An Alternate Approach For The Synthesis of 2-Substituted-Arylimidazo[4,5-*b*]Pyridines And Their Anti-Bacterial Activity

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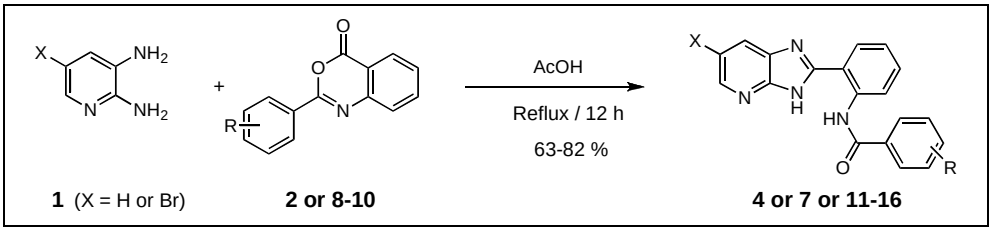

An alternate method for the convenient preparation of the imidazo[4,5-*b*]pyridines from 2,3-pyridinediamine and 2-aryl-3(1)-benzoxazine-4*H*-one has been illustrated. The mechanistic pathway for the formation of the product **4** has been proposed. All the compounds prepared herein were screened for their anti- bacterial properties.

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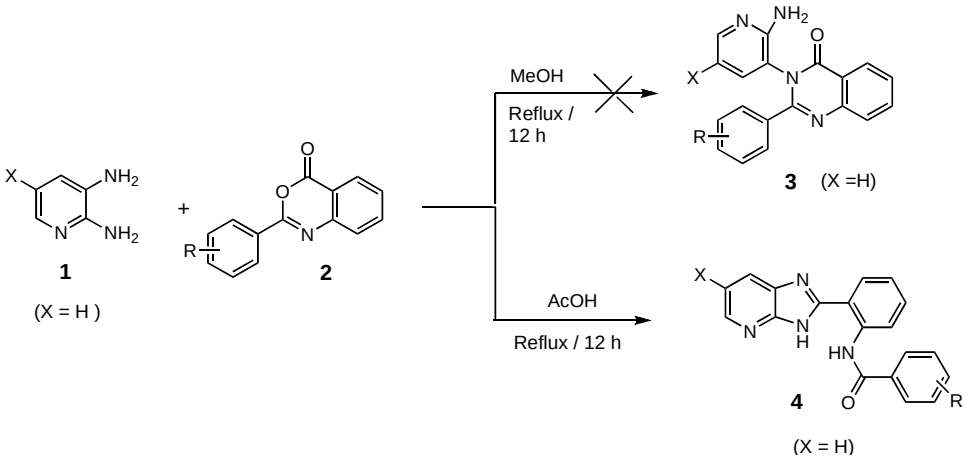
INTRODUCTION

Imidazopyridines constitute a potent class of bio-active compounds that are found in several natural and non-natural products [1]. Further, these are the aza-analogs of another biologically active molecules, the benzimidazoles [2]. The biological activities of both benzimidazoles [3] and imidazopyridines [4] have been very well documented in the literature. Our interest in the chemistry of imidazopyridines [5] and their carbocyclic analogues [6] has been continued owing to their potential biological activities. In the present work, we described our efforts towards the synthesis of some biologically active derivatives obtained by the reaction of 2,3-pyridine-diamines with 2-aryl-3(1)-benzoxazine-4H-ones.

RESULTS AND DISCUSSION

Condensation of 2,3-pyridinediamine [7] (**1**)(X=H) with 2-phenyl-3(1)-benzoxazine-4*H*-one [8] (**2**) was carried out in methanol in anticipation of preparing the analogues of the biologically active compounds obtained by the reaction of compound **2** with primary amines [9]. However, we did not observe any progress in the reaction unlike in the case of the reaction of compound **2** with primary amines. We, then tried the reaction of **1** (X=H) and **2** in glacial acetic acid initially at RT for 6 hr and then at reflux temperature for 12 hr, which showed the formation of some new product on TLC. The reaction mixture was then worked up and characterized with spectral data. The IR spectrum of the product did not show the expected frequencies for -NH_2 group stretchings

