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Synthesis of Novel Hybrid 4*H*-Pyran-lipoic and 4*H*-Pyran-azetidine Derivatives

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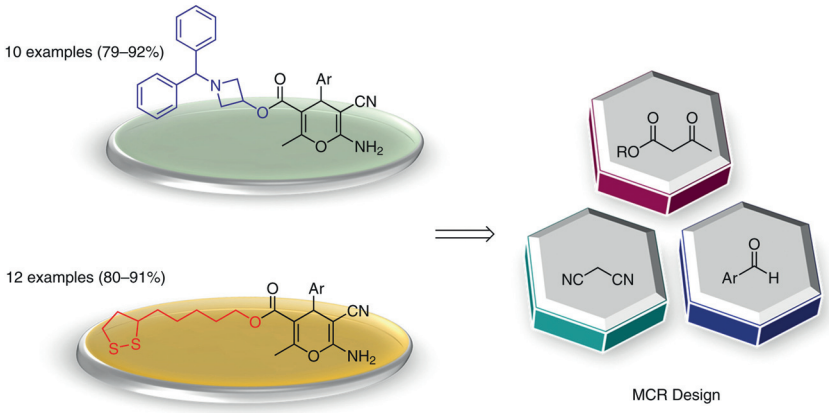

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Abstract In this study, a molecular hybridization strategy was used to design and synthesize two novel series of hybrid compounds: 4*H*-pyran-lipoic and 4*H*-pyran-azetidine, employing ammonium hydroxide and involving the participation of aldehydes, malononitrile, and compounds derived from β-ketoesters to obtain the products with good yields.

Key words molecular hybridization, multicomponent reaction, 4*H*-pyran-lipoic, 4*H*-pyran-azetidine core

One of the current trends in organic and medicinal chemistry fields is the design, synthesis, and development of novel potential drugs. Such compounds should present better pharmacological properties for the treatment of illnesses and also exhibit low toxicity. One of the strategies employed to generate these types of compounds has been the use of molecular hybridization (MH), which is based either on the combination of different pharmacophoric fragments already studied or on the combination of various substances with previously known biological activity; this union generates a new hybrid compound which can have a better activity than its predecessor.[1]

Several methodologies have been reported on the applications of MH to generate new hybrid compounds,[2–6] some of which concern the synthesis of hybrid compounds using lipoic acid, for example, tacrine-lipoic (**1**),[7] polyphenols-lipoic (**2**),[8] ibuprofen-lipoic (**3**),[9] and Trolox-lipoic (**4**).[10] In these reports, the compounds exhibited improved biological activity compared with those of the starting compounds. There are also reports on hybrid compounds using the azetidine core, for instance, propranolol-azetidine derivatives (**5**),[11] fluoroquinolones-azetidine (**6**),[12] and 1,4-dihydropyridine-azetidine (azelnidipine) (**7**);[13] some of these compounds are in the preclinical phase while another privileged group is already used for the treatment of some diseases (Figure 1).

On the other hand, various studies have shown that the 4*H*-pyran core exhibits a wide range of biological activities such as antibacterial,[14] antiproliferative,[15] antipyretic,[16] and anti-inflammatory activity.[17] Our research group has conducted previous studies regarding this core, showing that this skeleton has vasorelaxant activity.[18,19] Furthermore, it was demonstrated that if an electron-withdrawing group was incorporated into the structure, the biological activity can be increased. Their physiological mechanism was also determined and found to proceed through inhibitors of calcium channels.[20] Likewise, some studies revealed that if an ester group was modified in a base structure, the biological activity could be affected.[21,22] In contrast, the increase of the chain size of different esters drastically changed the stability of the compound in the presence of enzymes.[23]

According to this background, the syntheses of two new series of hybrid compounds were performed in the present work; the first one includes a fragment of lipoic acid attached to a 4*H*-pyran core and the second corresponds to 4*H*-pyran-azetidine derivatives. By applying this modification and varying the ester size, it was expected that a clear correlation would be found between structure and biological activity of the molecules. Addressing the approaches to obtain them, the multi-component reaction (MCR) strategy is considered a convenient option[24] because it provides both high selectivity and atomic economy of the products.

