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Solid phase synthesis of isoxazole and isoxazoline-carboxamides via [2+3]-dipolar cycloaddition using resin-bound alkynes or alkenes

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ABSTRACT

An efficient approach for the parallel solid phase synthesis of isoxazole and isoxazoline derivatives has been developed. The isoxazoles and isoxazolines were constructed through a 1,3-dipolar cycloaddition reaction of nitrile oxides, with resin-bound alkynes or alkenes. The cycloaddition reaction conditions performed on solid phase supports was optimized, and an array of resin-bound carboxylic acid building blocks was utilized for distinct conversions. This methodology presents a new alternative to the diversity oriented synthesis of disubstituted isoxazoles and isoxazolines different from existing routes which are limited in structural diversity.

Heterocycles display an array of significant bioactive properties,[1–3] and heterocyclic scaffolds are present in a wide variety of drugs as well as drug like molecules of pharmaceutical relevance.[4,5] Among the family of heterocyclic compounds, isoxazoles and isoxazolines are an important class of heterocycles displaying a wide variety of biological properties including antiviral,[6] antitubulin,[7] as well as anti-inflammatory activity.[8] The synthesis of this family of heterocycles continues to attract the attention of synthetic organic and medicinal chemists.[9] The isoxazoline framework is a prevalent feature of several natural products **1**–**6**,[10,11] and the isoxazole structural motif is found in the COX II inhibitors, bextra **7** and parecoxib **8** (Fig. 1).[9a,12] A plethora of methodologies exist toward the synthesis of isoxazoles and isoxazolines,[13,14] and most of them endeavor nitrile oxide cycloaddition (NOC) as a key step.[15]

On the other hand, combinatorial chemistry and high-throughput screening have changed the scale on which drug discovery programs are carried out.[4,5] The inherent potential of this technique aids to accelerate the drug discovery process through rapid synthesis and subsequent screening of much larger numbers of compounds than previously possible.[16] The versatile and potential capability afforded by the tea-bag approach,[17] has led to the isolation and recognition of an array of bioactive peptides, including antibacterials, antigenic peptides, opioid receptor agonists and antagonist inhibitors, and several heterocyclic compounds of biomedical importance.[18] In continuation of our research investigation toward the design, and development of novel heterocycles, we developed a parallel solid phase nitrile oxide cycloaddition (NOC) strategy to synthesize a variety of isoxazoles and isoxazolines utilizing 1,3-dipolar cycloaddition chemistry.[9,15] The hydroximoyl chlorides **11** for the 1,3-dipolar cycloaddition are not commercially available and were conveniently synthesized in two steps utilizing solution phase chemistry.[8,9a] This methodology presents a new alternative to the diversity oriented synthesis of disubstituted isoxazoles and isoxazolines different from the existing routes which, are limited in structural diversity.[19,20]

We envisioned the synthesis of isoxazole **9** and isoxazolines **10** via 1,3-dipolar cycloaddition of in situ generated nitrile oxides with alkyne **12** or alkenes **13**. The required alkyne and alkene precursors are synthesized from the corresponding resin-bound carboxylic acid. The retrosynthetic rationale for the parallel solid phase synthesis of isoxazoles and isoxazolines is illustrated in Scheme 1.

The parallel solid phase synthesis of all compounds was carried out utilizing Houghten's tea-bag approach, wherein the resin is packed within sealed polypropylene mesh packets.[17] The first position of diversity was introduced by coupling several carboxylic acids to *p*-methylbenzhydrylamine resin. The generated secondary amide **14** was then alkylated in the presence of lithium *t*-butoxide and an alkylating agent (allyl bromide or propargyl bromide).[21] The parallel synthesis of the resin-bound isoxazoles **9** and isoxazolines **10** was initiated by the nitrile oxide cycloaddition of the resin-bound alkynes and alkene derivatives. Structurally diverse combinations of carboxylic acids (cyclopentanecarboxylic acid, 1-cyclopenteneacetic acid, benzoic acid, 2-nitrobenzoic acid,

