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SYNTHESIS OF 1,4-BENZODIAZEPINE-2,5-DIONE DERIVATIVES

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Abstract-A synthesis of a series of 1,4-benzodiazepine-2,5-dione derivatives with a carboxy group at the 3-position is realized in good yields by using methyl malonylchloride as a key reagent and intramolecular nucleophilic substitution as ring closure reaction.

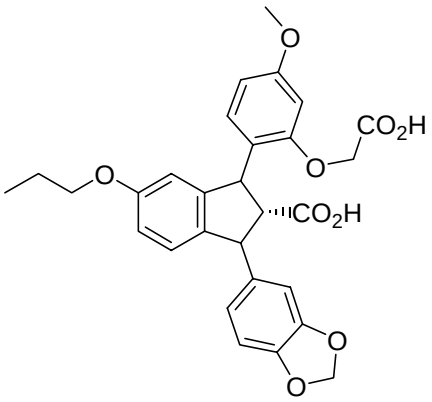
1,4-Benzodiazepine-2,5-dione (BZD) and its derivatives whether it is natural[1,2] or synthetic[3,4,5] represent one of the most important bioactive molecules. The BZD systems exhibit bioactivities such as anticonvulsant,[3] anxiolytic,[4] antitumor[1,5] pain releasing,[6] platelet aggregation inhibiting[7,8] and even anti-AIDS activities.[9]

It was recently reported that[10,11] the human receptor ET_A subtype is selective to endothelin-1 (ET-1), a 21 amino acid peptide. ET-1 exhibits profound endogenous vasoconstriction and mitogenic activities. Antagonism on the vasoconstrictor endothelin is a potential new approach to the treatment of a variety of human diseases including ischemia, hypertension, congestive heart failure, pulmonary hypertension and subarachnoid hemorrhage. In the process of searching for the non-peptide antagonists selective for ET_A and ET_B receptors, it was found by Elliott[12] that two phenyls on the indane derivative SB 209670 (Figure 1) are restricted dipeptide mimetic to Try-13 and Phe-14 of ET-1.

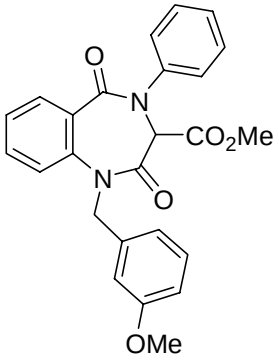
By molecular modeling, we have found that the *N*-phenyl and *N*-benzyl group of the BZD ring can be a perfect match to the two phenyls of SB209670. Thus it is possible that compound (**1**) (Scheme 3) and its derivatives may serve as alternative candidates for the non-peptide antagonists of ET_A.

Many efforts have been devoted toward the synthesis of this bioactive BZD and its derivatives.[9,13-15] For example, Keating and Armstrong recently published[3] a new synthetic method for BZD by using rearrangement (Scheme 1). In a primary attempt (Scheme 2), the *N*-benzylisatoic anhydride (**2**) was reacted with aniline to afford the amide (**3**). Then **3** was reacted with dimethyl chloromalonate to give **4**. However, cyclization to seven membered ring by intramolecular amide formation to **5** from **4** was not successful.

Figure 1. Non-peptide antagonists, SB209670 and several synthesized BZD derivatives.



SB 209670



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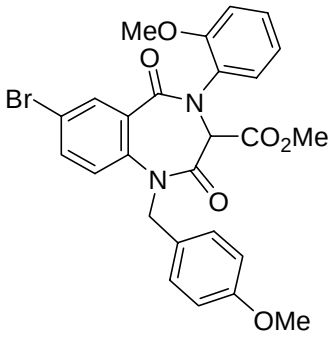
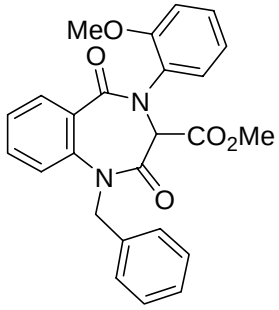


