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Application of vinylogous carbamates and vinylogous aminonitriles to the regiospecific synthesis of uniquely functionalized pyrroles and quinolones

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ABSTRACT

Pyrroles and quinolones represent core structures, which are routinely found in both natural and synthetic bioactive substances. Consequently, the development of efficient and regiospecific methods for the preparation of such heterocycles with unique functionality is of some importance. We describe herein the regiospecific synthesis of 1,2,3,4-tetrasubstituted pyrroles containing polar substituents and such products are prepared from vinylogous carbamates and vinylogous aminonitriles. We also describe the regiospecific synthesis of 3-aryl containing 1,3,6-trisubstituted quinolones from vinylogous carbamates. The use of an amine exchange reaction to prepare precursors for the pyrrole and quinolone forming cyclizations represents a key factor in the strategy.

1. Introduction

New and efficient methods for the preparation of pyrrole [1] and quinolone [2] scaffolds continue to be of significant interest to the organic chemical community. The need to have ready access to such materials is the result of their pharmacological properties. A few notable examples are given in Fig. 1.

Lamellarin D trimethyl ether [3] (1, Fig. 1) represents a potent anti-proliferative agent that targets topoisomerase 1 and lamellarin O [4] (2, Fig. 1) functions as an inhibitor of P-glycoprotein efflux pumps. Ciprofloxacin [5] (3, Fig. 1) is one of the more important quinolone anti-infective drugs on the commercial market while Endochin [6] (4, Fig. 1) exhibits significant anti-malarial properties. All of the substances shown in Fig. 1 contain hydrogen bond donor and hydrogen bond acceptor sites, which facilitate binding to appropriate proteins and plays an import role in contributing to desirable solubility properties [7]. Such pharmaceutical attributes require the ability to synthesize compounds with polar functional groups and hydroxy, acetoxy, amine and amide groups have historically served this function extremely well. We have recently reported [8] on the amine exchange reaction of vinylogous amides with glycinate esters, which produced intermediates that were used for the regiospecific preparation of 1,2,3,4-tetrasubstitutedpyrroles.

We now describe the use of the amine exchange process to generate similar precursors to 1,2,3,4-tetrasubstituted pyrroles, which contain the aforementioned polar groups. We also report the use of the amine exchange process to prepare 3-aryl containing 1,3,6-trisubstituted quinolones, which have recently been described as novel azaisoflavones [9], function as phytoestrogen mimetics and are inhibitors [10] of NO production in microglia.

2. Results and discussions

N,N-Dimethylformamide dimethylacetal (DMFA) is a very useful reagent [11] for the introduction of the vinylogous amide group and for methylation of carboxylic acids. We anticipated that reacting DMFA with a series of 2-arylacetic acids would generate the corresponding 2-arylvinylogous carbamates. Such substances could then serve as building blocks for novel pyrrole synthesis and

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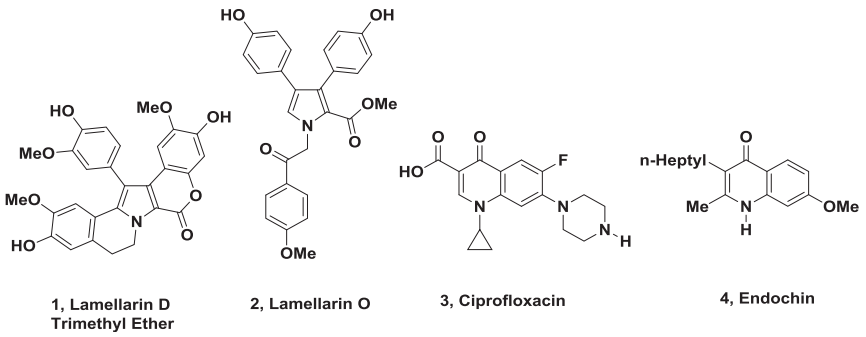


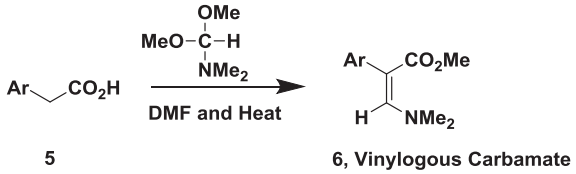
Fig. 1. Biologically active pyrroles and Quinolines.

complement our recently reported [8] vinylogous amide studies. These results are presented in Scheme 1 and Table 1. The requisite 2-arylsubstituted vinylogous carbamates were produced in very good yield (91–99%) with little if any purification required.

With a variety of vinylogous carbamates in hand, we attempted to use our recently reported [8] acetic acid mediated condensation conditions that were previously applied to a series of vinylogous amides Reaction with sarcosine ethyl ester hydrochloride under such conditions did not produce the expected pyrrole but did produce a vinyl acetate (7, Scheme 2). Upon slight modification of the reaction conditions (Scheme 2) we were able to generate the vinyl acetate cleanly and in good yield.

We subsequently decided to employ a different approach, which involved doing an amine exchange reaction with sarcosine hydrochloride and the vinylogous carbamates under milder conditions as presented in Scheme 3, Table 2.

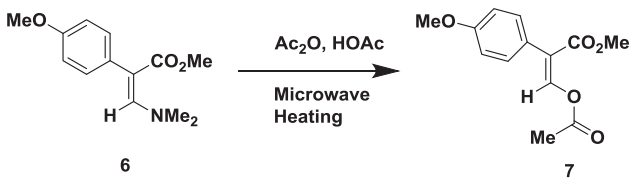
The reactions as reported in Scheme 3 and Table 2 gave excellent yields and the crude products were quite pure requiring minimal purification by flash chromatography. We have had some success in the past with base-mediated cyclization conditions [12] as applied to pyrrole synthesis. Consequently, we next attempted the use of sodium ethoxide in THF at room temperature for the cyclization of the amine exchanged vinylogous carbamates (8, Scheme 3) and the results are reported in Scheme 4 and Table 3. Prior to work up of the reaction mixtures listed in Table 3, all of the reactions were quenched with acetic anhydride allowing for acylation of the anionic product formed during the course of the reaction. Consequently the pyrrole forming cyclization with an acylation work up produced an acetoxy group at the 3-position of the pyrrole [13]. The 3-acetoxypyrroles produced in this manner were quite stable and exhibited no degradation of their purity over time. The acetoxy group was chosen, since it has the ability to provide unique functionality, greater molecular polarity and prodrug characteristics [7], which make it very useful in an SAR guided drug discovery process. Most of the reaction yields (Table 3) were in a reasonable range (52–99%) and no extensive optimization studies were subsequently conducted. In addition, NOESY NMR analysis was carried out on compound **9a** in Table 3 in order to verify the regiochemical nature of the various substituents and the results were consistent with the assigned structure.



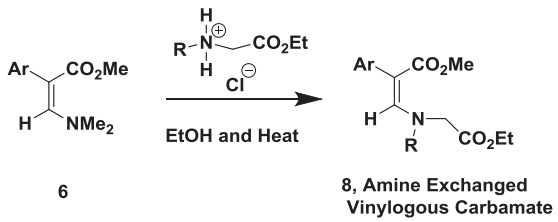
Scheme 1. Preparation of 2-Arylvinylogous Carbamates.

Table 1
Preparation of 2-arylvinylogous carbamates, 6a-g.

Compound Number	Ar	% Yield
6a	4-MeOPh	91
6b	4-MePh	91
6c	4-ClPh	98
6d	4-BrPh	97
6e	3,4-$(OMe)_2$Ph	99
6f	3,4,5-$(OMe)_3$Ph	97
6g	Ph	92



Scheme 2. Preparation of Vinyl Acetate.



Scheme 3. Preparation of Amine Exchanged Vinylogous Carbamates.

Table 2
Preparation of amine exchanged vinylogous carbamates, 8a-h.

Compound Number	Ar	R	% Yield
8a	4-MeOPh	Me	91
8b	4-MePh	Me	92
8c	4-ClPh	Me	99
8d	4-BrPh	Me	95
8e	3,4-$(OMe)_2$Ph	Me	99
8f	3,4,5-$(OMe)_3$Ph	Me	94
8g	Ph	Me	91
8h	4-MeOPh	Bz	88

We next turned our attention to developing a method for the incorporation of an amino/amide group at the 3-position of the pyrrole [14]. It was anticipated that such a functional group would provide additional enhancement to the desirable properties previously described for the acetoxy substituent of pyrrole **9**.

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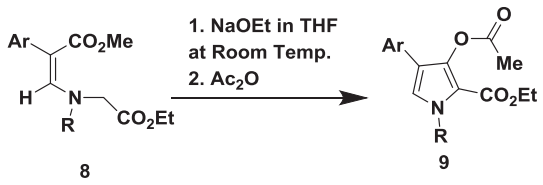


Scheme 4. Base Mediated Cyclization of Amine Exchanged Vinylogous Carbamates.

Table 3
Preparation of 1,2,3,4-tetrasubstituted pyrroles with polar 3-acetoxy functionality, 9a-h.

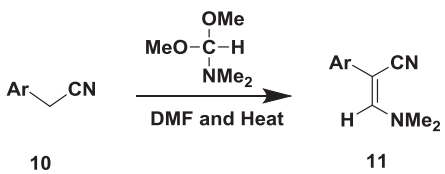
Compound Number	Ar	R	% Yield
9a	4-MeOPh	Me	69
9b	4-MePh	Me	58
9c	4-ClPh	Me	59
9d	4-BrPh	Me	99
9e	3,4-$(OMe)_2$Ph	Me	65
9f	3,4,5-$(OMe)_3$Ph	Me	52
9g	Ph	Me	86
9h	4-MeOPh	Bz	25

We selected aryl substituted acetonitriles (10, Scheme 5) as our starting materials given the ability of the cyano group to be transformed into an amine or amide functionality. Reaction of these aryl substituted acetonitriles (10, Scheme 5) with DMF acetal gave excellent yields of the corresponding vinylogous aminonitriles as presented in Scheme 5 and Table 4.

Since the amine exchange process (Scheme 3) had worked well for the synthesis of the 3-acetoxypyrroles, we planned to extrapolate the strategy to the vinylogous aminonitriles as depicted in Scheme 6 and Table 5. We had previously used ethanol as the preferred solvent for such reactions but for the vinylogous aminonitriles this proved unsuccessful. However, utilization of acetic acid as the solvent gave very good yields and purity (Table 5) of the desired amine exchanged products (Scheme 6 and Table 5) and these substances also exhibited good shelf life stability. It is also noteworthy that we did not observe any acetoxy derivatives under these reaction conditions as was the case for the vinylogous carbamates (Scheme 2) when treated with acetic acid.

Cyclization studies were then carried out on the amine exchanged vinylogous aminonitriles (Scheme 7, Table 6) and sodium hydride was found to be a superior base as compared to sodium ethoxide (Scheme 4). The yields for the cyclization reactions depicted in Scheme 7 and Table 6 were quite reasonable (60–99%). For examples **13j** and **13k** the crude reaction products were quenched with acetic anhydride and methane sulfonic anhydride, respectively to give amides (71%yield) and sulfonamides (47%yield). In an analogous manner to the 3-acetoxypyrroles (Scheme 4), compound **13d** in Table 6 was subjected to NOESY NMR analysis and the regiochemical assignment as depicted in Scheme 7 was confirmed. These 3-aminopyrroles were also quite stable and exhibited a very good shelf life.

