Synthesis of 3,5-Disubstituted 1,2,4-Triazoles Containing Trimethoxyphenyl Groups: Potential Antagonists of Platelet Activating Factor

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In an effort to develop a new class of Platelet Activating Factor antagonists, 3,5-disubstituted 1,2,4-triazoles containing trimethoxyphenyl groups have been synthesized. The synthesis of symmetrical triazoles **5** and **6**, as well as two methods of synthesizing unsymmetrical triazole **7**, are reported.

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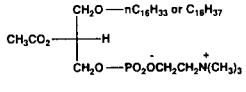
Platelet Activating Factor (PAF) **1** is a biologically active phospholipid which has been linked to a number of pathophysiological events in the lung including bronchoconstriction, airway obstruction and pulmonary edema [1,2], as well as other processes such as cardiac and renal dysfunction [3,4]. PAF has been proposed to be a critical mediator in asthma, as well as allergic and anaphylactic reactions [5-7]. Much evidence supports the existence of PAF receptors on cell membranes [8,9]; therefore, the development of PAF receptor antagonists represents a rational strategy for treatment of these problems.



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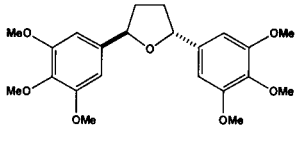
There currently exists a wide variety of structurally diverse PAF antagonists [10]. One of the most potent is L-652,731, **2**, a tetrahydrofuran which has shown high *in vitro* and *in vivo* biological activity [11,12]. Early structure activity relationship studies indicated the importance of the trimethoxyphenyl rings in imparting good biological activity to these molecules [11]. Another important class of antagonists are the triazolobenzodiazepines, which are generally of use clinically for their psychotropic activities. The triazolobenzodiazepines triazolam **3** and alprazolam **4** have been shown to be potent and specific inhibitors of PAF-induced platelet aggregation and shape change [13-16]. However, benzodiazepines which lack the triazole ring, such as diazepam and flunitrazepam, show very weak PAF antagonistic activity [13,17].

There currently exists a great need for potent and safe PAF antagonists in therapy as well as for elucidation of the role of PAF in other disease states. We became interested in the possibility of developing new PAF antagonists through the synthesis of heterocyclic ring analogs of L-652,731. We were interested in the possibility of using a triazole ring in place of the tetrahydrofuran. Since this ring plays a major role in conveying PAF antagonistic action to the benzodiazepine structure, we were hopeful that such a strategy might result in compounds of synergistic biological activity. Corey has recently synthesized chiral nonracemic analogs of L-652,731 and discovered the receptor did not discriminate enantiomeric forms [8]. This, coupled with the wide structural diversity of current PAF antagonists [10], suggests the existence of flexibility in binding of the PAF receptor to antagonists and warrants



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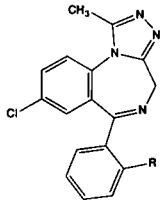
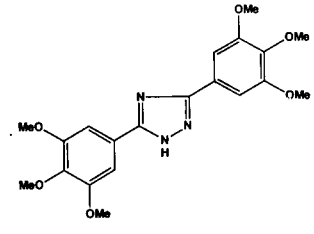


3 R = Cl

4 R = H



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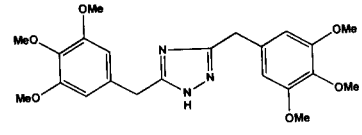

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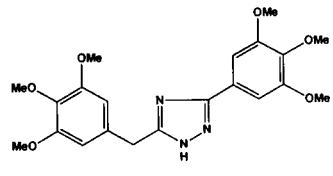