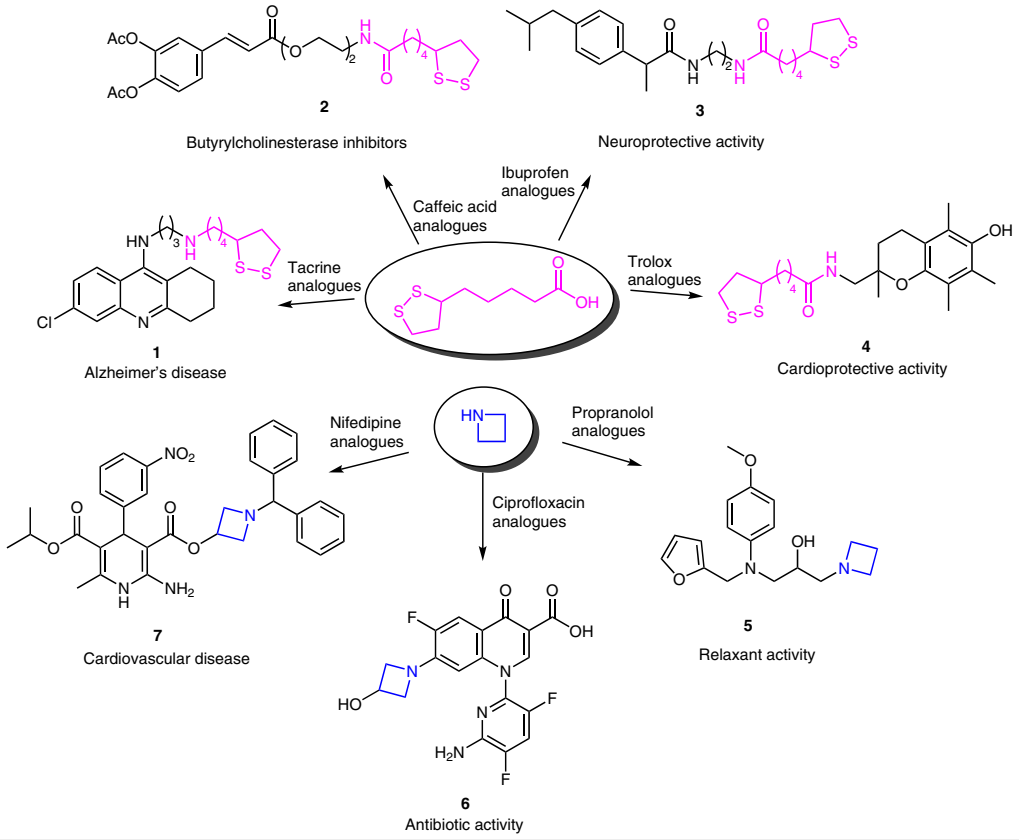
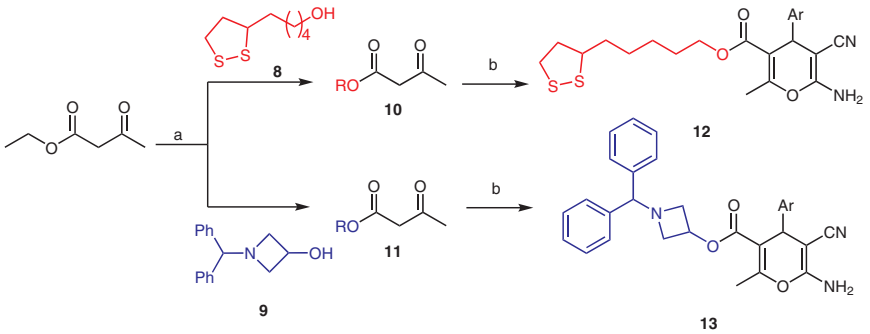


Figure 1 Examples of hybrid compounds

These features have motivated an interest to extend its application not only for pyran scaffolds but also other classes of cores.[25–27]

To obtain the target compounds **12** and **13**, the synthetic route used is depicted in Scheme 1. Compounds **8** and **9** were accomplished by using published methodologies. Based on the above considerations, alcohol **8** was obtained by reduction of lipoic acid using lithium aluminum hydride (LAH) and tetrahydrofuran as solvent; after that, disulfide bond formation was carried out using copper chloride in an ethanol/water mixture. The yields of compound **8** were similar to those already reported.[28]

Formation of alcohol **9** was carried out through reaction between diphenylmethanamine and epichlorohydrin as the first step, the mixture was stirred with isopropanol at room temperature to generate the epoxide opening product; upon completion of this reaction (TLC), the solvent was evaporated and an acetonitrile/methanol mixture was added in combination with triethylamine as base, then heated to reflux until **9** was obtained in equal yields as reported.[29]



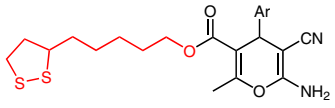
Scheme 1 *Reagents and conditions.* (a) I_2 (30 mol%), PhMe, reflux, 12 h; (b) ArCHO, malononitrile, NH_4OH (10 mol%), MeCN, r.t., 2 h.

To obtain compounds **10** and **11**, a transesterification reaction was used, in which ethyl acetoacetate was reacted with the corresponding alcohol (**8**/**9**) using molecular iodine as catalyst and toluene as solvent.[30] The mixture was heated at reflux and, after 12 hours, the corresponding 1,3-dicarbonyl compound was formed in 80 and 75% yield, respectively. Before continuing, both were characterized by NMR spectroscopic analysis and other techniques, showing distinctive signals for each one.

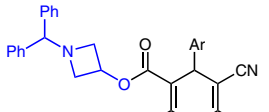
Our research group previously reported the synthesis of 4*H*-pyrans using infrared irradiation.[24] Based on this, we wanted to obtain the desired compounds by a MCR in which an aldehyde, malononitrile, and a 1,3-dicarbonyl system reacted using ammonium hydroxide as base, which had already been determined as the best base to promote this kind of reaction. In the present study, several solvents were tested to optimize the conditions. When ethanol was employed, the transesterification product was formed as the main component of the mixture; on the other hand, dichloromethane prevented this problem but the yield remained low (15%). Acetonitrile proved to be the best option, allowing an efficient transformation toward the target product (90%) after 2 hours of stirring at room temperature.