The success of the previously described amine exchange/



Scheme 5. Preparation of Vinylogous Aminonitriles

Table 4
Preparation of vinylogous Aminonitriles.11a-g.

Compound Number	Ar	% Yield
11a	4-MeOPh	96
11b	4-MePh	95
11c	4-ClPh	84
11d	4-BrPh	100
11e	4-FPh	95
11f	Ph	99
11g	3,4-$(OMe)_2$Ph	98

cyclization sequence to prepare the 3-acetoxypyrroles (Scheme 4) and the 3-aminopyrroles (Scheme 7) suggested there may be additional applications of this strategy to other important heterocycles. Consequently, we were attracted to the synthesis of quinolones [2,9,10] in anticipation that exchange reactions between anilines and vinylogous carbamates (Scheme 8, Table 7) would be possible. Application of the glycine/carbamate exchange reaction (Scheme 3) conditions to an aniline/carbamate exchange (Scheme 8, Table 7) worked quite well (63–93% yields) and the addition of a small amount of acetic acid to the ethanol mixture significantly accelerated the reaction rate. The mild acid catalysis is presumably necessary due to the decreased nucleophilicity of the anilines.

We anticipated our approach would allow us to prepare 3-arylquinolones, which have been identified as novel azaisoflavonoids and function as phytoestrogen mimics and inhibitors of NO production in microglia. During the course of our studies we noticed that a vinylogous carbamate had been employed by Jamison [5] and coworkers to prepare the quinolone Ciprofloxacin hydrochloride (See Fig. 1) in a continuous flow process by a strategy different from ours.

With a variety of aniline exchanged vinylogous carbamates in hand we examined the use of triflic anhydride as an acidic mediator for intramolecular Friedel-Crafts acylation given our recent success [8] with this reagent. Results of these studies are presented in Scheme 9 and Table 8.

The triflic anhydride mediated cyclization of the aniline exchanged vinylogous carbamates (Scheme 9, Table 8) gave quite good yields of the 3-arylquinolones (59–94%). A base mediated workup of the crude reaction products with a mixture of aqueous bicarbonate and THF was employed to convert any triflated precursors to the desired 3-arylquinolnes. In addition, NOESY NMR analysis was carried out on one of the quinolones (16a, Table 8) and the indicated regiochemistry was confirmed.

3. Conclusions

We have described the use of an amine exchange strategy to couple amines to either vinylogous carbamates or vinylogous aminonitriles, which allows for base mediated cyclization to the respective 3-acetoxy pyrroles or 3-aminopyrroles/3-amidopyrroles. The vinylogous carbamates or vinylogous aminonitriles are easily prepared in one step from commercially available arylacetic acids or aryl substituted acetonitriles. The subsequent conversion of the vinylogous carbamates or vinylogous aminonitriles to the requisite pyrroles is accomplished in good overall yields with polar groups located at the 3-position. The indicated transformations provide the opportunity to increase both the solubility and binding properties of bioactive pyrroles by virtue of additional hydrogen bond donor and hydrogen bond acceptor groups. In addition the ability to obtain the functionalized pyrroles in three steps from commercially available starting materials should prove useful. The use of the amine exchange strategy was then applied to aniline exchanged vinylogous carbamates, which

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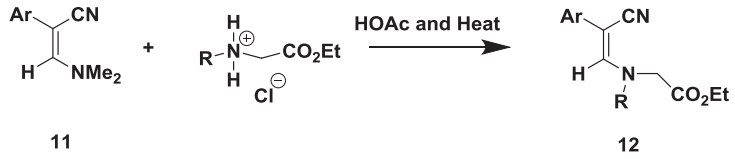
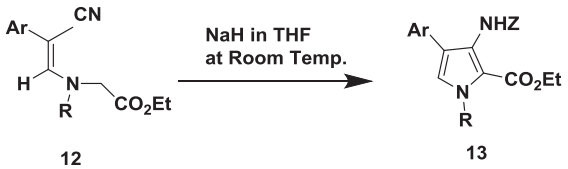


11 12

Scheme 6. Preparation of Amine Exchanged Vinylogous Aminonitriles

Table 5
Preparation of amine exchanged vinylogous aminonitriles, 12a-i.

Compound Number	Ar	R	% Yield
12a	4-MeOPh	Me	87
12b	4-MePh	Me	88
12c	4-ClPh	Me	88
12d	4-BrPh	Me	91
12e	4-FPh	Me	98
12f	Ph	Me	87
12g	3,4-$(OMe)_2$Ph	Me	92
12h	4-MeOPh	Bz	92
12i	4-MePh	Bz	58

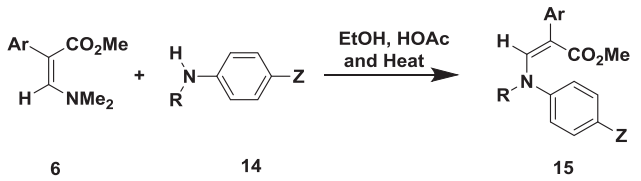


12 13

Scheme 7. Base Mediated Cyclization of Amine Exchanged Vinylogous Aminonitriles.

Table 6
Preparation of 1,2,3,4-tetrasubstituted pyrroles with polar 3-amino and 3-amido functionality, 13a-k.

Compound Number	Ar	R	Z	% Yield
13a	4-MeOPh	Me	H	99
13b	4-MePh	Me	H	74
13c	4-ClPh	Me	H	60
13d	4-BrPh	Me	H	79
13e	4-FPh	Me	H	75
13f	Ph	Me	H	83
13g	3,4-$(OMe)_2$Ph	Me	H	97
13h	4-MeOPh	Bz	H	63
13i	4-MePh	Bz	H	82
13j	4-MeOPh	Me	$COCH_3$	71
13k	4-MeOPh	Me	SO_2CH_3	47



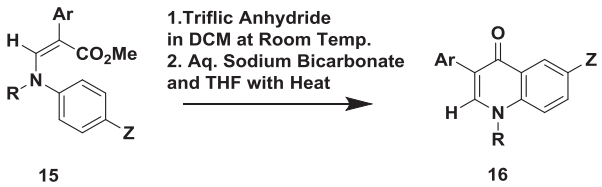
6 14 15

Scheme 8. Prearation of Aniline Exchanged Vinylogous Carbamates.

cyclized via triflic anhydride to the corresponding 3-arylquinolones. The rapid two step reaction sequence from the vinylogous carbamates provides an efficient preparation of the quinolones by the aniline exchange strategy and should bode well for use in SAR guided synthesis of novel quinolones containing a 3-aryl group.

Table 7
Preparation of aniline exchanged vinylogous carbamates, 15a-j.

Compound Number	Ar	R	Z	% Yield
15a	4-MeOPh	Me	Me	93
15b	4-MePh	Me	Me	73
15c	4-ClPh	Me	Me	81
15d	4-BrPh	Me	Me	85
15e	3,4-$(OMe)_2$Ph	Me	Me	82
15f	3,4,5-$(OMe)_3$Ph	Me	Me	63
15g	Ph	Me	Me	85
15h	4-MeOPh	Et	Me	69
15i	4-MeOPh	Me	MeO	81
15j	4-BrPh	Me	MeO	78



15 16

Scheme 9. Prearation of 3-Arylquinolones from Aniline Exchanged Vinylogous Carbamates.

Table 8
Preparation of 3-arylquinolones, 16a-j.

Compound Number	Ar	R	Z	% Yield
16a	4-MeOPh	Me	Me	83
16b	4-MePh	Me	Me	94
16c	4-ClPh	Me	Me	90
16d	4-Br-Ph	Me	Me	92
16e	3,4-$(OMe)_2$Ph	Me	Me	88
16f	3,4,5-$(OMe)_3$Ph	Me	Me	83
16g	Ph	Me	Me	92
16h	4-MeOPh	Et	Me	59
16i	4-MeOPh	Me	MeO	74
16j	4-MeOPh	Me	Br	78

4. Experimental

4.1. General

All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific). All solvents were dried over 4 Å molecular sieves prior to their use. NMR spectra were obtained on either a Bruker 300 MHz spectrometer, or a Bruker 500 MHz spectrometer in either $CDCl_3$, d_6-DMSO or d_6-acetone solutions. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer with an HATR attachment. High resolution mass spectra were obtained on a Shimadzu IT-TOF mass spectrometer at the University of Richmond. Low resolution GC-MS spectra were obtained on a Shimadzu QP 5050 instrument. Melting points and boiling points are uncorrected. Chromatographic purifications were carried out on a Biotage SP-1 instrument or a Biotage Isolera instrument (both equipped with a silica cartridge). Gradient elution

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with ethyl acetate/hexane was accomplished in both instances. The reaction products were normally eluted within the range of 4–8 column volumes of eluant with a gradient mixture of 60–80% ethyl acetate in hexane. TLC analyses were conducted on silica plates with hexane/ethyl acetate as the eluant. All purified reaction products gave TLC results, flash chromatograms, and ^{13}C NMR spectra consistent with a sample purity of >95%.

4.1.1. Z-2-(4-Methoxyphenyl)-3-dimethylaminoacrylic acid methyl ester (**6a**)

Into a 100 mL a round bottom flask equipped with magnetic stir bar and reflux condenser was added 4-methoxyphenyl acetic acid (3.0 g, 18.05 mmol), N,N-dimethylformamide dimethyl acetal (12.91 g, 108 mmol), and dimethylformamide (25 mL). The reaction mixture was heated to reflux for 4 h and the solvent was removed *in vacuo*. To the crude residue was added water (20 mL) and ethyl acetate (15 mL) and the phases were separated. The aqueous layer was extracted with additional ethyl acetate (2 × 15 mL) and the combined organic layers were washed with aqueous lithium chloride (20 mL) and dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed *in vacuo* to give an orange solid (3.85 g, 91% yield), which exhibited the following properties: mp 63–65 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.55 (s, 1H), 7.11 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 3.82 (s, 3H), 3.64 (s, 3H) and 2.69 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 158.1, 149.2, 133.0, 128.6, 112.8, 98.4, 55.1, 51.0 and 42.8; IR (neat) 1675 and 1603 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{13}H_{18}NO_3$ 236.1281 found 236.1301.

4.1.2. Z-3-Dimethylamino-2-p-tolylacrylic acid methyl ester (**6b**)

This compound was prepared by procedure **4.1.1** with the exception that *p*-tolylacetic acid was used in the reaction, in which case a 91% yield of a yellow solid was obtained, which exhibited the following properties: mp 76–77 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56 (s, 1H), 7.10 (s, 4H), 3.64 (s, 3H), 2.69 (s, 6H) and 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 149.2, 135.7, 133.4, 131.9, 128.1, 98.8, 51.0, 42.9 and 21.2; IR (neat) 1686 and 1584 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{13}H_{18}NO_2$ 220.1332 found 220.1307.

4.1.3. Z-2-(4-Chlorophenyl)-3-dimethylaminoacrylic acid methyl ester (**6c**)

This compound was prepared by procedure **4.1.1** with the exception that 4-chlorophenylacetic acid was used in the reaction, in which case a 98% yield of a pale yellow solid was obtained, which exhibited the following properties: mp 74–76 °C; ^1H NMR (acetone-d_6, 300 MHz) δ 7.57 (s, 1H), 7.29 (d, $J = 8.6$ Hz, 2H), 7.17 (d, $J = 8.6$ Hz), 3.54 (s, 3H), and 2.74 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 149.5, 135.2, 133.3, 132.0, 127.5, 97.6, 51.1, 43.1; IR (neat) 1665 and 1609 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{12}H_{15}ClNO_2$ 240.0786 found 240.0766.

