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The isoxazole as a linchpin for molecules that target folded DNA conformations: selective lateral lithiation and palladation

Xiaochun Han, Chun Li, Kevin C. Rider, Alex Blumenfeld, Brendan Twamley and N. R. Natale*

301 Renfrew Hall, Department of Chemistry, University of Idaho, Moscow, ID 83844-2343, USA

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Abstract—3-(10′-Halo-9′-anthracenyl)-5-methyl-4-isoxazolecarboxylic acid ethyl esters served as a useful scaffold for highly efficient lateral metalation at the C(5), and Suzuki–Fu palladium catalyzed cross coupling at the C(10′). © 2002 Published by Elsevier Science Ltd.

We previously reported tripartite aryl-isoxazole-lexitropins,[1] which required doubly activated amidation for efficient preparation.[2] One of these molecules, NSC D 694332, was found to exhibit promising biological activity: single digit micromolar inhibition of a dozen cancer cell lines in the National Cancer Institute's 60 cell line screening protocol.[3–5] Experimentally, a DNA array study with human genomic DNA showed a spectroscopic shift on exposure to NSC D 694332, consistent with our expectation that this molecule would act as an intercalating minor groove binding agent with B-DNA.[6] Therefore, we performed a COMPARE[7,8] analysis with the NCI Standard Agent Database. Surprisingly, this compound did not give a significant correlation with agents of known mechanism of action (Pairwise Correlation Coefficients ≤ 0.5); in contrast to strong correlations usually observed for intercalating agents. Therefore, we considered other possible DNA targets.[9] Our current working hypothesis resulted from a molecular graphics study conducted with the coordinates of human G-quadruplex DNA provided from the recent breakthrough reported by Neidle (Fig. 1),[10] and indicated several potential promising modes[11] of interaction with NSC D 694332. A binding study with Hurley's G-4a oligonucleotide sequence[12] indicated a fluxional potassium ion and time dependent fluorescence quenching that unquestionably evidences drug–oligonucelotide interaction. Based on literature precedent, this spectroscopic behavior can be explained by binding in an external stacking orientation to this putative molecular target. In order to use the isoxazole as a scaffold to construct highly functionalized molecules to bind folded DNA conformations, we now required the development of synthetic methodology that would work selectively and effectively in a very sterically demanding environment. We herein report promising progress towards that goal.

Lateral metalation has been used for the preparation of functionalized isoxazoles.[13,14] Previous reports have indicated that lithium diisopropylamide (LDA) is usually required in the presence of an ester moiety, and *n*-butyl lithium is known to add to esters selectively in the presence of an alkyl isoxazole.[14e]

Initial studies (see Scheme 1 and Table 1) with LDA indicated that good yields were possible for lateral metalation and electrophilic quenching, even in the presence of 10′-halogen groups on the anthracene ring, including 10′-bromo (**1b**). The deprotonation we observed proceeds more quickly than most of the lateral metalations that we have previously studied, and only 5–10 minutes are required. The orange to orange–red anion color dissipates upon addition of electrophile, which should be added slowly as the quenching is exothermic. Deliberate introduction of 2 equiv. of base, and 2 equiv. of benzyl bromide produces double electrophile incorporation, an opportunity if subsequent metalation is desired. We were gratified to observe that *n*-butyl lithium also cleanly deprotonated non-halogenated anthracenyl isoxazole ester (**1a**), in somewhat higher yield, a case wherein the steric bulk of the anthracene likely serves to 'protect' the ester group from nucleophilic attack by the alkyl lithium.

Furthermore, the presence of a 10′-chloro on the anthracene ring, as in (**1c**) served to improve the yield, and products were obtained in synthetically useful

* Corresponding author.

