# Synthesis of New Substituted 6-(morpholin-4-yl)-1H-Benzimidazole Derivatives 

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#### Abstract

A series of various substituted benzimidazole derivatives containing fluoro and morpholino substituents at the 5 and 6 positions was synthesized and their structures were identified by spectroscopic techniques.


Key Words: benzimidazole, synthesis

## Introduction

Because of its synthetic utility and broad range of pharmacological activities, the benzimidazole nucleus is an important heterocyclic ring. Some benzimidazole derivatives with different pharmacological effects, including antifungal ${ }^{1}$, anthelmintic ${ }^{2}$, anti-HIV ${ }^{3}$, antihistaminic ${ }^{4-6}$, antiulcer ${ }^{7,8}$, cardiotonic ${ }^{9}$, antihypertensive ${ }^{10,11}$ and neuroleptic ${ }^{12}$, are in clinical use. In order to obtain more effective chemotherapeutic agents, a variety of reports have been presented on the synthesis and biological evaluation of new benzimidazole derivatives ${ }^{13}$. Many reports have revealed that the influence of the substitution at the 1,2 and 5 positions of the benzimidazole ring is very important for their pharmacological effects ${ }^{14,15}$. 2-(substitutedphenyl)benzimidazoles with various types of biological activities, such as antibacterial ${ }^{16}$, antiviral ${ }^{17}$, antitumoral ${ }^{18,19}$ and antiinflammatory ${ }^{20}$, have been reported.

In connection with these studies, a series of new 2-aryl substituted benzimidazoles was prepared by condensation of sodium metabisulfite adduct of appropriate aldehydes ${ }^{21}$ with the corresponding ophenylenediamines for evaluation of their biological activities.

## Experimental

All melting points were determined using a Büchi SMP-20 melting point apparatus and were uncorrected. IR spectra were recorded on a Jasco FT/IR 420 spectrophotometer as potassium bromide disks. ${ }^{1} \mathrm{H}$ NMR and MS analyses were performed with a Bruker AC400NMR spectrometer and VG Platform II mass spectrometer, respectively (TÜBİTAK, Instrumental Analysis Lab., Ankara). Silica gel plates (Merck $\mathrm{F}_{254}$ ) and silica gel 60 (Merck; 230-400 mesh ATSM) were used for analytical and column chromatography, respectively. The

2,5-difluoroaniline and 3-chloro-4-fluoroaniline used in this study were purchased from Aldrich Chemical Co. N-(5-Chloro-4-fluoro-2-nitrophenyl)acetamide (2), ${ }^{22}$ 5-chloro-4-fluoro-2-nitro-N-propylaniline (3c), ${ }^{23} 4$ -fluoro-5-morpholin-4-yl-2-nitro-aniline (4a), ${ }^{24}$ propyl-(4-fluoro-5-morpholin-4-yl-2-nitrophenyl)amine (4c) ${ }^{23}$ and 4-fluoro-5-morpholin-4-yl-benzene-1,2-diamine (5a) ${ }^{24}$ were synthesized according to the literature.

5-Chloro-4-fluoro-2-nitro-N-ethylaniline (3b): A solution of $\mathbf{1}(0.5 \mathrm{~g}, 2.58 \mathrm{mmol})$ in a mixture of triethylamine ( 5 ml ) and ethylamine $(0.175 \mathrm{~g}, 3.9 \mathrm{mmol})$ was stirred at room temperature. The reaction mixture was diluted with EtOAc and extracted with water. The organic layer was washed with water. After drying and evaporation, the residue was recrystallized from EtOH , affording $0.48 \mathrm{~g}(85.7 \%)$ of $\mathbf{3 b}$. mp: $95-97^{\circ} \mathrm{C} . \mathrm{IR} \mathrm{cm}{ }^{-1}: 3370(\mathrm{NH}) .{ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}\right) \delta 1.3\left(\mathrm{t}, 3 \mathrm{H},-\mathrm{CH}_{2}-\mathrm{CH}_{3}\right), 3.2\left(\mathrm{q}, 2 \mathrm{H},-\mathrm{CH}_{2}-\mathrm{CH}_{3}\right), 6.8(\mathrm{~d}$, $1 \mathrm{H}, \mathrm{J}_{m}=6.5 \mathrm{~Hz}, \mathrm{H}-6$ ), 7.8 (br.s., $1 \mathrm{H}, \mathrm{NH}$ ), 7.9 (d, $1 \mathrm{H}, \mathrm{J}_{o}=9.3 \mathrm{~Hz}, \mathrm{H}-3$ ).