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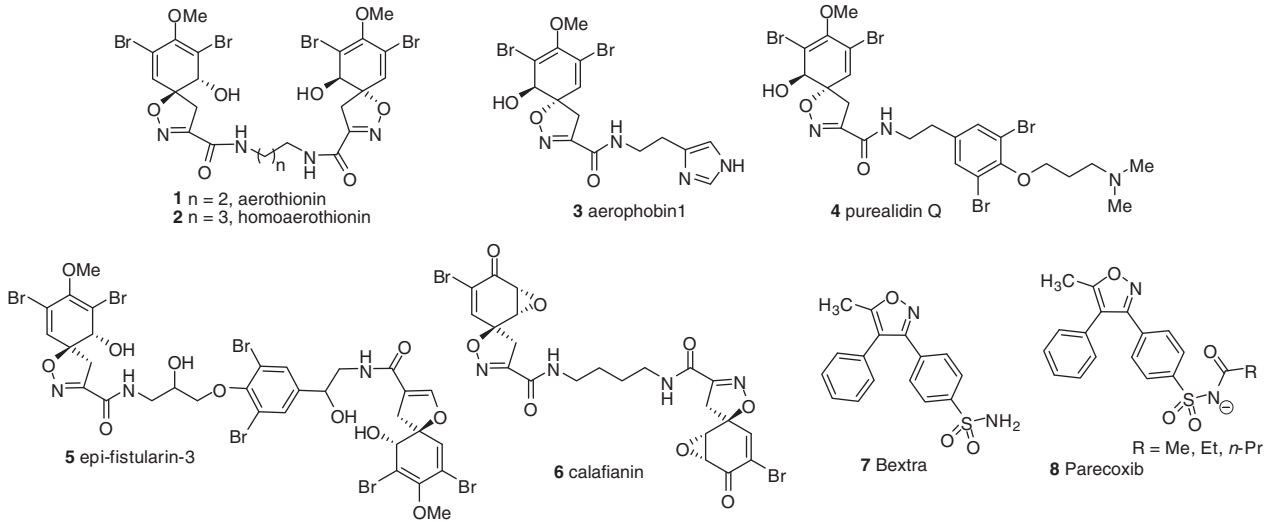
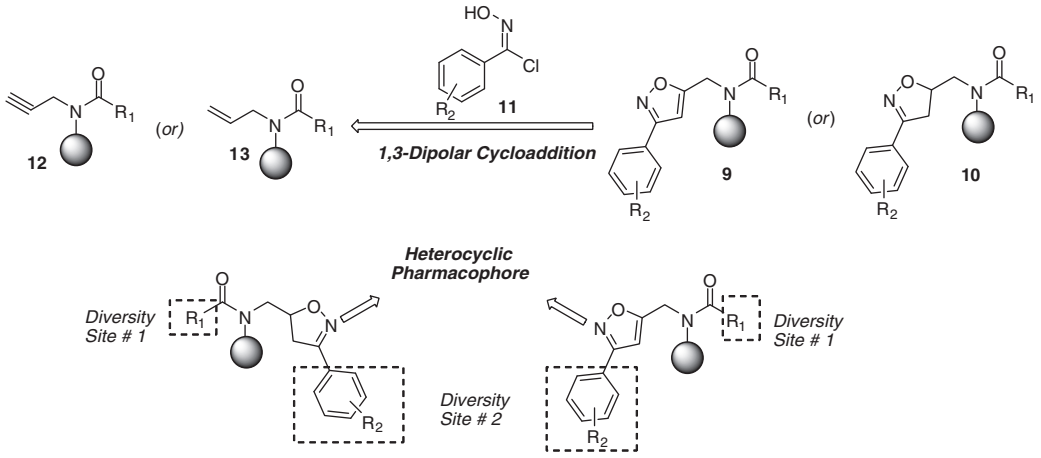


Figure 1. Naturally occurring isoxazolines and pharmaceutically relevant isoxazoles.



Scheme 1. Retrosynthetic illustration of structurally diverse isoxazoles and isoxazolines.