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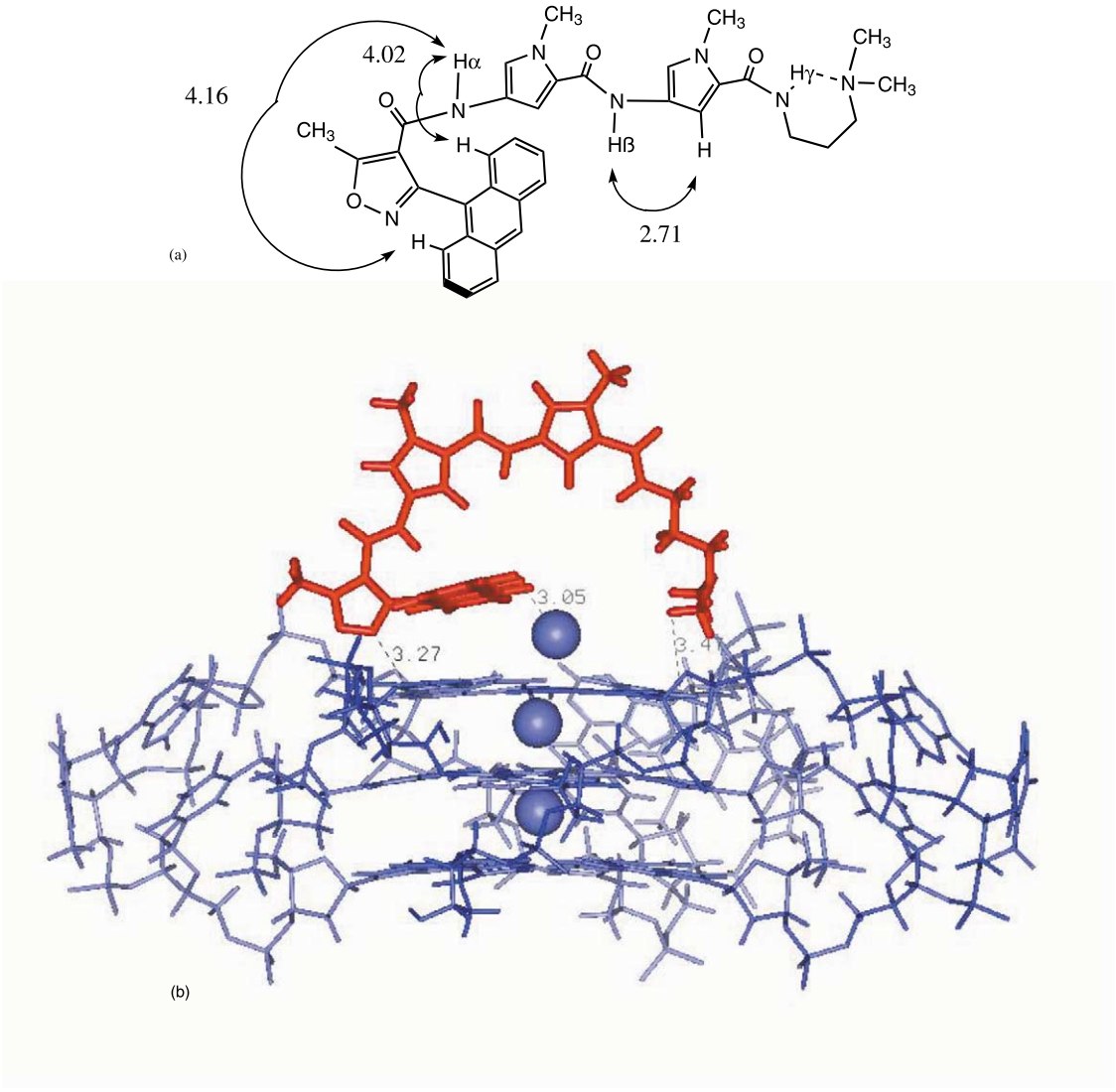
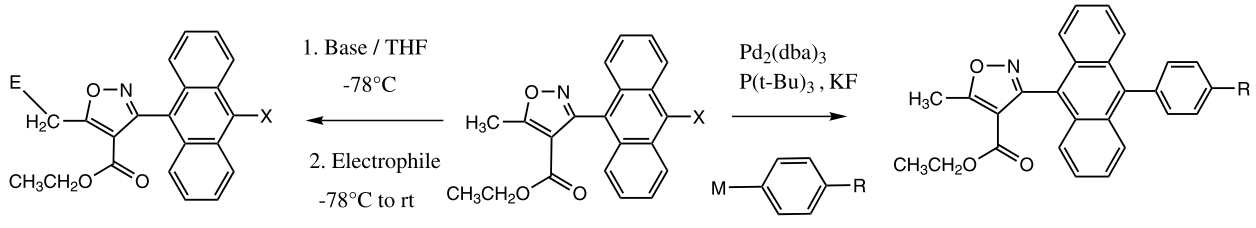