Ethyl-(4-fluoro-5-morpholin-4-yl-2-nitro-phenyl)amine (4b): Compound 3b (1 g, 4.6 mmol$)$ and morpholine ( $0.4 \mathrm{~g}, 4.6 \mathrm{mmol}$ ) were dissolved in triethylamine ( 5 ml ) and stirred at $60^{\circ} \mathrm{C}$ for 10 h . The resulting suspension was partitioned between water and EtOAc. The organic layer was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated. The residue was crystallized from EtOH, yielding $1.1 \mathrm{~g}(88.7 \%)$ of $\mathbf{4 b} \mathrm{mp}: 154-$ $156^{\circ} \mathrm{C}$. IR cm ${ }^{-1}: 3363(\mathrm{NH}) .{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right) \delta 1.4\left(\mathrm{t}, 3 \mathrm{H},-\mathrm{CH}_{2}-\mathrm{CH}_{3}\right), 3.4\left(6 \mathrm{H},-\mathrm{CH}_{2}-\mathrm{CH}_{3}\right.$ and morpholine $\mathrm{CH}_{2}$ ), $3.9\left(4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right), 6.0\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{m}=7.5 \mathrm{~Hz}, \mathrm{H}-6\right), 7.9\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{o}=14.2 \mathrm{~Hz}, \mathrm{H}-3\right), 8.1$ (br.s., 1 H , $\mathrm{NH})$.

Synthesis of substituted o-phenylenediamines (5a-c) A solution of 4a-c ( 1 mmol ) in concentrated hydrochloric acid ( 5 ml ) was treated portionwise with $\mathrm{SnCl}_{2}(6 \mathrm{mmol})$ and the resulting solution was stirred at room temperature for 30 min . The reaction mixture was poured into ice-water and neutralized with $10 \% \mathrm{NaOH}$ solution, extracted with EtOAc , washed with water, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and evaporated and used for the next step without further purification.

## 2-Substituted aryl-5-fluoro-6-(morpholin-4-yl)-1H-benzimidazoles (6-14)

To a suspension of related o-phenylenediamine ( $5 \mathbf{a}-\mathbf{c}$ ) ( 1 mmol ) in DMF ( 5 ml ), sodium metabisulfite adduct of appropriate aldehyde ( 1 mmol ) was added and the mixture was heated under nitrogen atmosphere for 4 h at $60^{\circ} \mathrm{C}$. Water was added to the reaction medium and the solid product obtained was collected by filtration and washed with water. The purification process is shown in the Table.

