Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 2787–2790

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

A Novel Pyridazinone Derivative as a Nonprostanoid PGI_2 Agonist

Kazunori Tsubaki,[a,†] Kiyoshi Taniguchi,[a,*] Seiichiro Tabuchi,[a] Osamu Okitsu,[a] Kouji Hattori,[a] Jiro Seki,[b] Kazuo Sakane[a] and Hirokazu Tanaka[a]

[a]*Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co., Ltd, 1-6, 2-Chome, Kashima, Yodogawa-ku, Osaka 532-8514, Japan*

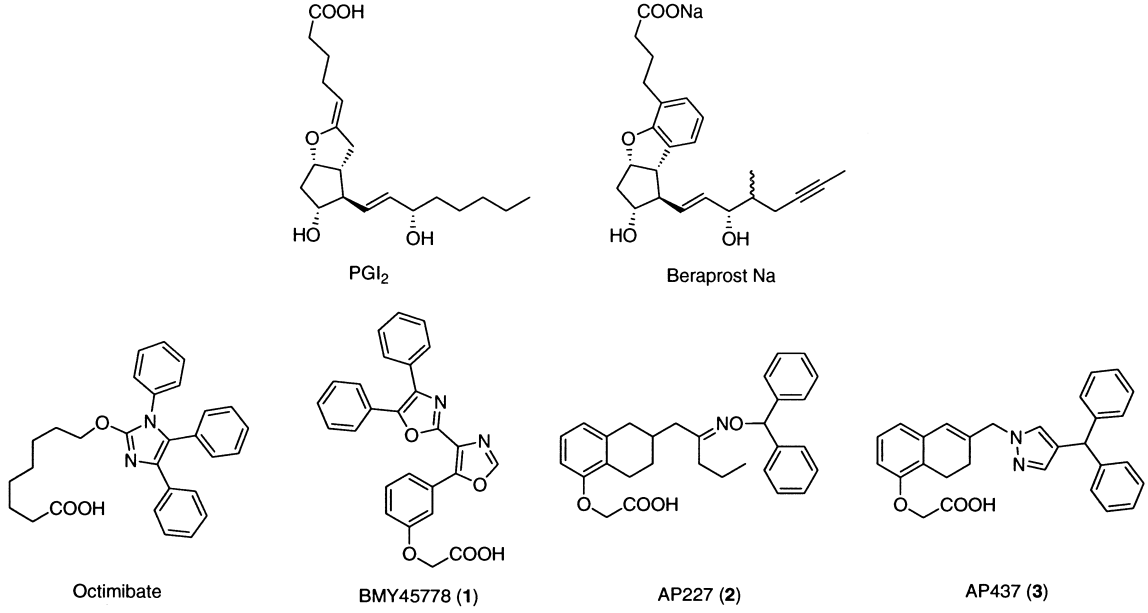
[b]*Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd, 1-6, 2-Chome, Kashima, Yodogawa-ku, Osaka 532-8514, Japan*

Received 22 August 2000; accepted 2 October 2000

Abstract—A novel optically pure pyridazinone derivative was synthesized and identified as a nonprostanoid PGI_2 agonist. It inhibited ADP-induced aggregation of human platelets with an IC_{50} value of 0.081 μM and has high oral bioavailability (56%) with a long half-life (4.3 h) in rats.

Introduction

PGI_2 (prostacyclin) is a powerful endogenous inhibitor of platelet function and a potent vasodilator.[1] Although these actions are considered to be clinically useful, its therapeutic application is limited by both chemical and metabolic instability.[1b] Thus the preparation of PGI_2 analogues with modified chemical and biological prop-

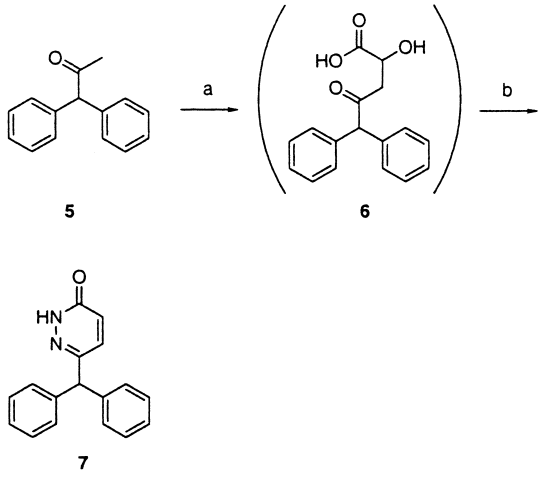


*Corresponding author. Tel: +81-6-6390-1141; fax: +81-6-6304-5435; e-mail: kiyoshi_taniguchi@po.fujisawa.co.jp
†Present address: Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan.

