Novel Synthesis of Heterocycle-Annulated Azocine Derivatives of Biological Relevance by Aromatic Aza-Claisen Rearrangement and Intramolecular Heck Reaction

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Abstract: A synthetic strategy based on the sequential application of an aromatic aza-Claisen rearrangement and an intramolecular Heck reaction sequence as the key steps has been developed for the synthesis of various hitherto unreported coumarin- and quinolone-annulated benzazocine derivatives in excellent yields.

Key words: aza-Claisen rearrangement, Heck reaction, benzazocine, coumarin, quinolone, palladium catalyst

The importance of medium-sized rings in synthetic organic chemistry is exemplified by their presence as the structural core moiety in a large number of biologically important natural products.[1] Moreover, these units have served as target molecules in numerous synthetic studies.[2] Medium-sized nitrogen heterocycles, especially eight-membered azocines, are key intermediates for many natural products.[3,4] For example, nakadomarin A[5] (Figure 1) has a range of potentially useful bioactivities (anticancer, antifungal, and antibacterial), but limited availability of natural material has restricted further screening. The polycyclic alkaloid manzamine A (Figure 1),[6] isolated from a sponge, shows cytotoxic activity (IC_{50} = 0.07 μg/mL) against the P-388 mouse leukemia cell.

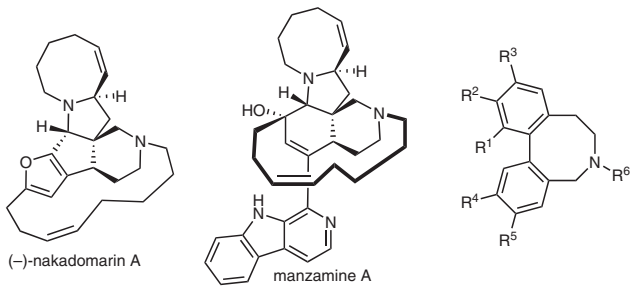

Figure 1 Nakadomarin A and manzamine A and a biologically important azocine backbone

In addition, medium-sized heterocycles fused to aryl rings are found in many drugs and preclinical leads. Despite their biological activity, azocine-fused systems are not sufficiently investigated, perhaps due to the lack of satisfactory synthetic procedures.[7] Recently, the search for new to newer methods for the construction of organic molecules from simple starting materials has become an ongoing challenge. In general, the number of methods available for the synthesis of medium-sized heterocycles is small. Among various synthetic protocols, the palladium-catalyzed intramolecular Heck reaction has become a useful technique due to its excellent functional-group tolerance and high stereoselectivity. The reaction can be catalyzed by palladium complexes with or without phosphine ligands (phosphine-assisted vs. phosphine-free catalysis). A primary role of the phosphine ligands is to support palladium in its zero oxidation state in the form of stable PdL_4 or PdL_3 species. The phosphine-assisted approach is a classical and well-established method, which gives excellent results in the majority of cases. Moreover, although there are many examples of the formation of medium-sized oxa heterocycles,[8,9] syntheses of medium-sized nitrogen heterocycles by use of intramolecular Heck reactions are rare and thus still a significant synthetic challenge. It has been reported[10] that the palladium-catalyzed cyclization by application of the intramolecular Heck reaction requires harsh reaction conditions when a nitrogen-containing compound is used as the starting material. Guy et al.[11] reported the synthesis of eight-membered azocines by the intramolecular Heck reaction by the 8-*endo*-trig mode of cyclization starting from highly activated precursors, but none from unactivated allylic substrates. It has also been reported[12–15] that coumarin and quinolone moieties are found in a large number of natural products that possess a broad spectrum of biological activities such as antifungal, antibacterial, antiviral, and antimicrobial properties. All these findings prompted us to investigate the synthesis of biologically interesting coumarin- and quinolone-annulated azocines by the application of the palladium-mediated intramolecular Heck reaction.