## 4-(5-Fluoro-6-morpholin-4-yl-1H-benzimidazole-2-yl)-phenol (15)

A solution of $\mathbf{6}(0.3 \mathrm{~g}, 0.74 \mathrm{mmol})$ in $\mathrm{EtOH}(10 \mathrm{ml})$ was hydrogenated in a Parr apparatus (room temperature, 40 psi ), using $10 \% \mathrm{Pd} / \mathrm{C}$ as the catalyst. After cessation of $\mathrm{H}_{2}$ uptake, the reaction was stopped. The catalyst was filtered through a bed of Celite and washed with EtOH. After the evaporation of EtOH , the residue was chromatographed $\left[\mathrm{CHCl}_{3}\right.$ :isoprop.(10:3)], affording $0.18 \mathrm{~g}(78 \%)$ of $\mathbf{1 5} \mathrm{mp}:>270^{\circ} \mathrm{C}$. ${ }^{1} \mathrm{H}$ NMR ( $\mathrm{DMSO}_{\mathrm{d}}^{6}$ ) $\delta 3.0\left(\mathrm{t}, 4 \mathrm{H}\right.$, morpholine $\mathrm{CH}_{2}$ ), $3.8\left(\mathrm{t}, 4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right), 6.9(\mathrm{~d}, 2 \mathrm{H}, \mathrm{J}=8.56 \mathrm{~Hz}$, $\mathrm{H}-\mathrm{b}), 7.15\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{m}=8 \mathrm{~Hz}, \mathrm{H}-7\right), 7.25\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{o}=12.5 \mathrm{~Hz}, \mathrm{H}-4\right), 7.9(\mathrm{~d}, 2 \mathrm{H}, \mathrm{J}=8.6 \mathrm{~Hz}, \mathrm{H}-\mathrm{a}), 12.6$ (br.s, 1H). MS: $m / z 313$ ( $\mathrm{M}^{+}, 100$ ), 255 (88), 127 (21).

## Results and Discussion

4-Chloro-2,5-difluoronitrobenzene (1), required in this work, was synthesized from 2,5-difluoroaniline via N -acylation, followed by nitration and subsequent deacylation, according to published procedures ${ }^{25,26}$. The amine group of the deacylation product was converted to a chlorine atom using Sandmeyer's reaction ${ }^{25}$.



6-14

Scheme 1. Synthesis of the compounds 6-14. a: ethyl or $n$-propylamine/triethylamine, $\mathbf{b}: \mathrm{H}_{2} \mathrm{SO}_{4} / \mathrm{H}_{2} \mathrm{O}$, $\mathbf{c}$ : morpholine, $\mathbf{d}: \mathrm{SnCl}_{2} / \mathrm{HCl}$, e: $\mathrm{DMF}, \mathbf{f}: \mathrm{NaHSO}_{3}$.

Substitution of $\mathbf{1}$ with ethyl or $n$-propylamine gave 5 -chloro-N-ethyl-4-fluoro-2-nitro aniline ( $\mathbf{3} \mathbf{b}$ ), and 5 -chloro-4-fluoro-2-nitro-N-propylaniline ( $\mathbf{3 c})^{23}$, respectively (Scheme 1). 3a was synthesized starting from 3 -chloro-4-fluoroaniline according to the literature ${ }^{22}$ by a few steps. Substitution of 3a-c with morpholine gave $\mathbf{4 a} \mathbf{- c}$ and the reduction of these compounds afforded o-phenylenediamines $\mathbf{5 a} \mathbf{a} \mathbf{- c}$. The reaction of $\mathbf{5 a - c}$ with sodium metabisulfite adduct of appropriate aldehydes yielded the targeted compounds (6-14) (Scheme 1). O-Debenzylation of $\mathbf{6}$ in the presence of $\mathrm{H}_{2}$ and $\mathrm{Pd} / \mathrm{C}$ afforded $\mathbf{1 5}$ in good yield (Scheme 2). The structures, melting points, yields, purification methods used and spectroscopic data are given in the Table.

Because of the instability of $\mathbf{5 a - c}$, these compounds were used for the next step without purification and their further reactions ( $\mathbf{6 - 1 4}$ ) were carried out under nitrogen atmosphere. This method provides mild reaction conditions and moderate to good yield of the desired benzimidazoles.

