-propio-nic acid (6d). Yield: 94%; IR (film, cm^{-1}) 3420, 2957, 2930, 2869, 1723, 1631, 1591, 1548. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ = 1.05 (s, 3H), 1.10 (s, 3H), 1.21 (t, 1H, ^{3}J = 7.2 Hz), 2.18 (s, 3H), 2.23 (d, 1H ^{2}J = 16.2 Hz), 2.32 (d, 1H ^{2}J = 16.2 Hz), 2.54 (d, 1H, ^{2}J = 16.2 Hz), 2.68 (d, 1H, ^{2}J = 16.2 Hz), 3.05 (dd, 1H, ^{3}J = 10.2, ^{2}J = 14.1 Hz), 3.32 (dd, 1H, ^{3}J = 6, ^{2}J = 14.1 Hz), 4.65 (dd, 1H, ^{3}J = 5.4, ^{2}J = 10.5 Hz), 6.23 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.8, 26.2, 27.6, 28.9, 35.5, 36.6, 51.3, 61.9, 103.7, 118.1, 131.5, 144.4, 173, 194.6. FABHRMS *m*/*z*: observed, 282.1175; estimated, 282.1164.

4.2.1.5. 2-(2,6,6-Trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-3-phenyl-propionic acid (6e). Yield: 77%; mp = 217–220 °C; IR (film, cm^{-1}) 3427, 3026, 2964, 2928, 2874, 1723, 1603. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ = 0.83, (br, 3H), 1.08 (br, 3H), 1.98 (br, 3H), 2.17 (d, 1H, ^{2}J = 16.5 Hz), 2.34 (d, 1H, ^{2}J = 16.2 Hz), 2.55 (d br, 1H), 3.17 (dd, 1H, ^{3}J = 11.4 Hz, ^{2}J = 14.1 Hz), 3.60 (dd, 1H, ^{3}J = 4 Hz, ^{2}J = 14.1 Hz), 4.80 (dd, 1H, ^{3}J = 4.0 Hz, 11.4 Hz), 6.20 (s, 1H), 6.91 (m, 2H), 7.20 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.9, 28.0, 29.2, 35.9, 37.0, 37.7, 51.7, 60.1, 104.5, 118.8, 127.5, 129.1, 129.4, 132.2, 137.2, 145.2, 171.6, 195.8. FABHRMS *m*/*z*: observed, 326.1745; estimated, 326.1756.

4.2.1.6. 2-(6,6-Dimethyl-4-oxo-2-phenyl-4,5,6,7-tetrahydro-indol-1-yl)-3-mercapto-propionic acid ethyl ester (7a). Yield: 90%; IR (film, cm^{-1}) 2958, 2935, 2871, 2558, 1738, 1659, 1465. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.10 (s, 1H), 1.18 (s, 1H), 1.27 (t, 3H), 2.26 (d, 1H, ^{2}J = 16.2 Hz), 2.35 (d, 1H, ^{2}J = 16.2 Hz), 2.45 (d, 1H, ^{2}J = 16.0 Hz), 2.57 (d, 1H, ^{2}J = 16.0 Hz), 3.0 (m, 1H), 3.2 (m, 1H), 4.23 (m, 2H), 4.94 (dd, 1H, ^{3}J = 6.0 Hz, 9.3 Hz), 6.55 (s, 1H), 7.4 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.0, 25.6, 27.6, 29.3, 35.8, 37.3, 51.7, 60.4, 62.3, 105.6, 120.4, 128.3, 128.5, 130.0, 131.9, 137.6, 142.3, 168.6, 193.3. FABHRMS *m*/*z*: observed, 372.1640; estimated, 372.1633.