12



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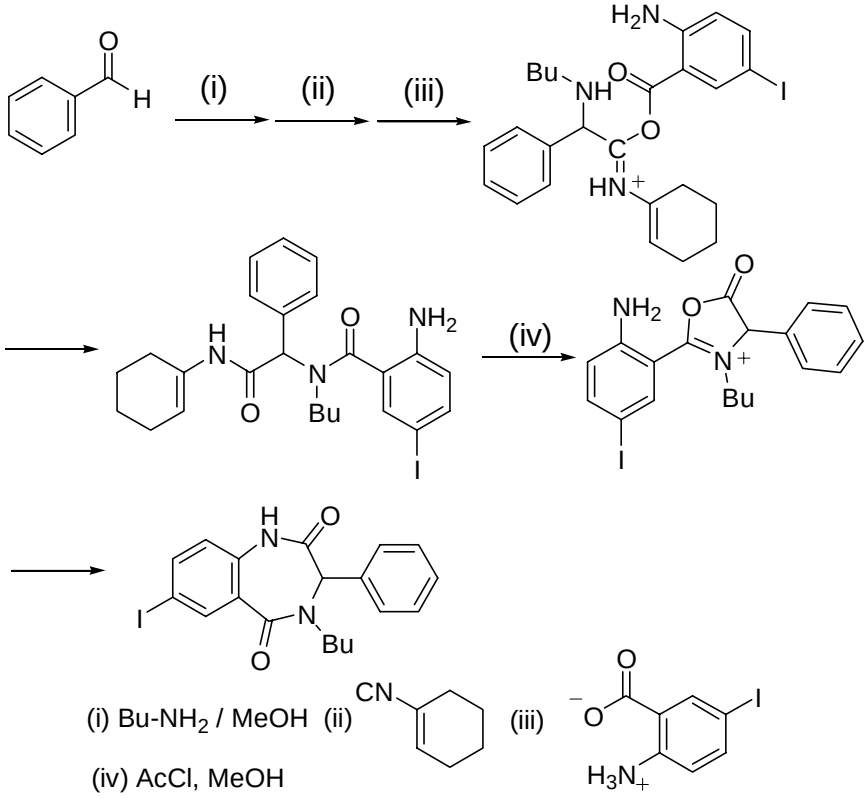
Scheme 1. Synthetic approach to BZD by using rearrangement.



A successful method to achieve the ring closure is shown in Scheme 3. Isatoic anhydride was reacted with *p*-methoxyaniline in DMF to form amide (**6**) in 78% yield. The aniline part of the amide (**6**) was alkylated with 3-methoxybenzyl chloride to afford **7** in 72% yield. The secondary amine part of **7** was acylated with methyl malonylchloride to yield **8** (96%). In order to activate the methylene carbon of the malonamide (**8**), a bromine atom is introduced to give **9**. By using two equivalents of bulky base, sodium *t*-butoxide, the ring closure occurred to afford the 1,4-benzodiazepine-2,5-dione (**10**) in 82% yield from compound (**8**) without isolation of **9**. The hydrolysis to the carboxylic acid (**1**) was achieved by lithium hydroxide in 90% yield.

In summary, a synthetic approach to a series of BZD derivatives has been described by using methyl malonylchloride as a key reagent through the intramolecular nucleophilic substitution to achieve the 1,4-benzodiazepine-2,5-dione in good yield. The possible bioactivities are being determined.