0960-894X/00/$ - see front matter
PII: S0960-894X(00)00571-0

erties has been encouraged.[1c] Beraprost Na, a clinically useful synthetic PGI_2, is a chemically stable and orally active drug, but its duration is still short owing to its metabolic instability.[2]

Recently, nonprostanoid PGI_2 mimetics with chemical and metabolic stability have been reported.[3,4] Octimibate was shown to be a PGI_2 mimetic.[3a,b] A Bristol-Myers Squibb group demonstrated BMY45778 (**1**) as a nonprostanoid PGI_2 mimetic[3d] and an Ono group showed that AP227 (**2**) and AP437 (**3**) were orally active PGI_2 agonists.[4a–c] Thus we aimed to find a nonprostanoid PGI_2 mimetic possessing an alternative structure and having long duration superior to that of beraprost Na.



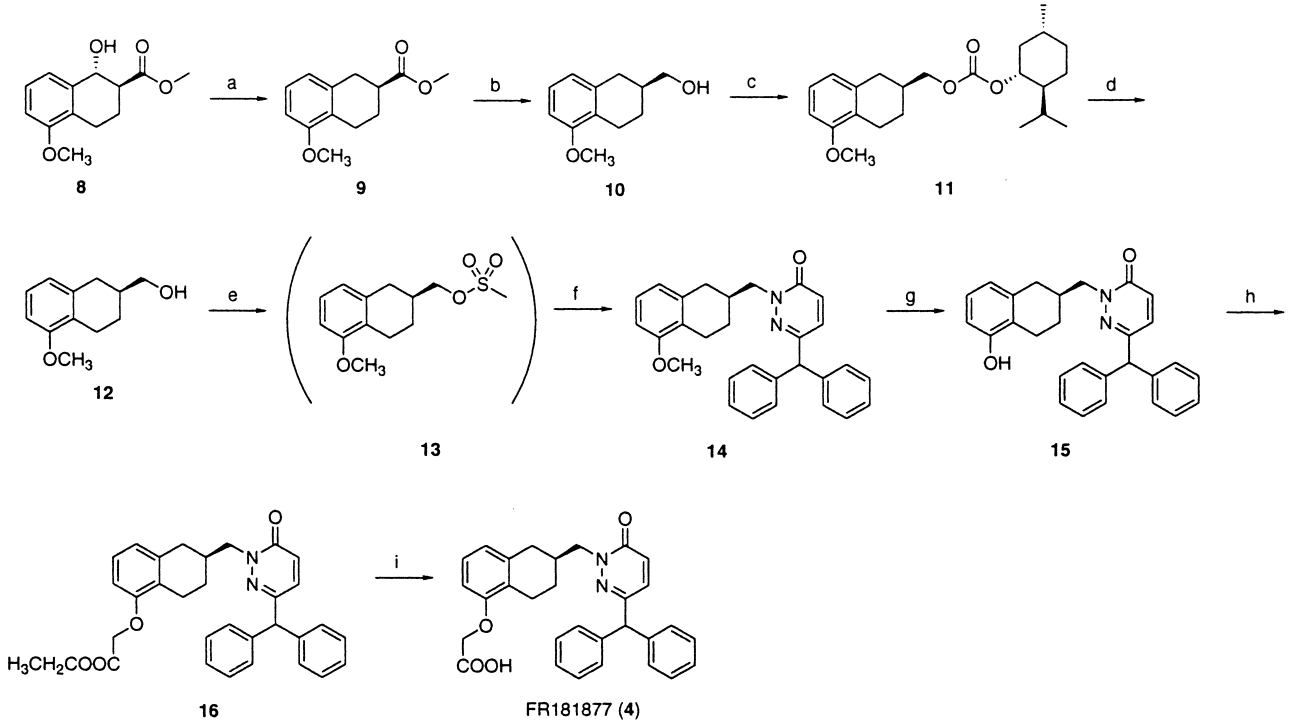
Scheme 1. Reagents and conditions: (a) HCOCOOH H_2O, DME, reflux, 3 days; (b) NH_2NH_2 H_2O, water, reflux, (20% two steps).