When the MCR approach was used, it was shown that by changing the nature of the aldehydes, the yields were similar. However, a slight increase in yield was observed with electron-releasing groups in the aromatic moiety. The presence of halogens in the aldehyde caused yields to diminish. In contrast, reaction with heteroaromatic aldehydes resulted in good yields (Table 1).

Table 1 Preparation of 4*H*-Pyran Hybrid Compounds



12



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Product	Ar	Yield (%)	Product	Ar	Yield (%)
12a	C_6H_5	90	**13a**	C_6H_5	85
12b	4-$O_2NC_6H_4$	87	**13b**	4-$O_2NC_6H_4$	90
12c	3-$O_2NC_6H_4$	88	**13c**	3-$O_2NC_6H_4$	92
12d	2-$ON_2C_6H_4$	85	**13d**	2-$O_2NC_6H_4$	87
12e	4-ClC_6H_4	83	**13e**	4-ClC_6H_4	89
12f	4-BrC_6H_4	81	**13f**	4-BrC_6H_4	86
12g	2,4-$Cl_2C_6H_3$	86	**13g**	2,4-$Cl_2C_6H_3$	79
12h	C_5H_4N	85	**13h**	C_5H_4N	92
12i	C_4H_3S	83	**13i**	C_4H_3S	80
12j	4-FC_6H_4	85	**13j**	4-$MeOC_6H_4$	86
12k	3-ClC_6H_4	86			
12l	C_4H_3O	91			

All compounds obtained were characterized by using a range of analytical techniques. The ^{1}H NMR spectra exhibited two singlets between δ = 4.5 and 5.0 ppm that correspond to the hydrogen of the 4-position and the hydrogen atoms of the amine group; all compounds also exhibited characteristic signals according to their identity. A single-crystal determination for compound **13g** allowed us to confirm its molecular construction (Figure 2). The X-ray structure showed that the compound was co-crystallized with an acetonitrile molecule and showed disorder in a portion of the molecule. On the other hand, the structure also indicated that the 4*H*-pyran core presents almost a coplanarity in the system with a deviation of 6.92°. A short hydrogen bond (2.142 Å) was also observed between the amine group of one molecule and the nitrile group of another. Finally, the torsion angle of the aryl group at the 4-position among the carbons C(1), C(6), C(10), and C(25) was 84.81°.

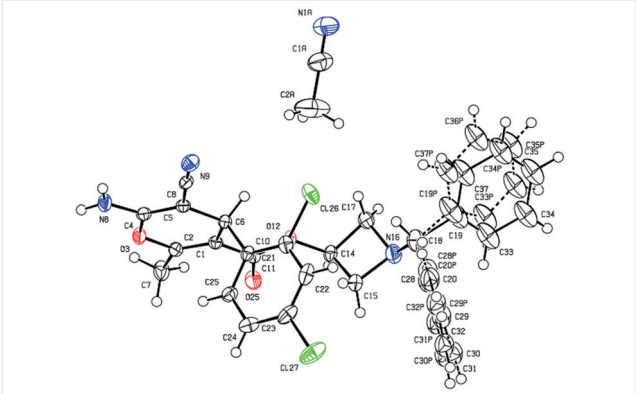

Figure 2 Structure of **13g** with thermal ellipsoids at the 30% probability level (CCDC 1514593).

To our knowledge, these 4*H*-pyran hybrids **12a–l** and **13a–j** have not been reported; for our research, the chain on ester group is important for biological studies. In fact, the in vivo studies on 4*H*-pyran derivatives with an ethyl ester moiety showed that vasorelaxant activity is decreased or even lost, probably when the chain in the ester group is too short.[23] We envisioned that if the size in the ester chain were lengthened the stability could be increased. All these findings will soon be reported.

In conclusion, a novel series of 4*H*-pyran-lipoic **12a–l** and 4*H*-pyran-azetidine **13a–j** hybrid compounds were synthesized using a MCR strategy under mild conditions, and good yields were observed for products with potential biological activity. With respect to the scope of the reaction, the methodology has enormous potential in synthesis and could be extended to obtain other types of hybrid molecules.

All chemicals, reagents, and solvents were of commercially high purity grade purchased from Sigma–Aldrich. Melting points were obtained in open glass capillaries with an Electrothemal digital 90100 melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel $60F_{254}$ plates and visualized using UV light and iodine vapor as visualizing reagent. Column chromatography was performed with silica gel (230–400 mesh) Machery–Nagel Co. using hexane/EtOAc. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) as internal standard with Bruker UltraShield (500 MHz) and Bruker Ascend (400 MHz) instruments. Chemical shift values are given in ppm (δ) relative to TMS as internal reference and coupling constants (*J*) in hertz. The splitting pattern abbreviations are assigned as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) or bs (broad singlet). High-resolution mass spectra were recorded with a spectrometer Bruker ESI-QTOFMS maXis impact and the samples were analyzed in combination with methyl stearate as an internal standard.