4.1.4. Z-2-(4-Bromophenyl)-3-dimethylaminoacrylic acid methyl ester (**6**)

This compound was prepared by procedure **4.1.1** with the exception that 4-bromophenylacetic acid was used in the reaction, in which case a 97% yield of a yellow solid was obtained, which exhibited the following properties: mp 94–96 °C; ^1H ($CDCl_3$, 500 MHz) δ 7.57 (s, 1 H), 7.41 (d, $J = 8.4$ Hz, 2 H), 7.08 (d, $J = 8.4$ Hz, 2 H), 3.64 (s, 3 H) and 2.70 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.0, 149.5, 135.7, 133.7, 130.5, 120.2, 97.7, 51.1 and 43.2; IR (neat) 1670 and 1603 cm-1; HRMS (ES, M+H) *m/z* calcd for $C_{12}H_{15}BrNO_2$ 284.0281 found 284.0256.

4.1.5. Z-3-Dimethylamino-2-(3,4-dimethoxyphenyl)acrylic acid methyl ester (**6e**)

This compound was prepared by procedure **4.1.1** with the exception that 3,4-dimethoxyphenylaceticacid was used in the reaction, in which case a 99% yield of an orange solid was obtained, which exhibited the following properties: mp 102–105 °C; ^1H NMR ($CDCl_3$, 300 MHz) 7.52 (s, 1H), 6.79 (d, $J = 8.6$ Hz, 1H), 6.70–6.73 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.62 (s, 3H) and 2.71 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 149.2, 147.9, 147.6, 129.0, 124.4, 115.5, 110.3, 98.7, 55.8, 55.8, 51.1, 42.8; IR (neat) 1674 and 1594 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{14}H_{20}NO_4$ 266.1387 found 266.1390.

4.1.6. Z-3-Dimethylamino-2-(3,4,5-trimethoxyphenyl)acrylic acid methyl ester (**6f**)

This compound was prepared by procedure **4.1.1** with the exception that (3,4,5-trimethoxyphenyl)acetic acid was used in the reaction, in which case a 97% yield of an orange solid was obtained, which exhibited the following properties: mp 110–111 °C; ^1H NMR (acetone-d_6, 300 MHz) δ 7.48 (s, 1H), 6.45 (s, 2H), 3.80 (s, 6H), 3.74 (s, 3H), 3.54 (s, 3H) and 2.75 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 152.2, 149.1, 136.6, 131.9, 109.4, 98.8, 60.7, 56.0, 51.0 and 42.7; IR (neat) 1676 and 1593 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{15}H_{22}NO_5$ calcd for 296.1492 found 296.1484.

4.1.7. Z-3-Dimethylamino-2-phenylacrylic acid methyl ester (**6g**)

This compound was prepared by procedure **4.1.1** with the exception that phenylacetic acid was used in the reaction, in which case a 92% yield of a yellow/orange solid was obtained, which exhibited the following properties: mp 38–40 °C; ^1H NMR (CDCl3, 300 MHz) δ 7.53 (s, 1H), 7.15–7.27 (m, 5H), 3.53 (s, 3H) and 2.70 (s, 6H); ^{13}C NMR (CDCl3, 75 MHz) δ 170.4, 149.24 136.6, 132.1, 127.3, 126.2, 98.9, 51.0, 42.9; IR (neat) 1679 and 1592 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{12}H_{16}NO_2$ 206.1176 found 206.1170.

4.1.8. Z-3-Acetoxy-2-(4-methoxyphenyl) acrylic acid methyl ester (**7**)

Into a 20 mL microwave vial equipped with magnetic stir bar and crimping cap was added 2-(4-methoxy-phenyl)-3-dimethylaminoacrylic acid methyl ester (580 mg, 2.46 mmol), acetic acid (7 mL) and acetic anhydride (3 mL). The resulting mixture was heated in a Biotage Initiator Microwave system for 1 h at 100 °C. The reaction mixture was diluted with a water (25 mL)/ethyl acetate (20 mL) mixture and the phases were separated. The aqueous phase was extracted with additional ethyl acetate (2 × 20 mL) and the combined organic phases were washed with saturated, aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed *in vacuo* to give a yellow oil (572 mg, 92.7% yield). An analytical sample was prepared by flash chromatography on a Biotage Isolera system, resulting in an oil, which exhibited the following properties: bp 150 °C at 0.330 torr; ^1H NMR (CDCl, 500 MHz) δ 8.45 (s, 1H), 7.30 (d, $J = 8.8$ Hz, 2H), 6.94 (d, $J = 8.8$ Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H) and 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.3, 166.9, 159.2, 143.8, 131.1, 123.8, 117.6, 113.4, 55.2, 52.0 and 20.6; IR (neat) 1776 and 1710 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{13}H_{14}O_5Na$ 273.0733 found 273.0752.

4.1.9. 2-(4-Methoxyphenyl)-3-(ethoxycarbonylmethyl-methylamino)acrylic acid methyl ester (**8a**)

Into a 20 mL microwave vial equipped with a magnetic stir bar and crimping cap was added 2-(4-methoxyphenyl)-3-dimethylaminoacrylic acid methyl ester (1.07 g, 4.55 mmol), sarcosine ethyl ester hydrochloride (2.10 g, 13.64 mmol), and ethanol (20 mL). The resulting mixture was heated in a Biotage Initiator microwave system for 2 h at 100 °C. The solvent was removed *in*

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vacuo and the crude residue was dissolved in a mixture of water (25 mL) and ethyl acetate (15 mL) and the phases were separated. The aqueous phase was extracted with additional ethyl acetate (2 × 15 mL) and the combined organic phases were washed with brine (15 mL), and dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed *in vacuo* to give a yellow solid (1.27 g, 91% yield), which exhibited the following characteristics: bp 180 °C @ 0.58 torr; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (s, 1H), 7.13 (d, J = 8.4, 2H), 6.84 (d, J = 8.4, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 2H), 3.69 (s, 3H), 2.75 (s, 3H) and 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 169.0, 158.4, 148.5, 132.8, 127.9, 113.1, 100.8, 61.2, 56.0, 55.1, 51.3, 42.34 and 14.1; IR (neat) 1743 and 1685 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{16}H_{22}NO_5$ 308.1492 found 308.1501.

4.1.10. 3-(Ethoxycarbonylmethyl-methylamino)-2-p-tolylacrylic acid methyl ester (**8b**)

This compound was prepared by the procedure **4.1.9** with the exception that 3-dimethylamino-2-*p*-tolylacrylic acid methyl ester was used in the reaction, in which case a 92% yield of a pale yellow solid was obtained, which exhibited the following properties: mp 51–52 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (s, 1H), 7.09 (s, 4H), 4.12 (q, J = 7.15 Hz, 2H), 3.66 (s, 2H), 3.63 (s, 3H), 2.74 (s, 3H), 2.35 (s, 3H) and 1.24 (t, J = 7.15 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 169.0, 148.4, 136.2, 132.7, 131.7, 128.3, 101.1, 61.1, 55.9, 51.3, 42.4, 21.2, 14.1; IR (neat) 1745 and 1681 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{16}H_{22}NO_4$ 292.1543 found 292.1512.

4.1.11. 2-(4-Chlorophenyl)-3-(ethoxycarbonylmethyl-methylamino) acrylic acid methyl ester (**8c**)

This compound was prepared by procedure **4.1.9** with the exception that 2-(4-chlorophenyl)-3-dimethylaminoacrylic acid methyl ester was used in the reaction, in which case a 99% yield of an orange solid was obtained that exhibited the following properties: mp 70–72 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (s, 1H), 7.27 (d, J = 8.5, 2H), 7.17 (d, J = 8.5, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.70 (s, 2H), 3.65 (s, 3H), 2.74 (s, 3H) and 1.27 (t, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 168.8, 148.9, 134.4, 133.2, 132.6, 127.7, 100.1, 61.3, 53.6, 51.3, 42.4 and14.1; IR (neat) 1747 and 1681 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{15}H_{19}ClNO_4$ 312.0997 found 312.0986.

4.1.12. 2-(4-Bromophenyl)-3-(ethoxycarbonylmethyl-methylamino)acrylic acid methyl ester (**8d**)

This compound was prepared by procedure **4.1.9** with the exception that 2-(4-bromophenyl)-3-dimethylaminoacrylic acid methyl ester was used in the reaction, in which case a 95% yield of an orange solid was obtained, which exhibited the following properties: mp 83–85 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (s, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 4.15 (q, J = 7.15 Hz, 2H), 3.70 (s, 2H), 3.65 (s, 3H), 2.74 (s, 3H) and 1.27 (t, J = 7.15 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 168.8, 148.9, 134.9, 133.6, 130.7, 120.7, 100.0, 61.3, 56.4, 51.3, 42.44 and 14.08; IR (neat) 1748 and 1692 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{15}H_{19}BrNO_4$ 356.0492 found 356.0503.

4.1.13. 3-(Ethoxycarbonylmethyl-methylamino)-2-(3,4-dimethoxyphenyl)acrylic acid methyl ester (**8e**)

This compound was prepared by procedure **4.1.9** with the exception that 3-dimethylamino-2-(3,4-dimethoxyphenyl)acrylic acid methyl ester was used in the reaction, in which case a 99% yield of an orange solid was obtained, which exhibited the following properties: mp 88–91 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (s, 1H), 6.81 (d, J = 8.7 Hz, 1H), 6.74–6.77 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.67 (s, 2H), 3.65 (s, 3H), 2.77 (s, 3H) and 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 169.0, 148.6, 148.1, 147.9, 128.2, 124.1, 115.1, 110.5, 101.0, 61.1, 55.8, 51.3, 42.2 and 14.0; IR (neat) 1732 and 1686 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{17}H_{23}NO_6Na$ 360.1418 found 360.1389.

4.1.14. 3-(Ethoxycarbonylmethyl-methylamino)-2-(3,4,5-trimethoxyphenyl) acrylic acid methyl ester (**8f**)

This compound was prepared by procedure **4.1.9** with the exception that 3-dimethylamino-2-(3,4,5-trimethoxyphenyl) acrylic acid methyl ester was used in the reaction, in which case a 94% yield of a yellow solid was obtained, which exhibited the following properties: mp 84–85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (s, 1H), 6.45 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.87 (s, 2H), 3.86 (s, 3H), 3.85 (s, 6H), 3.68 (s, 3H), 2.82 (s, 3H) and 1.23 (t, J = 7.15 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0, 169.1, 152.4, 148.6, 136.9, 131.2, 109.0, 101.2, 61.1, 60.8, 56.0, 51.3, 42.5 and 14.05; IR (neat) 1742 and 1693 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{18}H_{25}NO_7Na$ 390.1523 found 390.1497.

4.1.15. 3-(Ethoxycarbonylmethyl-methylamino)-2-phenylacrylic acid methyl ester (**8g**)

This compound was prepared by procedure **4.1.9** with the exception that 3-dimethylamino-2-phenylacrylic acid methyl ester was used in the reaction, in which case a 91% yield of a yellow solid was obtained, which exhibited the following properties: mp 41–43 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (s, 1H), 7.19–7.31 (m, 5H), 4.13 (q, J = 7.1 Hz, 2H), 3.66 (s, 2H), 3.64 (s, 3H), 2.73 (s, 3H) and 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 168.9, 148.5, 135.8, 131.9, 127.6, 126.7, 101.3, 61.2, 56.0, 51.3, 42.4 and 14.1; IR (neat) 1746 and 1680 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{15}H_{20}NO_4$ 278.1387 found 278.1405.