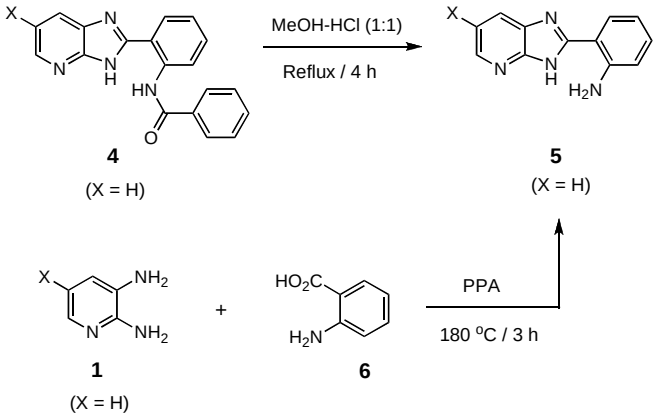
Scheme 1



and instead showed a broad –NH band in the range of 3000 cm^{-1}, characteristic of imidazole type ring formation [3]. The ^{1}H-NMR analysis also supported the formation of imidazole ring system rather than the simple replacement product **3** of the ring oxygen of compound **2** with the nitrogen of the reacting amine partner. Further, electron impact mass spectra of the product showed molecular ion peak at 314 (M^+), which was again in accordance with a different structure rather than that of compound **3** as usually expected. Based on the spectral data the structure of the product was assigned as *N*-(2-(3*H*-imidazo[4,5-*b*]-pyridin-2-yl)phenyl)benzamide **4** [10] (Scheme-1).

The structure of compound **4** was further authenticated by a simple hydrolysis of the latter with methanolic - HCl to the corresponding free amino compound **5** (X=H), which could be easily synthesized [11] by the acid catalysed condensation of compound **1** with anthranilic acid (**6**) (Scheme-2).

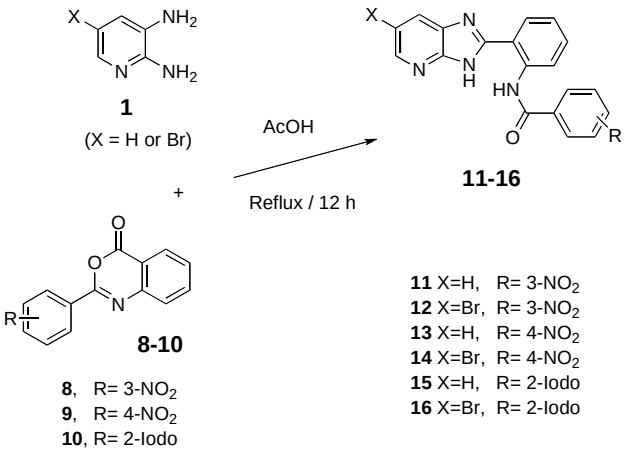
Scheme 2



The probable mechanistic pathway for the formation of **4** from **1** has been proposed in the following Figure-1.

Having confirmed the structure of compound **4** both by spectral and chemical methods, we have extended the above reaction of **1** (X=Br) with **2** and characterized the product thus obtained to be **7** analogous to compound **4** above. Similarly, the reaction of **1** (X=H and Br) was further elaborated with other 2-substituted derivatives of **2** *ie.*, **8** [12], **9**[13] **& 10** [14] (Scheme-3) and the products **11 - 16**, thus obtained were all well characterized with their respective spectral and analytical data (Table-1).

Scheme 3



After the synthesis of the compounds described above, we considered testing the compounds towards their anti-bacterial activities presuming that the compounds may exhibit some activity towards the testing microbial stains as imidazo[4,5-*b*]pyridine derivatives were shown to exhibit potential antimicrobial properties [15].

