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RAPID SYNTHESIS OF NEW AZAHETEROCYCLIC HYDROXY-MALONATE DERIVATIVES USING TDAE APPROACH

Marc Montana, Maxime D. Crozet, Caroline Castera-Ducros, Thierry Terme, and Patrice Vanelle*

Laboratory of Pharmaceutical Organic Chemistry, CNRS-UMR 6517, University of Méditerranée, Faculty of Pharmacy, 27 bd Jean Moulin, 13385 Marseille cedex 5, France. E-mail: patrice.vanelle@pharmacie.univ-mrs.fr

Abstract – A new series of azaheterocyclic hydroxymalonate derivatives was synthesized from reaction between chloromethyl azaheterocycles and diethyl oxomalonate using tetrakis(dimethylamino)ethylene (TDAE).

INTRODUCTION

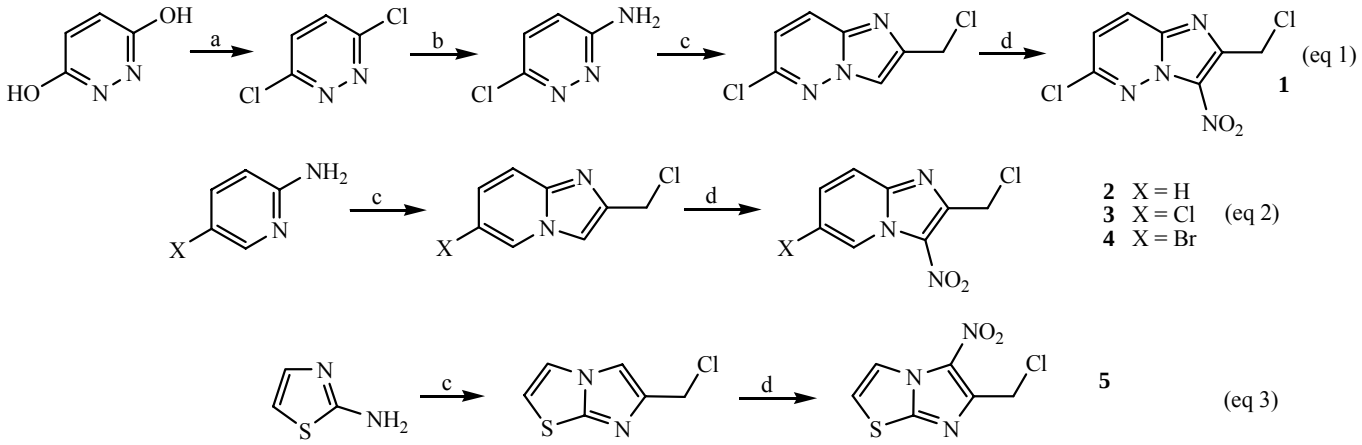
Substituted malonate derivatives are important synthons, especially in the field of bioactive molecule synthesis. Since 2004, we have developed various strategies using electron transfer reaction[1] such as $S_{RN}1$ or *via* a Vicarious Nucleophilic Substitution of hydrogen (VNS) followed by a direct Julia olefination reaction,[2] in order to obtain new substituted nitroheterocycles which possess a malonate or methylenemalonate moiety in an *ortho*-like position with respect to the nitro group. These derivatives are good candidates for reduction-cyclization reaction to form new polycyclic pyridones.[2] Concerning the hydroxymalonate derivative syntheses from diethyl oxomalonate, a general method was developed by Salomon[3] for arylhydroxymalonate derivatives but for benzylic hydroxymalonate derivatives, only a few methods were established.[4] Tetrakis(dimethylamino)ethylene (TDAE) is a reducing agent which reacts with halogenated derivatives to generate, under mild conditions, an anion *via* a single electron transfer (SET).[5] We have recently shown that from *o*- or *p*-nitrobenzyl chloride, TDAE could generate a nitrobenzyl carbanion which is able to react with various electrophiles such as aromatic aldehydes,[6] ketones, α-keto-esters, α-ketolactams and diethyl oxomalonate.[7] In continuation of our program directed towards the preparation of new substituted malonate derivatives *via* electron transfer methodologies, we applied the TDAE strategy in heterocyclic series with diethyl oxomalonate as an electrophile to form new hydroxymalonate derivatives.