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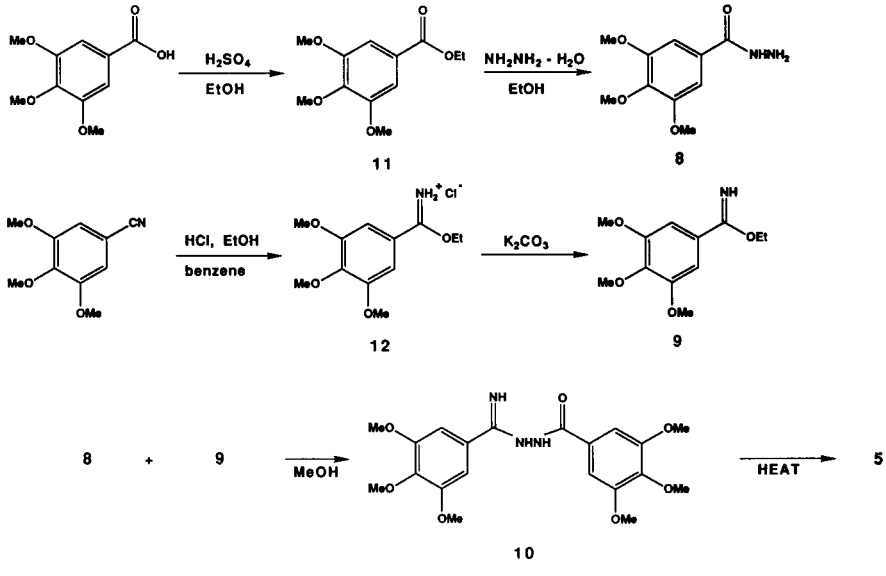
an examination as to the types of heterocyclic analogs of L-652,731 which may be accommodated by the receptor. In this report, we describe the synthesis of symmetrical triazoles **5** and **6**, as well as two methods of preparing unsymmetrical triazole **7**.

The synthesis of diaryl triazole **5** is indicated on Scheme 1. The general strategy involved condensation of acyl hydrazide **8** with imidate **9** to afford acylamidrazone **10**, followed by thermal cyclization to provide the desired triazole [18,19]. Although hydrazide **8** was a known compound [20,21], we found the reported synthesis [21] to require some slight modification for optimum results. 3,4,5-Trimethoxybenzoic acid was transformed into ethyl ester **11** in 81% yield as described [21]. Treatment of the ester with hydrazine hydrate in refluxing ethanol overnight afforded hydrazide **8** which was often contaminated with unreacted starting ester. This problem was easily remedied by washing the product with ethanol, as the ester was quite soluble in ethanol while the pure hydrazide was not (64% yield). Imidate **9** was obtained *via* Pinner reaction

SCHEME 1



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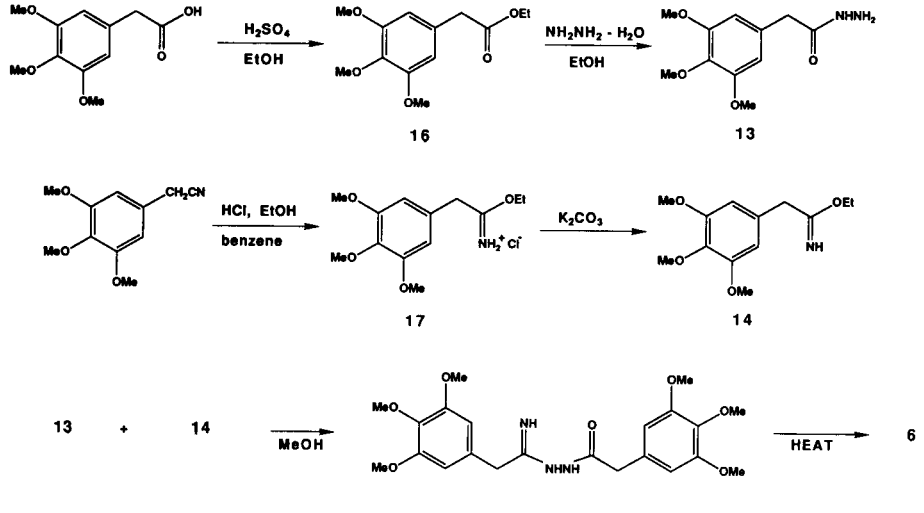

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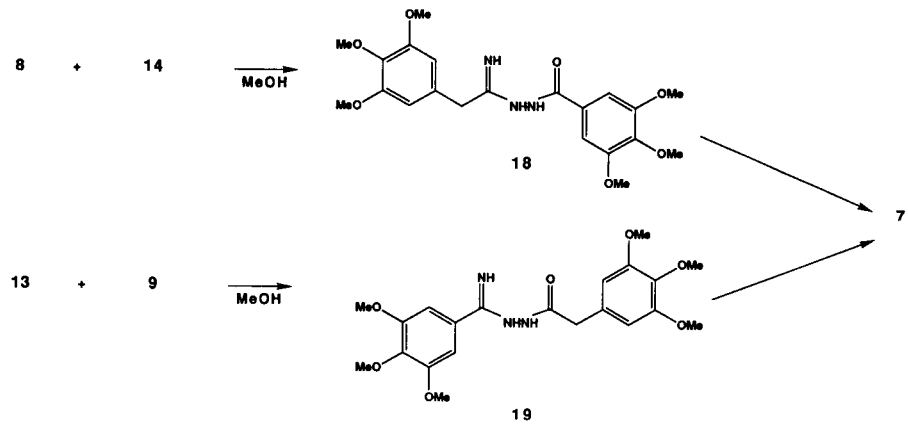

chemistry [22]. Treatment of 3,4,5-trimethoxybenzonitrile with ethanol and hydrochloric acid gas in benzene afforded imidate salt **12** in 80% yield after a reaction time of 72 hours. Shorter reaction times led to lower yields. Neutralization with potassium carbonate, followed by extractive isolation, provided the requisite imidate **9**.