Figure 1. (a) Solution structure of NSC D 694332, and distances calculated from NOE experiments for the predominant *endo* conformation. The assignment rests primarily on the prominent NOE observed for the Hα proton and the *peri*-protons of the anthracene, and the NOE distance between Hβ and the protons of the adjacent pyrroles. (b) Side view of the results of a SGI INSIGHT 2000 docking study, the minimum energy structure of NSC D 694332 and G-quadrulex DNA. It is apparent from this model that the next logical SAR avenue for study is the C-5 of the isoxazole, and C-10 of the anthracene.



2 a,b,c (E=CH_3)
3 a,b,c (E=CH_2Ph)
4 a,b,c (E=CH(OH)Ph)

a (X=H)
b (X=Br)
c (X=Cl)

1a (X=H)
1b (X=Br)
1c (X=Cl)

d R=H, M=$B(OH)_2$
e R=OMe, M=$B(OH)_2$
f R=NHAc, M=

6 (R=H)
7 (R=OMe)
8 (R=NHAc)

Scheme 1.

Table 1. Lateral metalation of 3-(10′-halo-9′-anthracenyl)-5-methyl-4-isoxazolecarboxylic acid ethyl esters[18]

Product	X	Base	Electrophile	Yield (%)
2a	H	LDA	Iodomethane	50
		n-BuLi	Iodomethane	59
3a	H	LDA	Benzylbromide	58
		n-BuLi	Benzylbromide	68
4a	H	LDA	Benzaldehyde	69
		n-BuLi	Benzaldehyde	76
2b	Br	LDA	Iodomethane	55
3b	Br	LDA	Benzylbromide	62
4b	Br	LDA	Benzaldehyde	70
2c	Cl	LDA	Iodomethane	58
		n-BuLi	Iodomethane	69
3c	Cl	LDA	Benzylbromide	71
		n-BuLi	Benzylbromide	75
4c	Cl	LDA	Benzaldehyde	77
		n-BuLi	Benzaldehyde	82

yields after isolation and purification. The X-ray structure of **3c** (see Fig. 2) indicates the orientation of each moiety in this benzyl bromide adduct to ethyl 3-(10′-chloro-9′-anthracenyl)-5-methyl-4-isoxazole-carboxylate (**1c**). The orthogonal relationship of isoxazole and anthracene rings, and shielding of the carbonyl, is clearly indicated.

Alas, the 10′-bromo (**1b**) with *n*-butyl lithium, appears to undergo fast halogen–metal exchange, and subsequent proton transfer from the C-5 methyl group, for de-halo product (**1a**) was observed. To confirm this, we examined the quenching of this metalation with benzaldehyde, and the 10′-dehalogenated adduct (**4a**) was observed.