RESULTS AND DISCUSSION

Herein, we present the preparation of several chloromethyl derivatives in imidazo[1,2-*b*]pyridazine, imidazo[1,2-*a*]pyridine, imidazo[2,1-*b*]thiazole and pyrido[1,2-*a*]pyrimidin-4-one series and their reactivity with diethyl oxomalonate in the presence of TDAE, leading to the corresponding hydroxymalonate derivatives.

The 6-chloro-2-chloromethyl-3-nitroimidazo[1,2-*b*]pyridazine (**1**) was prepared in a four-steps synthesis from 3,6-dihydroxypyridazine *via* dichlorination, amination, condensation with 1,3-dichloroacetone and nitration reaction (Scheme 1, eq 1).[8] The imidazo[1,2-*a*]pyridines **2**, **3** and **4** were obtained from corresponding 2-amino-5-halopyridine *via* condensation with 1,3-dichloroacetone and nitration (Scheme 1, eq 2).[9] The imidazo[2,1-*b*]thiazole substrate **5** was prepared from 2-aminothiazole according to the same procedure, dichloroacetone condensation followed by nitration reaction (Scheme 1, eq 3).[10]

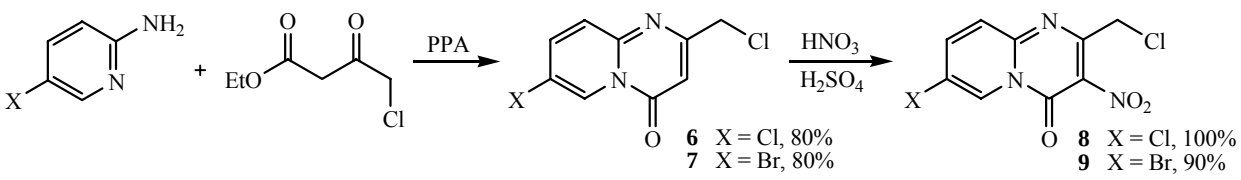
Scheme 1



(a) $POCl_3$; (b) NH_4OH; (c) 1,3-dichloroacetone; (d) HNO_3/H_2SO_4

The two pyrido[1,2-*a*]pyrimidin-4-one derivatives **8** and **9** were synthesized by condensation of corresponding 2-amino-5-halopyridine with ethyl 4-chloroacetoacetate in polyphosphoric acid (PPA) according to Ferrarini's procedure[11] to form the pyrido[1,2-*a*]pyrimidin-4-ones **6** and **7** followed by nitration reaction (Scheme 2).

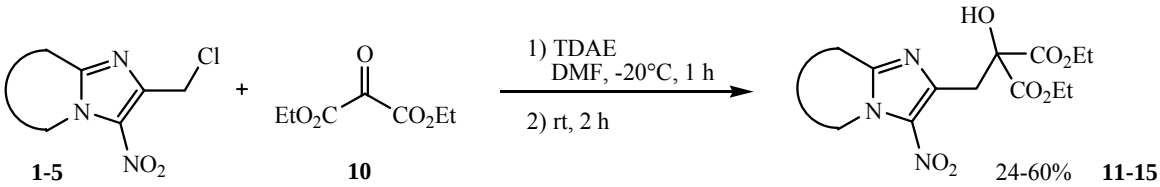
Scheme 2



The reaction of chloride derivatives **1**-**5** with 3 equivalents of diethyl oxomalonate (**10**) in presence of TDAE at – 20°C for 1 h followed by 2 h at room temperature led to the corresponding hydroxymalonate

