Bioorganic & Medicinal Chemistry Letters 23 (2013) 1274–1278

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis, crystal structure and antibacterial activity of new highly functionalized ionic compounds based on the imidazole nucleus

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ARTICLE INFO

Article history:
Received 18 October 2012
Revised 21 December 2012
Accepted 2 January 2013
Available online 11 January 2013

Keywords:
Haloimidazole
Nitroimidazole
Imidazolium salt
Halogenation
Crystal structure
Antibacterial activity

ABSTRACT

Several new highly functionalized imidazolium derivatives were synthesized, via appropriate synthetic routes, using imidazole, 1-methylimidazole and 2-phenyl-1-methylimidazole as key intermediates. The antibacterial activity of the prepared compounds was evaluated against: *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella thipymurium* using disk-diffusion and MIC methods. Crystal X-ray structures are reported for six compounds.

Heterocyclic compounds have so far been synthesized mainly due to the wide range of biological activities. Much attention was paid to the synthesis of heterocyclic compounds bearing nitrogen and oxygen containing ring system, like pyrazole, oxazole, coumarine, and pyrrole derivatives mainly due to their higher pharmacological activity.[1–3] At present, the role of heterocyclic compounds has become increasingly important in designing new class of structural entities of medicinal importance.[4–7]

Imidazole nucleus forms the main structure of some well-known components of human organisms, that is, histidine, Vit-B12, a component of DNA base structure and purines, histamine and biotin. It is also present in the structure of many natural or synthetic drug molecules.[8–10] For example, Lepidiline A and B exhibit significant cytotoxicity against various types of human cancer cell lines at micromolar concentrations.[11] Dacarbazine,[12] Zoledronic acid,[13] Tipifarnib[14,15] and Azathioprine[16] are also potent anticancer agents bearing an imidazole ring.

On the other hand, imidazolium salts are known for the wide-range of their biological activity. A large variety of these salts have been used as anti-inflammatory, antibacterial, antifungal and thromboxane synthetase inhibitior.[17]

Furthermore, Haloimidazoles are used as synthons for the production of various condensed heterocyclic systems[18] and some of them are known to possess remarkable and significant biological applications as drugs,[19] pharmaceuticals and agrochemicals.[20]

In the present work, a variety of functionalized imidazolium compounds were prepared (variations on C2, C4 and C5) and their antibacterial activity was studied. The structure elucidation of some prepared compounds was performed by X-ray diffraction.

First, the key intermediates **2**, **4**, **6** and **8** were prepared incorporating two bromine, iodine atoms or nitro group on the imidazole unit. Synthesis of these compounds was accomplished as outlined in Schemes 1 and 2.

According to a known procedure,[21] the hydroxymethylation of the commercially available 1-methylimidazole leads to the corresponding (1-methyl-1*H*-imidazol-2-yl)methanol **1**. Then, the resulting compound was subjected to bromination reaction using $Br_2/KHCO_3$ in DMF to give the desired (4,5-dibromo-1-methyl-1*H*-imidazol-2-yl)methanol **2**.[22]

The key intermediates 4,5-dibromo-2-methyl-1-methylimidazole **4a** and 4,5-dibromo-2-phenyl-1-methylimidazole **4b**, were obtained from the reaction of 2-methylimidazole or 2-phenylimidazole with bromine in DMF and in presence of $KHCO_3$,[22] followed by methylation reaction using Me_2SO_4.[23]

The 1-methyl-4,5-diiodoimidazole derivatives **6a** and **6b** were synthesized by reacting 2-methylimidazole and imidazole with