1,3-Dicarbonyl Compounds 10, 11; General Procedure

To a solution of compound **8**/**9** (1 mmol) in toluene (15 mL) was added ethyl acetoacetate (1.1 mmol) and iodine (0.3 mmol), and the reaction mixture was heated at reflux using a Dean–Stark apparatus for 12 h until the reaction was complete (progress monitored by TLC). The resulting mixture was extracted with dichloromethane. The organic layer was washed with a saturated solution of sodium thiosulfate, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 8:2) to afford **10**/**11**.

5-(1,2-Dithiolan-3-yl)pentyl 3-oxobutanoate (10)

Yield: 80%; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.14 (t, *J* = 6.7 Hz, 2 H), 3.60–3.54 (m, 1 H), 3.45 (s, 2 H), 3.24–3.05 (m, 2 H), 2.50–2.44 (m, 1 H), 2.27 (s, 3 H), 1.96–1.88 (m, 1 H), 1.76–1.59 (m, 4 H), 1.55–1.33 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.7, 167.3, 65.5, 56.7, 50.3, 40.5, 38.7, 35.0, 30.4, 29.1, 28.5, 25.9.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{12}H_{21}O_3S_2]^+$: 277.0927; found: 277.0934.

1-Benzhydrylazetidin-3-yl 3-oxobutanoate (11)

Yield: 75%; yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (m, 4 H), 7.38 (m, 4 H), 7.17 (m, 2 H), 5.13 (q, *J* = 10.0 Hz, 1 H), 4.37 (s, 1 H), 3.60 (d, *J* = 15.0 Hz, 2 H), 3.45 (s, 2 H), 3.04 (d, *J* = 15.0 Hz, 2 H), 2.26 (s,3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.3, 166.6, 141.3, 128.6, 127.2, 78.3, 64.9, 60.0, 49.9, 30.3.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{20}H_{22}NO_3]^+$: 324.1594; found: 324.1595.

4*H*-Pyran-lipoic Hybrids (12a–l); General Procedure

The appropriate aldehyde (1.0 mmol), malononitrile (1.0 mmol), β-ketoester compound (**10**; 1.0 mmol) and ammonium hydroxide (0.1 mmol) in acetonitrile (5.0 mmol) was stirred for 2 h. Upon completion of the reaction (monitored by TLC), a solid product was formed. The formed product was filtered and washed well with warm hexane to afford the pure products in excellent yields (80–91%).

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate (12a)

Yield: 90%; white solid; mp 135–136 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.28 (m, 2 H), 7.23–7.28 (m, 3 H), 4.48 (s, 2 H), 4.43 (s, 1 H), 4.04–3.98 (m, 1 H), 3.96–3.90 (m, 1 H), 3.55–3.48 (m, 1 H), 3.21–3.09 (m, 2 H), 2.48–2.39 (m, 1 H), 2.38 (s, 3 H), 1.92–1.87 (m, 1 H), 1.63–1.54 (m, 2 H), 1.49–1.41 (m, 2 H), 1.39–1.25 (m, 2 H), 1.17–1.06 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 157.4, 157.2, 143.8, 128.7, 127.3, 127.2, 118.9, 107.7, 64.5, 62.5, 56.5, 40.3, 38.7, 38.5, 34.7, 28.9, 28.3, 25.6, 18.5.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{22}H_{27}N_2O_3S_2Na]^+$: 453.1277; found: 453.1277.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4*H*-pyran-3-carboxylate (12b)

Yield: 87%; yellow solid; mp 131–132 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (t, *J* = 29.8 Hz, 2 H), 7.38 (d, *J* = 8.1 Hz, 2 H), 4.57 (m, 3 H), 4.15–3.86 (m, 2 H), 3.54 (m, 1 H), 3.18–3.11 (m, 2 H), 2.44 (s, 4 H), 1.89 (s, 1 H), 1.58 (s, 2 H), 1.52–1.42 (m, 2 H), 1.43–1.24 (m, 2 H), 1.12 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3, 158.3, 157.6, 151.1, 147.1, 128.3, 124.1, 118.2, 106.7, 64.9, 61.1, 56.4, 40.3, 38.8, 38.5, 34.7, 28.8, 28.3, 25.7, 18.7.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{22}H_{26}N_3O_5S_2Na]^+$: 498.1128; found: 498.1136.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4*H*-pyran-3-carboxylate (12c)

Yield: 88%; yellow solid; mp 95–96 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 7.9 Hz, 1 H), 8.05 (s, 1 H), 7.58 (d, *J* = 7.2 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 1 H), 4.58 (s, 3 H), 4.00 (m, 2 H), 3.52 (s, 1 H), 3.22–3.03 (m, 2 H), 2.45 (s, 3 H), 1.90 (dd, *J* = 12.2, 6.2 Hz, 1 H), 1.58 (d, *J* = 9.6 Hz, 3 H), 1.48 (d, *J* = 6.4 Hz, 2 H), 1.45–1.23 (m, 3 H), 1.23–1.06 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.3, 157.2, 156.6, 147.6, 145.1, 132.9, 128.6, 121.4, 117.2, 105.8, 63.9, 60.4, 55.5, 39.3, 37.8, 37.5, 33.7, 27.8, 27.3, 24.7, 17.7.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{22}H_{26}N_3O_5S_2Na]^+$: 498.1128; found: 498.1133.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-5-cyano-2-methyl-4-(2-nitrophenyl)-4*H*-pyran-3-carboxylate (12d)