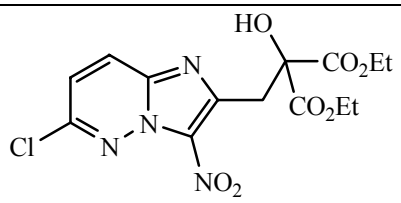
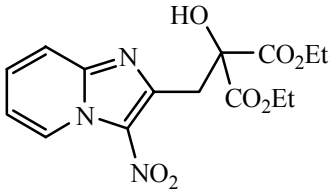
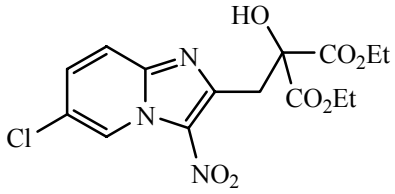
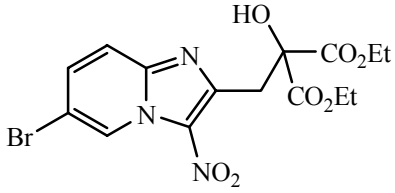
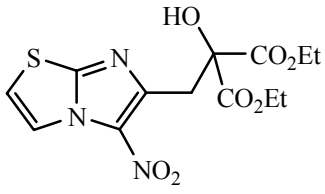
11-15 in moderate to good yields (24%-60%) as shown in Table 1 (Scheme 3). The formation of these hydroxymalonates (**11-15**) may be explained by nucleophilic addition of carbanion, formed by action of TDAE with chloride derivatives **1-5**, on central carbonyl group of diethyl oxomalonate (**10**).[7]

Scheme 3



1-5 **10** **11-15**

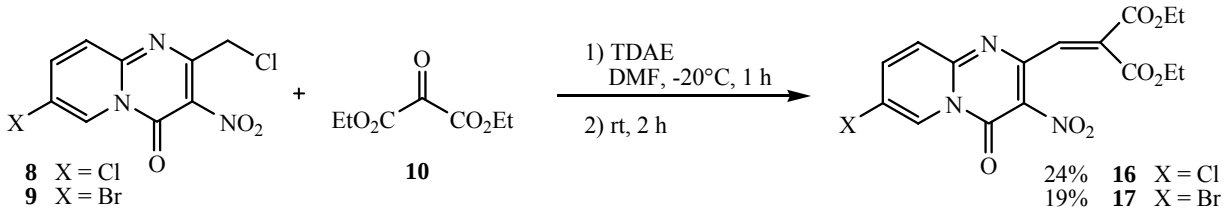
Table 1

Chloride	Product		Yield (%)
1		**11**	40
2		**12**	24
3		**13**	36
4		**14**	48
5		**15**	60

However, from chlorides **8** and **9**, the reaction with diethyl oxomalonate (**10**), according to the same protocol, furnishes the corresponding methylenemalonate derivatives **16-17** in poor yields (19-24%),

resulting from a dehydration of unstable hydroxymalonate intermediates (Scheme 4). This dehydration and instability of hydroxymalonate, only observed in pyrido[1,2-*a*]pyrimidin-4-one series, seems to be explained by the basic properties of TDAE[12] associated to the higher acidity of the benzylic hydrogen due to the presence on the same cycle of two electronwithdrawing groups (nitro and carbonyl groups).

Scheme 4



8 X = Cl
9 X = Br

10

24% **16** X = Cl
19% **17** X = Br

In conclusion, we present herein a rapid, original and mild method to prepare new heterocyclic hydroxymalonate derivatives. After our previous studies in benzylic series,[7] the generalization of this reaction in heterocyclic series shows the general character of this TDAE/diethyl oxomalonate method to obtain hydroxymalonate derivatives. However, the presence of several electronwithdrawing groups on the heterocycle favors the formation of methylenemalonate derivatives as shown in pyrido[1,2-*a*]pyrimidin-4-one series. The pharmacological evaluation of all compounds is under active investigation.

EXPERIMENTAL

Melting points were determined on Büchi B-540 and are uncorrected. ^{1}H and ^{13}C NMR spectra were determined on Bruker ARX 200 spectrometer. The ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm with respect to $CHCl_3$ 7.26 ppm (^{1}H) and 76.9 ppm (^{13}C). Elemental analyses were performed by the Spectropole of the University of P. Cezanne. The following adsorbent was used for column chromatography: silica gel 60 (Macherey Nagel, 0.063-0.2 mm). TLC was performed with silica gel Macherey Nagel Alugram Sil G UV254.