Table 1
Isoxazoles from resin-bound alkynes

Entry	R_1	R_2	Mass calcd/found	Yields[a] (%)
15a	Piperonyl	H	322.3/323.2 (MH^+)	87
15b	Cyclopentyl	H	270.3/271.4 (MH^+)	66
15c	1-Cyclopenteneacetyl	H	282.3/283.2 (MH^+)	91
15d	4-Biphenyl	H	354.4/355.2 (MH^+)	63
15e	Syringyl	H	354.4/356.0 (MH^+)	54
15f	1-Phenyl-1-cyclopropyl	H	318.3/319.6 (MH^+)	52
15g	Diphenylacetyl	H	368.4/369.5 (MH^+)	75
15h	Phenyl	4-Ph	354.4/355.2 (MH^+)	90
15i	Piperonyl	4-Ph	398.4/399.3 (MH^+)	83
15j	Cyclopentyl	4-Ph	346.4/347.4 (MH^+)	93
15k	1-Cyclopenteneacetyl	4-Ph	358.4/359.2 (MH^+)	94
15l	2-Nitrophenyl	4-Ph	399.4/400.4 (MH^+)	55
15m	4-Biphenyl	4-Ph	430.5/431.4 (MH^+)	63
15n	1-Phenyl-1-cyclopropyl	4-Ph	394.5/395.3 (MH^+)	75
15o	Diphenylacetyl	4-Ph	444.5/445.3 (MH^+)	62
15p	Syringyl	4-Ph	430.4/453.2 (MH^+)	63
15q	1-Napthyl	4-Ph	404.5/405.4 (MH^+)	73
15r	2-Nitrophenyl	2,6-diCl	392.2/393.5 (MH^+)	70
15s	Piperonyl	2,6-diCl	391.2/392.4 (MH^+)	91
15t	Phenyl	2,6-diCl	347.4/349.3 (MH^+)	92
15u	Cyclopentyl	2,6-diCl	415.4/416.3 (MH^+)	79
15v	1-Phenyl-1-cyclopentyl	2,6-diCl	415.3/438.2 (MNa^+)	75
15w	4-Biphenyl	2,6-diCl	423.3/446.1 (MNa^+)	86

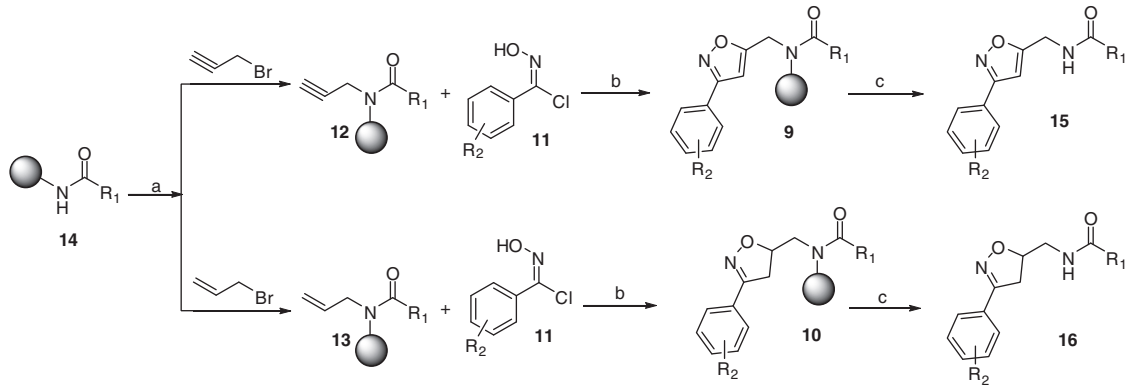
The products were run on a Vydac column, gradients 5–95% formic acid in Acetonitrile in 7 min.

[a] The yields are based on the weight of purified products and are relatives to the initial loading of the resin. (The purity of the purified compounds is higher than 95% for all the compounds).