4.1.16. 3-(Benzylethoxycarbonylmethylamino)-2-(4-methoxyphenyl)acrylic acid methyl ester (**8h**)

Into a 20 mL microwave vial equipped with a magnetic stir bar and crimping cap was added 2-(4-methoxyphenyl)-3-dimethylaminoacrylic acid methyl ester (521 mg, 2.21 mmol), N-benzylglycine ethyl ester (1.07 g, 5.54 mmol), triflouroacetic acid (505 mg, 4.43 mmol) and ethanol (10 mL). The resulting mixture was heated in a Biotage Initiator microwave system for 2 h at 100 °C. The solvent was removed *in vacuo*, the crude residue was dissolved in a water (25 mL)/ethyl acetate (15 mL) mixture and the phases were separated. The aqueous phase was extracted with additional ethyl acetate (2 × 15 mL) and the combined organic phases were washed with brine (15 mL), and dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed *in vacuo* to give a crude residue (1.35 g). The crude residue was purified via flash chromatography with a Biotage Isolera system to give a white solid (752 mg, 88% yield), which exhibited the following properties: mp 69–71 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (s, 1H), 7.30–7.36 (m, 3H), 7.19 (d, J = 6.6 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 4.34 (s, 2H), 4.05 (q, J = 7.15 Hz, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 3.52 (s, 2H) and 1.19 (t, J = 7.15 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 168.9, 158.5, 148.3, 136.3, 132.7, 128.8, 127.9, 127.8, 127.7, 113.3, 101.1, 61.0, 59.0, 55.1, 51.4, 50.0, 14.0; IR (neat) 1751 and 1689 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{22}H_{26}NO_5$ 384.1805 found 384.1828.

4.1.17. 3-Acetoxy-4-(4-methoxphenyl)-1-methyl-1H-pyrrole-2-carboxylic acid ethyl ester (**9a**)

Into a 3-neck round bottom flask equipped with a magnetic stirring bar, reflux condenser, and under a nitrogen atmosphere was added sodium hydride (262 mg, 10.9 mmol), anhydrous ethanol (523 mg, 11.3 mmol), and anhydrous tetrahydrofuran (50 mL). The resulting mixture was stirred at room temperature for 30 min and 2-(4-methoxyphenyl)-3-(ethoxycarbonylmethyl-

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methylamino)-acrylic acid methyl ester (840 mg, 2.73 mmol) was added and the reaction mixture stirred for 4 h. Acetic anhydride (2.23 mg, 21.9 mmol) was added and the reaction mixture stirred for an additional 12 h and quenched with 60 mL of water. The aqueous mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic phases were dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the solvent was removed *in vacuo* to give a crude residue. The crude residue was purified via a Biotage Isolera system to give a yellow/orange solid (548 mg, 69% yield), which exhibited the following properties: mp 72–73 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.85 (s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.82 (s, 3H), 2.30 (s, 3H), and 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 160.2, 158.5, 138.7, 128.0, 124.8, 124.6, 116.7, 114.2, 113.7, 59.9, 55.2, 37.9, 20.8 and 14.4; IR (neat) 1762 and 1694 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{17}H_{19}NO_5Na$ 340.1155 found 340.1166.

4.1.18. 3-Acetoxy-1-methyl-4-p-tolyl-1H-pyrrole-2-carboxylic acid ethyl ester (9b)

This compound was prepared by procedure **4.1.17** with the exception 3-(ethoxycarbonylmethyl-methylamino)-2-*p*-tolylacrylic acid methyl ester was used in the reaction, in which case a 58% purified yield of an off-white solid was obtained, which exhibited the following properties: mp 79–81 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.88 (s, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H) and 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$,75 MHz) δ 169.2, 160.3, 138.8, 136.2, 129.4, 129.3, 126.7, 124.7, 116.9, 113.8, 59.9, 38.0, 21.1, 20.8 and 14.4; IR (neat) 1761 and 1686 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{17}H_{19}NO_4Na$ 324.1206 found 324.1154.

4.1.19. 3-Acetoxy-4-(4-chlorophenyl)-1methyl-1H-pyrrole-2-carboxylic acid ethyl ester (9c)

This compound was prepared by procedure **4.1.17** with the exception 2-(4-chlorophenyl)-3-(ethoxy-carbonylmethyl-methylamino)acrylic acid methyl ester was used in the reaction, in which case a yellow/orange solid (59% yield) was obtained, which exhibited the following properties: mp 96–98 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (d, J = 10.0 Hz, 2H), 7.33 (d, J = 10.0 Hz, 2H), 6.90 (s, 1H), 4.31 (q, J = 7.15 Hz, 2H), 3.95 (s, 3H), 2.31 (s, 3H) and 1.37 (t, J = 7.15 Hz, 3H); ^{13}C NMR (CDCl3, 75 Hz) δ 169.1, 160.1, 138.8, 132.4, 130.8, 128.8, 128.0, 124.7, 115.9, 114.1, 60.1, 38.1, 20.8 and 14.4; IR (neat) 1751 and 1693 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{16}H_{17}NO_4Cl$ 322.0841 found 322.0881.

4.1.20. 3-Acetoxy-4-(4-bromophenyl)-1methyl-1H-pyrrole-2-carboxylic acid ethyl ester (9d)

This compound was prepared procedure **4.1.17** with the exception 2-(4-bromophenyl)-3-(ethoxy-carbonylmethyl-methylamino) acrylic acid methyl ester was used in the reaction, in which case an off-white solid was obtained (99% yield), which exhibited the following properties: mp 108–110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 6.90 (s, 1H), 4.31 (q, J = 7.2 Hz), 4.13 (s, 3H), 2.31 (s, 3H) and 1.37 (t, J = 7.2 Hz);^{13}C NMR ($CDCl_3$, 75 Hz) δ 169.1, 160.1, 138.7, 131.8, 131.3, 128.3, 124.6, 120.4, 115.9, 114.2, 60.1, 38.1, 20.8 and 14.4; IR (neat) 1768 and 1693 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{16}H_{17}NO_4Br$ 366.0335 found 366.0347.

4.1.21. 3-Acetoxy-1-methyl-4-(3,4-dimethoxyphenyl)-1H-pyrrole-2-carboxylic acid ethyl ester (9e)

This compound was prepared by procedure **4.1.17** with the exception 3-(ethoxycarbonylmethyl-methylamino)-2-(3,4-dimethoxyphenyl)acrylic acid methyl ester was used in the reaction, in which case a yellow/orange solid (65% yield) was obtained, which exhibited the following properties: mp 108–109 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98–6.95 (m, 2H), 6.86–6.88 (m, 2H), 4.30 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H). 2.30 (s, 3H) and 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl3, 75 Hz) δ 169.2, 160.2, 149.01, 148.0, 137.0,125.1, 124.6, 119.3, 116.9, 113.7, 111.6, 110.5, 59.9, 55.9, 55.8, 37.9, 20.8 and14.34; IR (neat) 1768 and 1690 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{18}H_{21}NO_6Na$ 370.1261 found 370.1232.

4.1.22. 3-Acetoxy-1-methyl-4-(3,4,5-trimethoxyphenyl)-1H-pyrrole-2-carboxylic acid ethyl ester (9f)

This compound was prepared by procedure **4.1.17** with the exception 3-(ethoxy-carbonylmethyl-methylamino)-2-(3,4,5-trimethoxyphenyl)acrylic acid methyl ester was used in the reaction, in which case a yellow/orange solid (52% yield) was obtained, which exhibited the following properties: mp 129–131 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.89 (s, 1H), 6.66 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 3.88 (s, 9H). 2.30 (s, 3H) and 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 160.2, 153.4, 138.6, 137.1, 127.8, 124.7, 117.1, 113.9, 104.3, 60.9, 60.0, 56.1, 38.0, 20.8 and 14.4; IR (neat) 1756, and 1685 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{19}H_{23}NO_7Na$ 400.1367 found 400.1394.

4.1.23. 3-Acetoxy-1-methyl-4-phenyl-1H-pyrrole-2-carboxylic acid ethyl ester (9g)

This compound was prepared by procedure **4.1.17** with the exception 3-(ethoxycarbonylmethyl-methylamino)-2-phenylacrylic acid methyl ester was used in the reaction, in which case an off-white solid (86% yield) was obtained, which exhibited the following properties: mp 74–75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44 (d, J = 9.0 Hz, 2H), 7.37 (t, J = 9.0 Hz, 2H), 7.28 (t, J = 9.0 Hz, 1H), 6.91 (s, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.95 (s, 3H), 2.31 (s, 3H) and 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 160.2, 138.9, 132.3, 128.7, 126.8, 126.5, 124.89, 117.0, 113.9, 60.0, 38.0, 20.8 and 14.4; IR (neat) 1764 and 1679 cm-1; HRMS (ES, M+Na) *m/z* calcd for $C_{16}H_{17}NO_4Na$ 310.1050 found 310.1038.

4.1.24. 3-Acetoxy-1-benzyl-4-(4-methoxyphenyl)-1H-pyrrole-2-carboxylic acid ethyl ester (9h)

Into a 3-neck round bottom flask equipped with a magnetic stirring bar, reflux condenser and under a nitrogen atmosphere was added sodium hydride (245 mg, 1.02 mmol), anhydrous ethanol (490 mg, 1.07 mmol), anhydrous tetrahydrofuran (25 mL) and the mixture was stirred at room temperature for 30 min. 3-(Benzyle-thoxycarbonylmethylamino)-2-(4-methoxyphenyl)acrylic acid methyl ester was added and the resulting reaction mixture was stirred for 4 h at room temperature. Acetic anhydride was then added (2.08 g, 20.4 mmol) to the reaction mixture and stirring was continued at room temperature for 12 additional hours. The reaction was quenched with 30 mL of brine, extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the solvent was removed *in vacuo* to give an orange/brown residue The crude residue was purified via a Biotage Isolera flash system to give a yellow solid (245 mg, 25% yield), which exhibited the following characteristics: mp 72–74 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.30 (m, 5H), 7.17 (d, J = 9.0 Hz, 2H), 6.88–6.94 (m, 3H), 5.55 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.30 (s, 3H) and 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 169.0, 160.0, 158.5, 139.2, 137.5, 128.7, 128.0, 127.6, 127.0, 124.7, 123.9, 117.4, 114.2, 113.5, 60.0, 55.3, 53.1, 20.8 and 14.3; IR (neat) 1772 and 1693 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{23}H_{23}NO_5Na$ 416.1468 found 416.1494.

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*4.1.25. Z-3-Dimethylamino-2-(4-methoxyphenyl)acrylonitrile **(11a)***

To a round bottom flask, equipped with a reflux condenser and a magnetic stirring bar, was added 4-methoxybenzyl acetonitrile (0.5 g, 3.40 mmol), *N*,*N*-dimethylformamide dimethyl acetal (1.630 g, 13.6 mmol), and DMF (15 mL). The reaction mixture was refluxed for 4 h and diluted with aqueous lithium chloride (30 mL). The mixture was extracted with ethyl acetate (3 × 20 mL) and washed with aqueous lithium chloride (30 mL). The solution was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to give an orange solid (0.660 g, 96% yield), which exhibited the following properties: mp 60–62 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.78 (s, 1H), 3.81 (s, 3H), and 3.22 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 149.1, 129.2, 125.5, 121.3, 114.2, 55.4 and 42.4; IR (neat) 2178 and 1620 cm^{-1}; HRMS (ES, M+Na) *m*/*z* calcd for $C_{12}H_{14}N_2ONa$ 225.0998 found 225.0938.