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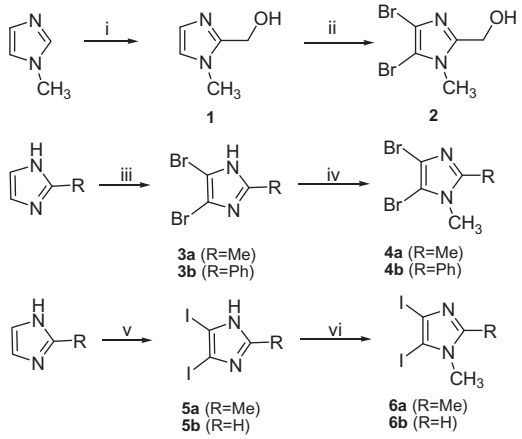
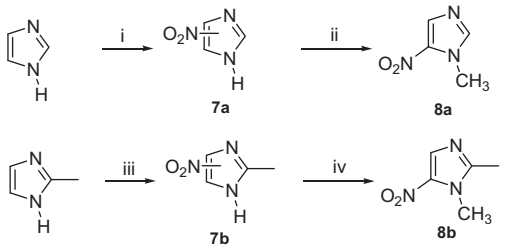
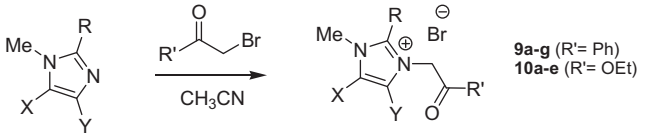
http://dx.doi.org/10.1016/j.bmcl.2013.01.004



Scheme 1. Reagents and conditions: (i) CH_2O/H_2O, DMSO, 48 h (43%); (ii) Br_2, $KHCO_3$, DMF, 0–100 °C, 72 h (30%); (iii) for **3a** and **3b**: Br_2, $KHCO_3$, DMF, 0–100 °C, 72 h (36% and 61% respectively); (iv) for **4a** and **4b**: Me_2SO_4, NaOH/H_2O, 40 °C, (91% and 39%); (v) for **5a** and **5b**: I_2, NaOH, KI/H_2O, then AcOH, 24 h (60% and 70% respectively); (vi) for **6a** and **6b**: Me_2SO_4, NaOH/H_2O, 40 °C, (78% and 86% respectively).



Scheme 2. Reagents and conditions: (i) H_2SO_4, HNO_3 100%, 100 °C (85%); (ii) $MeSO_4$, 100 °C then neutralization at rt with NH_4OH, (72%); (iii) H_2SO_4, 0 °C then HNO_3 100%/Ac_2O, 140 °C (39%); (iv) Me_2SO_4, HCOOH, reflux, 4 h, (87%).



Scheme 3. Reagents and conditions: (i) $BrCH_2COR'$ (1.2 equiv R′ = Ph; 1.8 equiv R′ = OEt), CH_3CN, reflux, 48 h.

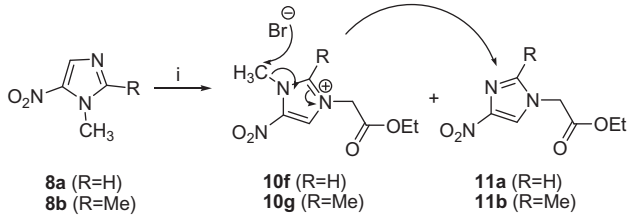
iodine in water in presence of KI and NaOH,[24] followed by treatment of the obtained 4,5-diiodo-1*H*-imidazole derivatives **5a** and **5b** with dimethylsulfate in aqueous NaOH solution.

Next, we considered the synthesis of imidazole units containing a nitro group. Some nitroimidazoles were found to be useful biological synthons and endowed with numerous important activities.[25–27] 1-Methyl-5-nitroimidazole **8a** and 1,2-dimethyl-5-nitroimidazole **8b** were obtained via a nitration/methylation sequence (Scheme 2).

Having in hand these various functionalized derivatives, we turned our attention to the synthesis of corresponding imidazolium salts using a quaternization reaction. Following the standard methodology, compounds **9a–9g** were obtained in moderate to good yields by reacting the corresponding products **2**, **4a–b**, **6a–b** and **8a–b** with 1.5 equiv of 2-bromoacetophenone at reflux of acetonitrile (Scheme 3). In similar manner, when 1.8 equivalent of ethyl bromoacetate was used as quaternization agent, the compounds **2**, **4a–b** and **6a–b** react correctly and give the imidazolium compounds **10a–e**.