The requisite precursors **3a–c** for our present syntheses were prepared in good to excellent yields by the aromatic aza-Claisen rearrangement of *N*-allylcoumarins and *N*-allylquinolones **2a–c** in the presence of the boron trifluoride–diethyl ether complex as catalyst in xylene at 130 °C in a sealed tube (Scheme 1). These coumarins and quinolones **2a–c** were, in turn, prepared by the reaction of different *N*-alkylcoumarins and -quinolones **1a–c** with allyl bromide in anhydrous methyl ethyl ketone in the presence of potassium carbonate and sodium iodide (Scheme 1).

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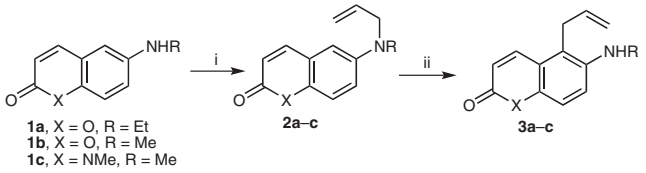
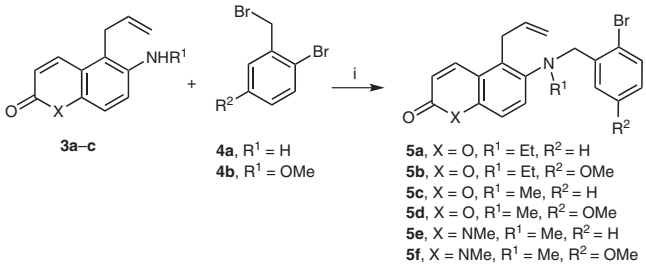


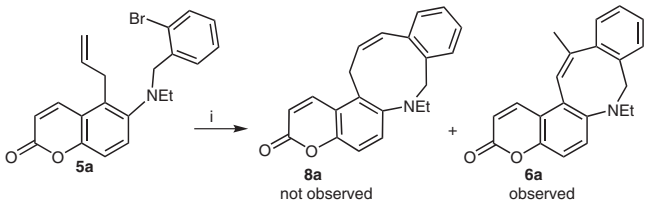
Scheme 1 *Reagents and conditions*: (i) AllBr, MEK, K_2CO_3, NaI, reflux, 9 h; (ii) $BF_3{\cdot}OEt_2$ (2 equiv), xylene, 130 °C, 6 h.

The required Heck precursors **5a**,**b** for our present study were synthesized in 76–80% yields by refluxing 5-allyl-6-(ethylamino)coumarin **3a** with benzyl bromides **4a**,**b** in anhydrous methyl ethyl ketone for about 14 hours in the presence of anhydrous potassium carbonate and a small amount of sodium iodide (Finkelstein conditions) (Scheme 2).[16]



Scheme 2 *Reagents and conditions*: (i) K_2CO_3, MEK, NaI, reflux, 14 h.

The intramolecular Heck reactions were performed in anhydrous *N*,*N*-dimethylformamide in the presence of potassium acetate as a base, tetrabutylammonium bromide as a promoter, triphenylphosphine as ligand, and palladium(II) acetate as catalyst under a nitrogen atmosphere at 90 °C for about six hours. All the reactions afforded the eight-membered heterocyclic compounds **6a**–**f** fused with aryl ring, coumarin, and quinolone moieties (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) $Pd(OAc)_2$ (10 mol%), Ph_3P (20 mol%), KOAc (2.5 equiv), TBAB (1.2 equiv), DMF, 90 °C, 6 h.

In the intramolecular Heck reaction, ring closure can occur by two possible modes, namely the *exo*-trig and the *endo*-trig mode. Of these two possible modes, an *exo* mode is usually favored for the formation of small- to medium-size (5–8) rings,[17] because the *endo* mode is sterically very demanding; the *endo* mode requires that the olefinic system moves into the loop of the substrate, generating an energetically favorable substituted alkene product. In our present work we have obtained only the endocyclic product **6a** via 8-*exo* cyclization followed by double-bond isomerization. The optimization of the reaction conditions was carried out with substrate **5a** and is summarized in Table 1.