Antibacterial activity: The antibacterial activity of all the compounds synthesized (Table-1) was evaluated using disc diffusion method [16]. All the experiments were carried out in triplicates. Nutrient agar plates were used to carry out all these screening tests. About 0.2 ml of 24 hrs old broth cultures of different strains (B.*subtilis* and E.*coli* both at 100 and 10 μg concentrations) of bacteria were spread over on solidified nutrient agar petri-plates. The discs containing different compounds were placed on petri-plates and were

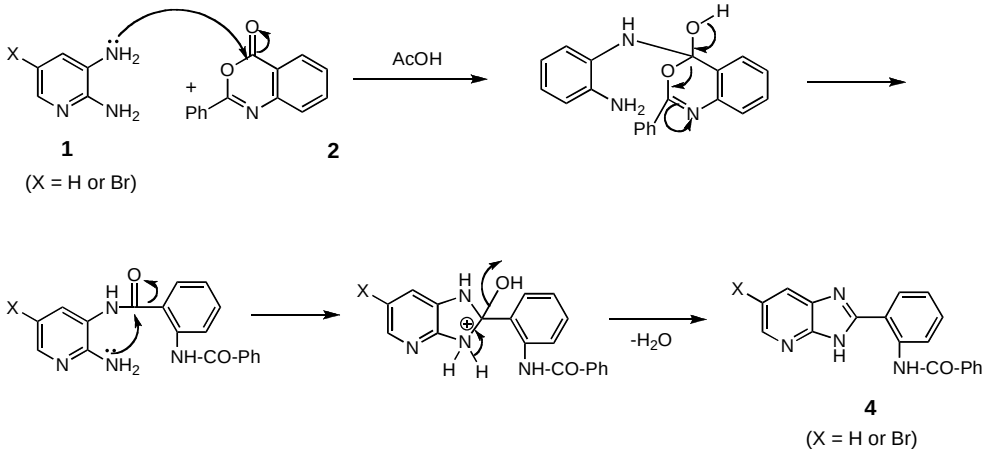


Figure 1

incubated for 48 hrs at 37 °C in a temperature controlled incubators. After 48 hrs of incubation, the zones of inhibition were measured and compared with the positive control *i.e.*, DMF and the results were compared with the standard Cephalexin as shown in Table-2.

EXPERIMENTAL

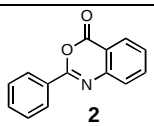
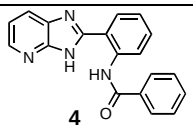
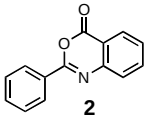
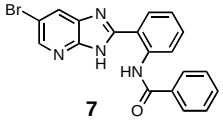
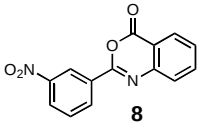
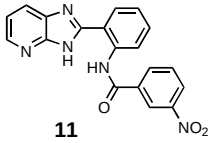
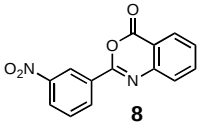
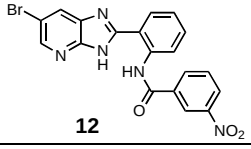
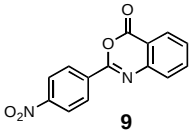
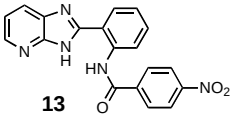
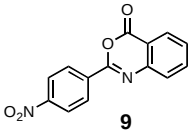
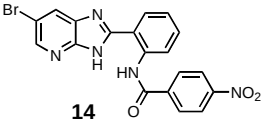
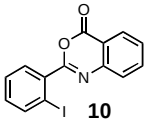
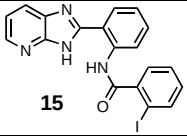
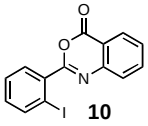
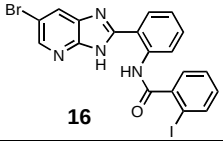
Melting Points are uncorrected and were determined in open capillaries in a sulphuric acid bath. The progress of the reaction was checked on glass plates coated with silica gel-G. IR spectra were recorded on a JASCO FT-IR 5300 spectrometer. ^{1}H-NMR spectra were recorded on a Jeol JNM 400 MHz spectrometer and the mass spectra on a Hewlett Packard Mass Spectrometer operating at 20 eV. As a safety precaution all the experiments should be carried out in well ventilated hood to avoid exposure to the hazardous chemicals.