To carry out the condensation reaction, a methanolic solution containing equimolar amounts of **8** and **9** was refluxed for one hour [18] to produce amidrazone **10** which crystallized out of the reaction mixture. The filtered product was heated at 200° for 20 minutes to effect cyclization, leading to formation of triazole **5** in 22% yield for the two steps, following chromatography.

The synthesis of symmetrical dibenzyl triazole **6** is indicated on Scheme 2 and parallels that of triazole **5**. Hydrazide **13** [23] was obtained from 3,4,5-trimethoxyphenylacetic acid *via* the intermediacy of the ethyl ester **16**. Pinner reaction on 3,4,5-trimethoxyphenylacetonitrile overnight afforded imidate salt **17** in 82% yield, which was neutralized with potassium carbonate to provide the free imidate **14**. A solution of **13** and **14** in methanol was refluxed one hour, leading to crystallization of amidrazone **15**. Isolation and thermal cyclization provided triazole **6** in 51% overall yield for the two steps.

Unsymmetrical triazole **7** could be obtained from either of the two unsymmetrical hydrazide-imidate combinations (Scheme 3). Condensation of hydrazide **8** with imidate **14** afforded amidrazone **18** which cyclized to triazole **7** in 33% overall yield. A similar transformation with hydrazide **13** and imidate **9** provided amidrazone **19** which underwent cyclization to **7** in a 31% overall yield.

All three triazoles proved to be inactive as PAF antagonists in an assay which involved a measurement of the compound's ability to inhibit PAF-induced aggregation of human platelets [13]. A possible explanation for this inactivity may lie in the planar aromatic nature of the triazole ring, which places the trimethoxyphenyl groups in orientations that differ significantly from those of L-652,731.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H nmr were recorded on a Bruker AC200 spectrometer (200 MHz) in deuteriochloroform or deuterioacetone with tetramethylsilane (TMS) or acetone as an internal reference. Data are reported as follows: chemical shift in ppm, multiplicity (br = broad, s = singlet), integration and interpretation. Infrared spectra were recorded on a Perkin-Elmer 683 spectrometer. Peaks are reported in reciprocal centimeter units. Mass spectra were obtained at the Ohio State University Chemical Instrument Center by use of a Kratos MS-30 mass spectrometer. Elemental analyses were performed by Desert Analytics of Tucson, Arizona.

Analytical thin-layer chromatography was performed on EM Science silica gel plates with F-254 indicator. Visualization was accomplished by uv light and iodine. Column chromatography was performed by using the method described by Still [24].

Ethyl 3,4,5-Trimethoxybenzoate (**11**).

This compound was prepared according to the procedure of Stenberg [21].

3,4,5-Trimethoxybenzhydrazide (**8**).

This compound was prepared by a modification of the procedure described by Stenberg [21] as follows:

To a solution of benzoate **11** (4.6 g, 19 mmoles) in 95% ethanol (10 ml) was added hydrazine monohydrate (2.5 g, 2.4 ml, 50 mmoles). The solution was stirred under reflux overnight. The reaction mixture was concentrated to a white solid on the rotary evaporator. Cold distilled water was added, and the suspension was filtered. The crude product was dissolved in hot 95% ethanol, cooled, and set in the freezer overnight. The suspension of recrystallized product was allowed to stand at room temperature for one hour and filtered. The solid product was washed with 95% ethanol to yield hydrazide **8** (4.3 g, 64%) as white needle-like crystals, mp 159.5-160° lit 162° [20].

Ethyl 3,4,5-Trimethoxybenzimidate (**9**).

Hydrochloric acid gas was bubbled into an ice cooled solution of ethanol (0.84 g, 14.5 mmoles) and 3,4,5-trimethoxybenzonitrile (1.96 g, 10.1 mmoles) in benzene (7.5 ml) over a period of 35 minutes with stirring. The reaction mixture changed from colorless to milky, to yellow, and finally to yellow-green during the addition (total 0.6 g hydrochloric acid). The solution was allowed to stand at room temperature for 30 minutes. The now deep green solution was placed in the refrigerator for 72 hours. A solid precipitate was observed after 48 hours. The resulting mixture was added to 200 ml of anhydrous ether and a white solid precipitated immediately. The mixture was set in the refrigerator for 2.5 hours. The resulting white solid was filtered and dried to give 2.2 g of imidate salt **12** (80%, mp 177-179°).