We focused our attention on AP227 and AP437. On the basis of similarities of the chemical structures of AP227 and AP437 to that of BMY45778, we speculated that the phenoxyacetic acid moiety and the benzhydryl group of the AP compounds played an important role in binding to the PGI_2 receptor (IP). The Ono group also reported that the chemical modifications of the oxime moiety to the other groups (ether, amide) or of the pyrazole moiety to the other 5-membered heteroaromatics greatly affected the PGI_2 mimetic activities.[4b–e] Thus we aimed to create a functional group alternative to the oxime group or the pyrazole group, key groups of the AP compounds. As a result, we generated a novel pyridazinone derivative, FR181877 (**4**). In this report, we describe the synthesis and pharmacological and pharmcokinetic properties of optically pure FR181877 and related compounds.

Synthesis

The objective 3-pyridazinone derivative, FR181877 (**4**), was prepared as shown in Schemes 1 and 2.

The right part of compound **4**, benzhydrylpyridazinone **7**, was prepared by cyclization of γ-oxopentanoic acid **6**, which was prepared by condensation of 1,1-diphenylacetone (**5**) with glyoxalic acid, with hydrazine as shown in Scheme 1.



Scheme 2. Reagents and conditions: (a) H_2 (3 atm), 10% Pd/C, MeOH, rt (78%); (b) $LiAlH_4$, THF, −70 °C (99%); (c) (1) (−)-Menthyl chloroformate, pyridine, 0 °C; (2) recrystallization from *n*-hexane (46%); (d) 3 N NaOH, THF–water, rt (99%); (e) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0 °C; (f) **7**, *tert*-BuOK, 18-crown-6, DMF, rt (77% two steps); (g) BBr_3, CH_2Cl_2, 0 °C–reflux (83%); (h) $BrCH_2COOCH_2CH_3$, K_2CO_3, DMF, rt–50 °C (95%); (i) 1 N NaOH, DME, 85 °C (82%).

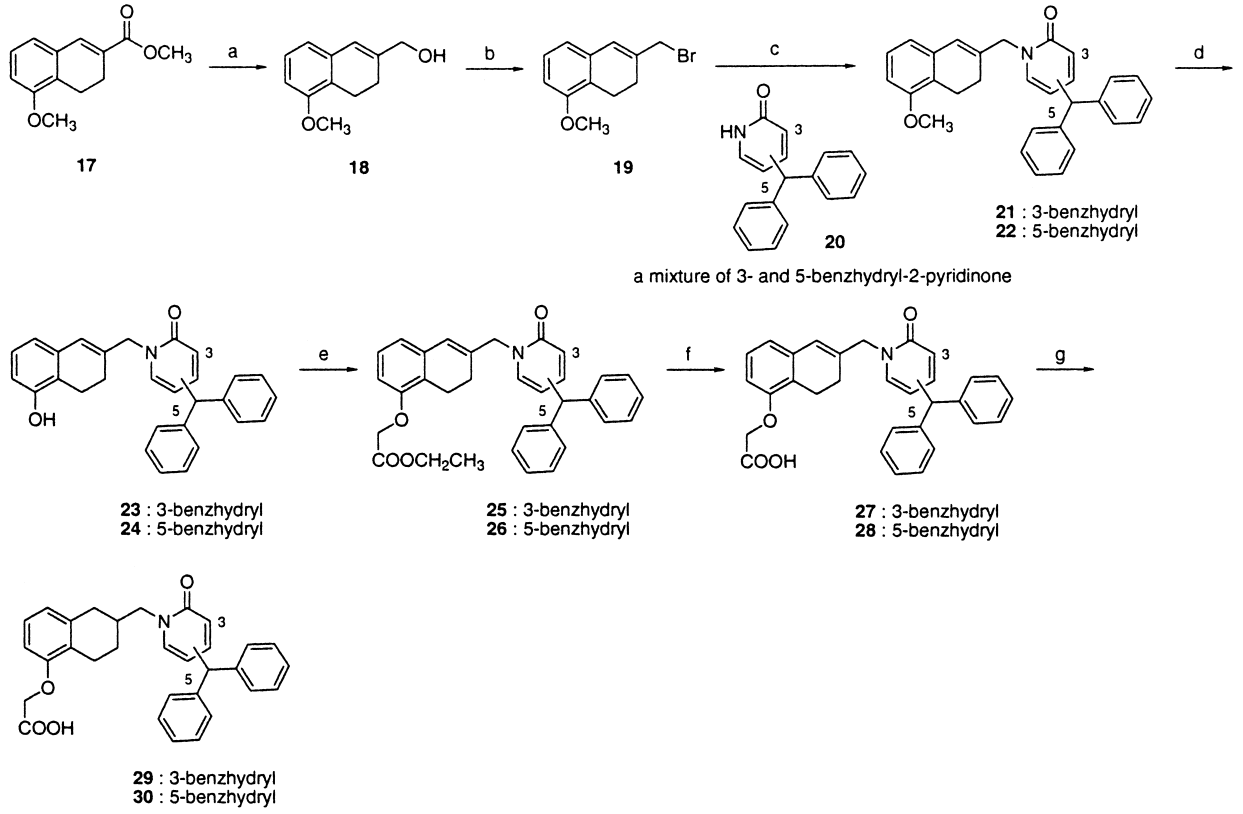
The key intermediate for the synthesis of compound **4**, optically pure (*S*)-2-tetralinemethanol **12**, was prepared as shown in Scheme 2. The starting material, (1*R*,2*S*)-1-hydroxy-2-tetralinecarboxylic acid methyl ester **8** (90% ee),[5] was dehydroxylated by hydrogenation on palladium/carbon to afford the corresponding 2-tetralinecarboxylic acid methyl ester **9**. The methyl ester **9** was reduced quantitatively to the corresponding (*S*)-2-tetralinemethanol **10** (70% ee) with lithium aluminum hydride. In order to obtain the optically pure methanol **12**, the obtained methanol **10** was acylated to the corresponding (−)-menthyl carbonate **11** to give a mixture of two diastereomers, the recrystallization of which from *n*-hexane resulted in an improvement of its diastereomeric excess. The recrystallized carbonate **11** was hydrolyzed with NaOH to afford the optically pure methanol **12**. Its optical purity was determined by HPLC with a chiral stationary-phase column (Chiralpak AD) to be > 99% ee. The methanol **12** was mesylated, and the resulting mesylate **13**, without isolation, was treated with the anion of benzhydrylpyridazinone **7** in the presence of 18-crown-6 to afford (*S*)-2-[(2-tetralinyl)methyl]-3(2*H*)-pyridazinone **14**. Compound **14** was demethylated with BBr_3 to provide the corresponding 5-hydroxytetralinyl derivative **15**, which was transformed to the objective compound **4** (FR181877)[6] by treatment with bromoacetic acid ethyl ester, followed by saponification. The optical purity of the 5-(ethoxycarbonylmethoxy)tetralinyl derivative **16** was determined by HPLC with a chiral stationary-phase column (Chiralcel AS) to be > 99% ee.