4.2.1.7. 2-(6,6-Dimethyl-4-oxo-2-phenyl-4,5,6,7-tetrahydro-indol-1-yl)-3-hydroxy-propionic acid ethyl ester (7b). Yield: 71%; mp = 167–168 °C; IR (film, cm^{-1}) 3357, 3060, 2959, 2934, 2872, 1738, 1639. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.03 (s, 3H), 1.13 (s, 3H), 1.23 (t, 3H), 2.21 (d, 1H, ^2J = 16.5 Hz), 2.29 (d, 1H, ^2J = 16.5 Hz), 2.43 (d, 1H, ^2J = 16.2 Hz), 2.68 (d, 1H, ^2J = 16.2 Hz), 3.96 (dd, 1H, ^3J = 7.8 Hz, ^2J = 11.7 Hz), 4.12 (m, 1H), 4.25 (m, 2H), 5.05 (dd, 1H, ^3J = 6.3 Hz, ^2J = 7.5 Hz), 6.45 (s, 1H), 7.36 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.9, 27.4, 29.4, 35.7, 37.4, 51.5, 59.6, 61.5, 62.1, 105.7, 120.1, 128.2, 128.6, 129.8, 130.0, 131.8, 137.5, 143.5, 169.2, 193.9. $C_{21}H_{25}NO_4$: calcd C 70.96, H 7.09; found C 70.78, H 7.26.

4.2.1.8. 2-(6,6-Dimethyl-4-oxo-2-phenyl-4,5,6,7-tetrahydro-indol-1-yl)-propionic acid methyl ester (7c). Yield: 50%; mp = 144–146 °C; IR (film, cm^{-1}) 3058, 2998, 2956, 2872, 1745, 1660. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 3H), 1.16 (s, 3H), 1.63 (d, 3H, ^3J = 7.32 Hz), 2.33 (d, 1H, ^2J = 16.1 Hz), 2.41 (d, 1H, ^2J = 14.1 Hz), 2.48 (d, 1H, ^2J = 14.0 Hz), 2.7 (d, 1H, ^2J = 16.1 Hz), 3.74 (s, 3H), 4.97 (c, 1H, ^3J = 7.32 Hz), 6.55 (s, 1H), 7.3–7.5 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.6, 27.6, 29.3, 35.8, 37.4, 51.8, 52.8, 53.2, 105.3, 120.3, 128.1, 128.7, 129.5, 132.0, 136.5, 142.8, 171.0, 193.5. $C_{21}H_{25}NO_4$: calcd C 73.82, H 7.12; found C 73.86, H 7.34.

4.2.1.9. 2-(6,6-Dimethyl-4-oxo-2-phenyl-4,5,6,7-tetrahydro-indol-1-yl)-3-mercapto-propionic acid (7d). Yield: 70%; (c = 0.5,CH_3OH); mp = 98–100 °C; IR (film, cm^{-1}) 3428, 3060, 2958, 2932, 2871, 1727, 1624. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.06 (s, 3H), 1.14 (s, 3H), 2.37 (d, 1H, ^2J = 16.5 Hz), 2.46 (d, 1H, ^2J = 16.5 Hz), 2.63 (d, 1H, ^2J = 15.9 Hz), 2.70 (d, 1H, ^2J = 15.9 Hz), 2.98 (m, 1H), 3.22 (m, 1H), 4.97 (dd, 1H, ^3J = 5.7 Hz, 10.2 Hz), 6.53 (s, 1H), 7.35 (m, 5H), 10.67 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.7, 27.7, 29.0, 36.0, 37.3, 51.1, 60.5, 105.7, 119.6, 128.5, 128.6, 130.1, 131.6, 138.4, 144.7, 170.1, 195.9. FABHRMS m/z: observed, 344.1313; estimated, 344.1320.