In this study, the synthesis of new ten targeted benzimidazole derivatives and two intermediates was performed and their structures were evaluated by spectroscopic techniques. The IR spectra of $\mathbf{3 b} \mathbf{b} \mathbf{c}$ and 4b-c revealed a sharp band at around $3370-3348 \mathrm{~cm}^{-1}$ as expected. The structures of the synthesized compounds are consistent with the ${ }^{1} \mathrm{H}$ NMR spectra. In case of the F-containing compounds, the structures
Table Structure, Physical and Spectroscopic Data of Compounds 6-14.

| $\begin{gathered} \text { Comp. } \\ \text { no. } \\ \hline \end{gathered}$ | R | R1 | Formulas | $\begin{aligned} & \hline \mathrm{Mp} \\ & \left({ }^{\circ} \mathrm{C}\right) \end{aligned}$ | Yield \% | Purification Method | ${ }^{1} \mathrm{H}$ NMR ( $\delta$, ppm, DMSO-d ${ }_{6}$ ) | Mass ( $\mathrm{M}^{+}$, \%) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 6 | H | $4-\mathrm{OCH}_{2}-\varnothing$ | $\mathrm{C}_{24} \mathrm{H}_{22} \mathrm{FN}_{3} \mathrm{O}_{2}$ | 217-219 | 86 | EtOAc:n-hexane (1:2) (flash chrom.) | 3.03 ( 4 H , morpholine $\mathrm{CH}_{2}$ ), $3.8\left(4 \mathrm{H}\right.$, morpholine $\mathrm{CH}_{2}$ ), $5.2\left(\mathrm{~s}, 2 \mathrm{H},-\mathrm{O}-\mathrm{CH}_{2}-\right), 7.2(\mathrm{~d}, 2 \mathrm{H}, \mathrm{J}=8.8 \mathrm{~Hz}, \mathrm{H}-3$ ' and $\mathrm{H}-$ $5^{\prime}$ ), 7.3-7.9 ( $7 \mathrm{H}, \mathrm{ArH}$ ), $8.1(\mathrm{~d}, 2 \mathrm{H}, \mathrm{J}=8.8 \mathrm{~Hz}, \mathrm{H}-2$ ' and H-6'), 12.6 (br.s., $1 \mathrm{H}, \mathrm{NH}$ ). | $\begin{gathered} \hline 403\left(\mathrm{M}^{+}, 100\right), 312(94), \\ 254(27), 226(8.6), \\ 91(60.7), 86(6) . \end{gathered}$ |
| 7 | H | 4-F | $\mathrm{C}_{17} \mathrm{H}_{15} \mathrm{~F}_{2} \mathrm{~N}_{3} \mathrm{O}$ | 211-213 | 93 | EtOAc:n-hexane (1:2) (flash chrom.) | $3.04\left(4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right), 3.8\left(4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right)$, $7.3\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{\mathrm{H} 7 . \mathrm{F}}=6,7 \mathrm{~Hz}\right), 7.4\left(2 \mathrm{H}, \mathrm{H}-3^{\prime}\right.$ and $\left.\mathrm{H}-5^{\prime}\right), 7.5$ $\left(\mathrm{d}, 1 \mathrm{H}, \mathrm{J}_{\mathrm{H} 4 \mathrm{~F}}=12.6 \mathrm{~Hz}\right), 8.1-8.2\left(2 \mathrm{H}, \mathrm{H}-2^{\prime}\right.$ and H-6'), 12.7 (br.s, 1H, NH). | $\begin{gathered} 315\left(\mathrm{M}^{+}, 100\right), 256(22), \\ 228(3), 95(2) . \end{gathered}$ |