Table 2
Isoxazolines from resin-bound alkenes

Entry	R_1	R_2	Mass calcd/found	Yields[a] (%)
16a	Cyclopentyl	H	272.3/273.1 (MH^+)	96
16b	1-Cyclopenteneacetyl	H	284.1/285.1 (MH^+)	92
16c	4-Biphenyl	H	356.4/357.3 (MH^+)	67
16d	1-Phenyl-1-cyclopropyl	H	320.3/321.2 (MH^+)	87
16e	Syringyl	H	356.3/357.2 (MH^+)	77
16f	Piperonyl	4-Ph	400.4/423.2 (MNa^+)	63
16g	Cyclopentyl	4-Ph	348.4/349.3 (MH^+)	93
16h	1-Cyclopenteneacetyl	4-Ph	360.4/361.3 (MH^+)	88
16i	2-Nitrophenyl	4-Ph	401.5/402.4 (MH^+)	84
16j	Phenyl	4-Ph	356.3/357.3 (MH^+)	84
16k	1-Phenyl-1-cyclopropyl	4-Ph	396.5/397.4 (MH^+)	77
16l	Diphenylacetyl	4-Ph	446.4/447.4 (MH^+)	82
16m	Syringyl	4-Ph	432.4/433.2 (MH^+)	87
16n	1-Napthyl	4-Ph	406.5/429.3 (MNa^+)	71
16o	4-Biphenyl	4-Ph	432.5/455.5 (MNa^+)	61
16p	1-Phenyl-1-cyclopentyl	4-Ph	424.5/447.3 (MNa^+)	72
16q	Phenyl	2,6-diCl	349.2/372.3 (MNa^+)	96
16r	2-Nitrophenyl	2,6-diCl	394.2/417.1 (MNa^+)	95
16s	Piperonyl	2,6-diCl	393.2/417.2 (MNa^+)	96
16t	Cyclopentyl	2,6-diCl	417.3/440.2 (MNa^+)	87
16u	1-Phenyl-1-cyclopentyl	2,6-diCl	417.3/440.1 (MNa^+)	77
16v	4-Biphenyl	2,6-diCl	425.3/447.4 (MNa^+)	78

The products were run on a Vydac column, gradients 5–95% formic acid in Acetonitrile in 7 min.
[a] The yields are based on the weight of purified products and are relatives to the initial loading of the resin (The purity of the purified compounds is higher than 95% for all the compounds).



Scheme 2. Solid phase synthesis of structurally diverse isoxazoles and isoxazolines. Reagents and conditions: (a) ^{t}BuOLi, DMSO, 5 h; (b) $(C_2H_5)_3N$, CH_2Cl_2, rt overnight; (c) anhydrous HF, 90 min, 0 °C.

piperonylic acid, syringyl, 4-biphenylcarboxylic acid, 1-napthalenecarboxylic, diphenylacetic acid, 1-phenyl-1-cyclopropylcarboxylic acid, and 1-phenyl-1-cyclopentanecarboxylic acid) were selected.

To investigate the feasibility of nitrile oxide cycloadditions (NOC) on solid support, three different hydroximoyl chlorides were freshly prepared and were treated with triethylamine to generate the corresponding nitrile oxides[9,13c,f,14i,5a,b] Treatment of resin-bound dipolarophiles **12**, **13** with the generated nitrile oxides proceeded in a 1,3-dipolar fashion and furnished diversified isoxazoles and isoxazolines.[22] In case of resin coupled with piperonylic acid, we also observed the formation of a diol (partially cleaved protected diol) in addition to the main product. All of the cycloadditions occurred in good yields and were isolated in high purities (Tables 1 and 2). The protocol for the parallel synthesis of structurally diverse isoxazoles and isoxazolines is outlined in Scheme 2.

In conclusion, we have developed an efficient parallel solid phase methodology to construct the diversity oriented isoxazoles and isoxazolines via 1,3-dipolar cycloaddition reaction.[22] Coupling of carboxylic acids to the resin introduced the first position of diversity in which, following N-alkylation with allyl bromide or propargyl bromide furnished several resin-bound alkenes and alkynes. 1,3-Dipolar cycloaddition of the resin-bound alkenes or alkynes with nitrile oxides led to the formation of the corresponding disubstituted isoxazole and isoxazolines.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.041.