4.2.1.10. 2-(6,6-Dimethyl-4-oxo-2-phenyl-4,5,6,7-tetrahydro-indol-1-yl)-3-phenyl-propionic acid (7e). Yield: 70%; mp = 140–142 °C; IR (film, cm^{-1}) 3426, 3062, 3029, 2958, 2871, 1606, 1474. ^1H NMR (300 MHz, $CDCl_3$+ CD_3OD) δ = 1.0, (s, 3H), 1.15 (s, 3H), 2.3 (d, 1H, ^2J = 16.2 Hz), 2.41 (d, 1H, ^2J = 16.2 Hz), 2.64 (d, 1H, ^2J = 16.2), 2.77 (d, 1H, ^2J = 16.2), 3.02 (dd, 1H, ^2J = 14.1 Hz, ^3J = 12 Hz), 3.40 (dd, 1H, ^2J = 14.1 Hz, ^3J = 3.6 Hz), 4.89 (dd, 1H, ^2J = 14.1 Hz, ^3J = 3.6 Hz), 6.29 (s, 1H), 6.62 (m, 4H), 7.11 (m, 6H), 8.32 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.4, 29.0, 36.3, 38.1, 38.3, 51.9, 62.2, 104.6, 119.6, 126.8, 128.0, 128.3, 128.7, 129.0, 130.1, 132.5, 138.0, 138.8, 144.9, 176.6, 195.9. FABHRMS m/z: observed, 388.1922; estimated, 388.1913.

4.2.1.11. 2-[6,6-Dimethyl-2-(4-nitrophenyl)-4-oxo-4,5,6,7-tetrahydro-indol-1-yl]-3-mercaptopropionic acid ethyl ester (8a). Yield: 12%; IR (film, cm^{-1}) 2959, 2936, 2871, 1739, 1661, 1598, 1518. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.10 (s, 3H), 1.19 (s, 3H), 1.13 (t, 3H), 2.36. (d, 1H, ^2J = 15.6 Hz), 2.45 (d, 1H, ^2J = 15.6 Hz), 2.54 (d, 1H, ^2J = 16.0 Hz), 2.67 (d, 1H, ^2J = 16.0 Hz), 2.98–3.33 (m, 2H), 4.30 (m, 2H), 4.94 (dd, 1H, ^2J = 14.7 Hz, ^3J = 8.5 Hz), 6.69 (s, 1H), 7.58 (d, 2H), 8.30 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.1, 25.8, 27.6, 29.3, 35.9, 37.4, 51.7, 60.8, 62.8, 107.6, 124.0, 130.2, 135.8, 138.5, 143.7, 147.2, 147.3, 168.3, 193.4. MS (EI) m/z: 416.

4.2.1.12. 2-[6,6-Dimethyl-2-(4-nitrophenyl)-4-oxo-4,5,-6,7-tetrahydro-indol-1-yl]-propionic acid methyl ester (8b). Yield: 26%; IR (film, cm^{-1}) 3410, 3101, 2958, 2934, 2872, 1745, 1660, 1343. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.10 (s, 3H), 1.18 (s, 3H), 1.67 (d, 3H), 2.35 (d, 1H, ^2J = 16.4 Hz), 2.43 (d, 1H, ^2J = 16.4 Hz), 2.50 (d, 1H, ^2J = 16.1 Hz), 2.73 (d, 1H, ^2J = 16.1 Hz), 3.78 (s, 3H), 4.96 (c, 1H), 6.7 (s, 1H), 7.5 (d, 2H), 8.28 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.6, 27.5, 29.3, 35.8, 37.5, 51.7, 53.06, 53.65, 107.7, 120.9, 124.1, 129.6, 134.3, 138.5, 144.5, 147.1, 170.5, 193.36. FABHRMS m/z: observed, 371.1600; estimated, 371.1607.

4.2.1.13. Ethyl-2-(4,5,6,7-tetrahydro-2,6,6-trimethyl-4-oxo-indo-1-yl)acrylate (11). ^1H NMR (200 MHz, $CDCl_3$) δ = 1.08 (s, 6H), 1.30 (t, 3H), 2.07 (s, 3H), 2.34 (s, 2H), 2.43 (s, 2H), 4.26 (c, 2H), 5.87 (s, 1H), 6.31 (c, 1H), 6.74 (s, 1H).

Acknowledgments

We thank DGAPAUNAM (IN-2281031) for financial support. We also thank UNAM for postdoctoral position (A. C. -S.), R. Patiño, H. Rios, A. Peña, N. Zavala, E. Huerta, E. García, L.Velasco, and J. Pérez for technical assistance, and Luis Miranda (IQ) for microwave system apparatus. Contribution No. 2643 from Instituto de Química, UNAM.