| 8 | H | 3,4-di-F | $\mathrm{C}_{17} \mathrm{H}_{14} \mathrm{~F}_{3} \mathrm{~N}_{3} \mathrm{O}$ | 242-244 | 86 | EtOAc:n-hexane (1:2) (flash chrom.) | $3.0\left(\mathrm{t}, 4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right), 3.77(\mathrm{t}, 4 \mathrm{H}$, morpholine $\left.\mathrm{CH}_{2}\right), 7.2\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{\mathrm{H} 7-\mathrm{F}}=6.5 \mathrm{~Hz}\right), 7.4(\mathrm{~d}, 1 \mathrm{H}$, $\left.\mathrm{J}_{\mathrm{H} 4-\mathrm{F}}=12.5 \mathrm{~Hz}\right), 7.5-7.66(\mathrm{q}, 1 \mathrm{H}, \mathrm{Ar}-\mathrm{H}), 7.95-8.1(2 \mathrm{H}$, $\mathrm{Ar}-\mathrm{H}$ ), 12.6 (br.s., 1H, NH). | $\begin{gathered} 333\left(\mathrm{M}^{+}, 100\right), 275(31.8), \\ 219(9), 105(9), 77(8.5) . \end{gathered}$ |
| 9 | H | 2,4-di-Cl | $\mathrm{C}_{17} \mathrm{H}_{14} \mathrm{FCl}_{2} \mathrm{~N}_{3} \mathrm{O}$ | 212-214 | 85 | EtOAc:n-hexane (1:2) (flash chrom.) | $3.02\left(4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right), 3.78\left(4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right)$, <br> 7.1-7.9 (5H, Ar-H), 12.6 (br.s., 1H, NH). | $\begin{gathered} 366\left(\mathrm{M}^{+}, 13.5\right), 368(\mathrm{M}+2,8), \\ 370(\mathrm{M}+4,1.4), 307(42), \\ 278(10), 171(19), 154(47), \\ 29(100) . \end{gathered}$ |
| 10 | H | $4-\mathrm{Cl}$ | $\mathrm{C}_{17} \mathrm{H}_{15} \mathrm{FClN}_{3} \mathrm{O}$ | 230-232 | 94 | EtOAc:n-hexane (1:2) (flash chrom.) | $3.0\left(4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right), 3.77\left(4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right)$, $7.0\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{\mathrm{H} 7-\mathrm{F}}=7.5 \mathrm{~Hz}\right), 7.2\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{\mathrm{H} 4 \mathrm{~F}}=12 \mathrm{~Hz}\right)$, (d, $2 \mathrm{H}, \mathrm{J}=8.5 \mathrm{~Hz}, \mathrm{H}-3^{\prime}$ 'and $\mathrm{H}-5$ '), $8.3(\mathrm{~d}, 2 \mathrm{H}$, $\mathrm{J}=8.5 \mathrm{~Hz}, \mathrm{H}-\mathbf{2}^{\prime}$ and $\mathrm{H}-6^{\prime}$ ), 12.55 (br.s, $1 \mathrm{H}, \mathrm{NH}$ ) | $\begin{gathered} 331\left(\mathrm{M}^{+}, 88\right), 333(\mathrm{M}+2, \\ 28), 273(50), 275(15), \\ 149(24), 136(39), \\ 31(100) . \\ \hline \end{gathered}$ |
| 11 | H | 3,4-di- $\mathrm{OCH}_{3}$ | $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FN}_{3} \mathrm{O}_{3}$ | 166-168 | 83 | EtOAc:n-hexane (1:1) (flash chrom.) | 3.07 ( 4 H , morpholine $\mathrm{CH}_{2}$ ), 3.75 ( 4 H , morpholine $\mathrm{CH}_{2}$ ), $3.8\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{O}-\mathrm{CH}_{3}\right), 3.85\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{O}-\mathrm{CH}_{3}\right), 7.15-7,75(5 \mathrm{H}$, Ar-H), 12.7 (br.s, 1H, NH). | $\begin{gathered} 357(\mathrm{M}+, 100), 299(49), \\ 284(12), 256(10), \\ 128(11), 85(5) . \\ \hline \end{gathered}$ |