Table 1
Products and yields of quaternization reactions

Products	R	X	Y	Yield (%)
9a	CH_2OH	Br	Br	27
9b	Me	Br	Br	78
9c	Ph	Br	Br	21
9d	Me	I	I	52
9e	H	I	I	66
9f	H	NO_2	H	76
9g	Me	NO_2	H	65
10a	CH_2OH	Br	Br	57
10b	Me	Br	Br	60
10c	Ph	Br	Br	83
10d	Me	I	I	82
10e	H	I	I	17



Scheme 4. Reagents and conditions: (i) 1.8 equiv $BrCH_2CO_2Et$, CH_3CN, reflux, 48 h.

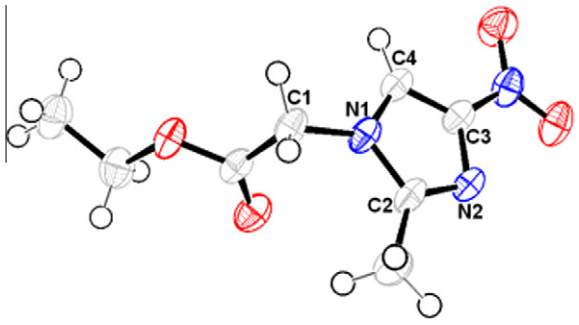


Figure 1. ORTEP plot of the X-ray crystal structure of **11b**. Displacement ellipsoids are drawn at the 50% probability level; selected bond lengths [Å]: N1–C2 1.379(3), C2–N2 1.317(3), N2–C3 1.370(3), N1–C1 1.450(3).[30]

Note that no purification was needed and the corresponding compounds **9a–g** and **10a–e** were isolated by simple filtration after crystallization during the reducing step of solvent volume. The prepared compounds and yields of the quaternisation reaction are shown in Scheme 3 and in Table 1 and their structures were established by spectroscopic and analytical methods.[28]

However, the reaction of compounds **8a** and **8b** (X = NO_2, Y = H) with ethyl bromoacetate afford the quaternized compounds **10f** and **10g** accompanied with unexpected products **11a** and **11b**, respectively, resulting from a demethylation reaction with bromide ion (Scheme 4). This result was previously observed by Crozet and co-workers.[29]

The structure determination of **11b** is based on an X-ray study of a suitable crystal obtained by slow evaporation at room temperature of a MeOH solution. An ORTEP representation of the crystal structure is shown in Figure 1.

On the other hand, crystallographic studies can contribute to understanding the reactivity, affinity and the binding properties of molecules.[31–33] Furthermore, numerous studies have demonstrated that the nature of substituents and substitution pattern on the imidazole unit may have a considerable impact on the pharmacological activities.[34,35] Thus it was considered of interest to

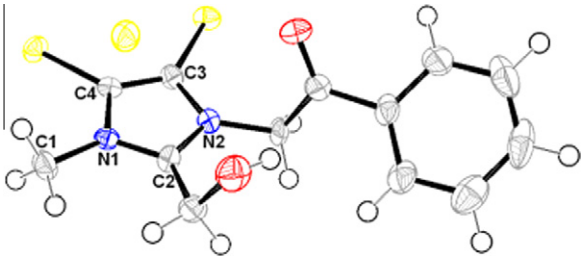


Figure 2. ORTEP plot of the X-ray crystal structure of **9a**. Displacement ellipsoids are drawn at the 50% probability level; selected bond lengths [Å]: N1–C2 1.336(8), C2–N2 1.349(8), N2–C3 1.385(8), C3–C4 1.349(9), C4–N1 1.392(8), N1–C1 1.460(8).[30]

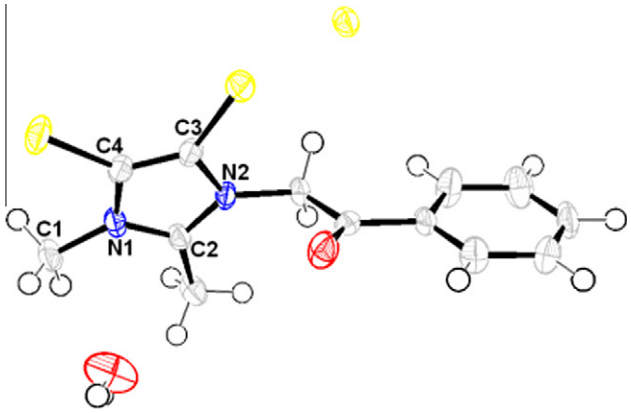


Figure 3. ORTEP plot of the X-ray crystal structure of **9b**. Displacement ellipsoids are drawn at the 50% probability level; selected bond lengths [Å]: N1–C2 1.337(3), C2–N2 1.344(3), N2–C3 1.390(3), C3–C4 1.342(4), C4–N1 1.388(3), N1–C1 1.463(3).[30]