Synthesis of compounds 4, 7 and 11-16 (General Procedure). A mixture of compound **1** (X = H or Br) (10 mmole) and respective 2-substitutedaryl-3,1-benzoxazin-4(*H*)-one **2** or **8-10** (10 mmole) in glacial acetic acid (10 ml) was refluxed together for 12 hr (tlc monitoring). The reaction mixture was then cooled to room temperature and poured onto crushed-ice, when a solid separated, which was filtered, washed with water (2 x 25 ml) and dried under vaccum to obtain the products **4**, **7** and **11-16** respectively. A small fraction of the crude products were recrystallised from hot aq. methanol to obtain pure products.

Hydrolysis of 4 to obtain 5. Compound **4** (10 mmole) was dissolved in methanolic-HCl (1:1, 30 ml) and refluxed on a water bath for 4 hr. The methanol in the reaction mixture was then evaporated and the acidic solution was neutralized with aq. ammonia. The separated solid was collected by filtration, washed with water (2 x 10 ml) and dried to obtain **5**. The crude products were purified by dissolving them in 10 % HCl and reprecipitation by the addition of aq. ammonia after charcoal treatment.

Table-1

List of Imidazo[4,5-*b*]pyridines prepared

Diamine Used	Reagent	Product	Yield (%)	M.P. (°C)
1 (X = H)	 **2**	 **4**	63	174-176[10]
1 (X = Br)	 **2**	 **7**	66	207-209[10]
1 (X = H)	 **8**	 **11**	76	241-242
1 (X = Br)	 **8**	 **12**	73	245-246
1 (X = H)	 **9**	 **13**	70	251-252
1 (X = Br)	 **9**	 **14**	82	205-206
1 (X = H)	 **10**	 **15**	78	--
1 (X = Br)	 **10**	 **16**	71	216-217

Alternate synthesis of compound 5 from 1. A mixture of **1** (X= H) (5 mmole), anthranilic acid (5 mmole) and polyphosphoric acid (10 ml) was heated in an oil bath maintained at 180 °C for 2 hr. The reaction mixture was then cooled to room temperature, poured into cold water (10 ml) and neutralized with aq. ammonia. The separated solid was filtered, washed with water (2 x 25 ml) and dried to obtain compound **5**. The crude product was purified as above, which was found to be identical (in TLC and IR) with the product obtained earlier.

Antibacterial activity. The antibacterial activity of all the compounds synthesised (Table-1) was evaluated using disc diffusion method [16]. All the experiments were carried out in triplicates. Nutrient agar plates were used to carry out all screening tests. About 0.2 ml of 24 hrs old broth cultures of different strains (B.*subtilis* and E.*coli* both at 100 and 10 μg concentrations) of bacteria were spreaded over on solidified nutrient agar petri-plates. The discs containing different compounds were placed on petri-plates and were incubated for 48 hrs at 37 °C in a temperature controlled incubators. After 48 hrs of incubation, the zones of inhibition were measured and compared with the the positive control ie., DMF and the results were compared with the standard Cephalexin as shown in Table-2.

Table-2

Anti-bacterial growth Inhibition activity of 2-(*o*-N-benzoylamino phenyl)imidazo(4,5-b)pyridines 4, 7, and 11-16 against B. *subtilis and* E. *coli in vitro*.

Test Compound	B. *subtilis* 100μg	B. *subtilis* 10μg	E. *Coli* 100μg	E. *Coli* 10μg	App. MIC
4	++	++	+++	+	100 μg/ml
7	+	+	++	++	100 μg/ml
11	+	-	++	-	100 μg/ml
12	++	+	+	+	100 μg/ml
13	+++	-	+	-	100 μg/ml
14	++	-	++	+	100 μg/ml
15	-	-	++	+	100 μg/ml
16	++	+	+	-	100 μg/ml
Cephalexin	++	+	++	+	100μg/ml

Symbols: +++ = Good inhibition zone (7-10 mm); + + = Moderate inhibition zone (5-7 mm); + = Partial inhibition zone (3-5 mm); - = No inhibition zone.

Spectral Data.