Table 1 Optimization of the Reaction Conditions for the Intramolecular Heck Reaction Giving **6a**[a]

Entry	Catalyst	Solvent[b]	Base	Ligand	Yield[c,d] (%)
1	$Pd(OAc)_2$	DMA	K_2CO_3	–	20
2	$Pd(OAc)_2$	DMA	KOAc	–	25
3	$Pd(OAc)_2$	DMF	KOAc	–	65
4[e]	**$Pd(OAc)_2$**	**DMF**	**KOAc**	**Ph_3P**	**79**
5	$Pd(OAc)_2$	DMF	K_2CO_3	–	26
6	$Pd(OAc)_2$	DMF	Ag_2CO_3	–	30
7	$PdCl_2$	DMF	KOAc	Ph_3P	35
8	$Pd(OAc)_2$	DMF	NaOAc	Ph_3P	48
9	$Pd(OAc)_2$	THF	Et_3N	–	n.r.
10	$PdCl_2$	dioxane	KOAc	–	n.r.

[a] Reagents and conditions: TBAB (1.2 equiv), 90 °C.
[b] DMA = *N*,*N*-dimethylacetamide.
[c] Isolated yield.
[d] n.r. = no reaction.
[e] Optimized reaction conditions.

From Table 1, it can be seen that the use of a ligand increases the reaction yield. Among the different bases used, potassium acetate has the largest effect on the reaction yield. Potassium carbonate and silver(I) carbonate show nearly similar effects. The reaction did not occur under the reaction conditions described in Table 1, entries 9 and 10. Among the various solvents, *N*,*N*-dimethylformamide is the best choice. The optimized reaction conditions therefore consist of the use of palladium(II) acetate (10 mol%), tetrabutylammonium bromide (1.2 equiv), potassium acetate (2.5 equiv), triphenylphosphine (20 mol%), and *N*,*N*-dimethylformamide at 90 °C. Other substrates **5b**–**f** were similarly treated under the optimized reaction conditions to afford the corresponding Heck cyclized products **6b**–**f** in 75–78% yields. The results are summarized in Table 2.

The exclusive formation of heterocycle-annulated azocine derivatives **6a**–**f** via the 8-*exo* mode of cyclization is quite unusual. Beletskaya and Cheprakov reported[18] that *endo* Heck cyclization can occur when the Heck precursor possesses a Michael-type olefinic fragment such as a highly activated double bond.

Here the exclusive formation of the endocyclic products **6a**–**f** may be rationalized to occur via two possible pathways, such as proceeding by the 8-*exo* mode of cyclization followed by double-bond isomerization and, alternatively, a double-bond isomerization prior to the Heck reaction leading to the subsequent 8-*endo* Heck cyclization (Scheme 4). It is worthwhile noting that in the

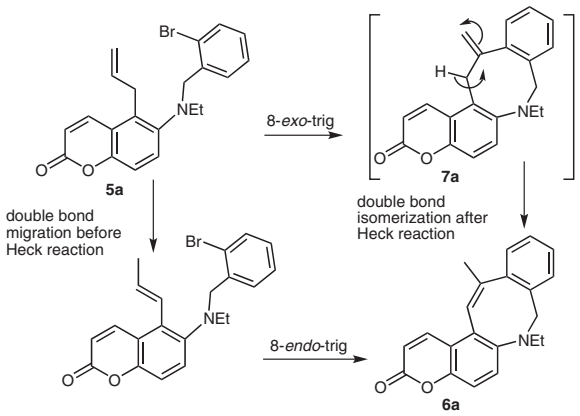
Table 2 Synthesis of Endocyclic Heck Products

Entry	Starting material	Product	Time (h)	Yield[a] (%)
1	**5a**	**6a**	6	79
2	**5b**	**6b**	6.5	77
3	**5c**	**6c**	7	76
4	**5d**	**6d**	7	78
5	**5e**	**6e**	7.5	75
6	**5f**	**6f**	6.5	78

[a] Isolated yield.

case of the formation of dibenzoazocine derivatives[19] this double-bond isomerization did not occur at all. There the reaction was achieved under ligand-free conditions, whereas in the present instance the yield of the reaction is affected by the absence of the triphenylphosphine ligand. The newly formed double bond is more substituted in products **6** than in intermediates **7**.