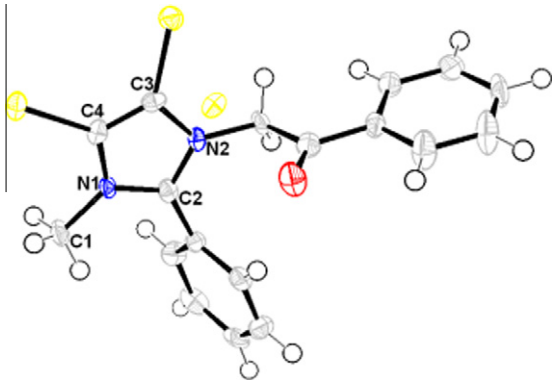


Figure 4. ORTEP plot of the X-ray crystal structure of **9c**. Displacement ellipsoids are drawn at the 50% probability level; selected bond lengths [Å]: N1–C2 1.343(4), C2–N2 1.345(4), N2–C3 1.386(4), C3–C4 1.345(4), C4–N1 1.379(4), N1–C1 1.458(4).[30]

carry out an X-ray diffraction analysis. In this context, some quaternized compounds were recrystallized. Suitable crystals of **9a**, **9b**, **9c**, **9d** and **9f** were grown by slow evaporation of water/methanol or isopropanol solution. The X-ray crystallographic analysis confirmed their respective structures and the refined X-ray crystal structures are shown in Figures 2–6.

Crystal data and structural details of new imidazolium salts are presented in Table 2. Compounds **9a**, **9b**, **9c**, **9d** and **9f** are composed of 4,5-dihalo or 5-nitro-1-methyl-3-(1-oxo-1-phenyleth-2-yl)imidazole cation and the bromide anion. The N2 atom adds a 1-oxo-1-phenyleth-2-yl entity to form the cation, and the anion bromide balances the charge. The benzene ring of the benzoyl fragment is also planar. The bond lengths of N–C are in the range [1.321(3)–1.343(4) Å] for N1–C2 and [1.341(3)–1.349(8) Å] for C2–N2. These values are shorter than normal C–N bond lengths, indicating that they have double bond characters. However, they are different from those of other neutral substituted imidazole compounds 1.379(3) Å for N1–C2 and 1.317(3) Å, for N2–C2 in **11b**. The others two C–N bond lengths in the imidazole ring are in the range 1.360(3)–1.393(3) Å, which is shorter than the single-bond length of 1.48 Å, but longer than the typical C = N length of 1.27 Å, indicating an appreciable charge delocalization in the ring.

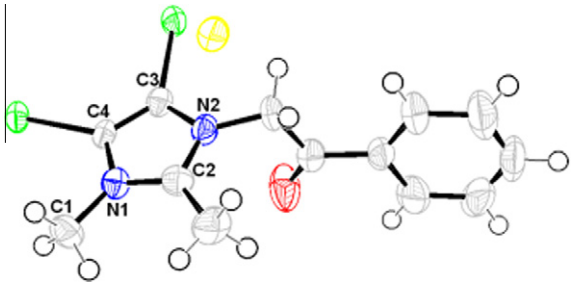


Figure 5. ORTEP plot of the X-ray crystal structure of **9d**. Displacement ellipsoids are drawn at the 50% probability level; selected bond lengths [Å]: N1–C2 1.327(4), C2–N2 1.343(5), N2–C3 1.387(4), C3–C4 1.357(5), C4–N1 1.389(4), N1–C1 1.453(4).[30]