| 12 | H | 2,5-di-F | $\mathrm{C}_{17} \mathrm{H}_{14} \mathrm{~F}_{3} \mathrm{~N}_{3} \mathrm{O}_{3}$ | 170-172 | 89 | EtOAc : n-hexane (1:2) (flash chrom.) | $3.0\left(\mathrm{t}, 4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right), 3.78(\mathrm{t}, 4 \mathrm{H}$, morpholine $\left.\mathrm{CH}_{2}\right), 7.2\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{\mathrm{H} 7-\mathrm{F}}=7.2 \mathrm{~Hz}\right), 7.35-7.6(3 \mathrm{H}, \mathrm{Ar}-\mathrm{H}), 7.9$ ( $1 \mathrm{H}, \mathrm{Ar}-\mathrm{H}$ ), 12.6 (br.s, $1 \mathrm{H}, \mathrm{NH}$ ). | $\begin{gathered} 333\left(\mathrm{M}^{+}, 100\right), 274(99), \\ 261(27), 139(31) . \end{gathered}$ |
| 13 | $\mathrm{C}_{3} \mathrm{H}_{7}$ | 3,4-di- $\mathrm{OCH}_{3}$ | $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{FN}_{3} \mathrm{O}_{3}$ | 177-179 | 81 | EtOAc:n-hexane (1:2) (flash chrom.) | $0.76\left(\mathrm{t}, 3 \mathrm{H},-\mathrm{CH}_{2}-\mathrm{CH}_{3}\right), 1.69\left(\mathrm{~m}, 2 \mathrm{H},-\mathrm{CH}_{2}-\mathrm{CH}_{2}-\mathrm{CH}_{3}\right)$, $3.0\left(\mathrm{t}, 4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right)$, $3.78(\mathrm{t}, 4 \mathrm{H}$, morpholine $\mathrm{CH}_{2}$ ), $3.8\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{O}-\mathrm{CH}_{3}\right), 3.85\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{O}-\mathrm{CH}_{3}\right), 4.26$ $\left(\mathrm{t}, 2 \mathrm{H},-\mathrm{CH}_{2}-\mathrm{CH}_{2}-\mathrm{CH}_{3}\right), 7.1\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{\mathrm{H} 7-\mathrm{F}}=8.5 \mathrm{~Hz}\right)$, 7.2-7.3 ( $3 \mathrm{H}, \mathrm{Ar}-\mathrm{H}$ ), $7.4\left(\mathrm{~d}, 1 \mathrm{H}, \mathrm{J}_{\mathrm{H} 4 . \mathrm{F}}=13 \mathrm{~Hz}\right)$. | $\begin{gathered} 399\left(\mathrm{M}^{+}, 100\right), 341(18), \\ 326(8), 298(8) . \end{gathered}$ |
| 14 | $\mathrm{C}_{2} \mathrm{H}_{5}$ | 4-F | $\mathrm{C}_{19} \mathrm{H}_{19} \mathrm{~F}_{2} \mathrm{~N}_{3} \mathrm{O}$ | 172-174 | 83 | EtOAc:n-hexane (1:2) (flash chrom.) | $1.1\left(\mathrm{t}, 3 \mathrm{H},-\mathrm{CH}_{2}-\mathrm{CH}_{3}\right)$, $3.0\left(4 \mathrm{H}\right.$, morpholine $\left.\mathrm{CH}_{2}\right), 3.8$ ( 4 H , morpholine $\mathrm{CH}_{2}$ ), $4.2\left(\mathrm{q}, 2 \mathrm{H},-\mathrm{CH}_{2}-\mathrm{CH}_{3}\right)$, 7.1-7.9 ( $6 \mathrm{H}, \mathrm{Ar}-\mathrm{H}$ ). | $\begin{gathered} 343\left(\mathrm{M}^{+}, 100\right), 285(58), \\ 270(9), 135(4), 95(3) . \end{gathered}$ |



Scheme 2. Synthesis of 15. a: $\mathrm{H}_{2}, \mathrm{Pd} / \mathrm{C}, \mathrm{EtOH}$.
were confirmed by the magnitude of the F-H coupling constant (J) in the ${ }^{1} \mathrm{H}$ NMR spectra. ${ }^{22}$ In the mass spectra of $\mathbf{9 , 1 0}$, isotopes of chlorine atoms are seen as expected. The assigned structures were substantiated by IR, ${ }^{1} \mathrm{H}$ NMR and MS data.

The targeted compounds 6-15 are undergoing biological investigation and their results will be published later.

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