Yield: 85%; yellow solid; mp 101–102 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.1 Hz, 1 H), 8.05 (d, *J* = 1.6 Hz, 1 H), 7.58 (d, *J* = 7.5 Hz, 1 H), 7.51 (t, *J* = 7.9 Hz, 1 H), 4.69 (s, 2 H), 4.57 (s, 1 H), 4.05–3.94 (m, 2 H), 3.56–3.49 (m, 1 H), 3.24–3.08 (m, 2 H), 2.51–2.40 (m, 4 H), 1.90 (ddq, *J* = 14.0, 6.9, 1.6 Hz, 1 H), 1.64–1.53 (m, 2 H), 1.53–1.44 (m, 2 H), 1.42–1.27 (m, 2 H), 1.23–1.08 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3, 158.2, 157.8, 148.6, 146.2, 133.9, 129.6, 122.4, 118.3, 106.8, 64.9, 61.1, 56.5, 40.3, 38.8, 38.5, 34.7, 30.9, 28.8, 28.3, 25.7, 18.7.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{22}H_{26}N_3O_5S_2Na]^+$: 498.1128; found: 498.1140.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (12e)

Yield: 83%; white solid; mp 137–138 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.4 Hz, 1 H), 7.13 (d, *J* = 8.4 Hz, 1 H), 4.53 (s, 2 H), 4.41 (s, 1 H), 4.12–3.89 (m, 2 H), 3.53 (m, 1 H), 3.25–3.06 (m, 2 H), 2.46 (m, 1 H), 2.39 (s, 3 H), 1.91 (d, *J* = 12.8 Hz, 1 H), 1.72–1.54 (m, 2 H), 1.54–1.40 (m, 2 H), 1.40–1.25 (m, 2 H), 1.10 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 157.6, 157.5, 142.6, 133.1, 129.0, 128.9, 118.7, 107.5, 64.8, 62.2, 56.7, 40.4, 38.4, 34.9, 29.0, 28.5, 25.8, 18.5.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{22}H_{26}ClN_2O_3S_2Na]^+$: 487.0887; found: 487.0905.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-5-cyano-4-(4-bromophenyl)-2-methyl-4*H*-pyran-3-carboxylate (12f)

Yield: 81%; yellow solid; mp 114–115 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.9 Hz, 2 H), 7.09 (d, *J* = 7.9 Hz, 2 H), 4.83 (s, 2 H), 4.40 (s, 1 H), 4.09–3.90 (m, 2 H), 3.54 (d, *J* = 6.4 Hz, 1 H), 3.25–3.08 (m, 2 H), 2.54–2.36 (m, 6 H), 1.60 (s, 2 H), 1.54–1.43 (m, 2 H), 1.42–1.23 (m, 2 H), 1.19–1.03 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 157.9, 143.1, 131.7, 129.1, 120.9, 118.7, 107.1, 64.6, 61.4, 56.5, 40.2, 38.4, 34.7, 28.9, 28.3, 25.6, 18.5.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{22}H_{26}BrN_2O_3S_2Na]^+$: 531.0382; found: 531.0405.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-5-cyano-4-(2,4-dichlorophenyl)-2-methyl-4*H*-pyran-3-carboxylate (12g)

Yield: 86%; yellow solid; mp 123–124 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (s, 1 H), 7.21 (d, *J* = 7.8 Hz, 1 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 5.01 (s, 1 H), 4.55 (s, 2 H), 4.09–3.84 (m, 2 H), 3.53 (d, *J* = 6.4 Hz, 1 H), 3.25–3.08 (m, 2 H), 2.42 (s, 3 H), 1.91 (s, 2 H), 1.59 (d, *J* = 5.6 Hz, 2 H), 1.51–1.23 (m, 4 H), 1.10–1.06 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4, 158.6, 157.6, 140.1, 133.7, 133.3, 130.5, 129.6, 127.8, 118.3, 106.4, 64.8, 60.8, 56.5, 40.3, 38.5, 35.0, 34.8, 28.9, 28.3, 25.7, 18.5.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{22}H_{26}Cl_2N_2O_3S_2Na]^+$: 521.0498; found: 521.0526.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-5-cyano-2-methyl-4-(pyridin-4-yl)-4*H*-pyran-3-carboxylate (12h)

Yield: 85%; red solid; mp 144–145 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 5.8 Hz, 2 H), 7.15 (d, *J* = 5.8 Hz, 2 H), 4.75 (s, 2 H), 4.43 (s, 1 H), 4.05–3.89 (m, 2 H), 3.53–3.51 (m, 1 H), 3.25–3.05 (m, 2 H), 2.52–2.35 (m, 4 H), 1.96–1.86 (m, 1 H), 1.70–1.55 (m, 2 H), 1.52–1.43 (m, 2 H), 1.38–1.22 (m, 2 H), 1.19–1.04 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4, 158.6, 158.6, 157.9, 152.6, 150.1, 122.4, 118.4, 106.3, 64.8, 60.6, 56.5, 40.3, 38.5, 38.3, 34.7, 30.9, 28.8, 28.2, 25.6, 18.6.