References and notes

1. Cohen, N. C. Lead Structures in Pharmacophore-Base Drug Design. In *Medicinal Chemistry Today and Tomorrow*; Yamazaki, M., Ed.; Blackwell Science: Oxford, 1997; pp 15–22.
2. Cohen, N. C. Molecular Mimics and Drug Design. In *Trends in Medicinal Chemistry*; Van der Goot, H., Domany, G., Pallos, L., Timmerman, H., Eds.; Elsevier Science: Amsterdam, 1989; pp 13–28.
3. Martínez, R.; Ávila, J. G.; Duran, M. E.; Ramírez, M. T.; Cañas, R. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1675.
4. Martínez, R.; Ávila, J. G.; Ramírez, M. T.; Pérez, A.; Martínez, A. *Bioorg. Med. Chem.* **2006**, *14*, 4007.
5. Liu, L.-Y.; Chen, R.-Y.; Huang, Y. *Heteroat. Chem.* **2005**, *16*, 33, and references therein.
6. Landowski, C. P.; Song, X.; Lorenzi, P. L.; Hilfinger, J. M.; Amidon, G. L. *Pharm. Res.* **2005**, *22*, 1510.
7. Kim, Y.; You, Y.-J.; Nam, N.-H.; Ahn, B.-Z. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3435.
8. Boger, D. L.; Boyee, C. W.; Labroll, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.

9. Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753.
10. Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817.
11. Lee, C.-F.; Yang, L.-M.; Hwu, T.-Y.; Feng, A.-S.; Tseng, J.-C.; Luh, T.-L. *J. Am. Chem. Soc.* **2000**, *122*, 4992.
12. Fürsnett, A. *Synlett* **1999**, 1523.
13. Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238.
14. Hansford, K. A.; Zanzarova, V.; Dörr, A.; Lubell, W. D. *J. Comb. Chem.* **2004**, *6*, 893.
15. Takaya, H.; Kojima, S.; Murahashi, S.-I. *Org. Lett.* **2001**, *3*, 421.
16. Rao, H. S. P.; Jothilingam, S. *Tetrahedron Lett.* **2001**, *42*, 6595.
17. Martínez, R.; López, G.; Ávila, J. G. *J. Heterocycl. Chem.* **1995**, *32*, 491, and references cited therein.
18. Negrón, G.; Ángeles, D.; Lomas, L.; Martínez, A.; Ramírez, M.; Martínez, R. *Heterocycles* **2004**, *63*, 367.
19. Werner, S.; Lyer, P. S.; Fodor, M. D.; Coleman, C. M.; Twining, L. A.; Mitasev, B.; Brummond, K. M. *J. Comb. Chem.* **2006**, *8*, 368.
20. Braun, R. U.; Zeitler, K.; Müller, T. J. *J. Org. Lett.* **2001**, *3*, 3297.
21. Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465.
22. Song, G.; Wang, B.; Wang, G.; Kang, Y.; Yang, T.; Yang, L. *Synth. Commun.* **2005**, *35*, 1051, and references cited therein.
23. Alongi, M.; Minetto, G.; Taddei, M. *Tetrahedron Lett.* **2005**, *46*, 7069.
24. Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. Eur. *J. Org. Chem.* **2005**, 5277.
25. Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389.
26. Dai, W.-M.; Guo, D.-S.; Sun, L.-P.; Huang, X.-H. *Org. Lett.* **2003**, *5*, 2919.
27. Danks, T. N. *Tetrahedron Lett.* **1999**, *40*, 3957.
28. Menes-Arzate, M.; Martínez, R.; Cruz-Almanza, R.; Muchowski, J. M.; Osornio, Y. M.; Miranda, L. D. *J. Org. Chem.* **2004**, *69*, 4001.
29. Maini, P. M.; Sammes, M. P.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 161.
30. Oae, S.; Kiritani, R. *Bull. Chem. Soc. Jpn.* **1965**, *8*, 1381.