Imidate salt **12** (1.01 g, 3.66 mmoles) was neutralized with 10% aqueous potassium carbonate solution (30 ml). The resulting mixture was extracted with methylene chloride (3 x 25 ml). The combined organic layers were dried with sodium sulfate and evaporated to afford imidate **9** as a yellow oil (0.85 g, 98%) which was used immediately in the next reaction.

3,4,5-Trimethoxyphenyl-β-3,4,5-trimethoxybenzoylamidrazone (**10**).

Imidate **9** (0.88 g, 3.7 mmoles) and benzhydrazide **8** (0.83 g, 3.7 mmoles) were dissolved in methanol (10 ml) and heated to reflux for 1 hour. A white solid began to precipitate after 30-40 minutes. The solid was collected from the cooled reaction mixture by suction filtration and washed with methanol to produce amidrazone **10** which was used immediately in the next reaction.

bis-3,5-(3,4,5-Trimethoxyphenyl)-1,2,4-triazole (**5**).

Solid amidrazone **10** was heated at 200° in a sand bath for 20 minutes. The white solid melted to leave a green oil which rapidly evolved water to leave a pale yellow oil. Isopropyl ether was added forming a white solid. This mixture was evaporated to dryness. This resulting white solid was dissolved in hot methylene chloride and purified by flash chromatography (ethyl acetate/hexane: 3/1) to yield triazole **5** (0.44 g, 22% from the imidate), mp 171-171.5; ^{1}H nmr (deuteriochloroform): 13.7-13.4 (br s, 1H, NH), 7.29 (s, 4H, aromatic), 3.86 (s, 6H, OCH_3), 3.75 (s, 12H, OCH_3); ir (potassium bromide): 3457, 3434, 2993, 2939, 2835, 1594, 1500, 1478, 1420, 1384, 1235, 1129, 1002, 879, 854, 761; ms: m/e (relative intensity) 402 (22), 401 (M^+, 100), 387 (14), 386 (59), 358 (18), 45 (29), 43 (16).

Anal. Calcd. for $C_{20}H_{23}N_3O_6$: C, 59.84; H, 5.77; N, 10.47. Found: C, 59.85; H, 5.78; N, 10.23.

Ethyl 3,4,5-Trimethoxyphenylacetate (**16**).

This molecule was prepared in 74% yield from 3,4,5-trimethoxyphenylacetic acid according to the general procedure used to prepare compound **11**. The crude product, obtained as an oil, was used as such in the next reaction.

3,4,5-Trimethoxyphenylmethylhydrazide (**13**).

To crude acetate **16** (1.7 g, 6.6 mmoles) in 95% ethanol (10 ml) was added hydrazine monohydrate (0.80 g, 0.78 ml, 16.4 mmoles). The solution was stirred under reflux overnight. The reaction mixture was concentrated to a residue on the rotary evaporator and vacuum dried for 1 hour to give a white solid. The crude product was dissolved in hot benzene [23], cooled, and set in the refrigerator overnight. The recrystallized product was suction filtered and washed with cold benzene to afford hydrazide **13** (1.3 g, 80%) mp 104-106.5° lit 104-106° [23].

Ethyl 3,4,5-Trimethoxyphenylmethylimidate (**14**).

Hydrochloric acid gas was bubbled into an ice cooled solution of ethanol (0.84 g, 14.5 mmoles) and 3,4,5-trimethoxyphenylacetonitrile (2.1 g, 10.1 mmoles) in benzene (7 ml) over a period of 30 minutes with stirring. The reaction mixture changed from a yellow color to a brown color during the addition (total 0.6 g of hydrochloric acid). The solution was allowed to stand in the refrigerator overnight. The resulting solution was added to 200 ml of anhydrous ether and a white solid precipitated immediately. The mixture was set in the refrigerator for 2 hours. The resulting solid was filtered and dried to give 2.4 g of imidate salt **17** (82%, mp 100-103°).

Imidate salt **17** (1.04 g, 3.58 mmoles) was neutralized with 10% aqueous potassium carbonate solution (30 ml). The resulting mixture was extracted with methylene chloride (3 x 25 ml). The combined organic layers were dried (sodium sulfate) and evaporated to afford imidate **14** as a yellow oil (0.83 g, 92%) which was used immediately in the next reaction.