The various heterocyclic chlorides, 6-chloro-2-(chloromethyl)-3-nitro-1*H*-imidazo[1,2-*b*]pyridazine (**1**), 2-(chloromethyl)-3-nitro-1*H*-imidazo[1,2-*a*]pyridine (**2**), 6-chloro-2-(chloromethyl)-3-nitro-1*H*-imidazo [1,2-*a*]pyridine (**3**), 6-bromo-2-(chloromethyl)-3-nitro-1*H*-imidazo[1,2-*a*]pyridine (**4**), 6-(chloromethyl)--5-nitroimidazo[2,1-*b*]thiazole (**5**), were prepared as previously described.[8-10]

Condensation of 2-amino-5-halopyridine and ethyl 4-chloroacetoacetate according Ferrarini's procedure:[11]

A mixture of polyphosphoric acid, 2-amino-5-halopyridine (2 mmol) and ethyl 4-chloroacetoacetate (2.8 mmol) was stirred at 110 °C for 30 min. After cooling with an ice-cold solution, the precipitate was

filtered and recrystallized from isopropanol giving 80% of corresponding 7-halo-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one as beige solid.

7-Chloro-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (6)

Beige solid; Yield 80%, mp 156 °C; ^{1}H NMR δ 4.51 (s, 2H, CH_2); 6.66 (s, 1H, CH); 7.59 (dd, *J* = 0.8 Hz and 9.5 Hz, 1H, CH); 7.70 (dd, *J* = 2.3 Hz and 9.5 Hz, 1H, CH); 9.06 (d, *J* = 2.3 Hz, 1H, CH). ^{13}C NMR δ 45.5; 103.2; 124.3; 125.0; 127.2; 138.1; 149.4; 157.0; 162.3. Anal. Calcd for $C_9H_6Cl_2N_2O$ (229.06): C, 47.19; H, 2.64; N, 12.23. Found: C, 47.32; H, 2.64; N, 12.65.

7-Bromo-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (7)

Beige solid; Yield 80%, mp 175 °C; ^{1}H NMR δ 4.50 (s, 2H, CH_2); 6.66 (s, 1H, CH); 7.50 (dd, *J* = 0.6 Hz and 9.4 Hz, 1H, CH); 7.80 (dd, *J* = 2.0 Hz and 9.4 Hz, 1H, CH); 9.15 (d, *J* = 2.0 Hz, 1H, CH). ^{13}C NMR δ 45.5; 103.4; 111.0; 127.2; 127.5; 140.1; 149.6; 157.0; 162.4. Anal. Calcd for $C_9H_6BrClN_2O$ (273.51): C, 39.52; H, 2.21; N, 10.24. Found: C, 39.93; H, 2.22; N, 10.49.

Nitration reaction of 7-halo-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **6** and **7**:

To a solution of 7-halo-2-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (1.5 mmol) in concentrated sulfuric acid (75 mmol), 65% nitric acid (7.5 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at rt for 1 h and poured into an ice-cold solution (50 mL). After filtration, the crude product was dried and recrystallized from isopropanol gave the corresponding 7-halo-2-(chloromethyl)-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one as yellow solid.

7-Chloro-2-(chloromethyl)-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (8)

Yellow solid; Yield 100%, mp 167 °C; ^{1}H NMR δ 4.74 (s, 2H, CH_2); 7.82 (dd, *J* = 0.7 Hz and 9.4 Hz, 1H, CH); 7.99 (dd, *J* = 2.3 Hz and 9.4 Hz, 1H, CH); 9.19 (dd, *J* = 0.7 Hz and 2.3 Hz, 1H, CH). ^{13}C NMR δ 42.5; 126.7; 127.4; 128.0; 141.1; 148.9; 150.2; 156.8. The C-nitro was not observed under these experimental conditions. Anal. Calcd for $C_9H_5Cl_2N_3O_3$ (274.06): C, 39.44; H, 1.84; N, 15.33. Found: C, 39.70; H, 1.72; N, 15.17.