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $[C_{21}H_{26}N_3O_3S_2]^+$: 432.1410; found: 432.1435.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-5-cyano-2-methyl-4-(thiophen-2-yl)-4*H*-pyran-3-carboxylate (12i)

Yield: 83%; yellow solid; mp 124–125 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 4.9 Hz, 1 H), 6.97–6.83 (m, 2 H), 4.79 (s, 1 H), 4.60 (s, 2 H), 4.13–4.04 (m, 2 H), 3.56–3.52 (m, 1 H), 3.20–3.11 (m, 2 H), 2.48–2.44 (m, 1 H), 2.35 (s, 3 H), 1.92–1.88 (m, 2 H), 1.71–1.52 (m, 4 H), 1.44–1.36 (m, 2 H), 1.31–1.16 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 158.1, 157.4, 148.4, 127.1, 124.6, 124.5, 118.8, 108.2, 64.9, 62.3, 56.6, 40.4, 38.6, 34.9, 33.9, 29.0, 28.5, 25.8, 18.6.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{20}H_{25}N_2O_3S_3Na]^+$: 459.0841; found: 459.0861.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-5-cyano-4-(4-fluorophenyl)-2-methyl-4*H*-pyran-3-carboxylate (12j)

Yield: 85%; white solid; mp 116–117 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.09 (m, 2 H), 6.99 (t, *J* = 8.6 Hz, 2 H), 4.48 (s, 2 H), 4.43 (s, 1 H), 4.06–3.99 (m, 1 H), 3.99–3.91 (m, 1 H), 3.52 (m, 1 H), 3.15 (m, 2 H), 2.46 (m, 1 H), 2.39 (s, 3 H), 1.93–187 (m, 1 H), 1.66–1.54 (m, 2 H), 1.52–1.43 (m, 2 H), 1.43–1.27 (m, 2 H), 1.18–1.08 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 163.1, 161.1, 157.4 (d, *J* = 24.9 Hz), 139.9, 129.0 (d, *J* = 8.1 Hz), 118.8, 115.5 (d, *J* = 21.5 Hz), 107.8, 64.8, 62.5, 56.6, 40.4, 38.6, 38.3, 34.9, 29.0, 28.5, 25.8, 18.6.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{22}H_{26}FN_2O_3S_2Na]^+$: 471.1183; found: 471.1198.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-4-(3-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (12k)

Yield: 86%; yellow solid; mp 137–138 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.19 (m, 2 H), 7.15 (s, 1 H), 7.12–7.08 (m, 1 H), 4.58 (s, 2 H), 4.41 (s, 1 H), 4.09–4.01 (m, 1 H), 3.98–3.91 (m, 1 H), 3.56–3.48 (m, 1 H), 3.23–3.08 (m, 2 H), 2.47–2.44 (m, 1 H), 2.40 (s, 3 H), 1.92–1.90 (m, 1 H), 1.64–1.55 (m, 2 H), 1.48–1.46 (m, 2 H), 1.41–1.27 (m, 2 H), 1.19–1.07 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 157.8, 157.7, 146.1, 134.6, 130.1, 127.7, 127.6, 125.9, 118.7, 107.3, 64.8, 62.0, 56.6, 40.4, 38.8, 38.6, 34.8, 29.0, 28.4, 25.8, 18.7.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{22}H_{26}ClN_2O_3S_2Na]^+$: 487.0887; found: 487.0905.

5-(1,2-Dithiolan-3-yl)pentyl 6-Amino-5-cyano-4-(furan-2-yl)-2-methyl-4*H*-pyran-3-carboxylate (12l)

Yield: 91%; orange solid; mp 126–127 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (s, 1 H), 6.28 (dd, *J* = 3.0, 1.8 Hz, 1 H), 6.08 (d, *J* = 2.9 Hz, 1 H), 4.61 (s, 3 H), 4.16–4.09 (m, 1 H), 4.08–4.00 (m, 1 H), 3.59–3.51 (m, 1 H), 3.23–3.08 (m, 2 H), 2.49–2.44 (m, 1 H), 2.36 (s, 3 H), 1.94–1.87 (m, 1 H), 1.71–1.61 (m, 2 H), 1.61–1.53 (m, 2 H), 1.46–1.37 (m, 2 H), 1.33–1.21 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 158.6, 158.1, 155.4, 141.9, 118.7, 110.4, 105.8, 105.6, 64.7, 59.3, 56.5, 40.2, 38.5, 34.8, 32.4, 28.9, 28.4, 25.7, 18.5.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $[C_{20}H_{24}N_2O_4S_2Na]^+$: 443.1070; found: 443.1089.

4*H*-Pyran-azetidine Hybrids (13a–j); General Procedure

A mixture of the appropriate aldehyde (1.0 mmol), malononitrile (1.0 mmol), β-ketoester compound (**11**; 1.0 mmol) and ammonium hydroxide (0.1 mmol) in acetonitrile (5.0 mmol) was stirred for 1 h. Upon completion of the reaction (monitored by TLC), the solid prod-

uct was formed. The formed product was filtered and washed well with warm hexane to afford the pure product in excellent yields (79–92%).