To summarize, we have developed a protocol which is simple, straightforward, and interesting. A synthetic route for the construction of heterocycle-annulated azocines from unactivated allylic substrates by the intramolecular Heck reaction has been developed.



Scheme 4 Probable mechanistic path of the Heck reaction

Melting points of samples were determined in open capillaries and are uncorrected. IR spectra of samples prepared as KBr discs (or neat for liquid samples) were obtained on a Perkin-Elmer 120-000A apparatus. NMR spectra of solns in $CDCl_3$ were determined on a

Bruker Ultrashield-400 spectrometer (TMS was used as an internal standard). HRMS was carried out on a Qtof Micro YA263 instrument. Silica gel (60–120 mesh) was used for chromatographic separations and silica gel G (E-Merck, India) was used for TLC. PE refers to the fraction with bp 60–80 °C.

6-[Allyl(ethyl)amino]coumarin (2a); Typical Procedure

A mixture of **1a** (2.0 g, 10.6 mmol), allyl bromide (1.34 mL, 15.8 mmol), and anhyd K_2CO_3 (4 g, 28.9 mmol) in anhyd MEK (50 mL) in the presence of NaI was refluxed for 9 h. After cooling, the reaction mixture was filtered and the solvent was removed in vacuo. The residual mass was extracted with EtOAc (3 × 10 mL), washed with H_2O (10 mL) and brine (10 mL), and dried (Na_2SO_4). Removal of the EtOAc gave a crude product which was chromatographed (silica gel, EtOAc–PE, 15:85); this gave **2a**. Compounds **2b**,**c** were prepared similarly.

5-Allyl-6-(ethylamino)coumarin (3a); Typical Procedure

A mixture of compound **2a** (1.2 g, 5.2 mmol) and $BF_3{\cdot}OEt_2$ (1.31 mL, 10.5 mmol) in xylene (4 mL) was heated in a sealed tube at 130 °C for 6 h. After cooling, the reaction mixture was neutralized with sat. aq $NaHCO_3$. Then it was extracted with EtOAc (3 × 10 mL), washed with H_2O (10 mL) and brine (5 mL), and dried (Na_2SO_4). Removal of EtOAc afforded a crude mass, which was purified by column chromatography (silica gel, EtOAc–PE, 20:80); this gave **3a**. Compounds **3b**,**c** were prepared similarly.

5-Allyl-6-[(2-bromobenzyl)(ethyl)amino]coumarin (5a); Typical Procedure

A mixture of **3a** (0.40 g, 1.7 mmol), 2-bromobenzyl bromide (**4a**; 0.52 g, 2.1 mmol), and anhyd K_2CO_3 (2.0 g) in anhyd MEK (50 mL) in the presence of NaI was refluxed for 14 h. The reaction mixture was cooled and filtered and the solvent was removed. The residual mass was extracted with CH_2Cl_2 (3 × 10 ml), washed with H_2O (10 mL) and brine (5 mL), and dried (Na_2SO_4). Removal of the CH_2Cl_2 gave a crude product, which was purified by chromatography (silica gel, EtOAc–PE, 15:85); this gave **5a**. Other substrates **5b**–**f** were prepared similarly.

Compound 5a

Yield: 80%; gummy liquid.