7-Bromo-2-(chloromethyl)-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (9)

Yellow solid; Yield 90%, mp 178 °C; ^{1}H NMR δ 4.73 (s, 2H, CH_2); 7.75 (d, *J* = 9.3 Hz, 1H, CH); 8.08 (dd, *J* = 2.2 Hz and 9.3 Hz, 1H, CH); 9.29 (d, *J* = 2.2 Hz, 1H, CH). ^{13}C NMR δ 42.5; 113.9; 127.9; 129.0; 143.2; 149.1; 150.2; 156.8. The C-nitro was not observed under these experimental conditions. Anal. Calcd for $C_9H_5BrClN_3O_3$ (318.51): C, 33.94; H, 1.58; N, 13.19. Found: C, 34.26; H, 1.58; N, 13.56.

General procedure for the reaction of diethyl oxomalonate (**10**) and chlorides **1-5, 8** or **9** using TDAE.

Into a two-necked flask equipped with a silica-gel drying tube and a nitrogen inlet was added, under nitrogen at −20 °C, 10 mL of anhydrous DMF solution of chloride **1-5, 8** or **9** (1.5 mmol) and diethyl oxomalonate (**10**) (4.5 mmol). The solution was stirred and maintained at this temperature for 30 min and

then was added dropwise (*via* a syringe) the TDAE (1.5 mmol). A red color immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred at −20 °C for 1 h and then warmed up to rt for 2 h. After this time TLC analysis (CH_2Cl_2) clearly showed that initial chloride **1-5, 8** or **9** was totally consumed. The orange–red turbid solution was filtered (to remove the octamethyl-oxamidinium dichloride) and hydrolyzed with 80 mL of H_2O. The aqueous solution was extracted with $CHCl_3$ (3 × 40 mL) and the combined organic layers were washed with H_2O (3 × 40 mL) and dried over $MgSO_4$. Evaporation of the solvent left an orange oil as crude product. Purification by silica gel chromatography (CH_2Cl_2) and recrystallization from isopropanol gave the corresponding hydroxymalonate derivatives **11-15** or methylenemalonate derivatives **16-17**.

Diethyl 2-[(6-Chloro-3-nitroimidazo[1,2-*b*]pyridazin-2-yl)methyl]-2-hydroxymalonate (11)

Yellow solid; Yield 40%, mp 100 °C; ^{1}H NMR δ 1.26 (m, 6H, 2xCH_3); 4.00 (s, 2H, CH_2); 4.26 (m, 4H, 2xCH_2); 7.42 (d, *J* = 9.5 Hz, 1H, CH); 7.99 (d, *J* = 9.5 Hz, 1H, CH). ^{13}C NMR δ 13.8; 34.4; 62.7; 78.0; 123.9; 127.4; 136.8; 145.2; 149.4; 169.2. Anal. Calcd for $C_{14}H_{15}ClN_4O_7$ (386.74): C, 43.48; H, 3.91; N, 14.49. Found: C, 43.54; H, 3.93; N, 14,81.

Diethyl 2-Hydroxy-2-[(3-nitro-1*H*-imidazo[1,2-*a*]pyridin-2-yl)methyl]malonate (12)

Yellow solid; Yield 24%, mp 101.7 °C; ^{1}H NMR δ 1.29 (m, 6H, 2xCH_3); 4.08 (s, 2H, CH_2); 4.30 (q, *J* = 7,2 Hz, 4H, 2xCH_2); 5.03 (s, 1H, OH); 7.27 (m, 1H, CH); 7.70 (m, 2H, 2xCH); 9.44 (m, 1H, CH). ^{13}C NMR δ 13.9; 34.9; 62.6; 78.4; 116.5; 117.9; 127.7; 130.9; 144.5; 148.6; 160.2; 169.4. Anal. Calcd for $C_{15}H_{17}N_3O_7$ (351.31): C, 51.28; H, 4.88 N, 11.96. Found: C, 51.51; H, 4.92; N, 12.18.

Diethyl 2-[(6-Chloro-3-nitro-1*H*-imidazo[1,2-*a*]pyridin-2-yl)methyl]-2-hydroxymalonate (13)

Beige solid; Yield 48%, mp 99.5 °C; ^{1}H NMR δ 1.29 (m, 6H, 2xCH_3); 4.07 (s, 2H, CH_2); 4.30 (q, *J* = 7.0 Hz, 4H, 2xCH_2); 4.76 (s, 1H, OH); 7.65 (m, 2H, 2xCH); 9.49 (m, 1H, CH). ^{13}C NMR δ 13.9; 34.8; 62.7; 78.3; 118.2; 125.1; 125.7; 132.0; 142.7; 148.7; 169.4. Anal. Calcd for $C_{15}H_{16}ClN_3O_7$ (430.21): C, 46.70; H, 4.18; N, 10.89. Found: C, 46.86; H, 4.18; N, 10.76.