1-Benzhydrylazetidin-3-yl 6-Amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate (13a)

Yield: 85%; yellow solid; mp 81–83 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.15 (m, 15 H), 4.92 (q, *J* = 6.0 Hz, 1 H), 4.48 (s, 2 H), 4.45 (s, 1 H), 4.14 (s, 1 H), 3.51 (t, *J* = 7.5 Hz, 1 H), 3.41 (t, *J* = 7.5 Hz, 1 H), 2.88–2.85 (m, 1 H), 2.48–2.46 (m, 1 H), 2.35 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3, 157.8, 157.3, 144.0, 141.9, 141.8, 130.1, 128.9, 128.6, 128.5, 127.8, 127.5, 118.8, 107.3, 78.3, 64.1, 62.7, 60.1, 59.6, 39.0, 18.5.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{30}H_{28}N_3O_3]^+$: 478.2125; found: 478.2127.

1-Benzhydrylazetidin-3-yl 6-Amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4*H*-pyran-3-carboxylate (13b)

Yield: 90%; yellow solid; mp 170–173 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.5 Hz, 2 H), 7.41 (d, *J* = 8.5 Hz, 2 H), 7.33–7.16 (m, 10 H), 4.93 (q, *J* = 5.5 Hz, 1 H), 4.64 (s, 2 H), 4.60 (s, 1 H), 4.14 (s, 1 H), 3.51 (t, *J* = 7.5 Hz, 1 H), 3.41 (t, *J* = 7.5 Hz, 1 H), 2.88–2.85 (m, 1 H), 2.53–2.51 (m, 1 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 158.9, 157.6, 151.1, 147.2, 141.6, 141.5, 128.6, 127.4, 127.3, 127.3, 127.2, 124.1, 118.2, 106.1, 78.3, 64.5, 60.8, 59.9, 59.6, 38.8, 18.6.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{30}H_{27}N_4O_5]^+$: 523.1976; found: 523.1974.

1-Benzhydrylazetidin-3-yl 6-Amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4*H*-pyran-3-carboxylate (13c)

Yield: 92%; yellow solid; mp 88–89 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.0 Hz, 1 H), 8.10 (s, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.35–7.14 (m, 10 H), 4.96 (q, *J* = 6.0 Hz, 1 H), 4.78 (s, 2 H), 4.57 (s, 1 H), 4.17 (s, 1 H), 3.51 (t, *J* = 7.5 Hz, 1 H), 3.42 (t, *J* = 7.5 Hz, 1 H), 2.91–2.89 (m, 1 H), 2.55–2.53 (m, 1 H), 2.37 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.7, 158.8, 157.9, 148.6, 146.3, 141.7, 141.6, 134.1, 129.8, 128.6, 127.4, 127.4, 122.7, 122.6, 118.4, 106.4, 78.3, 64.3, 60.7, 60.1, 59.7, 38.9, 18.7.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{30}H_{27}N_4O_5]^+$: 523.1976; found: 523.1975.

1-Benzhydrylazetidin-3-yl 6-Amino-5-cyano-2-methyl-4-(2-nitrophenyl)-4*H*-pyran-3-carboxylate (13d)

Yield: 87%; yellow solid; mp 90–91 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.0 Hz, 1 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.40–7.15 (m, 12 H), 5.29 (s, 1 H), 4.90 (q, *J* = 6.0 Hz, 1 H), 4.67 (s, 2 H), 4.25 (s, 1 H), 3.44 (t, *J* = 7.5 Hz, 1 H), 3.35 (t, *J* = 7.5 Hz, 1 H), 2.82 (t, *J* = 7.5 Hz, 1 H), 2.37–2.33 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.4, 158.9, 157.9, 149.0, 141.7, 139.1, 133.5, 130.6, 128.5, 128.4, 128.1, 127.5, 127.4, 127.2, 127.2, 124.4, 118.0, 106.6, 77.9, 63.9, 61.1, 59.8, 59.3, 33.1, 18.4.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{30}H_{27}N_4O_5]^+$: 523.1976; found: 523.1977.

1-Benzhydrylazetidin-3-yl 6-Amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (13e)

Yield: 89%; white solid; mp 87–89 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 14 H), 4.91 (q, *J* = 6.0 Hz, 1 H), 4.53 (s, 2 H), 4.44 (s, 1 H), 4.11 (s, 1 H), 3.51 (t, *J* = 7.5 Hz, 1 H), 3.43 (t, *J* = 7.5 Hz, 1 H), 2.85–2.82 (m, 1 H), 2.46–2.43 (m, 1 H), 2.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.0, 142.7, 141.8, 141.8, 133.3, 129.2, 129.1, 128.7, 128.6, 127.5, 127.4, 127.4, 118.6, 106.9, 78.4, 64.3, 62.0, 60.2, 59.6, 38.5, 18.5.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{30}H_{27}ClN_3O_3]^+$: 512.1735; found: 512.1730.