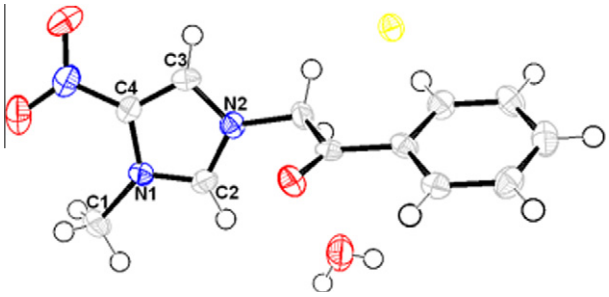


Figure 6. ORTEP plot of the X-ray crystal structure of **9f**. Displacement ellipsoids are drawn at the 50% probability level; selected bond lengths [Å]: N1–C2 1.321(3), C2–N2 1.341(3), N2–C3 1.360(3), C3–C4 1.355(3), C4–N1 1.393(3), N1–C1 1.473(3).[30]

Once the imidazolium salts **9** and **10** were in hand, they were evaluated for their antimicrobial activity against *Escherichia coli* **Ec** (ATTC-25922), *Staphylococcus aureus* **Sa** (ATTC-25923), *Pseudomonas aeruginosa* **Pa** (ATCC-27853) and *Salmonella thipymurium* **St** (ATCC-07095) using the disk-diffusion method.[36]

The disk-diffusion method was performed as follows: the bacterial suspension was spread on the surface of a Mueller–Hinton agar. Paper disks (6 mm) were charged with 200 µg of the tested compounds dissolved in DMSO and were placed on the agar surface. After overnight incubation at 37 °C, inhibition zones diameters were measured with a ruler and were recorded in millimeter. For comparison Spiramicyn was used as standard drug. The results of the antibacterial screening of the prepared compounds are summarized in Table 3. Most of the compounds tested were found to have moderate to good antibacterial activities against *Staphylococcus aureus* and *Escherichia coli* and *Pseudomonas aeruginosa*. However, activity of these compounds against *Salmonella thypimurium* was found to be less in comparison to reference compound. Moreover, comparison of antimicrobial data further

Table 2
Crystal data for characterized compounds

Compounds	**9a**	**9b**	**9c**	**9d**	**9f**
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	*Pcab*	$P2_1/c$	$C2/c$	$P2_1/a$	$P2_12_12_1$
a (Å)	7.1740(2)	5.4562(2)	31.8115(18)	10.8527(4)	6.0194(8)
b (Å)	11.9743(3)	18.0551(6)	7.9772(5)	9.6643(3)	11.8657(15)
c (Å)	35.0273(8)	16.4893(6)	14.3825(9)	16.4305(6)	19.396(2)
α (°)	90	90	90	90	90
β (°)	90	91.8320(10)	101.934(3)	106.3150(10)	90
γ (°)	90	90	90	90	90
V (Å^3)	3008.97(13)	1623.57(10)	3570.9(4)	1653.90(10)	1385.3(3)
Z	8	4	8	4	4

Table 3
In vitro antibacterial activity of compounds **9a**–**g** and **10a**–**e**

	MIC (μg/mL) (zones of inhibition in mm)			
Products	**Ec**	**Sa**	**Pa**	**St**
9a	25(7)	>250(7)	50(9)	>250(NI)
9b	12.5(9)	>250(7)	150(9)	>250(7)
9c	50(9)	250(12)	50(8)	150(7)
9d	12.5(9)	>250(15)	12.5(9)	25(8)
9e	25(12)	250(15)	25(8)	12.5(9)
9f	12.5(NI)	>250(NI)	12.5(9)	12.5(NI)
9g	50(9)	>250(9)	>250(10)	50(7)
10a	150(7)	>250(NI)	25(7)	>250(NI)
10b	25(NI)	>250(10)	250(NI)	>250(NI)
10c	50 (NI)	>250(9)	25(7)	25(7)
10d	25(NI)	>250(NI)	25(9)	>250(NI)
10e	6.2(NI)	250(NI)	6.2(9)	50(NI)
Spiramicyn*	9	22	0	9

NI: No inhibition zone.
* Disc charge 100 μg.

suggested that compounds possessing 1-oxo-1-phenyleth-2-yl linked to N2 (**9a**–**g**) have more antimicrobial activity compared to the corresponding ethyl ester derivatives **10a**–**e** (Table 3).

In series of brominated compounds **9a**–**c**, the best results were observed with 2-phenylimidazole quaternized with 1-oxo-1-phenyleth-2-yl) entity (compounds **9c**) which have shown a significant inhibition effect on the growth of Gram positive bacteria like *Staphylococcus aureus*.