*4.1.26. Z-3-Dimethylamino-2- p-tolylacrylonitrile **(11b)***

This compound was prepared by procedure **4.1.25** with the exception that 4-methylphenylacetonitrile was used in the reaction, in which case a 95% yield of a solid was obtained, which exhibited the following properties: mp 84–87 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.3 Hz, 2H), 6.89 (s, 1H), 3.23 (s, 6H), and 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4, 134.8, 133.7, 129.9, 124.1, 121.2, 42.5 and 20.8; IR (neat) 2176 and 1620 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{12}H_{15}N_2$ 187.1230 found 187.1213.

*4.1.27. Z-2-(4-Chlorophenyl)-3-dimethylaminoacrylonitrile **(11c)***

This compound was prepared by procedure **4.1.25** with the exception that 4-chlorophenylacetonitrile was used in the reaction, in which case a solid (84% yield) was obtained, which exhibited the following properties: mp 73–75 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J = 9.1 Hz, 2H), 7.24 (d, J = 9.1 Hz, 2H), 6.89 (s, 1H) and 3.26 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.8, 135.2, 131.1, 128.7, 125.1, 120.7 and 42.6; IR (neat) 2187 and 1633 cm^{-1}; HRMS (ES, M+Na) *m*/*z* calcd for $C_{11}H_{11}N_2ClNa$ 229.0503 found 229.0460.

*4.1.28. Z-2-(4-Bromophenyl)-3-dimethylaminoacrylonitrile **(11d)***

This compound was prepared by procedure **4.1.25** with the exception that 4-bromophenylacetonitrile was used in the reaction, in which case a solid (100% yield) was obtained, which exhibited the following properties: mp 84–86 °C; ^{1}H NMR (CDCl, 500 MHz) δ 7.41 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 6.89 (s, 1H) and 3.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.8, 135.7, 131.7, 125.4, 120.6, 118.4 and 31.4; IR (neat) 2184 and 1617 cm^{-1}; HRMS (ES, M+Na) *m*/*z* calcd for $C_{11}H_{11}N_2BrNa$ 272.9998 found 272.9950.

*4.1.29. Z-2-(4-Fluorophenyl)-3-dimethylaminoacrylonitrile **(11e)***

This compound was prepared by procedure **4.1.25** with the exception that 4-flourophenylacetonitrile was used in the reaction, in which case a solid (95% yield) was obtained, which exhibited the following properties: mp 52–53 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23–7.28 (m, 2H), 6.99 (t, J = 8.7 Hz, 2H), 6.81 (s, 1H) and 3.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.81 (d, J = 243.9 Hz), 149.8, 132.8 (d, J = 3.0 Hz), 125.6 (d, J = 7.5 Hz), 121.1115.4 (d, J = 21.8 Hz), 75.8 and 42.4; IR (neat) 2185 and 1610 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{11}H_{12}N_2F$ 191.0979 found 191.0984.

*4.1.30. Z-3-Dimethylamino-2-phenylacrylonitrile **(11f)***

This compound was prepared by procedure **4.1.25** with the exception that phenylacetonitrile was used in the reaction, in which case a solid was obtained (99% yield), which exhibited the following properties: mp 73–75 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.29 (m, 4H), 7.10–7.17 (m, 1H), 6.91 (s, 1H) and 3.24 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.8, 136.6, 128.7, 125.1, 124.0, 121.0 and 43.2; IR (neat) 2187 and 1614 cm^{-1}; HRMS (ES, M+Na) *m*/*z* calcd for $C_{11}H_{12}N_2Na$ 195.0893 found 195.0886.

*4.1.31. Z-2-(3,4-Dimethoxyphenyl)-3-dimethylaminoacrylonitrile **(11g)***

This compound was prepared by procedure **4.1.25** with the exception that 3,4-dimethoxyphenylacetonitrile was used in the reaction in which case a brown solid (98% yield) was obtained, which exhibited the following properties: mp 88–91 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.83 (broad m, 1H), 6.82–6.83 (m, 2H), 6.80 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H) and 3.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4, 149.1, 147.0, 129.8, 121.3, 116.3, 111.8, 108.3, 56.0, 55.9, 42.4; IR (neat) 2187 and 1617 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{13}H_{17}N_20_2$ 233.1285 found 233.1256.

*4.1.32. {[2-Cyano-2-(4-methoxyphenyl)vinyl]methylamino}acetic acid ethyl ester **(12a)***

Into a round bottom flask, equipped with a reflux condenser and magnetic stirring bar, was added 3-dimethyl-amino-2-(4-methoxyphenyl)acrylonitrile (0.685 g, 3.39 mmol), sarcosine ethyl ester hydrochloride (1.561 g, 10.2 mmol), and acetic acid (15 mL). The reaction mixture was heated at reflux for 6 h and diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. After removing the drying agent by filtration, the solvent was concentrated *in vacuo* and the crude residue was purified via a Biotage Isolera flash system to give an orange solid (0.929 g, 87% yield), which exhibited the following characteristics: mp 78–79 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.76 (s, 1H), 4.29 (q, J = 7.1, 2H), 4.13 (s, 2H), 3.81 (s, 3H), 3.29 (s, 3H), and 1.34 (t, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 158.0, 148.6, 128.6, 126.0, 120.3, 114.2, 79.4, 61.8, 56.4, 55.4, 41.4 and 14.2; IR (neat) 2181 and 1736 cm^{-1}; HRMS (ES, M+Na) *m*/*z* calcd for $C_{15}H_{18}N_2O_3Na$ 297.1210 found 297.1198.

*4.1.33. {[2-Cyano-2-p-tolylvinyl]methylamino}acetic acid ethyl ester **(12b)***

This compound was prepared by procedure **4.1.32** with the exception that 3-dimethylamino-2-*p*-tolylacrylonitrile was used in the reaction, in which case a solid (88% yield) was obtained, which exhibited the following properties: mp 84–85 °C; ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.23 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.3 Hz, 2H), 6.84 (s, 1H), 4.29 (q, J = 7.1, 2H), 4.13 (s, 2H), 3.30 (s, 3H), 2.33 (s, 3H) and 1.34 (t, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 149.7, 134.5, 133.8, 129.2, 123.8, 119.9, 77.9, 60.9, 56.3, 40.1, 19.9 and 13.6; IR (neat) 2181 and 1739 cm^{-1}; HRMS (ES, M+Na) *m*/*z* calcd for $C_{15}H_{18}N_2O_2Na$ 281.1260 found 281.1247.

*4.1.34. {[2-(4-Chlorophenyl)-2-cyanovinyl]methylamino}acetic acid ethyl ester **(12c)***

This compound was prepared by procedure **4.1.32** with the exception that 2-(4-chlorophenyl)-3-dimethylamino-acrylonitrile was used in the reaction, in which case a solid (88% yield) was obtained, which exhibited the following properties: mp 102–104 °C; ^{1}H NMR (acetone-d_6; 300 MHz) δ 7.42 (s, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 4.26 (s, 2H), 4.22 (q, J = 7.1, 2H), 3.37 (s, 3H) and 1.28 (t, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ; 168.44, 149.5, 134.67 131.2, 128.8, 125.6, 119.7, 78.6, 61.9, 56.4, 41.5 and 14.1; IR (neat) 2187 and 1749 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{14}H_{16}N_2O_2Cl$ 279.0895 found 279.0904.

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*4.1.35. {[2-(4-Bromophenyl)-2-cyanovinyl]methylamino}acetic acid ethyl ester **(12d)***

This compound was prepared by procedure **4.1.32** with the exception that 2-(4-bromophenyl)-3-dimethylaminoacrylonitrile was used in the reaction, in which case a solid (91% yield) was obtained, which exhibited the following properties: mp 112–114 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 6.87 (s, 1H), 4.30 (q, J = 7.1, 2H), 4.17 (s, 2H), 3.32 (s, 3H) and 1.34 (t, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4, 149.4, 135.1, 131.7, 125.9, 119.6, 119.2, 78.78, 61.9, 56.4, 41.7 and 14.1; IR (neat) 2186 and 1740 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{14}H_{15}N_2O_2BrNa$ 345.0209 found 345.0218.

*4.1.36. {[2-Cyano-2-(4-fluorophenyl)vinyl]methylamino}acetic acid ethyl ester **(12e)***

This compound was prepared by procedure **4.1.32** with the exception that 2-(4-flourophenyl)-3-dimethylamino-acrylonitrile was used in the reaction, in which case a solid (98% yield) was obtained, which exhibited the following properties: mp 83–84 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (dd, J = 8.7, 5.2 Hz, 2H), 7.00 (t, J = 8.7 Hz, 2H), 6.80 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.15 (s, 2H), 3.30 (s, 3H) and1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5, 161.2 (d, J = 245.1 Hz), 149.4, 132.1 (d, J = 3.2 Hz), 126.1 (d, J = 7.8 Hz), 120.0, 115.5 (d, J = 21.7 Hz), 78.7, 61.9, 56.3, 41.5, and14.1; IR (neat) 2186 and 1744 cm^{-1};HRMS (ES, M+Na) *m/z* calcd for $C_{14}H_{15}N_2O_2FNa$ 285.1010 found 285.1013.

*4.1.37. [(2-Cyano-2-phenylvinyl-methylamino)]acetic acid ethyl ester **(12f)***

This compound was prepared by procedure **4.1.32** with the exception that 3-dimethylamino-2-phenylacrylonitrile was used in the reaction, in which case a solid (87% yield) was obtained, which exhibited the following properties: mp 60–62 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.38 (d, J = 7.5 Hz, 2H), 7.35 (s, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.13 (t, J = 7.5 Hz, 1H), 4.36 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.36 (s, 3H) and 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$;, 75 MHz) δ 168.9150.2, 136.7, 128.6, 125.0, 123.8, 119.8, 77.9, 60.9, 56.3, 40.2 and 13.6; IR (neat) 2182 and 1724 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{14}H_{16}N_2O_2Na$ 267.1104 found 267.1098.

*4.1.38. {[2-Cyano-2-(3,4-dimethoxyphenyl)vinyl]methylamino} acetic acid ethyl ester **(12g)***

This compound was prepared by procedure **4.1.32** with the exception that 2-(3,4-dimethoxyphenyl)-3-dimethylaminoacrylonitrile was used in the reaction, in which case a solid (92% yield) was obtained, which exhibited the following properties: bp 130 °C, 0.305 torr; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.80–6.88 (m, 3H), 6.78 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.15 (s, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.25 (s 3H) and 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 149.2, 148.8, 147.6, 129.2, 121.0, 116.9, 111.6, 108.8, 79.6, 61.8, 56.3, 56.0, 55.9, 41.5 and 14.2; IR (neat) 2190 and 1740 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{16}H_{20}N_2O_4Na$ 327.1315 found 327.1309.