1-Benzhydrylazetidin-3-yl 6-Amino-4-(4-bromophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (13f)

Yield: 86%; white solid; mp 97–98 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.4 Hz, 2 H), 7.37–7.15 (m, 10 H), 7.11 (d, *J* = 8.4 Hz, 2 H), 4.92 (q, *J* = 6.0 Hz, 1 H), 4.54 (s, 2 H), 4.42 (s, 1 H), 4.11 (s, 1 H), 3.51 (t, *J* = 7.5 Hz, 1 H), 3.43 (t, *J* = 7.5 Hz, 1 H), 2.84–2.82 (m, 1 H), 2.46–2.43 (m, 1 H), 2.35 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.0, 158.3, 157.3, 143.2, 141.8, 141.7, 132.0, 129.5, 128.7, 128.6, 127.5, 127.4, 127.4, 121.4, 118.6, 106.7, 78.4, 64.3, 61.9, 60.2, 59.5, 38.5, 18.5.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{30}H_{27}BrN_3O_3]^+$: 556.1230; found: 556.1237.

1-Benzhydrylazetidin-3-yl 6-Amino-5-cyano-4-(2,4-dichlorophenyl)-2-methyl-4*H*-pyran-3-carboxylate (13g)

Yield: 79%; white solid; mp 114–115 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 2.0 Hz, 1 H), 7.37–7.10 (m, 13 H), 5.05 (s, 1 H), 4.98–4.87 (m, 1 H), 4.51 (d, *J* = 4.2 Hz, 2 H), 4.12 (s, 1 H), 3.51 (t, *J* = 7.5 Hz, 1 H), 3.42–3.36 (m, 1 H), 2.93 (dd, *J* = 8.5, 5.5 Hz, 1 H), 2.38 (s, 3 H), 2.31 (dd, *J* = 8.6, 5.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.7, 159.1, 157.6, 157.5, 141.9, 141.8, 140.3, 134.0, 133.7, 130.8, 129.7, 128.7, 128.6, 128.0, 127.5, 127.4, 127.3, 118.2, 106.0, 78.6, 64.2, 60.8, 60.3, 59.3, 35.1, 18.4.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{30}H_{26}Cl_2N_3O_3]^+$: 546.1346; found: 546.1248.

1-Benzhydrylazetidin-3-yl 6-Amino-5-cyano-2-methyl-4-(pyridin-4-yl)-4*H*-pyran-3-carboxylate (13h)g

Yield: 92%; yellow solid; mp 97–99 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 8.0 Hz, 2 H), 7.35–7.16 (m, 14 H), 4.93 (q, *J* = 6.0 Hz, 1 H), 4.84 (s, 2 H), 4.44 (s, 1 H), 4.15 (s, 1 H), 3.51 (t, *J* = 7.5 Hz, 1 H), 3.43 (t, *J* = 7.5 Hz, 1 H), 2.85–2.83 (m, 1 H), 2.57–2.53 (m, 1 H), 2.38 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.7, 159.2, 157.9, 152.7, 150.3, 147.7, 147.6, 128.7, 128.6, 127.4, 127.4, 122.7, 118.4, 105.8, 78.3, 64.5, 60.5, 60.0, 59.7, 38.5, 18.7.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{30}H_{28}N_3O_3]^+$: 479.2078; found: 479.2077.

1-Benzhydrylazetidin-3-yl 6-Amino-5-cyano-2-methyl-4-(thiophen-2-yl)-4*H*-pyran-3-carboxylate (13i)

Yield: 80%; orange solid; mp 65–67 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.16 (m, 11 H), 6.97–6.95 (m, 2 H), 5.04 (q, *J* = 6.0 Hz, 1 H), 4.82 (s, 1 H), 4.57 (s, 2 H), 4.27 (s, 1 H), 3.56 (t, *J* = 7.5 Hz, 1 H), 3.51 (t, *J* = 7.5 Hz, 1 H), 3.00–2.97 (m, 1 H), 2.78–2.75 (m, 1 H), 2.33 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.1, 157.9, 148.3, 141.9, 128.6, 127.5, 127.4, 127.1, 124.8, 124.7, 118.7, 107.6, 78.3, 64.4, 60.1, 59.8, 33.8, 18.6.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{28}H_{26}N_3O_3S]^+$: 489.1689; found: 489.1690.

1-Benzhydrylazetidin-3-yl 6-Amino-5-cyano-4-(4-methoxyphenyl)-2-methyl-4*H*-pyran-3-carboxylate (13j)

Yield: 86%; yellow solid; mp 95–96 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 10 H), 7.15 (d, *J* = 8.5 Hz, 2 H), 6.90 (d, *J* = 8.5 Hz, 2 H), 4.93 (q, *J* = 5.5 Hz, 1 H), 4.46 (s, 2 H), 4.41 (s, 1 H), 4.15 (s, 1 H), 3.81 (s, 3 H), 3.52 (t, *J* = 7.3 Hz, 1 H), 3.42 (t, *J* = 7.3 Hz, 1 H), 2.88–2.86 (m, 1 H), 2.48–2.46 (m, 1 H), 2.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 158.9, 157.4, 157.1, 141.9, 136.3, 128.9, 128.6, 127.5, 127.4, 127.4, 127.3, 119.0, 114.2, 107.5, 78.3, 64.1, 62.7, 60.1, 59.6, 55.4, 38.1, 18.4.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $[C_{31}H_{30}N_3O_4]^+$: 508.2231; found: 508.2232.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591730.

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