IR (neat): 2929, 1732, 1567 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7 Hz, 3 H, NCH_2CH_3), 3.01 (q, *J* = 7 Hz, 2 H, NCH_2CH_3), 3.79 (t, *J* = 2.6 Hz, 2 H, CH_2), 4.13 (s, 2 H, NCH_2), 4.73 (d, *J* = 17.1 Hz, 1 H, $CH{=}CH_aH_b$)), 4.98 (d, *J* = 10.5 Hz, 1 H, $CH{=}CH_aH_b$), 5.77–5.87 (m, 1 H, $HC{=}CH_2$), 6.35 (d, *J* = 9.8 Hz, 1 H, C_3-H of coumarin), 7.06 (t, *J* = 7.5 Hz, 1 H, ArH), 7.18–7.22 (m, 2 H, ArH), 7.32 (d, *J* = 7.5 Hz, 1 H, ArH), 7.48 (t, *J* = 9.8 Hz, 2 H, ArH), 7.83 (d, *J* = 9.8 Hz, 1 H, C_4-H of coumarin).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3, 30.5, 49.1, 59.1, 115.6, 115.8, 116.0, 118.58, 124.4, 127.2, 127.6, 128.5, 130.3, 132.8, 134.9, 136.6, 137.7, 141.6, 145.7, 151.6, 160.8.

ESI-HRMS: *m/z* calcd: 398.0750 $[M + H]^+$, 400.0732 $[M + H + 2]^+$; found: 398.0781 $[M + H]^+$, 400.0703 $[M + H + 2]^+$.

Anal. Calcd for $C_{21}H_{20}BrNO_2$: C, 63.33; H, 5.06; N, 3.52. Found: C, 63.54; H, 5.18; N, 3.45.

Compound 5b

Yield: 77%; gummy liquid.

IR (neat): 2932, 1732, 1568 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3 H, NCH_2CH_3), 3.00 (q, *J* = 7.1 Hz, 2 H, NCH_2CH_3), 3.71 (s, 3 H, OCH_3), 3.81 (d, *J* = 5.2 Hz, 2 H, CH_2), 4.08 (s, 2 H, NCH_2), 4.74 (d, *J* = 17.5 Hz, 1 H, $CH{=}CH_aH_b$)), 5.00 (d, *J* = 9.9 Hz, 1 H, $CH{=}CH_aH_b$), 5.82–5.91 (m, 1 H, $HC{=}CH_2$), 6.36 (d, *J* = 9.9 Hz, 1 H, C_3-H of coumarin), 6.96 (d, *J* = 2.8 Hz, 1 H, ArH), 7.21 (d, *J* = 8.9 Hz, 2 H, ArH), 7.37 (d, *J* = 8.7 Hz, 1 H, ArH), 7.46 (d, *J* = 9 Hz, 1 H, ArH), 7.84 (d, *J* = 9.8 Hz, 1 H, C_4-H of coumarin).

MS (EI, 70 eV): *m/z* = 427 $[M^+]$, 429 $[M + 2]^+$.

Anal. Calcd for $C_{22}H_{22}BrNO_3$: C, 61.69; H, 5.18; N, 3.27. Found: C, 61.95; H, 5.32; N, 3.26.

Compound 5c

Yield: 78%; solid; mp 101–102 °C.

IR (KBr): 2947, 1718, 1567 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.59 (s, 3 H, NCH_3), 3.75 (t, *J* = 3.2 Hz, 2 H, CH_2), 4.06 (s, 2 H, NCH_2), 4.70 (dd, *J* = 1.2 Hz, 1 H, *J* = 17.2 Hz, $=CH_aCH_b$), 4.97 (dd, *J* = 1.6 Hz, 1 H, *J* = 10.4 Hz, $=CH_aCH_b$), 5.82–5.92 (m, 1 H, $HC{=}CH_2$), 6.32 (d, *J* = 10 Hz, 1 H, C_3-H of coumarin), 7.02–7.07 (m, 1 H, ArH), 7.16–7.21 (m, 2 H, ArH), 7.36 (d, *J* = 7.6 Hz, 1 H, ArH), 7.41 (d, *J* = 8.8 Hz, 1 H, ArH), 7.47 (d, *J* = 8 Hz, 1 H, ArH), 7.78 (d, *J* = 9.6 Hz, 1 H, C_4-H of coumarin).

MS (EI, 70 eV): *m/z* = 383 $[M^+]$, 385 $[M + 2]^+$.

Anal. Calcd for $C_{20}H_{18}BrNO_2$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.48; H, 4.74; N, 3.44.