The observation that lateral metalation could proceed in the presence of the aryl halogen atom, suggested the opportunity for further elaboration of this scaffold via palladium catalyzed cross coupling. Suzuki coupling of aryl boronates with the 10′-bromo (**1b**) (see Scheme 1 and Table 2) proceeded readily with the modification

Table 2. Suzuki coupling of 3-(10′-halo-9′-anthracenyl)-5-methyl-4-isoxazolecarboxylic acid ethyl esters with aryl boronates[18]

Product	Aryl halide	Reaction conditions	Yield (%)
6	**1b**	THF, rt, 72 h	92
	1c	DMF, 120–125°C, 24 h	78
7	**1b**	THF, rt, 72 h	96
	1c	DMF, 120–125°C, 24 h	91
8	**1b**	THF, rt, 72 h	93
	1c	DMF, 120–125°C, 24 h	88

pioneered in Fu's laboratory[15], namely, 2% $Pd_2(dba)_3$ and 4% P(*t*-Bu)$_3$ at room temperature, and produced the cross coupling products in excellent yields. While the 10′-chloro (**1c**) required higher temperature (120–125°C), the yields were also excellent. While previous reports of Suzuki type cross-coupling of anthracenyl bromides, and anthraquinone triflates have appeared, this—to the best of our knowledge—is the first report of the use of anthracenyl chlorides.[16,17] Furthermore, while the Suzuki reaction in the presence of other heterocyclic systems have been reported—only a very few of them π-deficient—this is the first instance in which the transformation has been performed in the presence of the isoxazole ring, a ring notorious for the lability of the O–N bond in the presence of low valent metals.

Application of these methods towards optimization of the biological activity of analogs of NSC D 694332 is being studied in our laboratories, and our progress will be reported in due course.

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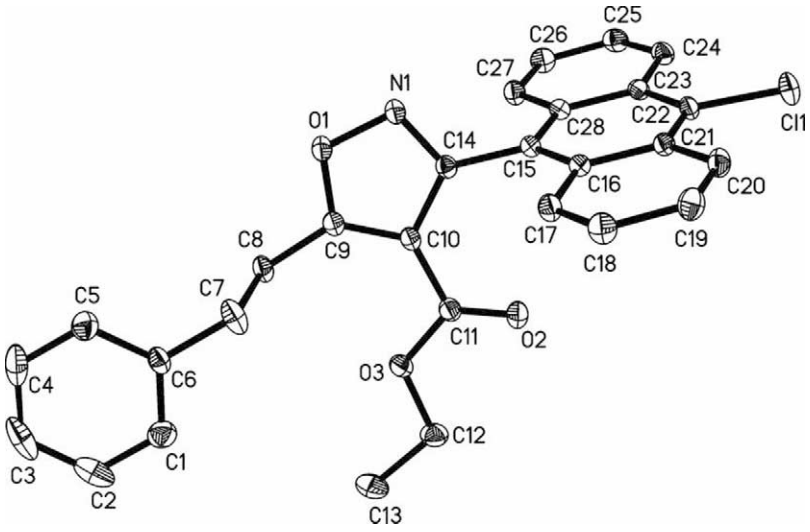

Figure 2. The X-ray structure of **3c**.

and Andrzej J. Paszczynski of the Environmental Biotechnology Institute, University of Idaho, for use of their computational facility. Dr. Dan Zaharevitz assisted us with the COMPARE calculation and interpretation. N.R.N. thanks the National Institute of Neurological Disease and Stroke for Grant 2R15-NS38444. X.H., C.L. and K.C.R. acknowledge the Malcolm and Carol Renfrew Scholarship Endowment, University of Idaho. We would like to thank Professor Kin Shing Chan of The Chinese University of Hong Kong for helpful discussions.