ACKNOWLEDGEMENTS

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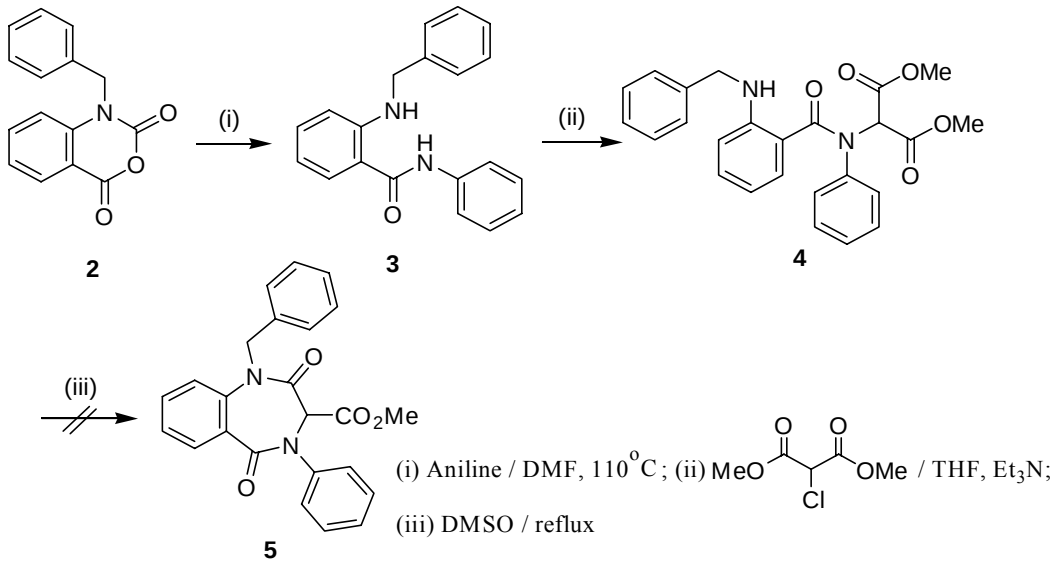
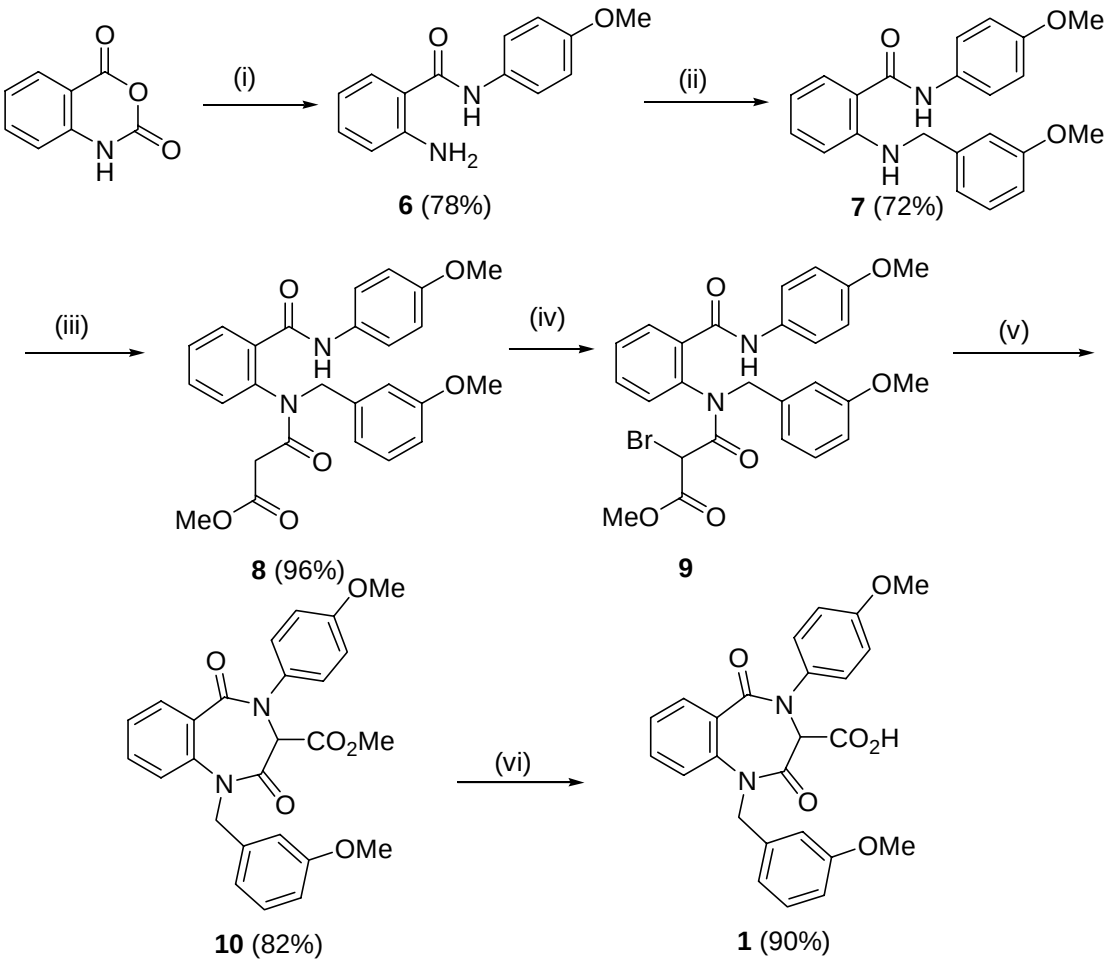
Scheme 2. Primary attempt to the BZD derivative (**5**).