Compound 5d

Yield: 76%; liquid.

IR (neat): 2939, 1732, 1559 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.66 (s, 3 H, NCH_3), 3.77 (s, 3 H, OCH_3), 3.82 (t, *J* = 2.7 Hz, 2 H, CH_2), 4.08 (s, 2 H, NCH_2), 4.78 (dd, *J* = 0.9 Hz, 1 H, *J* = 17.1 Hz, $=CH_aCH_b$), 5.05 (dd, *J* = 0.9 Hz, 1 H, *J* = 10.2 Hz, $=CH_aCH_b$), 5.90–6.03 (m, 1 H, $HC{=}CH_2$), 6.39 (d, *J* = 9.6 Hz, 1 H, C_3-H of coumarin), 6.69 (dd, *J* = 2.7 Hz, 1 H, *J* = 8.7 Hz, ArH), 7.06 (d, *J* = 2.7 Hz, 1 H, ArH), 7.21 (d, *J* = 7.2 Hz, 1 H, ArH), 7.42 (d, *J* = 8.7 Hz, 1 H, ArH), 7.48 (d, *J* = 8.7 Hz, 1 H, ArH), 7.86 (d, *J* = 9.6 Hz, 1 H, C_4-H of coumarin).

MS (EI, 70 eV): *m/z* = 413 $[M^+]$, 415 $[M + 2]^+$.

Anal. Calcd for $C_{21}H_{20}BrNO_3$: C, 60.88; H, 4.87; N, 3.38. Found: C, 60.64; H, 4.90; N, 3.35.

Compound 5e

Yield: 77%; solid; mp 73–74 °C.

IR (KBr): 2939, 1655, 1567 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3 H, NCH_3), 3.66 (s, 3 H, NCH_3), 3.84 (t, *J* = 2.8 Hz, 2 H, CH_2), 4.10 (s, 2 H, NCH_2), 4.70 (dd, *J* = 1.2 Hz, 1 H, *J* = 17.2 Hz, $=CH_aCH_b$), 4.95 (dd, *J* = 1.2 Hz, 1 H, *J* = 10.4 Hz, $=CH_aCH_b$), 5.86–5.94 (m, 1 H, $HC{=}CH_2$), 6.62 (d, *J* = 10 Hz, 1 H, C_3-H of quinolone), 7.04 (t, *J* = 7.2 Hz, 1 H, ArH), 7.23 (d, *J* = 9.2 Hz, 2 H, ArH), 7.42 (d, *J* = 7.2 Hz, 1 H, ArH), 7.47 (dd, *J* = 3.6 Hz, 2 H, *J* = 8.8 Hz, ArH), 7.78 (d, *J* = 10 Hz, 1 H, C_4-H of quinolone).

MS (EI, 70 eV): *m/z* = 396 $[M^+]$, 398 $[M + 2]^+$.

Anal. Calcd for $C_{21}H_{21}BrN_2O$: C, 63.48; H, 5.33; N, 7.05. Found: C, 63.53; H, 5.56; N, 6.87.

Compound 5f

Yield: 76%; gummy liquid.

IR (neat): 2924, 1649, 1569 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.65 (s, 3 H, NCH_3), 3.72 (s, 3 H, NCH_3), 3.77 (s, 3 H, OCH_3), 3.84 (t, *J* = 2.7 Hz, 2 H, CH_2), 4.10 (s, 2 H, NCH_2), 4.78 (d, *J* = 16.8 Hz, 1 H, $=CH_aH_b$), 5.03 (d, *J* = 10.2 Hz, 1 H, $=CH_aH_b$), 5.93–6.05 (m, 1 H, $CH{=}CH_2$), 6.69 (d, *J* = 9.9 Hz, 1 H, C_3-H of quinolone), 7.10 (d, *J* = 2.4 Hz, 1 H, ArH), 7.30

(d, J = 9.9 Hz, 2 H, ArH), 7.42 (d, J = 8.4 Hz, 1 H, ArH), 7.54 (d, J = 9.0 Hz, 1 H, ArH), 7.85 (d, J = 9.9 Hz, 1 H, C_4-H of quinolone).