3,4,5-Trimethoxyphenylmethyl-β-3,4,5-trimethoxyphenylacetylamidrazone (**15**).

Imidate **14** (0.78 g, 3.1 mmoles) and hydrazide **13** (0.74 g, 3.1 mmoles) were dissolved in methanol (10 ml) and heated to reflux for 1 hour. A white solid began to precipitate after less than 10 minutes. The solid was collected by suction filtration and washed with methanol to produced amidrazone **15** which was used immediately in the next reaction.

bis-3,5-(3,4,5-Trimethoxyphenylmethyl)-1,2,4-triazole (**6**).

Solid amidrazone **15** was heated in a sand bath at 200° for 15-20 minutes. The white solid melted and rapidly evolved water to leave a pale yellow oil. The cooled oil was dissolved in methylene chloride. Isopropyl ether was added and the solution was allowed to stand in the freezer overnight. The resulting white solid was suction filtered and dried to give triazole **6** (0.68 g, 51% from the imidate), mp 153-155°; ^{1}H nmr (deuteriochloroform): 11.8-10.5 (br s, 1H, N-H), 6.48 (s, 4H, aromatic), 3.88 (s, 4H, CH_2), 3.80 (s, 6H, OCH_3), 3.76 (s, 12H, OCH_3); ir (potassium bromide): 3133, 2973, 2958, 2939, 2907, 2886, 2841, 2825, 1594, 1509, 1466, 1428, 1349, 1333, 1254, 1238, 1125, 1065, 1011, 806; ms: m/e (relative intensity) 430 (24), 429 (M^+, 100), 414 (41), 386 (11), 264 (25), 263 (47), 248 (34), 207 (10), 181 (16), 87 (14), 69 (13), 59 (12), 55 (10), 45 (79), 43 (88), 41 (24), 39 (11).

Anal. Calcd. for $C_{22}H_{27}N_3O_6$: C, 61.53; H, 6.34; N, 9.78. Found: C, 61.45; H, 6.48; N, 9.73.

3-(3,4,5-Trimethoxyphenylmethyl)-5-(3,4,5-trimethoxyphenyl)-1,2,4-triazole (**7**).

Via Amidrazone **18**.

Imidate **14** (0.83 g, 3.3 mmoles) and benzhydrazide **8** (0.75 g, 3.3 mmoles) were dissolved in methanol (10 ml) and heated to reflux for 1 hour. A white solid began to precipitate after less than 10 minutes. The solid was collected by suction filtration and washed with methanol to give amidrazone **18** which was used immediately in the next reaction.

Solid amidrazone **18** was heated in a sand bath at 200° for 20 minutes. The white solid melted to leave a green oil which rapidly evolved water to leave a pale yellow oil. The cooled oil was dissolved in methylene chloride. Isopropyl ether was added and the solution was set in the freezer overnight to crystallize. The crude product was filtered and recyrstallized from methylene chloride/isopropyl ether to produce triazole **7** (0.45 g, 33% from the imidate).

Via Amidrazone **19**.

Imidate **9** (0.9 g, 3.8 mmoles) and hydrazide **13** (0.92 g, 3.8 mmoles) were dissolved in methanol (10 ml) and heated to reflux for 1 hour. A white solid began to precipitate after less than 10 minutes. The cooled reaction mixture was suction filtered and washed with methanol to produce amidrazone **19** which was used immediately in the next reaction.

Solid amidrazone **19** was heated in a sand bath at 200° for 20 minutes. The white solid melted and rapidly evolved water to afford a pale yellow oil. The cooled oil was dissolved in hot methylene chloride. Isopropyl ether was added and the solution was set in the freezer overnight. The white solid was suction filtered and dried. Recrystallization from methylene chloride/isopropyl ether afforded triazole **7** (0.54 g, 31% from the imidate), mp 186°; ^{1}H nmr (deuteriochloroform): 12-11.75 (br s, 1H, N-H), 7.27 (s, 2H, aromatic), 6.45 (s, 2H, aromatic), 4.08 (s, 2H, CH_2), 3.88 (s, 6H, OCH_3), 3.85 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.73 (s, 6H, OCH_3); ir (potassium bromide): 3405, 1631, 1591, 1578, 1500, 1461, 1339, 1232, 1130, 1113, 1101, 1004; ms: m/e (relative intensity) 416 (24), 415 (M^+, 100), 401 (16), 400 (61), 372 (15).

Anal. Calcd. for $C_{21}H_{25}N_3O_6$: C, 60.71; H, 6.07; N, 10.11. Found: C, 60.57; H, 6.01; N, 10.11.

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