*4.1.39. {Benzyl-[2-cyano-2-(4-methoxyphenyl)vinyl]amino}acetic acid ethyl ester **(12h)***

Into a round bottom flask, equipped with a reflux condenser and magnetic stirring bar, was added 3-dimethylamino-2-(4-methoxyphenyl)acrylonitrile (1.00 g, 0.0043 mol), N-benzyl glycine (1.64 g, 0.0085 mol), and acetic acid (20 mL). The reaction mixture was heated at reflux for 6 h and diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate until gas evolution ceased. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue (0.624 g, 92% yield) was purified using a Biotage Isolera flash chromatography system to give a pale yellow solid, which exhibited the following properties: mp 93–94 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (t, J = 10.0 Hz, 2H), 7.36 (t, J = 10.0 Hz Hz, 1H), 7.30 (d, J = 10.0 Hz, 2H), 7.27 (d, J = 10.0 Hz, 2H), 6.97 (s, 1H), 6.88 (d, J = 10.0 Hz, 2H), 4.63 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 4.24 (s, 2H), 3.82 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 158.1, 148.2, 135.4, 129.0, 128.5, 128.4, 128.0, 126.0, 119.9, 114.2, 79.5, 61.8, 59.4, 55.3, 50.9 and 14.1; IR (neat) 2176 and 1741 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{21}H_{22}N_2O_3Na$ 373.1523, found 373.1515.

*4.1.40. [Benzyl(2-cyano-2-p-tolylvinyl)amino]acetic acid ethyl ester **(12i)***

This compound was prepared by procedure **4.1.39** with the exception that 3-dimethylamino-2-*p*-tolylacrylonitrile and N-benzyl glycine were used in the reaction, in which case a 58% yield of a solid was obtained, which exhibited the following properties: mp 76–78 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.35 (m, 3H), 7.31–7.28 (m, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 7.05 (s, 1H), 4.63 (s, 2H), 4.31–4.23 (m, 4H), 2.34 (s, 3H) and 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 148.7, 135.5, 133.1, 1295, 129.0, 128.4, 128.1, 124.3, 119.9, 79.55, 61.8, 59.5, 51.1, 20.9 and 14.2; IR (neat) 2180 and 1741 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{21}H_{22}N_2O_2Na$ 357.1573 found 357.1583.

*4.1.41. 3-Amino-4-(4-methoxyphenyl)-1-methyl-1H- pyrrole-2-carboxylic acid ethyl ester **(13a)***

Into a 3-neck round bottom flask, equipped with a magnetic stirring bar and under an inert atmosphere, were added sodium hydride (0.219 g, 0.00547 mol) and anhydrous THF (20 mL).{[2-Cyano-2-(4-methoxyphenyl)vinyl]methylamino}acetic acid ethyl ester (0.600 g, 0.00219 mol) was added drop wise in THF and the reaction mixture stirred at room temperature for 12 h. The reaction was quenched with brine, extracted with ethyl acetate (3 × 15 mL) and dried over anhydrous sodium sulfate. The ethyl acetate extract was filtered and concentrated *in vacuo* to give a give pale yellow solid (0.591 g, 99% yield), which exhibited the following properties: mp 48–49 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (d, J = 8.7, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.64 (s, 1H), 4.60 (s, 2H), 4.36 (q, J = 7.1, 2H), 3.85 (s, 3H), 3.83 (s, 3H) and 1.41 (t, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1158.0, 128.4, 127.1, 126.5, 114.4, 111.7, 107.6, 59.3, 55.3, 37.4 and 14.7; IR (neat) 3420, 3322 and 1650 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{15}H_{19}N_2O_3$ 275.1390 found 275.1395.

*4.1.42. 3-Amino-1-methyl-4-p-tolyl-1H- pyrrole-2-carboxylic acid ethyl ester **(13b)***

This compound was prepared by procedure **4.1.41** with the exception that 3-{[2-cyano-2-*p*-tolylvinyl]methyl-amino}acetic acid ethyl ester was used in the reaction, in which case a 74% yield of a solid was obtained, which exhibited the following properties: mp 69–70 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.67 (s, 1H), 4.64 (s, 2H), 4.36 (d, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.38 (s, 3H) and 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.7, 141.3, 134.7, 131.7, 129.3, 127.5, 126.5, 111.2, 107.3, 58.6, 36.7, 20.2 and 14.1; IR (neat) 3469, 3367 and 1642 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{15}H_{19}N_2O_2$ 259.1441, found 259.1437.

*4.1.43. 3-Amino-4-(4-chlorophenyl)-1-methyl-1H- pyrrole-2-carboxylic acid ethyl ester **(13c)***

This compound was prepared by procedure **4.1.41** with the exception that 3-{[2-(4-chlorophenyl)-2-cyanovinyl]methylamino} acetic acid ethyl ester used in the reaction, in which case a 60% yield of a solid was obtained, which exhibited the following properties:

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mp 69–70 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (broad s, 4H), 6.68 (s, 1H), 4.63 (s, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), and1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1, 140.3, 132.6, 131.6, 129.1, 128.2, 127.1, 110.8, 107.9, 59.4, 37.6 and 14.6; IR (neat) 3458, 3347 and 1641 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{14}H_{16}N_2O_2Cl$ 279.0895 found 279.0920.

4.1.44. 3-Amino-4-(4-bromophenyl)-1-methyl-1H- pyrrole-2-carboxylic acid ethyl ester **(13d)**

This compound was prepared by procedure **4.1.41** with the exception that {[2-(4-bromophenyl)-2-cyanovinyl]methylamino} acetic acid ethyl ester was used in the reaction, in which case a 79% yield of a solid was obtained, which exhibited the following properties: mp 79–80 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (d, J = 8.6 Hz, 2 H), 7.32 (d, J = 8.6 Hz, 2H), 6.68 (s, 1H), 4.63 (s, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H) and 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.0, 140.3, 133.1, 131.9, 128.4, 127.1, 119.4, 110.7, 107.9, 59.4, 37.6 and 14.7; IR (neat) 3429, 3334 and 1653 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{14}H_{16}N_2O_2Br$ 323.0390 found 323.0405.

4.1.45. 3-Amino-4-(4-fluorophenyl)-1-methyl-1H- pyrrole-2-carboxylic acid ethyl ester **(13e)**

This compound was prepared by procedure **4.1.41** with the exception that {[2-cyano-2-(4-fluorophenyl)-vinyl]methylamino} acetic acid ethyl ester was used in the reaction, in which case a 75% yield of a solid was obtained, which exhibited the following properties: mp 57–59 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (dd, J = 8.9 Hz, J = 5.4 Hz, 2H), 7.09 (t, J = 8.9 Hz, 2H), 6.65 (s, 1H), 4.62 (broad s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H) and 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1, 161.3 (d, J = 247.5 Hz), 140.2, 130.1 (d, J = 3.8 Hz), 128.6 (d, J = 7.5 Hz), 127.1, 115.7 (d, J = 21.0 Hz), 111.0, 107.7, 59.4, 37.5 and 14.7; IR (neat) 3403 and 1659 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{14}H_{16}N_2O_2F$ 263.1190 found 263.1176.

4.1.46. 3-Amino-4-phenyl-1-methyl-1H- pyrrole-2-carboxylic acid ethyl ester **(13f)**

This compound was prepared by procedure **4.1.41** with the exception that [(2-cyano-2-phenylvinyl)methylamino]- acetic acid ethyl ester was used in the reaction, in which case an 83% yield of a solid was obtained, which exhibited the following properties: mp 36–38 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, J = 8.3 Hz, 2H), 7.41 (t, J = 8.3 Hz, 2H), 7.25 (t, J = 8.3 Hz, 1H), 6.70 (s, 1H), 4.67 (broad s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H) and 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.2, 140.4, 134.2, 128.9, 127.3, 127.0, 125.9, 111.9107.7, 59.3, 37.5 and 14.7; IR (neat) 3413, 3334 and 1651 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{14}H_{17}N_2O_2$ 245.1285 found 245.1279.

4.1.47. 3-Amino-4-(3,4-dimethoxyphenyl)-1-methyl-1H- pyrrole-2-carboxylic acid ethyl ester **(13g)**

This compound was prepared by procedure **4.1.41** with the exception that {[2-cyano-2-(3,4-dimethoxyphenyl)vinyl]methylamino}acetic acid ethyl ester was used in the reaction, in which case a 97% yield of a solid was obtained, which exhibited the following properties: mp 107–109 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00–6.96 (m, 2H), 6.93 (d, J = 8.7 Hz, 1H), 6.66 (s, 1H), 4.62 (broad s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.92 (s, 6H), 3.84 (s, 3H) and 1.41 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$,75 MHz) δ 162.2, 149.3, 147.6, 140.1, 127.1, 126.9, 119.5, 111.9, 111.87, 110.8, 107.7, 59.3, 56.0, 55.9, 37.4 and 14.7; IR (neat) 3437, 3354 and 1663 cm^{-1}; HRMS (ES, M+Na) m/z calcd for $C_{16}H_{20}N_2O_4Na$ 327.1315, found 327.1311.

4.1.48. 3-Amino-1-benzyl-4-(4-methoxyphenyl)-1H-pyrrole-2-carboxylic acid ethyl ester **(13h)**

This compound was prepared by procedure **4.1.41** with the exception that {benzyl-[2-cyano-2-(4-methoxyphenyl)vinyl] amino}acetic acid ethyl ester was used in the reaction, in which case a 63% yield of a solid was obtained, which exhibited the following properties: bp 111 °C at 0.385 torr; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, J = 8.7 Hz, 2H), 7.34–7.23 (m, 3 H), 7.14 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.76 (s, 1H), 5.42 (s, 2H), 4.68 (broad s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H) and 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.9, 158.1, 141.0, 138.8, 128.5, 128.4, 127.2, 126.8, 126.6, 126.4, 114.1, 112.5, 107.0, 59.3, 55.3, 52.8 and 14.5; IR (neat) 3480, 3349 and 1664 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{21}H_{23}N_2O_3$ 351.1703 found 351.1709.

4.1.49. 3-Amino-1-benzyl-4-p-tolyl-1H-pyrrole-2-carboxylic acid ethyl ester **(13i)**

This compound was prepared by procedure **4.1.41** with the exception that [benzyl(2-cyano-2-*p*-tolylvinyl)amino]-acetic acid ethyl ester was used in the reaction, in which case an 82% yield of a solid was obtained, which exhibited the following properties: bp 92 °C at 0.365 torr; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (d, J = 7.2 Hz, 2H), 7.23–7.31 (m, 3H), 7.21 (d, J = 7.2 Hz, 2H), 7.13 (d, J = 7.2 Hz, 2H), 6.80 (s, 1H), 5.43 (s, 2H), 4.72 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H) and 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.9, 141.2, 138.8, 135.7, 131.0, 129.7, 128.5, 127.2, 127.1, 126.6, 112.7, 107.0, 59.3, 52.9, 21.2 and 14.6; IR (neat) 3472, 3368 and 1660 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{21}H_{23}N_2O_2$ 335.1754 found 335.1735.

4.1.50. 3-Acetylamino-4-(4-methoxyphenyl)-1-methyl-1H-pyrrole-2-carboxylic acid ethyl ester **(13j)**

This compound was prepared by procedure **4.1.41** with the exception that {[2-cyano-2-(4-methoxy-phenyl)vinyl]methylamino}acetic acid ethyl ester was used in the reaction. In addition, acetic anhydride (3.5 eq.) was added to the reaction mixture followed by two additional hours of stirring prior to reaction workup, in which case a 71% yield of a solid was obtained. This material exhibited the following properties: mp 133–136 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.76 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.13 (s, 3H), 3.81 (s, 3H), 3.29 (s, 3H) and 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 168.8, 160.7, 158.3, 128.2, 126.7, 125.5, 121.4, 117.9, 113.6, 59.3, 54.6, 36.9, 22.4 and 13.8; IR (neat) 3258, 1685 and 1650 cm^{-1}; HRMS (ES, M+Na) m/z calcd for $C_{17}H_{20}N_2O_4Na$ 339.1515 found 339.1519.