SUPPORTING INFORMATIONS

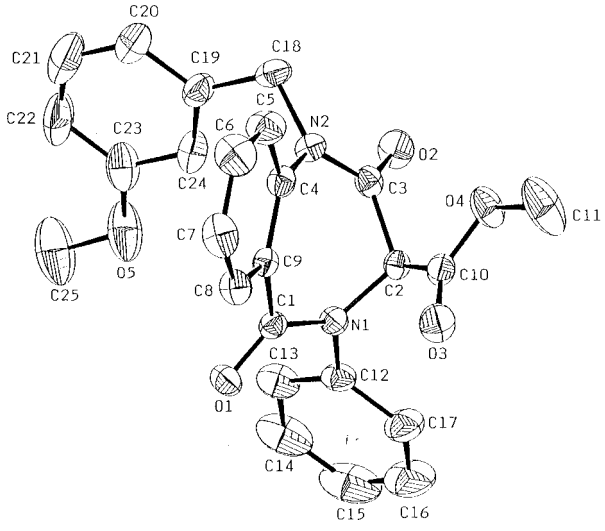
^{1}H and ^{13}C NMR spectral data of compounds (**1**, **7**, **8**, **10**)[16] are available. The single crystal X-Ray diffraction data are also included.

Scheme 3. Novel synthetic approach to a new BZD derivative (**1**).



(i) *p*-Anisidine / DMF; (ii) 3-Methoxybenzyl chloride / THF; (iii) Methyl malonylchloride / THF, 0^0C; (iv) $PyHBr_3$ / THF, H^+; (v) *t*-BuONa / DMF; (vi) LiOH, H_2O, 0^0C

Figure 2. Perspective view of X-Ray crystal structure of **11.**



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16. **Spectral data for 11** (mp 148-150 °C (ethyl acetate)): IR(KBr) 3065, 3040, 2953, 1757, 1662, 1601, 1490, 1322, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.87 (d, *J* = 1.5 Hz, 1H), 7.43 – 7.15 (m, 9H), 6.87 – 6.77 (m, 3H), 5.27(d, *J* = 15.8 Hz, 1H), 5.19 (s, 1H), 4.99 (d, *J* = 15.8 Hz, 1H), 3.74 (s, 3H), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.1, 164.9, 158.9, 141.6, 137.5, 136.9, 131.5, 130.3, 128.7, 128.4, 128.0, 126.9, 125.5, 125.2, 120.5, 118.9, 117.6, 111.9, 110.9, 67.8, 54.1, 51.9, 50.8; MS m/z (70 eV, EI) 430 (M^+, 60), 278 (10), 146 (100), 221(90). HR-MS Calcd for $C_{25}H_{22}N_2O_5$ 430.1528, found 430.1545.

Spectral data for 1 (white powder): IR (KBr) 3485, 1732, 1682, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, *J* = 7.7 Hz , 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.30-7.19 (m, 4H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.82-6.76 (m, 3H), 5.37 (s, 1H), 5.23 (d, *J* = 16.3 Hz, 1H,), 5.15 (d, *J* =

16.3 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.0, 166.6, 165.8, 159.5, 158.1, 138.7, 138.2, 135.8, 132.6, 130.9, 129.6, 129.1, 127.5, 126.0, 122.0, 118.7, 114.3, 112.8, 111.7, 68.4, 55.4, 54.9, 49.9; FABMS: 417.1 (M+1).