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22. *General procedure for the 1,3-Dipolar cycloaddition*: Resin-bound carboxylic acid coupling and *N*-alkylation using allyl bromide or propargyl bromide were performed according to the literature precedents.[21] Resin-bound alkyne (alkene) and the hydroximoyl chloride (10 equiv) in 10 mL of dry dichloromethane (DCM) was treated with triethylamine (0.16 mL, 10 equiv) and the reaction mixture was stirred overnight. The excess solution was decanted, and the resin was washed with DCM (2 × 5 mL). The resin was cleaved with anhydrous HF (10 mL) for 90 min at 0 °C, and the desired isoxazole (isoxazoline) was obtained following extraction with 95% AcOH in H_2O and lyophilization as a colorless powder. The isoxazole (isoxazoline) was purified by preparative reverse-phase HPLC. *Cyclopentanecarboxylic acid (3-phenyl-isoxazol-5-ylmethyl)-amide (**15b**)*: ^{1}H NMR (500 MHz; DMSO-d_6): δ 1.50–1.52 (m, 2H), 1.61–1.67 (m, 4H), 1.77–1.79 (m, 2H), 2.61–2.64 (m, 1H), 4.44 (d, J = 6.0 Hz, 2H), 6.81 (s, 1H), 7.49–7.52 (m, 3H), 7.84–7.87 (m, 2H), 8.49 (t, J = 6.0 Hz, 1H); MS (ESI) m/z calcd for $C_{16}H_{18}N_2O_2$ [M+H$^+$]: 270.3; found: 271.4. *Benzo[1,3]dioxole-5-carboxylic acid (3-biphenyl-4-yl-isoxazol-5-ylmethyl)-amide (**15i**)*: ^{1}H NMR (500 MHz; DMSO-d_6): δ 1.23 (s, 2H), 4.64 (d, J = 5.5 Hz, 2H), 6.55 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 7.0 Hz, 1H), 7.45 (s, 1H), 7.50 (q, J = 8.0 Hz, 3H), 7.74 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.0 Hz, 2H), 9.07 (t, J = 6.0 Hz, 1H); MS (ESI) m/z calcd for $C_{24}H_{18}N_2O_4$ [M+H$^+$]: 398.4; found: 399.3. *Cyclopentanecarboxylic acid (3-biphenyl-4-yl-isoxazol-5-ylmethyl)-amide (**15j**)*: ^{1}H NMR (500 MHz; DMSO-d_6): δ 1.23 (s, 4H), 1.50–1.52 (m, 1H), 1.63–1.68 (m, 2H), 1.77–1.80 (m, 1H), 2.62–2.65 (m, 1H), 4.46 (t, J = 5.8 Hz, 2H), 6.88 (s, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 7.74 (t, J = 9.5 Hz, 2H), 7.81 (t, J = 8.1 Hz, 2H), 7.95 (t, J = 10.5 Hz, 2H), 8.49–8.51 (m, 1H); MS (ESI) m/z calcd for $C_{22}H_{22}N_2O_2$ [M+H$^+$]: 346.4; found: 347.4. *Benzo[1,3]dioxole-5-carboxylic acid [3-(2,6-dichloro-phenyl)-isoxazol-5-ylmethyl]-amide (**15s**)*: ^{1}H NMR (500 MHz; DMSO-d_6): δ 4.69 (d, J = 5.5 Hz, 2H), 6.10 (s, 2H), 6.59 (s, 1H), 7.01 (d, J = 8.5 Hz, 1H), 7.43 (s, 1H), 7.50 (d, J = 10.0 Hz, 1H), 7.54–7.63 (m, 1H), 7.64–7.65 (m, 2H), 9.1 (t, J = 5.5 Hz, 1H); MS (ESI) m/z calcd for $C_{17}H_{12}Cl_2N_2O_4$ [M+H$^+$]: 391.2; found: 393.2. *Biphenyl-4-carboxylic acid [3-(2,6-dichloro-phenyl)-isoxazol-5-ylmethyl]-amide (**15w**)*: ^{1}H NMR (500 MHz; DMSO-d_6): δ 4.75 (d, J = 4.5 Hz, 2H), 6.62 (s, 1H), 7.41 (m, 1H), 7.50 (t, J = 7.0 Hz, 2H), 7.56 (t, J = 8.0 Hz, 1H), 7.64 (t, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 8.01 (d, J = 8.5 Hz, 2H), 9.31 (t, J = 6.0 Hz, 2H); MS (ESI) m/z calcd for $C_{23}H_{16}Cl_2N_2O_2$ [M+Na$^+$]: 423.2; found: 446.1. *Cyclopentanecarboxylic acid (3-phenyl-4,5-dihydro-isoxazol-5-ylmethyl)-amide (**16a**)*: ^{1}H NMR (500 MHz; DMSO-d_6): δ 1.44–168 (m, 8H), 2.54 (t, J = 7.5 Hz, 1H), 3.13 (dd, J = 7.0 Hz, 17 Hz 1H), 3.22–3.24 (m, 1H), 3.44 (dd, J = 11.0 Hz, 17 Hz 1H), 4.72–4.78 (m, 1H), 7.43–7.46 (m, 3H), 7.62–7.65 (m, 2H), 8.04 (t, J = 6.0 Hz, 1H); MS (ESI) m/z calcd for $C_{23}H_{16}Cl_2N_2O_2$ [M+H$^+$]: 272.3; found: 273.1. *Benzo[1,3]dioxole-5-carboxylic acid (3-biphenyl-4-yl-4,5-dihydro-isoxazol-5-ylmethyl)-amide (**16f**)*: ^{1}H NMR (500 MHz; DMSO-d_6): δ 3.40 (dd, J = 7 Hz, 17.5 Hz, 1H), 3.61–3.70 (m, 1H), 3.77–3.81 (m, 1H), 4.34 (dd, J = 5.5 Hz, 12 Hz, 1H), 4.43 (dd, J = 3.5 Hz, 12 Hz, 1H), 5.07–5.13 (m, 1H), 6.11 (s, 2H), 6.80–6.82 (m, 1H), 6.98–7.00 (m, 2H), 7.09–7.10 (m, 1H), 7.32 (s, 1H), 7.40–7.42 (m, 1H), 7.48–7.54 (m, 4H), 7.72–7.74 (m, 2H); MS (ESI) m/z calcd for $C_{24}H_{20}N_2O_4$ [M+Na$^+$]: 400.4; found: 423.2. *Cyclopentanecarboxylic acid (3-biphenyl-4-yl-4,5-dihydro-isoxazol-5-ylmethyl)-amide (**16g**)*: ^{1}H NMR (500 MHz; DMSO-d_6): δ 1.45–1.69 (m, 6H), 2.55–2.58 (m, 1H), 3.15–3.19 (m, 1H), 3.24–3.32 (m, 1H), 3.46–3.51 (m, 1H), 4.74–4.80 (m, 1H), 7.4 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.71–7.73 (m, 4H), 7.77–7.78 (m, 2H), 8.05 (t, J = 6.0 Hz, 1H); MS (ESI) m/z calcd for $C_{22}H_{24}N_2O_2$ [M+H$^+$]: 348.4; found: 349.3. *N-[3-(2,6-Dichloro-phenyl)-4,5-dihydro-isoxazol-5-ylmethyl]-2-nitro-benzamide (**16r**)*: ^{1}H NMR (500 MHz; DMSO-d_6): δ 3.14 (dd, J = 6.5 Hz, 17.5 Hz, 1H), 3.41–3.55 (m, 3H), 4.96–5.00 (m, 1H), 7.52–7.55 (m, 1H), 7.61–7.64 (m, 3H), 7.8 (t, J = 7.5 Hz, 1H), 8.05 (d, J = 10 Hz, 1H), 9.06 (t, J = 6.0 Hz, 1H); MS (ESI) m/z calcd for $C_{17}H_{13}Cl_2N_3O_4$ [M+Na$^+$]: 394.20; found: 417.1. *Benzo[1,3]dioxole-5-carboxylic acid [3-(2,6-dichloro-phenyl)-4,5-dihydro-isoxazol-5-ylmethyl-]-amide (**16s**)*: ^{1}H NMR (500 MHz; DMSO-d_6): δ 3.14 (dd, J = 6.5 Hz,17.5 Hz, 2H), 3.64–3.48 (m, 2H), 3.55–3.61 (m, 1H), 4.98–5.0 (m, 1H), 6.1 (s, 2H), 6.99 (d, J = 10 Hz, 2H), 7.43 (s, 1H), 7.48–7.58 (m, 2H), 7.60 (d, J = 5.0 Hz, 2H), 8.65 (t, J = 6.0 Hz, 1H); MS (ESI) m/z calcd for $C_{18}H_{14}Cl_2N_2O_4$ [M+Na$^+$]: 393.22; found: 417.2.