4.1.51. 3-Methanesulfonylamino-4-(4-methoxyphenyl)-1-methyl-1H- pyrrole-2-carboxylic acid ethyl ester **(13k)**

Into a 3-neck round bottom flask, equipped with a magnetic stirring bar and under an inert atmosphere, was added sodium hydride (0.110 g, 0.00457 mol), ethanol (0.220 g, 0.00471 mol) and anhydrous THF (30 mL). The reaction mixture stirred for 30 min and cooled in an ice bath.{[2-Cyano-2-(4-methoxyphenyl)vinyl]methylamino}acetic acid ethyl ester (0.250 g, 0.00091 mol) in a minimal amount of dry THF was slowly added to the reaction mixture and the resulting solution was stirred for 4 h. Methane sulfonic anhydride (0.960 g, 0.00349) in a minimal amount of dry THF was added dropwise and the resulting reaction mixture stirred for 12 h. The reaction was quenched with brine (20 mL), extracted with ethyl acetate (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a crude residue. The crude residue was purified using a Biotage Isolera flash chromatography system to produce a brown solid (0.150 g, 47% yield), which exhibited the following properties: mp 139–141 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.79 (s, 1H), 4.41 (q,

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$J = 7.1$ Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 2.60 (s, 3H) and 1.44 (q, $J = 7.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 160.9, 158.7, 129.4, 126.4, 125.7, 125.2, 121.4, 117.3, 114.0, 60.7, 55.2, 40.3, 38.0 and14.3; IR (neat) 3266 and 1695 cm^{-1}; HRMS (ES, M+Na) m/z calcd for $C_{16}H_{20}N_2O_5SNa$ 375.0985 found 375.0982.

4.1.52. 2-(4-Methoxyphenyl)-3-(methyl-p-tolylamino)acrylic acid methyl ester **(15a)**

To a round bottom flask, equipped with a reflux condenser and a magnetic stirring bar, was added 3-dimethyl-amino-2-(4-methoxyphenyl)acrylic acid methyl ester (1.0 g, 0.00425 mol), N-methyl *p*-toluidine (1.03 g, 0.0085 mol), ethanol (20 mL), and acetic acid (0.5 mL). The reaction mixture was refluxed overnight and the solvent was removed *in vacuo*. Water (20 mL) and ethyl acetate (15 mL) were added to the reaction mixture and the phases were separated. The aqueous layer was extracted with additional ethyl acetate (3 × 15 mL) and the combined organic phases were washed with aqueous 1% HCl (20 mL) followed by a wash with saturated aqueous sodium bicarbonate (20 mL). The resulting organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a yellow solid (1.24 g, 93% yield), which exhibited the following characteristics: mp 86–88 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (s, 1H), 7.14 (m, 4H), 6.99 (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H) 3.83 (s, 3H), 3.71 (s, 3H), 2.87 (s, 3H) and 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 158.4, 145.3, 145.1133.4, 132.4, 129.7, 128.3, 119.7, 113.1, 105.4, 55.2, 51.5, 38.7 and 20.6; IR (neat) 1692 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{19}H_{22}NO_3$ 312.1594 found 312.1586.

4.1.53. 3-(Methyl-p-tolylamino)-2-p-tolylacrylic acid methyl ester **(15b)**

This compound was prepared by procedure **4.1.52** with the exception that 3-dimethylamino-2-*p*-tolyl-acrylic acid methyl ester was used in the reaction, in which case a 73% yield of a pale yellow solid was obtained, which exhibited the following properties: mp 105–108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (s, 1H), 7.17–7.11 (m, 6H), 7.00 (d, $J = 8.5$ Hz, 2H), 3.71 (s, 3H), 2.86 (s, 3H), 2.37 (s, 3H) and 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 145.3, 145.2, 136.3, 133.4, 133.1, 131.3, 129.7, 128.4, 119.7, 105.7, 51.2, 38.7, 21.3 and 20.6; IR (neat) 1685 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{19}H_{22}NO_2$ 296.1645 found 296.1639.

4.1.54. 2-(4-Chlorophenyl)-3-(methyl-p-tolyamino)acrylic acid methyl ester **(15c)**

This compound was prepared by procedure **4.1.52** with the exception that 2-(4-chlorophenyl)-3-dimethyl-aminoacrylic acid methyl ester was used in the reaction, in which case an 81% yield of a yellow solid was obtained, which exhibited the following properties: mp 97–99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (s, 1H), 7.24 (d, $J = 8.6$ Hz, 2 H), 7.09–7.15 (m, 4H), 6.96 (d, $J = 8.6$ Hz, 2H), 3.71 (s, 3H), 2.92 (s, 3H) and 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 146.0, 144.6, 134.6, 134.0, 132.7, 132.4, 129.7, 127.7, 120.3, 103.9, 51.5, 39.8 and 20.7; IR (neat) 1685 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{18}H_{19}ClNO_2$ 316.1099 found 316.1108.

4.1.55. 2-(4-Bromophenyl)-3-(methyl-p-tolylamino)acrylic acid methyl ester **(15d)**

This compound was prepared by procedure **4.1.52** with the exception that 2-(4-bromophenyl)-3-dimethyl-aminoacrylic acid methyl ester was used in the reaction, in which case an 85% yield of a yellow solid was obtained, which exhibited the following properties: mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (s, 1H), 7.39 (d, $J = 8.5$ Hz, 2H), 7.06–7.11 (m, 4H), 6.96 (d, $J = 8.5$ Hz, 2H), 3.71 (s, 3H), 2.93 (s, 3H) and 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 145.9, 144.6, 135.1, 134.1, 133.0, 130.6, 129.7, 120.5, 120.4, 103.9, 51.4, 40.0 and 20.6; IR (neat) 1685 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{18}H_{19}BrNO_2$ 360.0594 found 360.0614.

4.1.56. 2-(3,4-Dimethoxyphenyl)-3-(methyl-p-tolylamino)acrylic acid methyl ester **(15e)**

This compound was prepared by procedure **4.1.52** with the exception that 2-(3,4-dimethoxyphenyl)-3-dimethylaminoacrylic acid methyl ester was used in the reaction, in which case an 82% yield of an orange solid was obtained, which exhibited the following properties: mp 110–112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (s, 1H), 7.12 (d, $J = 8.6$ Hz, 2H), 7.00 (d, $J = 8.6$ Hz, 2H), 6.74–6.84 (m, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.72 (s, 3H), 2.89 (s, 3H) and 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 148.1, 147.9, 145.3, 145.1, 133.5, 129.7, 128.6, 123.9, 119.7, 144.8, 110.5, 105.3, 55.9, 55.8, 51.5, 38.6 and 20.6; IR (neat) 1690 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{20}H_{24}NO_4$ 342.1700 found 342.1707.

4.1.57. 3-(Methyl-p-tolylamino)-2-(3,4,5-trimethoxyphenyl)acrylic acid methyl ester **(15f)**

This compound was prepared by procedure **4.1.52** with the exception that 3-dimethylamino-2-(3,4,5-trimethoxyphenyl) acrylic acid methyl ester was used in the reaction, in which case a 63% yield of a yellow solid was obtained, which exhibited the following properties: mp 116–117 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (s, 1H), 7.11 (d, $J = 8.4$ Hz, 2H), 6.98 (d, $J = 8.4$ Hz, 2H), 6.43 (s, 2H), 3.86 (s, 3H), 3.83 (s, 6H), 3.73, (s, 3H), 2.97 (s, 3H) and 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 170.0, 152.4, 145.4, 144.8, 136.9, 133.7, 131.4, 129.6, 120.1, 108.9, 105.0, 60.8, 56.1, 51.5, 39.2 and 20.6; IR (neat) 1685 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{21}H_{26}NO_5$ 372.1805 found 372.1806.

4.1.58. 3-(Methyl-p-tolylamino)-2-phenylacrylic acid methyl ester **(15g)**

This compound was prepared by procedure **4.1.52** with the exception that 3-dimethylamino-2-phenylacrylic acid methyl ester was used in the reaction, in which case an 85% yield of a pale yellow solid was obtained, which exhibited the following properties: mp 95–97 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (s, 1H), 7.21–7.35 (m, 5H), 7.12 (d, $J = 8.5$ Hz, 2H), 7.00 (d, $J = 8.5$ Hz, 2H), 3.71 (s, 3H), 2.85 (s, 3H) and 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1, 145.5, 145.1, 136.2, 133.6, 131.5, 129.8, 127.6, 126.7, 119.9, 105.7, 51.5, 39.0 and 20.7; IR (neat) 1687 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{18}H_{20}NO_2$ 282.1489 found 282.1500.

4.1.59. 3-(Ethyl-p-tolylamino)-2-(4-methoxyphenyl)acrylic acid methyl ester **(15h)**

This compound was prepared by procedure **4.1.52** with the exception that N-ethyl p-toluidine was used in the reaction, in which case a 69% yield of a yellow oil was obtained, which exhibited the following properties: bp 126 °C at 0.970 torr; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (s, 1H), 7.01–7.07 (m, 4H), 6.90 (d, $J = 9.0$ Hz, 2H), 6.76 (d, $J = 9.0$ Hz, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 3.43 (q, $J = 6.0$ Hz, 2H), 2.29 (s, 3H) and 0.96 (t, $J = 6.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 158.2, 145.0, 143.2, 133.9, 132.0, 129.5, 128.2, 121.8, 113.1, 104.1, 55.1, 51.4, 46.2, 20.7 and 13.5; IR (neat) 1688 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{20}H_{24}NO_3$ 326.1751 found 326.1759.

4.1.60. 2-(4-Methoxyphenyl)-3-[(4-methoxyphenyl)methylamino] acrylic acid methyl ester **(15i)**

This compound was prepared by procedure **4.1.52** with the exception that 4-methoxyphenyl N-methyl aniline was used in the reaction, in which case a 91% yield of a yellow solid was obtained, which exhibited the following properties: mp 112–114 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.87 (s, 1H), 7.12 (d, $J = 9.0$ Hz, 2H), 7.01 (d, $J = 9.0$ Hz, 2H), 6.81–6.84 (m, 4H), 3.83 (s, 3H), 3.80 (s, 3H), 3.70 (s,

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3H) and 2.89 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 170.5, 158.3, 156.5, 145.9, 141.1, 132.4, 128.2, 121.9, 114.3, 113.0, 104.2, 55.6, 55.2, 51.4 and 39.7; IR (neat) 1688 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{19}H_{22}NO_4$ 328.1543 found 328.1542.

4.1.61. 3-[(4-Bromophenyl)methylamino]-2-(4-methoxyphenyl) acrylic acid methyl ester ***(15j)***

This compound was prepared by procedure **4.1.52** with the exception that 4-bromophenyl N-methyl aniline was used in the reaction, in which case a 78% yield of a yellow solid was obtained, which exhibited the following properties: mp 112–114 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.88 (s, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 3.73 (s, 3H) and 2.89 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 169.9, 158.6, 146.0, 144.1, 132.1, 132.0, 127.7, 120.6, 116.1, 113.3, 107.8, 55.2, 51.6 and 38.5; IR (neat) 1687 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{18}H_{19}NO_3Br$ 376.0543 found 376.0557.