Diethyl 2-[(6-Bromo-3-nitro-1*H*-imidazo[1,2-*a*]pyridin-2-yl)methyl]-2-hydroxymalonate (14)

Yellow solid; Yield 36%, mp 116 °C; ^{1}H NMR δ 1.29 (m, 6H, 2xCH_3); 4.00 (s, 2H, CH_2); 4.29 (q, *J* = 7.2 Hz, 4H, 2xCH_2); 4.75 (s, 1H, OH); 7.65 (m, 2H, 2xCH); 9.57 (m, 1H, CH). ^{13}C NMR δ 13.9; 34.8; 62.7; 78.3; 111.6; 118.4; 127.7; 134.2; 142.9; 148.5; 169.4. Anal. Calcd for $C_{15}H_{16}BrN_3O_7$ (430.21): C, 41.88; H, 3.75; N, 9.77. Found: C, 41.74; H, 3.75; N, 9.69.

Diethyl 2-Hydroxy-2-[(5-nitroimidazo[2,1-*b*]thiazol-6-yl)methyl]malonate (15)

Yellow solid; Yield 60%, mp 114.5 °C; ^{1}H NMR δ 1.30 (t, *J* = 7.1 Hz, 6H, 2xCH_3); 3.99 (s, 2H, CH_2); 4.30 (q, *J* = 7,1 Hz, 4H, 2xCH_2); 4.55 (s, 1H, OH); 7.16 (d, *J* = 4.5 Hz, 1H, CH); 8.26 (d, *J* = 4.5 Hz, 1H,

CH). ^{13}C NMR δ: 13.9; 34.4; 67.7; 78.3; 115.7; 121.3; 147.4; 152.1; 169.4. Anal. Calcd for $C_{13}H_{15}N_3O_7S$ (357.34): C, 43.69; H, 4.23; N, 11.76. Found: C, 43.85; H, 4.20; N, 11.80.

Diethyl 2-[(7-Chloro-3-nitro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methylene]malonate (16)

Beige solid; Yield 24%, mp 175 °C; ^{1}H NMR δ 1.34 (m, 6H, 2xCH_3); 4.36 (m, 4H, 2xCH_2); 7.62 (d, *J* = 9.4 Hz, 1H, CH); 7.73 (s, 1H, CH); 7.93 (d, *J* = 9.4 Hz, 1H, CH); 9.17 (s, 1H, CH). ^{13}C NMR δ 14.0; 14.1; 61.6; 62.5; 126.7; 127.1; 127.7; 131.6; 135.7; 140.9; 148.1; 150.2; 150.5; 162.6; 164.7; 168.4. Anal. Calcd for $C_{16}H_{14}ClN_3O_7$ (395.75): C, 48.56; H, 3.57; N, 10.62. Found: C, 48.56; H, 3.53; N, 10.47.

Diethyl 2-[(7-Bromo-3-nitro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)methylene]malonate (17)

Yellow solid; Yield 19%, mp 175 °C; ^{1}H NMR δ 1.29 (m, 6H, 2xCH_3); 4.36 (m, 4H, 2xCH_2); 7.55 (d, *J* = 9.4 Hz, 1H, CH); 7.73 (s, 1H, CH); 8.02 (d, *J* = 9.4 Hz, 1H, CH); 9.27 (s, 1H, CH). ^{13}C NMR δ 14.0; 14.1; 61.6; 62.5; 113.7; 127.6; 129.0; 131.6; 135.7; 143.1; 148.1; 150.1; 150.6; 162.6; 164.7; 168.4. Anal. Calcd for $C_{16}H_{14}BrN_3O_7$ (440.20): C, 43.66; H, 3.21; N, 9.55. Found: C, 43.66; H, 3.26; N, 9.33.

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