The 3- or 5-benzhydryl-2-pyridinone derivatives **29** and **30** were prepared as shown in Scheme 3.

The reduction of the starting material, 3,4-dihydro-2-naphthalenecarboxylic acid methyl ester[7] **17**, to 3,4-dihydro-2-naphthalenemethanol **18** with diisobutylaluminum hydride (DIBAL-H) was followed by treatment with carbon tetrabromide and triphenylphosphine to provide the corresponding bromide **19**. The bromide **19** was treated with the anion of a mixture of 3- and 5-benzhydryl-2-pyridinone[8] **20** in the presence of 18-crown-6 and the resulting products were separated by silica gel column chromatography to provide 3- and 5-benzhydryl-1-[(3,4-dihydro-2-naphthalenyl)methyl]-2(1*H*)-pyridinones **21** and **22**. Compounds **21** and **22** were demethylated with BBr_3 to provide the corresponding 5-hydroxydihydronaphthalenes **23** and **24**, respectively, which were transformed to the corresponding 5-car-

Table 1. Inhibition of ADP-induced aggregation of human platelets

Compounds	IC_{50} (μM)
4 (FR181877)	0.081
29	> 10
30	0.13



Scheme 3. Reagents and conditions: (a) DIBAL-H, toluene, 5 °C (quantitative); (b) CBr_4, PPh_3, CH_2Cl_2, rt (quantitative); (c) (1) *tert*-BuOK, 18-crown-6, DMF, rt; (2) SiO_2 column chromatography (separation); (13 and 31% for **21** and **22**, respectively); (d) BBr_3, CH_2Cl_2, 0 °C (66 and 99% for **23** and **24**, respectively); (e) $BrCH_2COOCH_2CH_3$, K_2CO_3, CH_3CN, reflux (72 and 83% for **25** and **26**, respectively); (f) 1 N NaOH, DME, rt (71 and 83% for **27** and **28**, respectively); (g) H_2 (1 atm), Pd/C, THF, rt (54 and 94%, for **29** and **30**, respectively).

boxymethoxydihydronaphthalene derivatives **27** and **28**, respectively, by treatment with bromoacetic acid ethyl ester and subsequent saponification. Hydrogenation of compounds **27** and **28** on palladium/carbon in THF provided the objective 3- and 5-benzhydryl-1-[(2-tetralinyl)methyl]-2-pyridinones **29**[9] and **30**,[10] respectively.