***N*-(2-(3*H*-Imidazo[4,5-*b*]pyridin-2-yl)phenyl)benzamide (4).** IR (KBr): 2970, 1680, 1640, 1610, 1540, 1500, 1410 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 7.1-8.2 (m, 11H), 8.9 (d, *J* =2.0 Hz, 1H), 12.4 (s, 1H). ^{13}C NMR (100 MHz): 115.85, 120.13, 120.19, 122.50, 127.43, 127.49, 128.66, 131.60, 131.78, 134.45, 134.50, 135.02, 142.06, 165.69, 170.86; EI-MS (m/z): 314 (M^+); Analysis: Calcd. For: $C_{19}H_{14}N_4O$, C- 72.60; H- 4.49; N-17.82; Found- C- 72.36 ; H- 4.09 ; N- 17.72.

***N*-(2-(6-Bromo-3*H*-imidazo[4,5-*b*]pyridin-2-yl)phenyl)-benzamide (7).** IR (KBr): 3063, 1680,1606, 1587, 1540, 1450, 1402, 1298 cm^{-1}. ^{1}H-NMR ($CDCl_3$ +DMSO-d_6/TMS): δ 7.0-8.3 (m, 10H), 8.9 (d, *J* =2.0 Hz, 1H), 12.4 (s, 1H). ^{13}C NMR (100 MHz): 115.89, 118.57, 120.10, 122.51, 127.42, 128.68, 131.60, 131.81, 134.42, 135.01, 142.05, 165.05, 170.85; EI-MS (m/z): 393 (M^+); Analysis: Calcd. For $C_{19}H_{13}BrN_4O$: C- 58.03; H- 3.33; N- 14.25; Found- C- 57.88; H-3.06 ; N- 13.97.

***N*-(2-(3*H*-Imidazo[4,5-*b*]pyridin-2-yl)phenyl)-3-nitrobenz-amide (11).** IR (KBr): 3089, 1666, 1585, 1526, 1413, 1350, 1230, 1080 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): **δ** 7.03 (t, *J* = 7.6Hz, 1H), 7.47 (t, *J*=7.8Hz, 2H), 7.58 (t, *J*= 8.0Hz, 1H), 8.03 (dd, *J* =7.8 & 1.4Hz, 1H), 8.25-8.30 (m, 3H), 8.74 (d, *J*=8.4Hz, 2H), 8.80 (s, 1H), 12.64 (s, 1H). ^{13}C NMR (100 MHz): 116.06, 120.04, 122.13, 123.18, 126.27, 130.04, 131.73, 133.79, 134.65, 136.69, 141.54, 148.38, 162.82, 171.48; EI-MS (m/z): 359 (M^+); Analysis: Calcd. For $C_{19}H_{13}N_5O_3$: C-63.51- ; H- 3.65; N- 19.49; Found- C-63.42 ; H- 3.59 ; N-19.28.

***N*-(2-(6-Bromo-3*H*-imidazo[4,5-*b*]pyridin-2-yl)phenyl)-3-nitrobenzamide (12).** IR (KBr): 3074, 2859, 1666, 1607, 1523, 1415, 1345, 1261, 1165, 1071, 909 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): **δ** 6.94 (t, *J* = 8.0Hz, 1H), 7.35-7.40 (m, 1H), 7.50 (t, *J*= 8.0Hz, 1H), 7.92 (dd, *J* =8.0 & 1.6Hz, 1H), 8.16-8.19 (m, 3H), 8.62 (d, *J*=8.4Hz, 2H), 8.68 (t, *J*=2.0Hz, 1H), 12.53 (s, 1H). ^{13}C NMR (100 MHz): 116.06, 119.97, 122.14, 123.15, 126.26, 130.10, 131.64, 133.57, 134.55, 136.58, 141.45, 148.34, 162.75, 171.31. EI-MS (m/z): 438 (M^+); Analysis: Calcd. For $C_{19}H_{12}BrN_5O_3$: C- 52.07; H- 2.76; N- 15.98; Found- C-51.85; H-2.55; N- 15.89.