The comparison of inhibition zone diameters in 4,5-dihalogenoimidazole series **9a**–**e** revealed that 4,5-diiododoimidazole **9d** and **9e** are more active than corresponding dibromoimidazole analogs and especially against *Staphylococcus aureus* and *Escherichia coli*.

To confirm the antibacterial activities of the synthesized compounds, the MICs tests were carried out. Bacterial inoculums were prepared by dilution of an overnight broth culture to give the equivalent of 10^6 cell/mL approximately. Minimum inhibitory concentrations (MICs) values (μg/mL) of each compound were determined after 1 day of exposure by a standardized agar dilution technique[37] (Table 3). The results obtained by the MIC method confirm those observed by the disc diffusion procedure. Indeed, most of the tested compounds have an interesting biological activity especially against Gram negative bacteria like *Escherichia coli* or *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Gram positive bacteria) are the less reactive. Compounds bearing the methyphenylketone at N2 were found more active than their analogs linked to the ester group. The best results were obtained with imidazolium bearing iodine atoms in imidazole nucleus and compound **10e** is the most promising antibacterial agent against Gram negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* (MIC $\leqslant$6.2 μg/mL). Furthermore, the non substituted imidazolium **9f** presents better inhibition compared to its methylated analog **9g**.

In conclusion, as demonstrated herein, the approaches developed in this work allow an efficient access to new haloimidazolium and nitroimidazolium salts using appropriate synthetic routes. These approaches allow a diverse range of compounds to be prepared in good yields. All the target compounds were evaluated for their in vitro antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella typhimurium*. In most cases, prepared ionic derivatives have shown moderate to significant antibacterial activities against especially Gram negative bacteria pathogens selected in this study and, iodinated compounds are the most promising antibacterial agents, and can serve as potential leads for further drug discovery study.

Acknowledgments

We thank MESRS (Ministère de l'Enseignement Supérieur et de la Recherche Scientifique) and ANDRU (Agence Nationale pour le Développement de la Recherche Universitaire) Algeria, for financial support.

Supplementary data

Supplementary data associated (analytical data for synthetic products) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.01.004.

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28. *Typical procedure for the synthesis of* ***9*** *and* ***10****:* To a solution of 1-methylimidazole derivatives (1 mmol) in adequate volume of acetonitrile, was added 1.5 mmol of 2-bromoacetophenone (1.8 mmol of ethylbromoactate). The reaction mixture was refluxed. When the reaction was over (TLC), the solvent volume was reduced and the crude product was then filtered off and washed with cold acetonitrile. Selected data for **9d**: ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.17–8.14 (m, 2H, Ar), 7.83–7.77 (m, 1H, Ar), 7.68–7.62 (m, 2H, Ar), 6.11 (s, 2H, CH_2), 3.89 (s, 3H, *N*-CH_3), 2.62 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 191.2 (C=O), 149.8 (C), 135.3 (C), 133.8 (CH), 129.5 (2 × CH), 128.9 (2 × CH), 95.8 (C), 95.6 (C), 57.3 (CH_2), 12.5 (CH_3), 12.4 (CH_3). Anal. Calcd for $C_{14}H_{15}Br_3N_2O_2$: C, 28.55; H, 2.40; N, 5.12; Found: C, 28.53; H, 2.64; N, 5.02. Selected data for **10c**: ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.84–7.67 (m, 5H, Ar), 5.06 (s, 2H, CH_2), 4.18 (q, *J* = 7.0 Hz, 2H, CH_2), 3.67 (s, 3H, *N*-CH_3), 1.11 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 166.0 (C=O), 147.6 (C), 133.7 (CH), 130.8 (2 × CH), 130.1 (2 × CH), 121.1 (C), 112.7 (C), 111.8 (C), 62.9 (CH_2), 50.1 (CH_2), 37.1 (CH_3), 14.3 (CH_3). Anal. Calcd for $C_{14}H_{15}Br_3N_2O_2$: C, 34.81; H, 3.13; N, 5.80; Found: C, 34.69; H, 3.23; N, 5.76.
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