MS (EI, 70 eV): m/z = 426 [M^+], 428 [M + 2]$^+$.

Anal. Calcd for $C_{22}H_{23}BrN_2O_2$: C, 61.83; H, 5.42; N, 6.56. Found: C, 61.90; H, 5.36; N, 6.44.

Compounds 6a–f by Heck Reaction; General Procedure

A mixture of **5a** (150 mg, 0.37 mmol), TBAB (145.9 mg, 0.45 mmol), fused KOAc (92.3 mg, 0.94 mmol), and Ph_3P (19.7 mg, 20 mol%) was taken up in anhyd DMF (10 mL), and N_2 was bubbled through the mixture. $Pd(OAc)_2$ (8.4 mg, 10 mol%) was added and the reaction mixture was stirred at 90 °C for 6 h. The reaction mixture was cooled, H_2O (20 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The EtOAc extract was washed with H_2O (4 × 10 mL) and brine (10 mL) and dried (Na_2SO_4). The solvent was distilled off to furnish a viscous mass, which was purified by column chromatography (silica gel, EtOAc–PE, 15:85) to afford **6a**. The other substrates **5b–f** were similarly treated to give the corresponding products **6b–f**.

Compound 6a

Yield: 79%; solid; mp 119–120 °C.

IR (KBr): 2924, 2850, 1726, 1567 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.0 Hz, 3 H, NCH_2CH_3), 2.24 (s, 3 H, CH_3), 3.34 (q, J = 7.1 Hz, 2 H, NCH_2CH_3), 4.33 (s, 2 H, NCH_2), 6.28 (d, J = 9.8 Hz, 1 H, C_3-H of coumarin), 6.44 (s, 1 H, =C*H*), 6.95 (d, J = 9.1 Hz, 1 H, ArH), 7.04 (d, J = 9.1 Hz, 1 H, ArH), 7.09–7.18 (m, 4 H, ArH), 7.79 (d, J = 9.7 Hz, 1 H, C_4-H of coumarin).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 24.5, 51.6, 56.7, 115.3, 116.1, 117.6, 123.4, 125.7, 127.5, 127.6, 128.9, 129.6, 130.2, 135.1, 141.3, 142.8, 143.1, 144.6, 149.3, 161.1.

ESI-HRMS: m/z calcd: 318.1489 [M + H]$^+$; found: 318.1484 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.30; H, 6.09; N, 4.36.

Compound 6b

Yield: 77%; gummy liquid.

IR (neat): 2923, 2852, 1726 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.39 (t, J = 7.5 Hz, 3 H, NCH_2CH_3), 2.23 (s, 3 H, CH_3), 3.33 (q, J = 6.9 Hz, 2 H, NCH_2CH_3), 3.74 (s, 3 H, OCH_3), 4.31 (s, 2 H, NCH_2), 6.29 (d, J = 9.6 Hz, 1 H, C_3-H of coumarin), 6.42 (s, 1 H, =C*H*), 6.73 (d, J = 6.3 Hz, 1 H, ArH), 6.79 (s, 1 H, ArH), 6.96–7.08 (m, 3 H, ArH), 7.82 (d, J = 9.6 Hz, 1 H, C_4-H of coumarin).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 24.7, 51.8, 55.2, 56.9, 113.3, 115.3, 116.1, 117.6, 123.0, 126.8, 128.0, 129.1, 129.9, 135.2, 136.6, 141.3, 142.6, 144.5, 149.4, 158.7, 161.1.

MS (EI, 70 eV): m/z = 347 [M^+]

Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 75.91; H, 6.13; N, 3.99.

Compound 6c

Yield: 76%; gummy liquid.