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18. All final compounds were characterized by ^{1}H, ^{13}C NMR, and HR MS or elemental analysis. Selected spectral data:
Compound **2a**: mp 96–98°C; ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.02 (dd, $J=7.1$, 2.0 Hz, 2H), 7.61 (dd, $J=7.1$, 2.0 Hz, 2H), 7.49–7.34 (m, 4H), 3.66 (q, $J=7.2$ Hz, 2H), 3.33 (q, $J=7.6$ Hz, 2H), 1.51 (t, $J=7.6$ Hz, 3H), 0.28 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 181.0, 161.9, 160.9, 131.4, 131.3, 129.0, 128.9, 126.7, 125.9, 125.6, 123.3, 110.8, 60.4, 21.6, 13.2, 11.9; MS (EI) m/z 176(9.24), 203(13.31), 214(12.02), 219(13.83), 243(23.65), 244(13.19), 345(100, M^+). Anal. calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.70; H, 5.66; N, 3.83.
Compound **3a**: mp 82–84°C; ^{1}H NMR ($CDCl_3$) δ 8.55(s, 1H), 8.03 (dd, $J=7.0$, 2.0 Hz, 2H), 7.53 (dd, $J=7.0$, 2.0 Hz, 2H), 7.48–7.24 (m, 4H), 3.67–3.57 (m, 4H), 3.50 (t, $J=7.5$ Hz, 2H), 0.27 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.8, 161.6, 160.8, 140.2, 131.4, 131.3, 129.0, 128.9, 128.8, 127.0, 126.7, 125.9, 125.6, 124.1, 123.2, 111.9, 60.4, 34.0, 29.5, 13.2; MS (EI) m/z 71(18.37), 149(96.13), 167(36.01), 243(21.04), 279(21.40), 375(14.53), 421(100, M^+). Anal. Calcd for $C_{28}H_{23}NO_3$: C, 79.79; H, 5.50; N, 3.32. Found: C, 79.98; H, 5.49; N, 3.41.
Compound **4a**: mp 145–147°C; ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.03 (dd, $J=7.1$, 2.0 Hz), 7.52 (dd, $J=7.1$, 2.0 Hz), 7.48–7.25 (m, 4H), 5.36 (m, 1H), 3.78–3.72 (m, 2H), 3.61 (q, $J=7.2$ Hz, 2H), 0.20 (t, $J=7.2$ Hz, 2H); ^{13}C NMR (acetone-d_6) δ 176.53, 160.72, 160.06, 144.10, 144.08, 131.16, 131.14, 130.77, 130.76, 128.46, 128.19, 127.46, 126.28, 126.27, 125.87, 125.42, 125.40, 125.33, 125.32, 123.29, 111.96, 71.72, 71.61, 59.65, 37.37, 37.33, 12.47; MS (EI) m/z 79(9.47), 107(12.19), 203(14.06), 219(15.74), 243(26.66), 285(21.19), 331(38.96), 437(100, M^+); HRMS (EI) calcd for $C_{28}H_{23}NO_4$ (M^+) 437.1628, found 437.1626.

Compound **2b**: Obtained as a yellow oil after chromatography on silica gel (R_f=0.26 in 3:2 benzene/hexane). ^{1}H NMR ($CDCl_3$) δ 8.56 (dd, J=6.9, 1.9 Hz, 2H), 7.59–7.40 (m, 6H), 3.64 (q, J=7.2 Hz, 2H), 3.29 (q, J=7.5 Hz, 2H), 1.46 (t, J=7.5 Hz, 3H), 0.29 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 181.2, 161.6, 160.7, 131.8, 130.5, 128.5, 127.5, 126.9, 126.3, 125.6, 124.2, 110.9, 60.5, 21.6, 13.3, 11.9; MS (EI) m/z 176(38.02), 214(38.20), 283(14.69), 297(16.52), 321(36.05), 423(93.38, M^+), 425(100, $(M+2)^+$); HRMS (EI) calcd for $C_{22}H_{18}BrNO_3$ (M^+, $(M+2)^+$), 423.0470, 425.0453, found 423.0470, 425.0439.