***N*-(2-(3*H*-Imidazo[4,5-*b*]pyridin-2-yl)phenyl)-4-nitrobenz-amide (13).** IR (KBr): 3010, 1658, 1528, 1427, 1350, 1252, 1019, 906 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): **δ** 7.03 (t, *J* = 8.0Hz, 1H), 7.21 (s, 2H), 7.47 (t, *J*= 8.0Hz, 1H), 8.02 (dd, *J* =8.0 & 1.6Hz, 2H), 8.07 (d, *J*=8.4Hz, 2H), 8.19 (d, *J*=8.4Hz, 2H), 8.73 (d, *J*=8.4Hz, 1H), 12.47 (s, 1H). ^{13}C NMR (100 MHz): 116.12, 120.14, 123.25, 123.87, 128.65, 131.73, 134.61, 140.62, 141.48, 149.73, 163.65, 171.07; EI-MS (m/z): 359 (M^+); Analysis: Calcd. For $C_{19}H_{13}N_5O_3$: C- 63.51; H- 3.65; N-19.49; Found- C-63.42 ; H-3.33; N-19.33.

***N*-(2-(6-Bromo-3*H*-imidazo[4,5-*b*]pyridin-2-yl)phenyl)-4-nitrobenzamide (14).** IR (KBr): 2925, 1669, 1604, 1524, 1439, 1349, 1271,1110, 902 cm^{-1}.^{1}H-NMR ($CDCl_3$ +DMSO-d_6/TMS): δ 6.82 (d, *J* = 2.8Hz, 1H), 6.95 (t, *J*=8.0Hz, 1H), 7.38 (t, *J*= 7.2Hz, 1H), 7.93 (d, *J* =8.0Hz, 1H), 7.98 (d, *J*=8.4Hz, 2H), 8.11 (d, *J*=8.4Hz, 2H), 8.19 (d, *J*=2.4Hz, 1H), 8.63 (d, *J*=8.4Hz, 1H), 12.39 (s, 1H). ^{13}C NMR (100 MHz): 98.59, 116.13, 120.05, 123.23, 123.84, 125.49, 126.62, 128.59, 130.05, 131.67, 134.52, 140.55, 141.39, 149.67, 156.59, 163.26, 169.09, 170.97; EI-MS (m/z): 438 (M^+); Analysis: Calcd. For $C_{19}H_{12}BrN_5O_3$: C- 52.07; H- 2.76; N- 15.98; Found- C-52.16; H-2.70; N-15.68.

***N*-(2-(3*H*-Imidazo[4,5-*b*]pyridin-2-yl)phenyl)-2-iodobenz-amide (15).** IR (KBr): 3110, 1650, 1521, 1407, 1353, 1252, 1009, 900 cm^{-1}. ^{1}H-NMR ($CDCl_3$+DMSO-d_6/TMS): δ 6.88 (d, *J* = 7.6Hz, 3H), 7.17 (t, *J*=7.6Hz, 1H), 7.26-7.34 (m, 4H), 7.65 (d, *J*=8.0Hz, 1H), 7.83 (d, *J*=8.0Hz, 1H), 8.54 (d, *J*=8.4Hz, 1H), 11.46 (s, 1H). ^{13}C NMR (100 MHz): 92.63, 116.20, 120.12, 123.01, 128.05, 128.30, 131.38, 131.48, 134.27, 140.19, 141.19, 141.29, 142.12, 167.51, 170.29. EI-MS (m/z): 440 (M^+); Analysis: Calcd. For $C_{19}H_{13}IN_4O$: C- 51.84; H- 2.98; N- 12.73; Found- C-52.02; H-2.96; N-12.68.

***N*-(2-(6-Bromo-3*H*-imidazo[4,5-*b*]pyridin-2-yl)phenyl)-2-iodo-benzamide (16).** IR (KBr): 3100, 1656, 1518, 1415, 1348, 1243, 1024, 905 cm^{-1}. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6/TMS): δ 6.86 - 6.91 (m, 2H), 7.17 (t, *J*=7.6Hz, 1H), 7.24-7.32 (m, 4H), 7.65 (d, *J* =7.6Hz, 1H), 7.84 (d, *J*=8.0Hz, 1H), 8.55 (d, *J*=8.4Hz, 1H), 11.47 (s, 1H). ^{13}C NMR (100 MHz): 92.63, 111.09, 116.23, 120.13, 123.01, 128.06, 128.31, 131.38, 131.49, 134.26, 140.20, 141.31, 142.15, 167.49, 170.29; EI-MS (m/z): 519 (M^+); Analysis: Calcd. For $C_{19}H_{12}BrIN_4O$: C- 43.96; H- 2.33; N- 10.79; Found- C-43.67; H-2.02; N-10.72.

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