4.1.62. 1,6-Dimethyl-3-(4-Methoxyphenyl)-1H-quinolin-4-one ***(16a)***

To a round bottom flask, equipped with a glass stopper and a magnetic stirring bar, was added 2-(4-methoxyphenyl)-3-(methyl-*p*-tolylamino)acrylic acid methyl ester (0.400g, 0.00128 mol), triflic anhydride (0.00256 mol) and anhydrous dichloromethane (20 mL). The reaction mixture was allowed to stir overnight and the solvent was removed *in vacuo*. To the crude residue was added 30 mL of a 50:50 mixture of THF and saturated aqueous sodium carbonate. The crude reaction mixture was heated at reflux for one hour, cooled to room temperature and water (20 mL) and ethyl acetate (15 mL) were added to the mixture. The phases were separated and the aqueous layer was extracted with additional ethyl acetate (3 × 15 mL) followed by a brine (15 mL) extraction. The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to yield an off white solid (0.297 g, 83% yield), which exhibited the following properties: mp 154–156 °C; ^{1}H NMR ($CDCl_3$;300 MHz) δ 8.38 (d, J = 1.5 Hz, 1H), 7.66–7.62 (m, 3H), 7.52 (dd, J = 8.6 Hz, J = 1.5 Hz, 1H), 7.34 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 3.86 (s, 6H) and 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 175.8, 158.7, 141.7, 138.1, 133.5, 133.3, 129.7, 128.1, 127.0, 126.9, 121.4, 114.9, 113.8, 55.3, 40.6 and 20.9; IR (neat) 1617 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{18}H_{18}NO_2$ 280.1332 found 280.1335.

4.1.63. 1,6-Dimethyl -3-p-tolyl-1H-quinolin-4-one ***(16b)***

This compound was prepared by procedure **4.1.62** with the exception that 3-(methyl-*p*-tolylamino)-2-*p*-tolylacrylic acid methyl ester was used in the reaction, in which case a 94% yield of a white solid was obtained, which exhibited the following properties: mp 160–163 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.33 (d, J = 1.5 Hz, 1H), 7.68 (s, 1H), 7.60 (d, J = 6.0 Hz, 2H), 7.52 (dd, J = 6.0 Hz, J = 1.5 Hz, 1 H), 7.33 (d, J = 6.0 Hz, 1H), 7.25 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.52 (s, 3H) and 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 175.7, 142.1, 138.0, 136.5, 133.4, 133.2, 132.7, 128.9, 128.4, 127.0, 126.8, 121.4, 115.1, 40.6, 21.2 and 20.9; IR (neat) 1614 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{18}H_{18}NO$ 264.1383 found 264.1377.

4.1.64. 3-(4-Chlorophenyl)-1,6-dimethyl-1H-quinolin-4-one ***(16c)***

This compound was prepared by procedure **4.1.62** with the exception that 2-(4-chlorophenyl)-3-(methyl-*p*-tolylamino)acrylic acid methyl ester was used in the reaction, in which case a 90% yield of a white solid was obtained, which exhibited the following properties: mp 173–174 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.36 (d, J = 1.5 Hz, 1H), 7.66 (s. 1H), 7.63 (d, J = 6.0 Hz, 2H), 7.53 (dd, J = 6.0 Hz, J = 1.5 Hz, 1H), 7.32–7.38 (m, 3H), 3.86 (s, 3H) and 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 175.4, 142.2, 138.0, 134.2, 133.8, 133.5, 132.4, 129.7, 128.2, 127.0, 126.6, 119.9, 115.2, 40.7 and 21.0; IR (neat) 1615 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{17}H_{15}NOCl$ 284.0837 found 284.0839.

4.1.65. 3-(4-Bromophenyl)-1,6-dimethyl-1H-quinolin-4-one ***(16d)***

This compound was prepared by procedure **4.1.62** with the exception that 2-(4-bromophenyl)-3-(methyl-*p*-tolylamino)acrylic acid methyl ester was used in the reaction, in which case a 92% yield of a white solid was obtained, which exhibited the following properties: mp 179–180 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.36 (broad s, 1H), 7.67 (s, 1H), 7.51–7.60 (m, 5H), 7.34 (d, J = 6.0 Hz, 1H), 3.86 (s, 3H) and 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 175.4, 142.1, 138.1, 134.6, 133.9, 133.5, 131.3, 130.2, 127.1, 126.9, 120.8, 120.3, 115.1, 40.7 and 21.0; IR (neat) 1614 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{17}H_{15}NOBr$ 328.0332 found 328.0317.

4.1.66. 3-(3,4-Dimethoxyphenyl)-1,6-dimethyl-1H-quinolin-4-one ***(16e)***

This compound was prepared by procedure **4.1.62** with the exception that 2-(3,4-dimethoxyphenyl)-3-(methyl-*p*-tolylamino) acrylic acid methyl ester. was used in the reaction, in which case an 88% yield of a yellow solid was obtained, which exhibited the following properties: mp 157–159 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.39 (d, J = 3.0 Hz, 1H), 7.70 (s, 1H), 7.53 (dd, J = 9.0, J = 3.0 Hz, 1H), 7.48 (d, J = 3.0 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 7.12 (dd, J = 9.0, J = 3.0 Hz, 1H), 6.94 (d, J = 9.0 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H) and 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 175.8, 148.6, 148.18, 141.9, 138.0, 133.6, 133.3, 128.6, 127.0, 126.8, 121.2, 120.3, 115.0, 112.6, 111.2, 56.0, 40.6 and 20.9; IR (neat) 1572 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{19}H_{20}NO_3$ 310.1438 found 310.1440.

4.1.67. 1,6-Dimethyl-3-(3,4,5-trimethoxyphenyl)-1H-quinolin-4-one ***(16f)***

This compound was prepared by procedure **4.1.62** with the exception that 3-(methyl-*p*-tolylamino)-2-(3,4,5-trimethoxyphenyl)acrylic acid methyl ester was used in the reaction, in which case an 83% yield of a yellow solid was obtained, which exhibited the following properties: mp 210–211 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.40 (d, J = 3.0 Hz, 1H), 7.71 (s, 1H), 8.40 (dd, J = 9.0, J = 3.0 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1 H), 6.96 (s, 2H), 3.93 (s, 6H), 3.90 (s, 3H), 3.89 (s, 3H) and 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 175.6, 153.0, 142.2, 138.0, 137.3, 133.8, 133.5, 131.3, 127.1, 126.8, 121.3, 155.1, 106.1, 60.8, 56.2, 40.7 and 20.9; IR (neat) 1582 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{20}H_{22}NO_4$ 340.1543 found 340.1547.

4.1.68. 1,6-dimethyl-3-phenyl-1H-quinolin-4-one ***(16g)***

This compound was prepared by procedure **4.1.62** with the exception that 3-(methyl-*p*-tolylamino)-2-phenylacrylic acid methyl ester was used in the reaction, in which case a 92% yield of a yellow solid was obtained, which exhibited the following properties: mp 150–151 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.39 (broad s, 1H), 7.69–7.71 (m, 3H), 7.53 (dd, J = 9.0, J = 2.0 Hz, 1H), 7.43 (t, J = 6.0 Hz, 2H), 7.32–7.37 (m, 2H), 3.87 (s, 3H) and 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 175.7, 142.4, 138.0, 135.7, 133.6, 133.3, 128.6, 128.2, 127.0, 126.8, 126.6, 121.3, 115.2, 40.6 and 21.0; IR (neat) 1609 cm^{-1}; HRMS (ES, M+H) *m*/*z* calcd for $C_{17}H_{16}NO$ 250.1226 found 250.1221.

4.1.69. 1-Ethyl-3-(4-methoxyphenyl)-6-methyl-1H-quinolin-4-one ***(16h)***

This compound was prepared by procedure **4.1.62** with the exception that 3-(ethyl-*p*-tolylamino)-2-(4-methoxy-phenyl) acrylic acid methyl ester was used in the reaction, in which case a 59% yield of a yellow oil was obtained, which exhibited the following properties: bp 202 °C @ 0.92 torr; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.39 (d, J = 2.0 Hz, 1H), 7.70 (s, 1H), 7.65 (d, J = 9.0 Hz,

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2H), 7.50 (dd, $J = 9.0$, $J = 2.0$ Hz, 1H), 7.37 (d, $J = 9.0$ Hz, 1H), 6.98 (d, $J = 9.0$ Hz, 2H), 4.24 (q, $J = 6.0$ Hz, 2H), 3.86 (s, 3H), 2.51 (s, 3H) and 1.54 (t, $J = 6.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 175.1, 158.7, 140.6, 136.9, 133.2, 133.1, 129.7, 128.3, 127.4, 127.1, 121.5, 114.9, 113.7, 55.3, 48.0, 20.9 and 15.6; IR (neat) 1608 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{19}H_{20}NO_2$ 294.1489 found 294.1452.

4.1.70. 6-Methoxy-3-(4-methoxyphenyl)-1-methyl-1H-quinolin-4-one (16i)

This compound was prepared by procedure **4.1.62** with the exception that 2-(4-methoxyphenyl)-3-[(4-methoxyphenyl)-methylamino]acrylic acid methyl ester was used in the reaction, in which case a 74% yield of a pale yellow solid was obtained, which exhibited the following properties: mp 158–160 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 7.98 (d, $J = 2.8$ Hz,1H), 7.65 (d, $J = 9.0$ Hz, 2H), 7.64 (s, 1H), 7.37 (d, $J = 9.0$ Hz, 1H), 7.29 (dd, $J = 9.0$ Hz, $J = 2.8$ Hz, 1H), 6.98 (d, $J = 9.0$ Hz, 2H), 3.95 (s, 3H) and 3.85 (s, 6 H) ^{13}C NMR ($CDCl_3$; 75 MHz) δ 175.2, 158.7, 156.4, 141.2, 134.6, 129.7, 128.3, 128.1, 122.6120.1, 116.7, 113.7, 106.6, 55.8, 55.3 and 40.8; IR (neat) 1609 cm^{-1}; HRMS (ES, M+Na) m/z calcd for $C_{18}H_{17}NO_3Na$ 296.1281 found 296.1281.

4.1.71. 6-Bromo-3-(4-methoxyphenyl)-1-methyl-1H-quinolin-4-one (16j)

This compound was prepared by procedure **4.1.62** with the exception that 3-[(4-bromophenyl)methylamino]- 2-(4-methoxyphenyl)acrylic acid methyl ester was used in the reaction, in which case a 78% yield of a yellow solid was obtained, which exhibited the following properties: mp 195–197 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 8.58 (d, $J = 2.0$ Hz, 1H), 7.63 (dd, $J = 9.0$ Hz, $J = 2.0$ Hz, 1H), 7.56 (s, 1H), 7.54 (d, $J = 9.0$ Hz, 2H), 7.20 (d, $J = 9.0$ Hz, 1H), 6.90 (d, $J = 9.0$ Hz, 2H) and 3.81 (s, 3H) and 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$; 75 MHz) δ 174.5, 158.8, 142.2, 138.5, 134.6, 129.7, 129.5, 128.2, 127.4, 121.9, 117.3, 117.1, 113.7, 55.3 and 40.67; IR (neat) 1577 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{17}H_{15}NO_2Br$ 344.0281 found 344.0284.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2018.10.078.

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