Compound **3b**: mp 146–148°C; ^{1}H NMR ($CDCl_3$) δ 8.54 (dd, J=7.0, 2.0 Hz, 2H), 7.55–7.25 (m, 6H), 3.63–3.56 (m, 4H), 3.22 (t, J=7.5 Hz, 2H), 0.29 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.9, 161.4, 160.6, 140.0, 131.8, 130.5, 129.0, 128.7, 128.5, 127.5, 127.0, 126.9, 126.3, 125.6, 124.1, 112.0, 60.5, 34.0, 29.5, 13.3; MS (EI) m/z 57(16.23), 70(11.01), 83(12.18), 91(21.42), 105(14.87), 131(9.84), 149(48.20), 176(37.33), 201(11.22), 214(25.70), 283(17.47), 323(29.30), 455(16.51), 499(94.35, M^+), 501(100, $(M+2)^+$); HRMS (EI) calcd for $C_{28}H_{22}BrNO_3$ (M^+, $(M+2)^+$) 499.0783, 501.0767, found 499.0772, 501.0787.

Compound **4b**: mp 113–114°C; ^{1}H NMR ($CDCl_3$) δ 8.53 (dd, J=7.0, 2.0 Hz, 2H), 7.55–7.29 (m, 6H), 5.33 (m, 1H), 3.80–3.64 (m, 2H), 3.56 (q, J=7.2 Hz, 2H), 0.22 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.7, 162.0, 160.5, 143.1, 131.8, 131.4, 131.3, 130.5, 129.1, 128.7, 128.6, 128.5, 127.5, 127.03, 127.01, 126.3, 126.1, 125.8, 125.7, 123.8, 113.0, 73.0, 60.9, 60.8, 37.54, 37.52, 13.2, 13.1; MS (EI) m/z 79(54.88), 107(58.02), 176(100), 203(34.75), 214(61.75), 297(34.07), 323(48.64), 365(29.29), 411(57.93), 437(33.12), 515(89.54, M^+), 517(90.18%, $(M+2)^+$); HRMS (EI) calcd for $C_{28}H_{22}BrNO_4$ (M^+, $(M+2)^+$) 515.0732, 517.0716, found 515.0725, 517.0723.

Compound **2c**: mp 99–101°C; ^{1}H NMR ($CDCl_3$) δ 8.61 (dd, J=7.1, 2.0 Hz, 2H), 7.68–7.51 (m, 6H), 3.73 (q, J=7.1 Hz, 2H), 3.37 (q, J=7.5 Hz, 2H), 1.56 (t, J=7.5 Hz, 3H), 0.39 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.8, 161.2, 160.2, 131.2, 131.0, 128.3, 126.7, 126.5, 125.9, 125.1, 122.8, 110.5, 60.1, 21.2, 12.9, 11.5; MS (EI) m/z: 83(7.79), 176(10.84), 214(11.71), 253(13.43), 277(21.53), 379(100, M^+), 380(19.63%, M+1), 381(25.86%, M+2). Anal. calcd for $C_{22}H_{18}ClNO_3$: C, 69.57; H, 4.78; N, 3.69. Found: C, 69.61; H, 4.66; N, 3.88.

Compound **3c**: Cubic crystals from cyclohexane: mp: 149–151°C; ^{1}H NMR ($CDCl_3$) δ 8.54 (dd, J=7.0, 2.1 Hz, 2H), 7.61–7.29 (m, 6H), 3.63 (m, 4H), 3.24 (t, J=7.5 Hz, 2H), 0.33 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.52, 161.00, 160.10, 139.62, 131.13, 130.98, 128.59, 128.58, 128.30, 126.67, 126.61, 126.50, 125.86, 125.04, 122.62, 111.57, 60.13, 33.56, 29.07, 12.90; MS (EI) m/z 77(3.99), 91(10.41), 176(9.29), 227(11.66), 277(26.66), 409(21.55), 455(100, M^+), 456(27.78%, $(M+1)^+$), 457(43.07%, $(M+2)^+$). Anal. calcd for $C_{28}H_{22}ClNO_3$: C, 73.76; H, 4.86; N, 3.07. Found: C, 73.91; H, 4.93; N, 2.98.