Spectral data for 10 (mp 151-152 °C (ethyl acetate)): IR(KBr) 3005, 2955, 2836, 1756, 1676, 1511, 1458, 1245, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.42-7.15 (m, 6H), 6.94-6.77 (m, 5H), 5.26 (d, *J* = 15.9 Hz, 1H), 5.1 (s, 1H), 4.96 (d, *J* = 15.9 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3, 166.1, 166.0, 159.9, 158.9, 138.0, 135.6, 132.5, 131.3, 129.8, 129.1, 127.5, 126.5, 121.4, 118.6, 114.6, 112.9, 111.9, 55.4, 69.2, 55.1, 52.9, 51.8 ,; MS (70 eV, EI) 260 (80), 401 (10), 254 (20), 146 (90), 121 (100); HR-MS Calcd for $C_{26}H_{24}N_2O_6$ 460.1634, found 460.1647.

Spectral data for 8 (mp 127-128 °C (ethyl acetate)): IR(KBr) 3298, 3061, 3001, 2952, 2836, 1741, 1656, 1600, 1537, 1411, 1321, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74-7.71 (m, 1H), 7.54-7.49 (m, 2H), 7.41-7.33 (m, 2H), 7.07-7.01 (m, 1H), 6.91-6.84 (m, 3H), 6.68-6.63 (m, 3H), 5.33 (d, *J* = 14.4 Hz, 1H), 4.39(d, *J* = 14.2 Hz, 1H), 3.78 (s, 3H), 3.66 (d, *J* = 15.3 Hz, 1H), 3.61 (s, 3H), 3.58 (s, 3H), 3.37(d, *J* = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 168.7, 166.0, 164.5, 159.2, 156.2, 138.2, 137.4, 134.8, 130.9, 130.8, 129.9, 129.3, 128.9, 128.6, 121.7, 120.8, 114.0, 113.6, 112.9, 55.0, 54.6, 52.5, 52.0, 41.3; MS (70 eV, EI) 462 (M^+, 10), 340 (10), 238 (10), 121 (100); HR-MS Calcd for $C_{26}H_{26}N_2O_6$ 462.1790, found 462.1804.

Spectral data for 7 (mp 125-126 °C (ethyl acetate)): IR(KBr) 3419, 3306, 3085, 3003, 2836, 1632, 1513, 1407, 1265, 820, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.49-7.38 (m, 3H), 7.29-7.17 (m, 2H), 6.95–6.84(m, 4H), 6.78 (dd, *J* = 7.3, 1.8 Hz, 1H), 6.65-6.58 (m, 2H), 4.38 (d, *J* = 5.6 Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168, 159.8, 156.6, 149.5, 140.6, 133, 130.7, 129.5, 127.2, 122.6, 119.9, 119.3, 115.4, 115.2, 114.1, 112.7, 112.4, 55.4, 55.1, 47.1; MS (70 eV, EI) 362 (M^+, 5), 240(30), 132 (10), 123(100). HR-MS Calcd for $C_{22}H_{22}N_2O_3$ 362.1630, found 362.1634.

Spectral data for 6 (mp 120-121 °C (ethyl acetate)): IR(KBr) 3466, 3363, 3280, 1635, 1601, 1545, 1570, 1030, 834, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.46-7.39 (m, 2H), 7.27-7.18 (m, 2H), 6.92-6.86 (m, 2H), 6.72-6.64 (m, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 156.4, 148.6, 132.4, 130.7, 127.1, 112.6, 117.3, 116.6, 116.2, 114.0, 55.3; MS (70 eV, EI) 242 (M^+, 50), 120 (100), 108 (20), 92 (40); HR-MS Calcd for $C_{14}H_{14}N_2O_2$ 242.1053, found 242.1053.