IR (neat): 2925, 2854, 1742 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.27 (s, 3 H, CH_3), 3.04 (s, 3 H, NCH_3), 4.36 (s, 2 H, NCH_2), 6.29 (d, J = 9.8 Hz, 1 H, C_3-H of coumarin), 6.49 (s, 1 H, =C*H*), 6.98–7.04 (m, 2 H, ArH), 7.12–7.19 (m, 2 H, ArH), 7.23 (d, J = 8.5 Hz, 1 H, ArH), 7.35 (d, J = 9.1 Hz, 1 H, ArH), 7.81 (d, J = 9.8 Hz, 1 H, C_4-H of coumarin).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 44.8, 60.3, 115.5, 116.1, 117.6, 123.5, 125.8, 126.2, 127.6, 127.8, 128.4, 130.1, 134.9, 141.3, 142.8, 143.5, 145.6, 148.9, 161.0.

MS (EI, 70 eV): m/z = 303 [M^+]

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.06; H, 5.64; N, 4.46.

Compound 6d

Yield: 78%; solid; mp 135–136 °C.

IR (KBr): 2924, 2854, 1729 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.24 (s, 3 H, CH_3), 3.03 (s, 3 H, NCH_3), 3.73 (s, 3 H, OCH_3), 4.33 (s, 2 H, NCH_2), 6.30 (d, J = 9.9 Hz, 1 H, C_3-H of coumarin), 6.45 (s, 1 H, =C*H*), 6.72–6.77 (m, 2 H, ArH), 6.99–7.06 (m, 3 H, ArH), 7.82 (d, J = 9.6 Hz, 1 H, C_4-H of coumarin).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 44.9, 55.2, 60.4, 113.3, 115.3, 115.5, 116.1, 117.6, 123.1, 126.5, 126.9, 128.5, 135.2, 136.4, 141.3, 143.0, 145.6, 149.0, 158.7, 161.0.

MS (EI, 70 eV): m/z = 333 [M^+]

Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.59; H, 5.78; N, 4.09.

Compound 6e

Yield: 75%; gummy liquid.

IR (neat): 2924, 2853, 1649 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 3.04 (s, 3 H, NCH_3), 3.60 (s, 3 H, NCH_3), 4.35 (s, 2 H, NCH_2), 6.57 (s, 1 H, =C*H*), 6.61 (d, J = 9.6 Hz, 1 H, C_3-H of quinolone), 7.07 (d, J = 8.8 Hz, 1 H, ArH), 7.11–7.16 (m, 2 H, ArH), 7.23 (d, J = 6.8 Hz, 1 H, ArH), 7.46–7.49 (m, 1 H, ArH), 7.64–7.69 (m, 1 H, ArH), 7.80 (d, J = 10 Hz, 1 H, C_4-H of quinolone).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 29.4, 44.9, 60.5, 114.0, 119.7, 120.8, 124.5, 125.9, 126.2, 127.3, 127.6, 128.4, 129.3, 130.0, 135.1, 135.9, 142.6, 143.0, 143.9, 161.7.

MS (EI, 70 eV): m/z = 316 [M^+]

Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.86; H, 6.34; N, 8.90.

Compound 6f

Yield: 78%; gummy liquid.

IR (neat): 2931, 2851, 1654 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2. 26 (s, 3 H, CH_3), 3.03 (s, 3 H, NCH_3), 3.60 (s, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 4.32 (s, 2 H, NCH_2), 6.54 (s, 1 H, =C*H*), 6.61 (d, J = 9.9 Hz, 1 H, C_3-H of quinolone), 6.71 (d, J = 8.1 Hz, 1 H, ArH), 6.77 (s, 1 H, ArH), 7.06 (t, J = 9 Hz, 2 H, ArH), 7.16 (d, J = 9.3 Hz, 1 H, ArH), 7.81 (d, J = 9.6 Hz, 1 H, C_4-H of quinolone).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 29.2, 44.6, 55.2, 61.6, 114.0, 119.7, 120.6, 123.9, 125.9, 126.4, 127.0, 127.6, 128.6, 129.4, 130.0, 134.9, 136.3, 141.7, 143.9, 157.8, 161.7.

MS (EI, 70 eV): m/z = 346 [M^+]

Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.24; H, 6.42; N, 8.05.

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