Biological Results

The activities of the PGI_2 agonists were evaluated in terms of inhibition against ADP-induced aggregation of human platelets in platelet-rich plasma (PRP) and against [^{3}H]-iloprost binding to human IP (PGI_2) receptor. Beraprost Na, AP227 (**2**), AP437 (**3**), and FR181877 (**4**) inhibited ADP-induced aggregation of human platelets with IC_{50} values of 4.3 nM, 0.15 μM, 0.041 μM, and 0.081 μM, respectively. Beraprost Na and FR181877 inhibited [^{3}H]-iloprost binding to the human IP receptor with K_i values of 0.080 and 0.094 μM, respectively.

The inhibitory activity of 2-pyridinones **29** and **30**, FR181877 analogues, against ADP-induced aggregation of human platelets is shown in Table 1 in comparison with that of FR181877. Replacement of the pyridazinone of FR181877 with pyridinone did not greatly affect the activity (compound **30**). Shifting the benzhydryl group of compound **30** from the 5-position to the 3-position resulted in complete loss of the activity (compound **29**). These facts show that the 1-position nitrogen atom of the pyridazinone ring of FR181877 is not essential in binding to the IP receptor but its benzhydryl group plays an important role in the binding.

FR181877 exhibited excellent pharmacokinetic properties, namely good oral bioavailability and a long half-life ($t_{1/2}\beta$). It was administered (10 mg/kg po ($n=3$), 3.2 mg/kg iv ($n=2$)) to fasted male rats. Its oral bioavailability is 56%, and its half-life ($t_{1/2}\beta$) is 4.3±0.2 h which is longer compared with that of beraprost Na (0.43 and 3.3 h in male and female rats, respectively).[2b]

Summary

FR181877 (**4**) possessing a pyridazinone group as a key functional group alternative to the oxime group of AP227 (**2**) or the pyrazole group of AP437 (**3**) was shown to be a novel nonprostanoid PGI_2 agonist. Its high optical purity was accomplished by increasing the diastereomeric excess of (−)-menthylcarbonate **11** transformed from 2-tetralinemethanol **10** (70% ee) by recrystallization. It exhibited potent PGI_2 mimetic functional activity in human platelets and has good oral bioavailability with a long half-life ($t_{1/2}\beta$) in rats.

Acknowledgements

We thank Mr. Yoshihiko Sakai of Biopharmaceutical and Pharmacokinetic Research Laboratories, Fujisawa Pharmaceutical Co., Ltd for performing the pharmacokinetic experiments.