Compound **4c**: mp 119–121°C; ^{1}H NMR ($CDCl_3$) δ 8.60 (dd, J=7.0, 2.0 Hz, 2H), 7.62–7.45 (m, 6H), 5.46 (m, 1H), 3.86–3.75 (m, 2H), 3.67 (q, J=7.2 Hz, 2H), 0.31 (t, J=7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 176.25, 161.10, 159.98, 142.74, 131.14, 131.09, 128.69, 128.297, 128.291, 128.20, 126.74, 126.70, 126.65, 126.56, 125.84, 125.82, 125.67, 125.06, 122.36, 112.65, 72.54, 60.48, 37.08, 12.78; MS (EI) m/z 77(13.45), 79(14.72), 105(19.34), 163(10.69), 176(14.33), 214(12.65), 277(23.69), 319(17.48), 365(44.89), 471(100, M^+), 472(35.78, $(M+1)^+$), 473(37.49%, $(M+2)^+$). Anal. calcd for $C_{28}H_{22}ClNO_4$: C, 71.26 H, 4.70; N, 2.97. Found: C, 71.08; H, 4.74; N, 2.84.

Compound **6**: Colorless crystals from cyclohexane: mp 191.5–193°C; ^{1}H NMR ($CDCl_3$) δ 7.63–7.27 (m, 13H), 3.68 (q, J=7.2 Hz, 2H), 2.88 (s, 3H), 0.33 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.6, 162.0, 161.2, 139.8, 139.1, 131.6, 131.5, 130.9, 130.1, 128.9, 128.8, 127.6, 126.3, 125.9, 125.5, 123.3, 111.9, 60.5, 13.8, 13.2; MS (EI) m/z 252(13.86), 295(12.85), 319(17.91), 407(100, M^+). Anal. calcd for $C_{27}H_{21}NO_3$: C, 79.59; H, 5.19; N, 3.44. Found: C, 79.94; H, 5.09; N, 3.57.

Compound **7**: Pale yellow crystals from 10:1 hexane/ethyl Acetate: mp 203–204°C; ^{1}H NMR ($CDCl_3$) δ 7.69–7.59 (m, 4H), 7.34–7.27 (m, 6H), 7.09–7.06 (m, 2H), 3.90 (s, 3H), 3.68 (q, J=7.2 Hz, 2H), 2.88 (s, 3H), 0.33 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.5, 162.0, 161.2, 159.6, 139.6, 132.7, 132.6, 131.1, 131.0, 130.5, 127.6, 126.3, 125.9, 125.4, 123.1, 114.4, 114.3, 111.9, 60.5, 55.83, 55.81, 13.8, 13.2; MS (EI) m/z 239(10.12), 325(12.01), 349(16.10), 437(100, M^+). Anal. calcd for $C_{28}H_{23}NO_4$: C, 76.87; H, 5.30; N, 3.20. Found: C, 76.64; H, 5.10; N, 3.24.

Compound **8**: Colorless needles from 5:1 hexane/ethyl acetate: mp 223–224°C; ^{1}H NMR ($CDCl_3$) δ 7.65–7.59 (m, 1H), 7.36–7.24 (m, 12H), 3.68 (q, J=7.2 Hz, 2H), 2.88 (s, 3H), 2.21 (s, 3H), 0.34 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.6, 168.8, 161.9, 161.2, 139.2, 137.9, 134.8, 132.24, 132.20, 130.9, 130.2, 127.5, 126.4, 125.9, 125.6, 123.3, 120.1, 111.9, 60.5, 25.0, 13.8, 13.3; MS (EI) m/z 119(8.90), 162(8.12), 266(11.10), 278(11.20), 304(10.23), 320(10.10), 335(15.12), 352(16.93), 376(30.01), 393(9.91), 421(12.03), 439(11.45), 464(100, M^+). Anal. calcd for $C_{29}H_{24}N_2O_4$: C, 74.98; H, 5.21; N, 6.03. Found: C, 75,21; H, 5.04; N, 6.25.