References and Notes

1. (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663. (b) Meanwell, N. A.; Romine, J. L.; Seiler, S. M. *Drugs Future* **1994**, *19*, 361. (c) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533.
2. (a) Kato, R.; Uji, Y.; Matsumoto, K. *Jpn. J. Clin. Pharmacol. Ther.* **1989**, *20*, 515. (b) Matsumoto, K.; Tajima, A.; Hirano, Y.; Ohno, K.; Yuge, T.; Hamasaki, T.; Hase, T.; Horiba, M. *Xenobio. Metabol. Dispos.* **1989**, *4*, 713. (c) Kato, R.; Uji, Y.; Ono, K.; Matsumoto, K.; Hisano, K.; Sakai, I.; Kagawa, Y.; Isai, M. *Jpn. J. Clin. Pharmacol. Ther.* **1986**, *17*, 267. (d) Kato, R.; Uji, Y.; Matsumoto, K. *Jpn. J. Clin. Pharmacol. Ther.* **1989**, *20*, 529. (e) Isaka, Y.; Handa, N.; Imaizumi, M.; Kimura, K.; Kamada, T. *Thromb. Haemost.* **1991**, *65*, 344.
3. (a) Seiler, S. M.; Brassard, C. L.; Arnold, A. J.; Meanwell, N. A.; Fleming, J. S.; Keely, S. L., Jr. *J. Pharm. Exp. Ther.* **1990**, *255*, 1021. (b) Merritt, J. E.; Hallam, T. J.; Brown, A. M.; Boyfield, I.; Cooper, D. G.; Hickey, D. M. B.; Jaxa-Chamiec, A. A.; Kaumann, A. J.; Keen, M.; Kelly, E.; Kozlowski, U.; Lynham, J. A.; Moores, K. E.; Murray, K. J.; MacDermot, J.; Rink, T. J. *Brit. J. Pharmacol.* **1991**, *102*, 251. (c) Meanwell, N. A.; Rosenfeld, M. J.; Kim Wright J. J.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming, J. S.; Seiler, S. M. *J. Med. Chem.* **1992**, *35*, 389. (d) Meanwell, N. A.; Romine, J. L.; Rosenfeld, M. J.; Martin, S. W.; Trehan, A. K.; Kim Wright, J. J.; Malley, M. F.; Gougoutas, J. Z.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming, J. S.; Gamberdella, M.; Hartl, K. S.; Zavoico, G. B.; Seiler, S. M. *J. Med. Chem.* **1993**, *36*, 3884.
4. (a) Kondo, K.; Hamanaka, N. *Folia Pharmacol. Jpn.* **1995**, *106*, 181. (b) Hamanaka, N.; Takahashi, K.; Nagao, Y.; Torisu, K.; Takada, H.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1071. (c) Hamanaka, N.; Takahashi, K.; Nagao, Y.; Torisu, K.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1083. (d) Hamanaka, N.; Takahashi, K.; Nagao, Y.; Torisu, K.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1077. (e) Nagao, Y.; Takahashi, K.; Torisu, K.; Kondo, K.; Hamanaka, N. *Heterocycles* **1996**, *42*, 517.
5. Genêt, J. P.; Pfister, X.; Ratovelomanana-Vidal, V.; Pinel, C.; Laffitte, J. A. *Tetrahedron Lett.* **1994**, *35*, 4559.
6. Physical data for compound FR181877 (**4**): mp 82–83 °C (AcOEt); $[\alpha]_D^{25}$ −27.6° (*c* 0.75, CH_2Cl_2); IR (Nujol) cm^{-1}: 1730, 1655, 1635, 1565; ^{1}H NMR (DMSO-d_6) δ: 1.34 (1H, m), 1.77 (1H, m), 2.20 (1H, m), 2.35–2.85 (4H, m), 3.90–4.10 (2H, m), 4.65 (2H, s), 5.57 (1H, s), 6.56–6.62 (2H, m), 6.92 (1H, d, $J=9.5$ Hz), 7.01 (1H, t, $J=7.9$ Hz), 7.20–7.37 (11H, m), 12.94 (1H, br s); (+)APCI-MS *m*/*z*: 481 ($M^+ + 1$).
7. Cook, C.; Cho, Y.; Jew, S.; Lee, Y.; Chung, T. *Soul Taehakkyo Yakhak Nonmunjip* **1983**, *8*, 1.
8. Sherlock, M. H.; Roebke, H. US Patent 4,138,488, 1979; *Chem. Abstr.* **1979**, *90*, 168465n.
9. Physical data for compound **29**: mp 185–187 °C (Et_2O); IR (Nujol) cm^{-1}: 1730, 1645, 1590, 1560; ^{1}H NMR (DMSO-d_6) δ: 1.35 (1H, m), 1.80 (1H, m), 2.15 (1H, m), 2.35–2.95 (4H, m), 3.89 (2H, m), 4.30 (2H, s), 5.64 (1H, s), 6.20 (1H, t, $J=6.7$ Hz), 6.54 (2H, d, $J=7.9$ Hz), 6.85 (1H, d, $J=6.7$ Hz), 6.95 (1H, t, $J=7.9$ Hz), 7.05–7.30 (10H, m), 7.62 (1H, d, $J=6.7$ Hz); (+)APCI-MS *m*/*z*: 480 ($M^+ + 1$).
10. Physical data for compound **30**: mp 162–163 °C (Et_2O); IR (Nujol) cm^{-1}: 1665, 1605, 1590; ^{1}H NMR (DMSO-d_6) δ: 1.30 (1H, m), 1.80 (1H, m), 2.10 (1H, m), 2.35–2.95 (4H, m), 3.70–3.95 (2H, m), 4.28 (2H, s), 5.39 (1H, s), 6.39 (1H, d, $J=10.1$ Hz), 6.48–6.56 (2H, m), 6.95 (1H, t, $J=7.9$ Hz), 7.14–7.35 (12H, m); (+)APCI-MS *m*/*z*: 480 ($M^+ + 1$).